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Antibody Response to mRNA SARS-COV-2 Vaccine (BNT162b) In Hemodialysis Patients: Utility of an Anti-Trimerics Immunoassay Detection

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Abstract

Objectives: The literature describes the attenuated SARS-CoV-2 vaccine response in hemodialysis (HD) patients. Most studies detected humoral response against the monomeric form of the SARS-CoV-2 spike (S) glycoprotein, which has a trimeric structure. In our HD population, we examined the antibody (ab) titer after the second and third dose of mRNA vaccine, using anti-trimericS abs.

Methods: Forty-one of 51 HD patients evaluated matched the enrollment criteria (no evidence of previous or current SARS-COV 2 disease) and completed the entire follow up. We assessed ab response before (T0) and 15, 30, 60, 90 and 210 days (T1, T2, T3, T4, T5) after the second dose of mRNA vaccine, as well as 30 and 60 days (T6, T7) after the third dose. We also evaluated ab response in 43 healthcare workers (HCWs) at T5 and T7.

Results: Anti-trimericS IgG were above the assay cut-off in 100% of patients at T1, 97,5% at T2, 95,1% at T3, 92,7% at T4, 80% at T5, 100% at T6. We observed a reduction in anti-trimericS abs from T1 to T5 and a significant rise at T6 compared to all previous times of observation ($p<0,0001$). The third dose resulted in a significant increase in anti-trimericS IgG ($p<0,0001$) in both HCWs and HD cohorts, without significant differences between the 2 groups.

Conclusions: In our HD patients, using anti-trimericS abs, we described a higher seroconversion rate after 2 mRNA vaccine doses than that reported in literature. We confirmed the efficacy of the third dose in terms of ab response in the HD cohort, with no significant differences from a control population of HCWs.

Keywords: Anti-Trimerics Immunoassay, SARS-CoV-2

Introduction

The SARS-CoV-2 pandemic has represented the world major health emergency in the past two years. As shown by epidemiological WHO data updated to October 2022, about 600 million people have been infected and about 6 million people have died worldwide because of COVID-19 [1]. Hemodialysis (HD) patients represent a high-risk category of mortality in the case of SARS-CoV-2 infection. A study performed in the pre-vaccination era on 2178 HD patients in North America showed a higher prevalence of COVID-19 infection among this group than in the general population (14% vs 2, 6%); the mortality rate of HD patients was about 28% and advanced age (>65 y/o), HD vintage (with an increased risk of 10% per year of treatment), male gender and low socio-economic conditions were found to be risk factors for high mortality [2]. A survey conducted on a cohort

of 4700 extracorporeal and peritoneal dialysis patients in Italy between April and October 2020 showed a COVID-19 infection prevalence of 1, 8% with a mortality rate of 31, and 7% [3]. The study of humoral immunity obtained by vaccination plays a key-role in the fight against this pandemic.

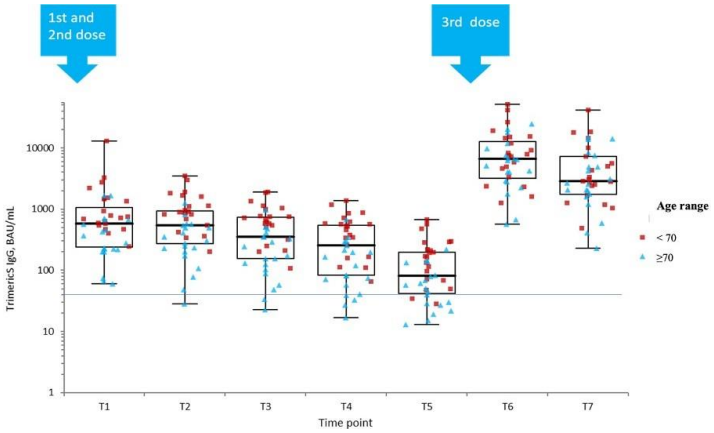

Figure 1: *Anti-trimericS IgG mean levels during the study follow-up: multiple comparisons using the Tukey-Kramer test. Boxplot displaying the minimum, maximum, sample median and first and third quartiles. Cut-off line: 33.8 BAU/ml. We registered a not statistically significant decline of anti-trimericS from T1 to T5. We observed a statistically significant rise following the 3rd vaccine dose (p<0.0001) at T6 compared to all previous times of observation. A T7 anti-trimericS IgG mean level, despite a significant decline compared to T6 (p=0.0005), remained significantly higher than all of the time points before the vaccine booster (p<0.001). Data are shown in Tables 2 and 3. Comparison by age was performed using two-way ANOVA with the Bonferroni test. Even if older patients (≥70 years) have lower levels of anti-trimericS IgG, differences between age ranges are not statistically significant.*

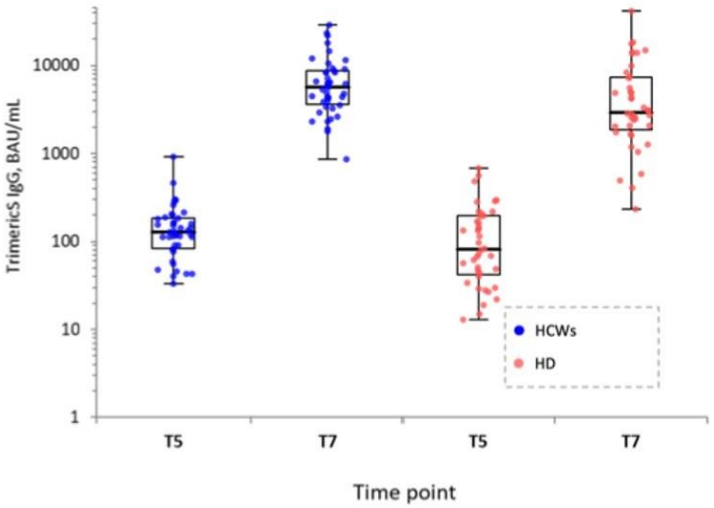

Figure 2: *Comparison between HCWs (healthcare workers) and HD (haemodialysis) patients before and after vaccine booster dose (3rd dose): two-way ANOVA analysis with the Bonferroni post-test for multiple comparisons. Vaccine booster dose results in a significant increase in IgG titers (p<0.0001) in both the HCW cohort as well as the HD cohort. No significant differences were measured at T5 and T7 when comparing HCWs versus HD patients, suggesting that this patient population responds similarly to apparently healthy subjects in terms of IgG levels after vaccination.*

The available mRNA vaccines produce an immune response by inducing cells to build the SARS-CoV-2 S glycoprotein, which has a trimeric structure with two functional subunits: S2 and S1. The S1 subunit contains the receptor binding domain (RBD), which directly interacts with the host ACE2 receptor and is considered a target of neutralizing antibodies (NAbs), defined as antibodies that defend a cell from a pathogen or infectious particle by neutralizing their biological effect [4-7]. Studies conducted on baseline anti-SARS-CoV-2 seronegative subjects revealed that immunogenicity after mRNA vaccination differed widely between recipients. Vaccine immunogenicity was found to be considerably attenuated in specific conditions such as chronic inflammatory diseases, malignancies, patients undergoing immunosuppressive treatments and in subjects with end-stage renal disease [8-10]. In the literature, a seroconversion rate after two doses of mRNA vaccine is reported in HD patients that is higher than 90%, although it is lower than in healthy controls [11-14]. Different studies reported that a third dose of mRNA vaccine substantially increases antibody levels in HD patients and allows seroconversion in most of the non-responders [15-21]. It is important to perform an accurate evaluation of antibody persistence over time and to identify the most appropriate serological test to monitor the humoral response induced by the SARS-CoV-2 vaccine. In our study, we have examined antibody titers after the second and third dose (booster) of mRNA vaccine in our HD population during a follow-up period of one year, using different immunoassays.

Patients and Methods

Patients

From the beginning of 2021, in our dialysis unit, humoral response to SARS- CoV-2 BNT162b2 vaccine was routinely monitored along with monthly blood tests before and after the three vaccine doses and periodically, depending on kit samples availability. We retrospectively evaluated 51 HD patients (17 female and 34 males) who received an mRNA Pfizer-BioNtech or BNT162b2 (Cominarty®) vaccine following the company's recommendation and assessed antibody response before (T0) and 15, 30, 60, 90 and 210 days (T1, T2, T3, T4 and T5) after the second dose of the mRNA vaccine (21 days between the two doses). We also assessed antibody response 30 (T6) and 60 (T7) days after the third dose of mRNA vaccine (administered 7 months after the second dose). No adverse reactions to SARS-CoV-2 vaccine occurred. Patients with evidence of previous or current SARS- CoV-2 disease were excluded from the study. To

better evaluate eventual asymptomatic patients or false negative nasopharyngeal swab RT-PCR tests, we performed total anti- NC (nucleocapsid) at T0 and during follow up and total anti-S1 Ab (IgA, IgG, IgM) at T0. Of the 51 patients enrolled, 41 completed the entire follow-up: 2 patients died (one with neoplastic complications and the other from septic shock), 2 left our dialysis unit, 2 underwent kidney transplantation and 4 patients had intercurrent SARS-CoV-2 infection (3 after two doses and 1 after one dose of mRNA vaccine). Demographic-anamnestic data of the definitive study populations are reported in Table 1. We used as control group a population of 43 health care workers whose antibody response was performed before (T5) and after (T7) the 3rd BNT162b2 vaccine dose in another study performed in our hospital.

Samples Collection

Blood samples were collected at T0, T1, T2, T3, T4, T5, T6 and T7 into serum-gel tubes (BD SST II Advance®, Becton Dickinson, NJ, USA) according to the standardized operating procedure and manufacturer's recommendations. Samples were centrifuged for 10 min at 1740 x g on a Sigma 3-16 KL centrifuge. Sera were liquidized, identified by a code to guarantee anonymity, and stored in the laboratory at -20°C. Frozen samples were thawed for 1 h at room temperature on the day of the analysis.

Detection of SARS-CoV-2 antibodies

Immunoassays used to study the time course of antibody response to anti-COVID-19 vaccines in HD patients were

Elecsys® Anti-SARS-CoV-2 antibodies (Roche) (99.80% specificity; sensitivity 99.5%) performed on the Cobas e411 analytical system (ECLIA) according to the manufacturer's instructions. This assay is based on a modified double-antigen sandwich immunoassay using recombinant N protein and is used for the specific detection of total SARS-CoV-2 antibodies, including IgM and IgG. Results are reported as signal sample/cutoff (COI) values and as qualitative results indicating non-reactivity (COI <1.0; negative) or reactivity (COI >1.0; positive).VITROS® Anti-SARS-CoV-2 Total (IgA, IgG, IgM) (100% specificity; 95% sensitivity) (Ortho Clinical Diagnostics), (HRP)-mediated chemiluminescence (CLIA), performed on the VITROS 3600 automated immunoassay analyzer according to the manufacturer's instructions. In this assay, specific antibodies against the recombinant S1 subunit of the S protein of SARS-CoV-2 are automatically analyzer. Results are reported as signal/cutoff (S/CO) values and as qualitative results indicating non-reactivity (S/CO <1.0; negative) or reactivity (S/CO >1.0; positive).LIAISON® SARS-CoV-2 TrimericS IgG (DiaSorin) (99.5% specificity; 98.7% sensitivity), performed on the analytical system LIAISON XL. It is a chemiluminescence immunoassay (CLIA), for the quantitative detection of anti-trimeric spike protein specific IgG antibodies to SARS-CoV-2. Results are expressed in BAU (Binding Antibody Unit)/ml: a sample ≥33.8 BAU/ml is considered reactive for IgG anti-SARS-CoV-2 antibodies. The test detects antibodies against the Trimeric complex, which includes the RBD site from the three subunits S1. According to the manufacturer package declarations, high LIAISON® doses (i.e. ≥520 BAU/mL) were compared to a higher microneutralization assay titer threshold of ≥1:80, to demonstrate concordance at high neutralizing antibody titers. Samples with values higher than 2080 BAU/ml were examined at the dilution of 1:20, as indicated in data sheet supplied by the company, and further tested at successive dilutions until the same value was obtained with each type of dilution (1:40, 1:80, 1:160) to exclude the hook effect. Furthermore, even samples< 2080 BAU/ml and close to the value of 500 BAU/ml were tested at the dilution of 1:20, obtaining the same value, to exclude the hook effect.

Statistical analysis

Data were analyzed using Analyse-it software for Microsoft Excel 4.60.1. Categorical variables are expressed as percentages/numbers; continuous variables are summarized as mean ± standard deviation (SD). The Tukey-Kramer multiple comparison analysis was performed to compare mean antibody levels at T1, T2, T3, T4, T5, T6 and T7. Two-way ANOVA and Bonferroni multiple comparison analyses were performed to compare mean antibody levels in different subgroups. Logistic regression analysis was performed to evaluate the effect of covariates on antibody response. A p value <0.05 was considered statistically significant.

Ethical approval

All study procedures were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by our institutional ethics committee (n. 0243678/2021). We used as control group a population of health care workers whose antibody response was monitored after the administration of BNT162b2 vaccine in a study performed in our hospital and approved by local ethics committee (n.0223816/2021). Informed consent was obtained from all individual participants included in the study.

Results

Of the 41 patients that completed the entire follow-up, 29 (70, 7%) were males and 12 (29, 3%) were females; the mean age was

69 (±11) years, the mean dialysis vintage was 87 (±69) months and the lymphocyte count at T0 was 1.29 (±0, 47) $10^3/\mu L$. In 6 (14,6%) patients, the ERSD cause was ADPKD, in 6 patients (14.6%) it was diabetes, in 15 subjects (36,6%) it was hypertension, in 12 patients (29,3%) it was glomerulonephritis and the cause of ERSD was unknown in 2 cases (Table 1).

Table 1: *Demographic and anamnestic data of the enrolled populations. HD: haemodialysis, ADPKD: autosomal dominant Polycystic Kidney Disease, HCWs: healthcare workers.*

Demographic/anamnestic data at T0		**HD patients (41)**	**HCWs** (43)
Males	n° (%)	29 (70,7)	29 (67,4)
Females	n° (%)	12 (29,3)	14 (32,6)
Age, years	mean (± SD)	69 (± 11)	57,2 (± 6,6)
Dialysis vintage, months	mean (± SD)	87 (± 69)	-
Lymphocyte count, $10^3/\mu L$	mean (± SD)	1,29 (± 0,47)	-
ERSD causes ADPKD	n° (%)	6 (14,6)	0 (0)
Diabetes	n° (%)	6 (14,6)	0 (0)
Hypertension	n° (%)	15 (36,6)	0 (0)
Glomerulonephritis	n° (%)	12 (29,3)	0 (0)
Unknown	n° (%)	2 (4,9)	-

Table 2: *Anti-trimericS IgG: seroconversion rate in the examined populations. Fifteen days after the second dose of m-RNA vaccine (T1), 100% of HD patients have a positive test. Over time, we observed a progressive reduction of anti-trimericS IgG mean levels from T1 to T5 and 8 patients (20%) became negative before the 3rd vaccine dose (data available only for 40 patients at T5). After the vaccine booster (T6, T7) 100% of patients had a positive test. A higher number of HD patients showed negative IgG results at 210 days after the second dose compared to HCWs (20% vs 2.3%), indicating that antibody persistence may be affected in some HD patients.*

Anti-TrimericS IgG		**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**
HD subjects	**Negative** (n°)	0	1	2	3	8	0	0
	Positive (n°)	41	40	39	38	32	41	41
	Prevalence Positive (%)	100%	97.5%	95.1%	92.7%	80%	100%	100%
	BAU/ml (mean ± SD)	1071,13 ± 2025,62	776,24 ± 744,25	508,46 ± 457,69	342,54 ± 321,58	141,49 ± 150,19	9945,54 ± 10609,90	5904,88± 7574,23
HCW subjects	**Negative** (n°)	-	-	-	-	1	-	0
	Positive (n°)	-	-	-	-	42	-	43
	Prevalence Positive (%)	-	-	-	-	97.7 %	-	100 %
	BAU/ml (mean ± SD)	-	-	-	-	159,84± 14,64	-	7360,81± 6054,45

Total anti-S1 Abs were absent at T0 (0, 08±0, 03), and total anti-NC Abs were negative from T0 (0, 08±0, 01) to T6 (0, 03±0, 02), confirming the absence of natural infection. Anti-trimericS IgG levels were above the assay cut-off (≥33,8 BAU/ml) in 100% patients (41/41) at T1, 97,5% (40/41) at T2, 95,1% (39/41) at T3, 92,7% (38/41) at T4 and 80% (32/40) at T5 (data available only for 40 patients at T5). After the third dose of mRNA vaccine (T6, T7), 100% of patients had a positive test (Table 2). Over time, we observed a reduction in anti-trimericS IgG mean levels from T1 to T5 and then a statistically significant increase was seen after the

third dose (T6) when compared to all previous times of observation (p<0,0001). We also registered a statistically significant reduction of anti-trimericS IgG mean levels at T7 when compared to T6 (p 0,005), but they remain significantly higher than those detected before the administration of the third dose (from T1 to T5) (Figure 1, Table 3). Older patients (≥70 years) generally had lower levels of anti-trimericS IgG, but differences between age ranges (<70 vs ≥70 years) were not statistically significant at all times of observation (Figure 1). We also evaluated anti- trimericS response before (T5) and after (T7) the 3rd vaccine dose (booster) in a cohort of healthcare workers (HCWs). Of the 43 HCWs enrolled 29 (67, 4%) were male, 14 (32, 6%) were female, mean age was 57, 2 (±6, 6) years. All subjects had normal renal function and declared that they had no other pathologies. Vaccine booster dose (3rd dose) results in a significant increase of IgG titers (p< 0, 0001) in both the HCWs cohort as well as the HD cohort. No significant differences were measured at T5 and T7 when comparing HCWs versus HD patients, even if at T5 a higher number of HD patients showed negative IgG results (20%) compared to HCWs (2,3%) (Figure 2). The logistic regression analysis did not show a significant effect on antibody response of the considered covariates: sex, age, dialysis vintage and cause of ERSD.

Discussion

In this study, we examined antibody titer after the second and third dose of anti-COVID-19 mRNA vaccine in our HD population, during a follow-up period of one year, with different immunoassays.

The combined use of serological tests directed towards different viral proteins (spike and nucleocapsid) was useful in discriminating immunization derived from vaccine and immunization derived from natural infection. In fact, we excluded patients with previous or current SARS- CoV-2 infection by performing total anti-S1 at T0 and total anti-NC total Abs during the entire follow- up.

In the literature, a seroconversion rate of about 95% is described in the general population 7 days after two doses of mRNA vaccine [22]. In the HD population, a seroconversion rate ranging from 82% to 93,4% is reported 2 to 6 weeks after the 2nd dose of mRNA vaccine [11-14]. A study showed that the use of the trimeric compared to the monomeric form of the S protein is associated with greater sensitivity in the detection of SARS-CoV-2 IgG antibody response in both the acute and post-infection phases [23]. In our study, most HD patients developed a substantial humoral response following two anti-SARS-CoV-2 mRNA vaccine doses (100% positive patients at T1, 97,7% at T2, 95,1% at T3) using an anti-trimericS abs. In literature is described that only 50% of neutralizing antibodies binds the RBD region, the other 50% binds the N-terminal part of the S protein.

Table 3: *Anti-trimericS mean difference during the study follow-up: multiple comparisons using the Tukey- Kramer test. Comparison between time point's post-vaccine booster (T6 and T7) and time point's pre-vaccine booster (from T1 to T5) were statistically significant, confirming the efficacy of the 3rd vaccine dose.*

Contrast	Anti-trimericS IgG (BAU/ml) mean difference	p-value
T1 - T2	294,89	1
T1 - T3	562,67	0,9987
T1 - T4	728,59	0,9946
T1 - T5	929,64	0,9811
T1 - T6	-8874,41	**<0,0001**
T1 - T7	-4833,75	**0,0003**
T2 - T3	267,78	1
T2 - T4	433,70	0,9997
T2 - T5	634,75	0,9976
T2 - T6	-9169,30	**<0,0001**
T2 - T7	-5128,64	**0,0001**
T3 - T4	165,92	1
T3 - T5	366,97	0,9999
T3 - T6	-9437,08	**<0,0001**
T3 - T7	-5396,42	**<0,0001**
T4 - T5	201,05	1
T4 - T6	-9603,00	**<0,0001**
T4 - T7	-5562,34	**<0,0001**
T5 - T6	-9804,05	**<0,0001**
T5 - T7	-5763,39	**<0,0001**
T6- T7	4040,66	**0,0057**

The trimeric assay can capture all the antibodies produced. Furthermore, mutations in the ACE2 binding region of RBD can affect neutralization capacity. In conclusion, anti-trimericS abs can evaluate a wider humoral response which includes both anti-RBD and antibodies against other epitopes of spike protein with neutralizing capacity [7,24]. These findings suggest that the anti-trimericS assay could be useful also to detect antibodies directed towards new SARS-CoV-2 variants with RBD mutations.

We observed a progressive decline of anti-trimericS mean levels. A similar decline of the anti-spike IgG titer is described in the literature 6 to 8 months after SARS-CoV-2 infection [26]. We also observed a negative titer of some previously positive patients during follow-up (100% positive patients at T1 vs 80% positive patients at T5). In the literature, it is reported that a booster dose of mRNA vaccine substantially increased antibody levels in the

HD population and allowed seroconversion in most non-responders [15-21]. About 7 months after the administration of the 2nd dose, a 3rd dose (booster) of mRNA vaccine was also given to our cohort of HD patients. Our study confirmed the presence of a substantial humoral response after the booster dose with 100% of patients reporting a positive test at T6 and T7 (30 and 60 days after booster), including all previously negative patients, with a statistically significant increase in anti-trimericS antibodies at T6 compared to all previous times of observation (from T1 to T5). A T7 anti-trimericS IgG mean level, despite a significant decline compared to T6 (p=0,0005), remained significantly higher than all the time points before the vaccine booster (p<0,001). According to the manufacturer package declarations, high LIAISON® doses (i.e. ≥520 BAU/mL) were compared to a higher microneutralization assay titer threshold of ≥1:80. In a study anti trimeric S IgG ≥ 1100 IgG BAU/mL were identified to reach a comparable serum neutralizing activity (≥1:250) against wilde-type virus and anti-trimericS IgG ≥ 1850 BAU/mL were found to predict a serum neutralizing activity against omicron BA.1 variant (≥1:10), suggesting a good humoral response of our cohort of HD patients which reach these targets after three dose of BNT162b2 vaccine. [28]. In the literature, older age is associated with lower antibody response to SARS-CoV-2 vaccine within the HD population [13,14]. In our study, even if older patients (≥70 years) had generally lower anti-trimericS levels, differences between age ranges (<70 vs ≥70 years) were not statistically significant. Sex, dialysis vintage and underling ERSD cause did not influence antibody response in our cohort of HD patients. In the literature, lower median anti-spike levels after two doses of the mRNA vaccine are reported in HD patients compared to healthy subjects [22]. In our study, vaccine booster dose results in a significant increase in IgG titers (p<0,0001) in both the HCW cohort as well as in the HD cohort. No significant differences were measured at T5 and T7 when comparing HCWs and HD patients, suggesting that this patient population responds similarly to apparently healthy subjects in terms of IgG levels after vaccination overall, even if a higher number of HD patients showed negative IgG results (20%) compared to HCWs (2,3%) at T5, indicating that antibody persistence may be affected in some dialysis patients.

To the best of our knowledge, our study is the first to evaluate the trend of antibody levels after SARS-CoV-2 vaccine in HD patients over a period of one year, with serial detection and using different assays. In our cohort of HD patients, we described a substantial humoral response following two vaccine doses, with a decay during the following 6 months, before the 3rd dose. Vaccine booster is effective in eliciting a significantly higher antibody response, which begins to decline 2 months after the 3rd dose, but with significantly higher Ab levels than those detected with a two-dose schedule.

The durability of the SARS-CoV-2 antibody response is not known. Most of SARS-CoV-2-infected individuals seroconverted at 1 month and the spike IgG levels were durable, with a modest decline in titers from 6 to 8 months [25-27]. The last question is whether the immune response can also be effective with lower Ab levels or against new COVID-19 variants. This study has some limitations: the small number of participants, the relatively short follow-up, and the absence of evaluation of the cellular response, which needs specific assays, and it is not easy to perform. Further investigations, longer follow-up and larger populations are needed to better explain the complex immune response to SARS-CoV-2 vaccine in this subset of patients. However, the baseline assessment followed by serial measurements after the last vaccine dose might help to identify low or non-responders to the vaccination and the antibody decay rate to better establish preventive measures or even vaccine boosters..

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