ISSN: 2754-5016

Journal of Immunology Research & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

COVID-19 Reinfection: Can Humoral or Cellular Immune Status Predict need for Vaccination and which Vaccine is more Effective: mRNA Booster or Inactivated whole Virus (VLA2001)?

Erpenbach K[1,2*], Erpenbach AS[2], Mayer W[3] and Seidl H[4]

[1]Private practice for General Medicine-internal medicine, Marienstraße 1, 50374 Erftstadt, Germany

[2]Institute for Medical Performance Optimization and Training Control, Marienstraße 1, 50374 Erftstadt, Germany

[3]Lab4More GmbH Bavariahaus, Augustenstraße 10, 80333 Munich, Germany

[4]Immundiagnostik AG, Stubenwald-Alle 8A, 64625 Bensheim, Germany

ABSTRACT

Background/Introduction: The SARS-CoV-2 B.1.1.529 variant (Omicron) has shown high infectivity worldwide, even in vaccinated patients. Little is known about how well naturally acquired immunity protect against further COVID-19 infections in unvaccinated or vaccinated patients. We investigated whether vaccination is still warranted, and if so, what type of vaccine should be used.

Methods: 36 patients with previous PCR-confirmed SARS-CoV-2-omicron infection (10 unvaccinated, 10 with Valneva booster vaccination and 16 triple vaccinated with mRNA), were included in this six-month prospective observational study from Oct2022 to Mar2023. SARS-CoV-2-Omicron immune status (SARS-CoV-2 immunoblot nucleoprotein IgG (BLOT-NP)) was analyzed four weeks after acute illness or Valneva booster vaccination, along with neutralizing antibodies IgG-S1 spike (NAB-S1) and T-cell response interleukin2 (ITT-BA5-IL2) or interferon (ITT-BA5-IFN) against Omicron-BA5 in blood samples. Endpoint at follow-up was PCR-confirmed reinfection with a SARS-CoV-2 variant. Wilcoxon-, Pearson-Chi-Square- and Whitney-U-tests were used for statistical analysis. $p \leq 0.05$ was assumed to be significant and $p \leq 0.01$ highly significant.

Results: The ten patients in the Valneva group, all older than 60 years (75.4 ± 13.3 y) showed no persisting humoral or cellular immunity to SARS-CoV-2-Omicon in their blood at baseline. These patients were boosted with inactivated whole virus vaccine VLA2001 against SARS-CoV-2. Immunity was fully restored within 4 weeks (BLOT-NP before 0 vs. after 1.2 ± 1.2 [p=0.026], ITT-BA5-IL2 before 5.7 ± 7.5 pg./mL vs. after 11.2 ± 9.9 pg./mL [p=0.063], ITT-BA5-IFN before 1.7 ± 2.6 pg./mL vs. after 5.5 ± 4.5 pg./mL [p=0.011]). There were no side effects of vaccination. Compared to the group of unvaccinated patients (N=10) or the triple mRNA-vaccinated patients (N=16), patients in the Valneva group suffered fewer reinfections with a SARS-CoV-2 variant during follow-up (40% vs. 25% vs. 20% [p=0.575]). All patients reinfected with SARS-CoV-2 (N=10) had either a metabolic syndrome (N=5: diabetes mellitus and obesity) or a neuro-degenerative-psychiatric disease [N=5: dementia (2), anxiety disorder (2), depression (1)]. In the BLOT-NP, patients with reinfection showed a significantly poorer immune response compared to patients without reinfection, both in the group of unvaccinated patients and in the group of Valneva-vaccinated patients, but not in the group of mRNA-vaccinated patients (BLOT-NP reinfection yes vs. no unvaccinated: 0.5 ± 0.7 vs. 1.38 ± 1.30 [p=0.041] / Valneva-vaccinated: 1.0 ± 0.82 vs 2.32 ± 0.82 [p=0.046] / mRNA-vaccinated: 2.0 ± 0.82 vs 2.42 ± 0.79 [p=n's.]). In ITT-BA5-IL2 and ITT-BA5-IFN, patients with reinfection showed significantly poorer cellular immunity to SARS-CoV-2-Omicron compared with patients without reinfection, not only within the Valneva-vaccinated group, but also in the groups of unvaccinated and mRNA-vaccinated patients (ITT-BA5-IL2 reinfection yes vs. no with Valneva vaccination vs. 0 vaccination vs. 3 vaccination: 0 vs. 14 ± 8.99 pg./mL [p=0.036] / 4.75 ± 5.5 vs. 17.5 ± 26.82 pg./mL [p=n's.] / 40.5 ± 31.98 vs. 47.25 ± 91.14 pg./mL [p=n's.] - ITT-BA5-IFN reinfection yes vs. no with Valneva vaccination vs. 0 vaccination vs. 3 vaccination: 0 vs. 6.88 ± 3.83 pg./mL [p=0.034] / 2.5 ± 4.36 vs. 4.83 ± 4.88 pg./ml [p=n's.] / 10.25 ± 8.18 vs. 30.17 ± 34.07 pg./mL [p=n's.]).

Conclusion: Recurrent mutations of the SARS-CoV2 virus continue to cause acute infection, the current variant EG5 triggering significantly more severe COVID-19 symptoms than the previous variant Omicron BA5. Patients over 65 years of age with high-risk underlying illnesses and a lack of humoral protection (SARS-CoV-2 nucleoprotein IgG antibodies) as well as limited or no cellular protection (ITT-BA5-IFN) are highly likely to experience reinfection. In this prospective study the whole virus vaccination VLA2001 was found to be effective in restoring humoral or cellular immune protection. mRNA vaccination, on the other hand, failed to restore humoral immune protection (SARS-CoV-2 nucleoprotein IgG antibodies) and can therefore no longer be recommended for immune boosting.

***Corresponding author**

Erpenbach K, Private Practice for General Medicine-Internal Medicine, Marienstraße 1, 50374 Erftstadt, Germany.

Received: February 05, 2024; **Accepted:** February 13, 2024; **Published:** February 19, 2024

Introduction

The SARS-CoV-2 B.1.1.529 variant (Omicron) with its 34 mutations in the spike protein showed a high infectivity and disease rate worldwide in 2022, even in vaccinated patients [1]. Triple vaccination with BNT162b2 or mRNA1273 or a combination of infection with Wuhan- or Delta-SARS-CoV-2 followed by vaccination, increased the concentration of neutralizing antibodies in serum compared to double-vaccinated or convalescent

patients. However, the neutralizing effect against Omicron- was drastically lower than against the Wuhan- or Delta-variants, which explains the high transmission rate of Omicron variant in vaccinated individuals [2-7]. Only antibodies against SARS-CoV-2 nucleoprotein IgG (BLOT-NP) and T-cell response (interleukin2 [IL2] or ß-interferon [IFN]) against the SARS-CoV-2 variant BA5 have been found to be therapeutically effective in protecting against further COVID-19 infection [8]. Patients immunized with the inactivated whole virus vaccine (VLA2001) against SARS-CoV-2 show these protective immune responses in the BLOT-NP as well as in the T-cell response IL2 or IFN [9,10]. The aim of this study was to compare humoral and cellular immune response and the occurrence of acute reinfection with SARS-CoV-2 variants in high-risk patients boosted using the whole virus vaccine VLA2001 with those of unvaccinated and triple mRNA (BNT162b2)-vaccinated patients after acute Omicron-SARS-CoV-2 infection. In addition, we sought to discover, whether immunological threshold values in the BLOT-NP or ITT-BA5-IL2/-IFN can be determined to predict the risk of reinfection and whether mRNA vaccination currently offers the best possible protection.

Methodology

Of the 36 patients with PCR-verified SARS-CoV-2-Omicron infection included in this prospective follow-up study, ten were unvaccinated, ten received a subsequent whole virus (VLA2001) booster vaccination, and 16 participants had received three mRNA (BNT162b2) vaccinations. All patients gave written informed consent to participation in the study. The ten participants boosted with VLA2001 no longer had detectable humoral (BLOT-NP) or cellular (ITT-BA5-IL2/IFN) immune status at the time of boosting. The SARS-CoV-2 Omicron immune status of the patients was tested in whole blood samples as follows 4 weeks after acute COVID-19 infection or VLA2001 booster vaccination: SARS-CoV-2 immunoblot nucleoprotein IgG (BLOT-NP), IgG-S1 neutralizing antibodies (NAB-S1), T cell response interleukin2 (ITT-BA5-IL2) or interferon (ITT-BA5-IFN) against Omicron-BA5. All patients were followed up for six months (October 2022 through March 2023). The follow-up endpoint was PCR-confirmed reinfection with a SARS-CoV-2 variant.

SARS-CoV-2 Blot Antibody (BLOT-NP)

Semi-quantitative detection of IgG antibodies against the nucleocapsid protein of SARS-CoV-2 was carried out according to the manufacturer's instructions using a commercial CE strip immunoassay from Mikrogen, Neuried (Recom Line SARS-CoV-2 IgG, article no. 7374) with recombinantly produced antigens. Results were evaluated automatically using the Recom-Scan software from the same manufacturer according to the manufacturer's instructions.

SARS-CoV-2 Neutralizing Antibody IgG-S1 (NAK-S1)

Quantitative detection of IgG antibodies against SARS-CoV-2 was carried out using the commercial, CE-labeled assay from Diasorin, Dietzenbach (SARS CoV-2 TrimericS IgG, article no. 311510) on their LIAISON® automated laboratory system according to the manufacturer's instructions.

T Cell Response (ITT) Omicron-BA5-IL2 / -IFN

Heparinized whole blood was diluted 1:1 with Roswell Park Memorial Institute (RPMI) medium and then left unstimulated (negative control), incubated with influenza antigen (positive control), or incubated with validated concentrations of commercially available SARS CoV-2-Omicron Spike S1 full antigen (amino acids 14-681) for 24 hours at 37°C. The supernatant of the whole blood cultures was taken and the concentration of the cytokines interferon-gamma (IFN) and interleukin 2 (IL2) was determined. Luminex technology and commercially available, CE-labeled reagent kits for IL2 (Art.No.171-B5003M) and IFN-γ (Art.No.171-B5019M) from Biorad Laboratories, Feldkirchen, were deployed according to the manufacturer's instructions.

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) 24 (IBM Corporation, Armonk, NY, USA) and Microsoft Excel 2016 (Microsoft Corporation, Redmond, WN, USA). Due to the small size of the subgroups, quantitative parameters were described by mean, median and minimum-maximum values. Pairwise comparisons were conducted using Wilcoxon- and the non-parametric Mann–Whitney-U test. Absolute and percentage frequencies were used to describe nominal values and the chi-square test was used to determine relationships between categorical variables. In all statistical tests, results were interpreted as statistically significant where p was less than 0.05, with $p \leq 0.01$ considered highly significant.

Results

36 patients who previously had a PCR-confirmed acute COVID-19 infection with the Omicron variant were included in the study. Ten patients (age: 50.2 ± 10.3 6 women - 4 men) were unvaccinated prior to acute COVID-19 infection with the Omicron variant and 16 patients (age: 57.6 ± 12.8, 11 women - 5 men) were vaccinated three times with an mRNA vaccine [BNT162b2 (Pfizer/BioNTech)]. Ten patients (age: 75.4 ± 13.3 6 women - 4 men), in whom neither humoral (BLOT-NP) nor cellular (ITT-BA5-IL2/IFN) immunity was detectable after infection with the Omicron variant before inclusion in the study, were vaccinated once with an inactivated whole virus (VLA2001) vaccine. These participants were considered high-risk patients (age > 65 years with one or more underlying diseases with increased risks) and were significantly older than the unvaccinated or triple mRNA-vaccinated participants. However, they did not differ in terms of gender (Table 1). In these ten patients a single vaccination of inactivated whole virus VLA2001 against SARS-CoV-2 led to restoration of immunity within 4 weeks (BLOT-NP before 0 vs. after 1,2 ± 1.2 [p=0.026], ITT-BA5-IL2 before 5.7 ± 7.5 pg/mL vs. after 11.2 ± 9.9 pg/mL [p=0.063], ITT-BA5-IFN before 1.7 ± 2.6 pg/ml vs. after 5.5 ± 4.5 pg/mL [p=0.011]). There were no vaccination side effects (Figure 1a-d).

Table 1: Demographic Characteristics (participants). N = Number, SD = Standard Deviation, Min = Minimum, Max = Maximum - * p=0.001 - † p=0.002 - § p=0.109

Characteristics	VLA2001-Vaccination	No Vaccination	3xBNT162b2- Vaccination
Age at baseline (years)			
N	10	10	16
Mean (SD)	75.4 (13.3) * †	50.2 (10.3)* §	57.6 (12.8) † §
Median	80.5	52.0	56.5
Min, Max	48, 89	35, 66	31, 75
Gender			
Male	4	4	5
Female	6	6	11
p=0,863			

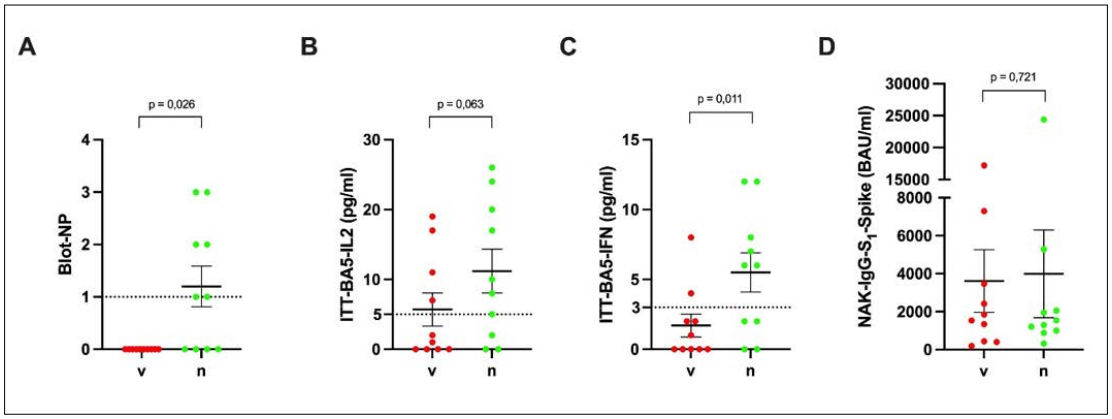

Figure1 a-d: MEAN Values of Neutralizing Antibodies (NAK) S1-IgG, Immunoblot Antibodies Against Nucleoprotein (Blot-NP), T Cell Response to SARS-CoV2-Omicron BA5-Interleukin2 (ITT_BA5-IL2) and -Interferon (ITT_BA5-IFN) before (red dots) and 4 weeks after Vaccination with VLA2001 (green dots) in 10 Selected Patients (< 60 years with risk diseases). v = Before Booster Vaccination with VLA2001 - n = after Booster Vaccination with VLA2001

Compared to the group of unvaccinated patients (N=10) or the triple BNT162b2-vaccinated patients (N=16), the patients in the Valneva group suffered fewer reinfections with a SARS-CoV-2 variant during follow-up (40% vs. 25% vs. 20% [p=0.575]) [Table 2]. All patients with SARS-CoV-2 reinfection (N=10) had either a metabolic syndrome (N=5: diabetes mellitus and obesity) or a neuro-degenerative-psychiatric disease [N=5: dementia (2), anxiety disorder (2), depression (1)]. In the IMMUNOBLOT antibody against nucleoproteins (BLOT-NP), patients with reinfection showed a significantly worse immune response compared to patients without reinfection both in the group of unvaccinated patients and in the group of VLA2001-vaccinated patients, but not in the group of triple mRNA-vaccinated patients (BLOT-NP reinfection vs. without reinfection - VLA2001-vaccinated: 0.5 ± 0.7 vs 1.38 ± 1.30 [p=0.041] / unvaccinated: 1.0 ± 0.82 vs 2.33 ± 0.82 [p=0.046] / 3xBNT162b2-vaccinated: 2.0 ± 0.82 vs 2.42 ± 0.79 [p=0.321]). In ITT-BA5-IL2 and ITT-BA5-IFN, T cell response indicated significantly poorer cellular immunity to SARS-CoV-2-Omicron in patients with vs. without reinfection only within the VLA2001-vaccinated group. In the groups of unvaccinated and BNT162b2-vaccinated patients, patients with reinfection also had worse cellular immunity than the patients without reinfection (ITT-BA5-IL2 reinfection vs. without reinfection - VLA2001 vaccination: 0 vs. 14 ± 8.99 pg/mL [p=0.036] / unvaccinated: 4.75 ± 5.5 vs. 17.5 ± 26.82 pg/mL [p=0.336] / 3xBNT162b2 vaccinated: 40.5 ± 31.98 vs. 47.25 ± 91.14 pg/mL [p=0.504] - ITT-BA5-IFN reinfection vs. without reinfection - VLA2001 vaccination: 0 vs. 6.88 ± 3.83 pg/mL [p=0.034] / unvaccinated: 2.5 ± 4.36 vs. 4.83 ± 4.88 pg/mL [p=0.330] / 3xBNT162b2-vaccinated: 10.25 ± 8.18 vs. 30.17 ± 34.07 pg/mL [p=0.300] [Table 2].

Table 2: Immunoblot Antibody Nucleoprotein, T Cell Response in the Immune Tolerance test (ITT)-OmicronBA5-Interleukin2 and -Interferon and IgG-S1-Spike Neutralizing Antibody of the 3 Groups (VLA2001-Vaccinated, Unvaccinated, 3xBNT162b2-Vaccinated) in Participants with Re-Infection Versus without Re-Infection. N = Number, SD = Standard Deviation, Min = Minimum, Max = Maximum

Characteristic	VLA2001 Vaccination N=10	No vaccination N=10	3x-BNT162b2 Vaccination N=16
Re-infection (%)	2/10 (20)	4/10 (40)	4/16 (25)
IMMUNBLOT antibody nucleoprotein (range: 0-3)			
with reinfection			
Mean (SD)	0.5 (0.71)	1.0 (0.82)	2.0 (0.82)
Median	0.5	1.0	2.0
Min, Max	0, 1	0, 2	1, 3
without reinfection			
Mean (SD)	1.38 (1.30)	2.33 (0.82)	2.42 (0.79)
Median	1.5	2.5	3.0
Min, Max	0, 3	1, 3	1, 3
Significance	**0.041**	**0.046**	0.321
IgG-S1-Spike Neutralizing Antibodies (norm < 34 BAU/ml)			
With Reinfection			
Mean (SD)	762 (633.57)	<34 (0)	9662.50 (6230.17)
Median	762	<34	9880
Min, Max	314, 1210	<34, <34	2790, 16100
Without Reinfection			
Mean (SD)	4799 (8042.68)	<34	15707.50 (11257.79)
Median	1745	<34	14400
Min, Max	876, 24400	<34, <34	1360, 32600
Significance	0.117	1.000	0.467

Discussion

Rapidly progressing mutations of the SARS-CoV-2 virus continue to cause acute COVID-19, with the current variant EG5 triggering significantly more severe symptoms than the previous variant, Omicron BA5. In particular, patients over 65 years of age with high-risk underlying disease and a lack of humoral protection (SARS-CoV-2 nucleoprotein IgG antibodies) as well as limited or no cellular protection (ITT-BA5-IFN) are extremely likely to experience reinfection. Since detection of the Omicron variant in 2022, new mutations of the SARS-CoV2 virus (BA1, BA4, BA5, XBB1.5, XBB1.9, XBB1.16, EG5, EG5.1) have emerged at increasingly shorter intervals. Characteristic for these mutations is that they bypass the spike protein, including a high resistance to IgG-S1-spike neutralizing antibodies and thus, a high rate of breakthrough infections [11]. Recently, an et al demonstrated that the SARS-CoV2 variants XBB1.5, XBB1.16, EG5 and EG5.1 showed significant resistance to vaccine-induced neutralizing immunity, with geometric mean titers (GMTs) close to or below the limit of detection (LOD) [12]. Thus, only therapeutically effective humoral antibodies against SARS-CoV2 nucleoprotein IgG (BLOT-NP) and a therapeutically effective T cell response (interleukin2 or ß-interferon) can protect against SARS-CoV-2 variants and thus against COVID-19 reinfections [8]. In previous research, patients administered a basic immunization with inactivated whole virus vaccine (VLA2001) against SARS-CoV-2 showed these protective immune responses in the BLOT-NP as well as in the IL2 or IFN T cell response and had no serious side effects related to the vaccine [9,10]. In our study, the single booster vaccination with VLA2001 was well tolerated, with no side effects even in patients with high-risk underlying diseases over 65 years of age. Patients boosted with VLA2001 developed significant, therapeutically effective humoral (BLOT-NP) and T cellular (ITTBA5-IL2 / -IFN) immune protection within 4 weeks. The VLA2001 vaccine proved significantly more effective in protecting against COVID-19 reinfection compared with either naturally acquired immunity following infection with the Omicron BA5 variant, or a triple BNT162b2 vaccination (reinfection 20% vs. 40% vs. 25%). Comparable studies are currently not available. Comparisons of humoral (BLOT-NP) or T cellular immunity (IL2/IFN) of patients with reinfection by SARS-CoV-2 variants versus patients without reinfection are also unavailable in the international literature. In our study, patients with reinfection - regardless of whether they were unvaccinated or vaccinated (either with the VLA2001 whole virus vaccination or triple BNT162b2 vaccination) - showed significantly worse humoral or T cellular immunity (Table 2). A vaccination recommendation can be derived from this, especially for patients over 65 years of age who are at increased risk due to existing underlying diseases (Figure 2). If humoral immunity in IMMUNOBLOT nucleoprotein ≤ 1 and the T cellular immune response in ITT-BA5 interleukin 2 is below 5 pg/mL and ITT-BA5 interferon is below 3 pg/mL, a single vaccination with the whole virus VLA2001 vaccine should be recommended, especially for patients over 65 years of age with or without additional health risks. This also applies to patients of any ages who suffer from metabolic syndrome, obesity with diabetes mellitus or neuro-degenerative diseases, or who are being treated with psychotropic drugs for depression, anxiety disorders or other psychiatric illnesses. Unfortunately, in december 2023,

the vaccination recommendation for VLA2001 was withdrawn and the manufacturer therefore stopped production.

Immunoblot antibodies against nucleoprotein (range: 0-3)	**T cell response ITT-BA5-Interleukin2** (norm > 3 pg/ml)	**T cell response ITT-BA5-Interferon** (norm > 3 pg/ml)
≤ 1	≤ 5	≤ 3

Figure 2: Threshold Values of Immunoblot Antibodies Against Nucleoprotein, T Cell Response in the Immunotolerance test (ITT)-Omicron-BA5-Interleukin2 or-Interferon (INF) for a Vaccination Recommendation in Patients > 65 years of age with these Additional Underlying Risk Factors:

- Metabolic syndrome
- Diabetes mellitus
- Obesity (BMI > 35)
- Heart failure
- COPD > grade 2 GOLD standard
- Neurodegenerative diseases (MS, dementia, Alzheimer´s, Parkinson´s, ALS)
- Patients undergoing psychotropic drug therapy (depression, anxiety disorder, obsessive-compulsive disorder, schizophrenia)
- Immunotherapy patients (malignoma, autoimmune diseases)

Summary

Whole virus (VLA2001) vaccination was found to be effective in restoring humoral or cellular immune protection against SARS-CoV-2-vaiants. mRNA vaccination, on the other hand, failed to restore humoral immune protection (SARS-CoV2 nucleoprotein IgG antibodies). Consequently, although vaccination with a bivalent mRNA vaccine can protect against fatality, it does not prevent infection with the EG5 variant [11]. Only antibodies against nucleoproteins (NP) appear to be therapeutically effective and can effectively protect against further COVID-19 infections. The mRNA vaccine can therefore no longer be recommended for immune boosting. Further studies in larger populations are need to confirm whether booster vaccination with a whole-virus vaccine is more useful and more effective in protecting against further COVID-19 infections than bivalent or multivalent mRNA vaccines.

Acknowledgment

The authors would like to express their thanks to Janet Collins (ICCC Rhein-Main, Frankfurt, Germany) for linguistic correction and editing of the manuscript.

References

1. Han P, Li L, Liu S, Wang Q, Zhang D, et al. (2022) Receptor binding and complex structures of human ACE2 to spike RBD from omicron and delta SARS-CoV-2. Cell 185: 630-640.
2. Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, et al. (2022) Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. Nature 602: 671-675.
3. Cameroni E, Bowen JE, Rosen LE, Saliba C, Zepeda SK, et al. (2022) Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. Nature 602: 664-670.
4. Dejnirattisai W, Huo J, Zhou D, Zahradnık J, Supasa P, et al. (2022) SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses. Cell 185: 467-484.
5. Dejnirattisai W, Shaw RH, Supasa P, Liu C, Stuart AS, et al. (2022) Reduced neutralization of SARS-COV-2 Omicron-B.1.1.529 variant by post-immunization serum. Lancet 399: 234-236.
6. Edara VV, Manning KE, Ellis M, Lai L, Moore KM, et al. (2022) mRNA-1273 and BNT162b2 mRNA vaccines have reduced neutralizing activity against the SARS-CoV-2 omicron variant. Cell Rep. Med 3: 100529.
7. Liu L, Iketani S, Guo Y, Chan JFW, Wang M, et al. (2022) Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2. Nature 602: 676-681.
8. Erpenbach K, Erpenbach AS, Mayer W, Weck M (2023) SARS-CoV-2-Omicron-variant Induced COVID-19-Infection in Unvaccinated and Vaccinated Patients: Impact on mmune Response, Symptomatology, and Risk of POST-COVID Syndrome. J Immuno Res Reports 3: 1-8.
9. LeGrand R, Galhaut M, Lundberg U, Marlin R, Bartuschka U, et al. (2023) High efficacy of VLA2001 vaccine against SARS-CoV2 infection in non-human primates. Research Square https://doi.org/10.21203/rs.3.rs-2867721/v1.
10. Taucher C, Lazarus R, Dellago H, Marer G (2022) Safety and immunogenicity against ancestral, Delta and Omicron virus variants following a booster dose of an inactivated whole-virus COVID-19 vaccine (VLA2001): Interim analysis of an open-label extension of the randomized, controlled, phase 3 COV-COMPARE trial. J Infection 85: 306-317.
11. Cobar O, Cobar S (2023) EG.5 Family of SARS-CoV-2; Will Overcome XBB.1.16 as the Most Prevalent Around the World? https://www.researchgate.net/profile/Oscar-Cobar/publication/373092876_EG5_Family_of_SARSCoV_Will_Overcome_XBB116_as_the_Most_Prevalent_Around_the_World/links/64d7c1f425837316ee094f64/EG5-Family-of-SARS-CoV-2-Will-Overcome-XBB116-as-the-Most-Prevalent-Around-the-World.pdf.
12. An Y, Zhou X, Tao L, Xie H, Yang C, et al. (2023) Neutralization of SARS-CoV-2 EG.5/EG.5.1 by sera from ZF2001 RBD-dimer and its next-generation vaccines. https://www.biorxiv.org/content/10.1101/2023.09.02.556038v1.