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Decaying of SARS-CoV-2 Antibodies with Time after Taking Booster Dose among the Doctors of Bangabandhu Sheikh Mujib Medical University

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Abstract **Original Research Article**

Background: SARS-CoV-2, the virus responsible for COVID-19, has prompted global vaccination efforts, including booster doses to enhance immunity. The persistence of antibodies following booster vaccination is a critical area of study. The decay rate of antibodies can vary based on vaccine type, age, and individual immune response. This study aimed to evaluate the temporal decline of SARS-CoV-2 antibodies post-booster dose among the doctors at Bangabandhu Sheikh Mujib Medical University. ***Methods:*** This prospective observational study was conducted at the Department of Biochemistry & Molecular Biology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2022 to February 2023. A total of 80 doctors of BSMMU aged between 25 to 65 years who had taken the COVID-19 booster dose about 6–8 months ago were enrolled in this study as the study subjects purposively. Data were analyzed by the SPSS version 26.0 program. ***Results:*** Comparing serum IgG levels 6-8 month's post-booster versus 3 months after, there was a significant decrease at 3-month intervals ($p<0.001$). This decline was consistent at 6, 7, and 8 months ($p<0.05$) across genders, infection and vaccination statuses, age groups (25-44 and 45-65), BMI categories (except normal weight participants $p>0.05$), and in those with comorbidities (DM, HTN). While all booster types showed a decrease, the Moderna vaccine showed a non-significant decline ($p>0.05$) compared to the others, which had significant reductions ($p<0.05$). ***Conclusion:*** The antibody level decays significantly with time after taking the booster dose. Serum IgG levels significantly decreased at 3 month's interval who had taken booster dose six to eight months before, consistent across age, gender, infection status, vaccination status, BMI (except normal weight individuals), diabetes, and hypertension. All booster types reduced IgG levels, but the decline with Moderna was insignificant, showing reduction varies depending on the vaccine type used.

Keywords: Antibodies, BSMMU, Booster dose, Decaying, Doctors, SARS-CoV-2, Serum IgG.

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which triggered the Coronavirus Disease 2019 (COVID-19) outbreak, was first identified in Wuhan, China, on December 31, 2019 [1]. By January 7, 2020, the virus was identified as a new coronavirus (2019-nCoV), believed to have originated from the Huanan seafood market [2]. The primary symptoms of COVID-19 include fever, cough, muscle aches, and fatigue, which are similar to those of SARS and MERS. Less common symptoms include sputum production, headache, coughing up blood, vomiting, and diarrhea [3]. Additionally, sore throat, runny nose, headache, and confusion may precede the fever, highlighting fever as an important, but not exclusive,

symptom of the infection [4]. Coronaviruses are a group of enveloped viruses characterized by a single-stranded positive-sense RNA genome, giving them a crown-like appearance when viewed under an electron microscope [5]. These spherical RNA viruses are classified under the Nidovirales order, within the Coronavirus family and the Ortho coronavirus subfamily, and have the largest genomes among RNA viruses, with sizes ranging from 26 to 32 kilobases [6]. The worldwide impact of the COVID-19 pandemic led to a rapid effort to develop a vaccine that is both safe and effective [7]. Currently, eight vaccines have reached phase 3 clinical trials and have been approved for emergency use against COVID-19 globally [8]. Testing for SARS-CoV-2 antibodies is crucial to assessing the virus's prevalence in the general population [7]. Antibody screening is important for assessing the necessity of boosters and global immunization strategies [9]. A cohort study conducted in Italy with 57 healthcare workers who received the COVID-19 vaccine showed that the mean anti-RBD IgG level was 294.7 BAU/mL on the day of the second dose (21 days after the first dose). By 51 days after the first dose, this value increased to 2583 BAU/mL, and then decreased to 320.4 BAU/mL six months after the first dose [10]. The virus responsible for COVID-19 has evolved into several variants, some of which are more contagious and can lead to more severe illness compared to the original SARS-CoV-2 strain. These variants include B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) [11]. As the COVID-19 pandemic continues into its third year, many countries have recommended administering a booster (third) vaccine dose to combat the outbreak [12]. This booster immunization has shown effectiveness against various SARS-CoV-2 variants, including the Omicron variant [13]. A study conducted in Singapore found that spike antibody titers peaked in all individuals 30 days after receiving the booster dose, reaching 25,220 BAU/mL. This represented a 30% increase from pre-booster levels. However, by 90 days post-booster, S-Ab titers decreased to 12,315 BAU/mL, marking a 51% drop [12]. In a study conducted in Israel, it was found that administering the third dose of the BNT162b2 vaccine significantly decreased the rates of confirmed SARS-CoV-2 infections and severe illness among 1,137,804 adults aged 60 or older who had previously received two doses, five or more months earlier [14]. As of January 29, 2023, in Bangladesh, 150,375,086 individuals had received their first dose, 135,108,210 completed the two-dose regimen, and 66,472,672 had received a booster dose (DGHS, 2023) [15]. In response to widespread outbreaks caused by the B.1.1.529 (Omicron) variant and evidence of waning immunity even after booster doses, several countries have started offering a fourth vaccine dose to those considered at risk. The study conducted in Israel highlighted that a fourth dose of the BNT162b2 vaccine effectively reduced short-term COVID-19-related risks in individuals who had received their third dose at least four months earlier [16]. However, there's a gap in knowledge regar0ding long-term antibody levels, particularly 6-8 months after a booster dose and at 3-month follow-up intervals. This lack of data is especially evident in specific regions like Bangladesh. As a result, the study aimed to investigate how antibody levels decline after a booster dose, specifically among doctors, to fill this knowledge gap.

METHODOLOGY

This was a prospective observational study that was conducted at the Department of Biochemistry & Molecular Biology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2022 to February 2023. In this study, 80 doctors from BSMMU, aged between 25 to 65 years, who had received their COVID-19 booster dose approximately 6-8 month's prior, were enrolled as participants. The researchers used a convenient purposive sampling technique to recruit the sample.

Inclusion Criteria:

Participants aged 25 to 65 years, regardless of gender, who are doctors and received a Covid-19 booster dose 6–8 months prior.

Exclusion Criteria:

Subjects with acute infections, systemic diseases such as chronic liver or kidney disease, pregnant women, individuals with immunosuppressive disorders like cancer, and those who contracted COVID-19 after providing the first sample.

This study explores how various variables, including Age, Sex, BMI, Blood Pressure, Random Blood Sugar, SARS-CoV-2 infection status, and types of vaccines, influence Serum Immunoglobulin G (IgG) levels against SARS-CoV-2. By examining these factors, we aim to understand their collective or individual impact on the immune response. The quantitative determination of SARS-CoV-2 specific IgG was done by Chemiluminescence Microparticle Immunoassay (CMIA) using Abbott Alinity Autoanalyzer (USA). Estimation of plasma glucose by Enzymatic (Hexokinase/G-6-PDH) method. The collected data were entered and processed by using Statistical Package for Social Science (SPSS) software version 26.0. Numerical data were presented as Mean ± SD for normally distributed data. The median, interquartile range, and number (%) were used for skewed data. Quantitative and qualitative data with a skewed distribution were analyzed using the Wilcoxon Signed Rank Sum test. P-value <0.05 was considered statistically significant.

RESULT

In the study, 80 participants included 44 (55%) SARS-CoV-2 infected vaccinated and 36 (45%) non-infected vaccinated individuals. Infected had more males, and non-infected had more females. The age was

43±10 for the infected and 36±6 for the non-infected. Serum IgG levels decreased by 21.3% at 3 month's interval among same individuals taken booster dose 6-8 months earlier (p <0.001). Serum IgG levels significantly declined (p <0.05) at 3 months follow up interval in comparison to 6-, 7-, and 8-months post-booster. The decaying percentage was 20.5% at 6 months, 24.3% at 7 months, and 27.8% at 8 months. In both males and females, levels declined significantly with 12.3% in males and 10.5% in females. Comparing serum IgG levels by SARS-CoV-2 infection history showed significant decay (p <0.05) in both infected and non-infected vaccinated participants. The IgG declined by 21.3% and 28.2% for infected and non-infected, respectively. By age, IgG decreased 17.4% in 25-44 years and 21.5% in 45-65 years, both significantly (p <0.05) in 3-month intervals. Comparing serum IgG levels by BMI, decays at 3-month intervals were 7.5% for normal weight, 17.9% for overweight, and 25.7% for obese individuals. The decline was significant for overweight and obese (p <0.05) but not for normal weight (p >0.05). IgG decreased in those with comorbidities: 25.6% for DM, 31.0% for HTN, and 35.8% for both, all significant (p <0.05) at 3-month intervals. The serum IgG decay at 3-month intervals was 29.2% for AstraZeneca, 20.8% for Pfizer, and 16.9% for Moderna booster recipients. While all boosters showed IgG reductions, the decline was significant for AstraZeneca and Pfizer (p <0.05), but not significant for Moderna (p >0.05).

Table 1: Distribution of the study subjects according to the history of SARS-CoV-2 infection.

History of SARS-CoV-2 infection	n	%
Infected and vaccinated	44	55
Non-infected and vaccinated	36	45
Total	80	100

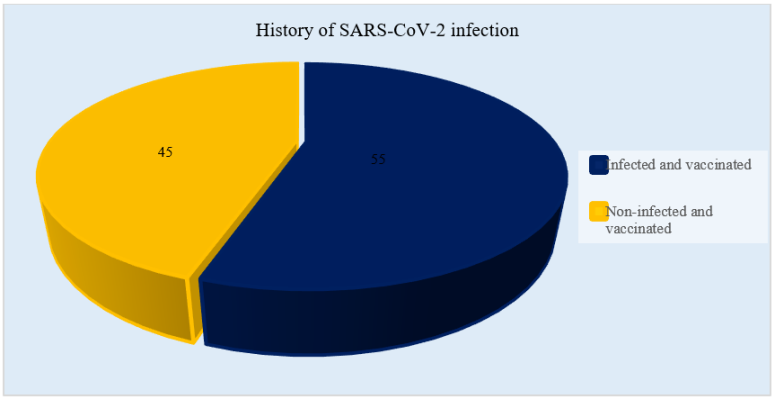

Figure I: Pie chart showing study subjects based on SARS-CoV-2 infection history

Table 2: Comparison of serum IgG levels: 6-8 months post-Booster vs. 3 months after

Antibody status	At initial stage	After 3 months	Decaying (%)	p-value
	IgG (AU/ml)			
Median (Range)	2563.4 (1602.4-5354.1)	2017.9 (1323.5-4144.3)	21.3%	<0.001

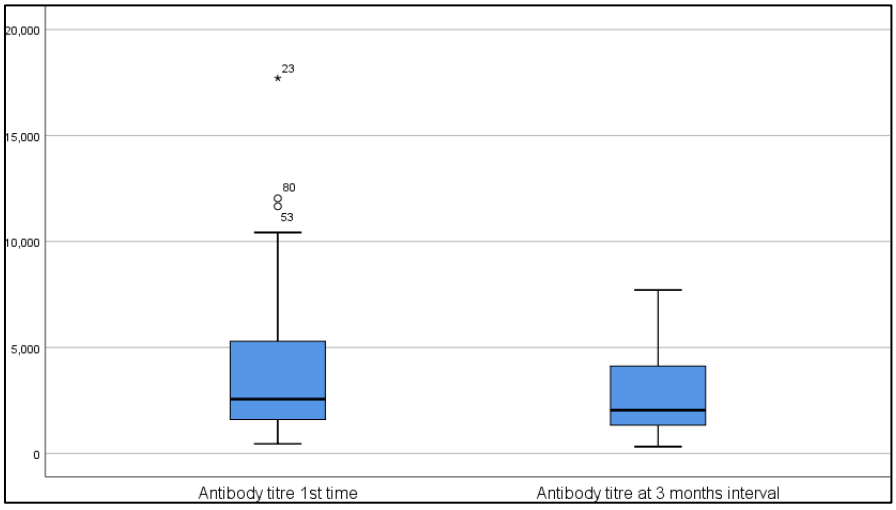

Figure II: Box and Whisker plot showing serum IgG level (AU/ml) at 6-8 months after Booster dose and in the same individual after 3 months

Table 3: Serum IgG levels at 6, 7, and 8 months after Booster vs. levels at 3-month intervals

Month interval	1st sample	2nd sample	Decaying (%)	p-value
		Taken after 3 months	At 3 months interval	
	(Median with IQR)			
	AU/ml			
6 months (n =25)	3350.2	2662.2	20.5%	0.032
	(1866.8.0-5724.9)	(1540.8-5300.2)		
7 months (n =25)	2886.3	2185.7	24.3%	0.026
	(1540.7-5472.3)	(1328.1-3795.8)		
8 months (n =30)	2690.1	1942.2	27.8%	0.002
	(1311.6-4642.3)	(1105.5-3603.7)		

Table 4: Comparison of serum IgG level (AU/ml) based on Gender

Gender	The booster dose was taken 6-8 months ago	Same individual at 3 months interval	p-value	Decaying % of S. IgG at 3 months interval
	(Median with IQR)	(Median with IQR)		
	AU/ml	AU/ml		
Male (n=38)	2451.7	2149.6	0.001	12.30%
	(1481.7-5682.8)	(1231.8-4132.3)		
Female (n=42)	2744.4	2455.6	0.005	10.50%
	(1608.5-4738.0)	(1424.0-4568.8)		

Table 5: Comparison of s. IgG level (AU/ml) as per the history of SARS-CoV-2 infection

SARS-CoV-2	At initial stage	After 3 months	Decaying (%)	p-value
(Infection status)	IgG (AU/ml) levels (Range)			
Infected vaccinated (n=44)	2877.3	2125.9	21.3%	0.003
	(1616.3-6029.9)	(1431.9-5388.9)		
Non-infected vaccinated (n=36)	2478	1779.3	28.2%	0.002
	(1415.3-4672.2)	(1191.9-3561.9)		

Table 6: Comparison of serum IgG level (AU/ml) based on age group

Age group	At initial stage	After 3 months	Decaying (%)	p-value
	IgG (AU/ml) levels (Range)			
25-44 (n=63)	2694.4	2225.6	17.4%	<0.001
	(1740.0-5897.7)	(1394.1-4868.2)		
45-65 (n=17)	2069.6	1625.1	21.5%	0.004
	(1423.2-3659.1)	(955.8-2229.1)		

Table 7: Comparison of serum IgG level (AU/ml) according to Body Mass Index

BMI	At initial stage	After 3 months	Decaying (%)	p-value
	IgG (AU/ml) levels (Range)			
Normal weight (n=16)	1851.1	1712.4	7.5%	0.301
	(1428.4-5177.7)	(1329.7-4556.6)		
Overweight (n=16)	3660.3	3005.1	17.9%	0.030
	(1743.7-6703.1)	(1433.5-5625.8)		
Obese (n=48)	2563.4	1905.9	25.7%	<0.001
	(1641.3-4903.8)	(1275.1-3880.4)		

Table 8: Comparison of serum IgG level (AU/ml) according to the comorbidity.

Comorbidities	At initial stage	After 3 months	Decaying (%)	p-value
	IgG (AU/ml) levels (Range)			
DM (n=12)	2574.2	1915.5	25.6%	0.023
	(1727.8-4933.1)	(1414.3-3017.8)		
HTN (n=10)	2315	1596.7	31.0%	0.005
	(988.3-5488.9)	(566.2-2682.8)		
Both DM & HTN (n=06)	2485.9	1596.7	35.8%	0.028
	(1614.9-5119.6)	(1149.7-2208.1)		

Table 9: Comparison of s. IgG levels based on Vaccine and Booster doses in study population

Vaccines	At initial stage	After 3 months	Decaying (%)	p-value
	IgG (AU/ml) levels (Range)			
AstraZeneca 3 times (8)	2218.7	1570.1	29.2%	0.026
	(1175.7-5717.3)	(1015.2-3586.0)		
AstraZeneca 2 times +Pfizer (49)	2692.8	2132.3	20.8%	<0.001
	(1602.5-5080.2)	(1397.5-4117.6)		
AstraZeneca 2 times + Moderna (23)	3014.5	2502.1	16.9%	0.068
	(1768.2-6074.0)	(1369.3-5996.0)		

DISCUSSION

The duration of COVID-19 vaccine protection remains unclear. Booster doses initially raise antibody levels significantly, but these decline over time [17]. Vaccine effectiveness wanes about six months after the primary series [18]. This study found median IgG levels dropped from 2563.4 AU/ml at 6-8 month's post-booster to 2017.9 AU/ml three months later, with a significant decline observed. Similarly, Kozakai *et al.,* (2022) [19] reported a 74.1% reduction in serum IgG six months after the third dose. We analyzed serum IgG levels among vaccine recipients at 6, 7, and 8 months, finding values of 3350.2 AU/ml, 2886.3 AU/ml, and 2690.1 AU/ml, respectively. Median antibody levels were higher at 6 months compared to 7 and 8 months. Similarly, Zember *et al.,* (2022) [20] reported a significant decline in IgG titers, from a median of 12,406.0 AU/ml at 3 months to 5550.6 AU/ml at 6 month's post-booster. This study found that 6-8 month's post-booster, serum IgG levels were 2451.7 AU/ml in males and 2744.4 AU/ml in females, with females showing higher antibody levels. Similarly, Phyu Pyar (2022) [21] observed in healthcare workers in Myanmar that females had higher anti-spike antibody levels (4857.67 U/ml) compared to males (3427.78 U/ml) after three COVID-19 vaccine doses. Infected-vaccinated individuals showed higher antibody levels than noninfected-vaccinated individuals, as natural immunity from COVID-19 infection boosts antibody levels. Phyu Pyar (2022) [21] also reported greater anti-Spike antibody levels in previously infected healthcare workers (4013.79 U/mL) compared to noninfected workers (3524.48 U/mL). In our study, serum IgG levels were 2125.9 AU/ml (1431.9–5388.9) in infected individuals and 1779.3 AU/ml (1191.9–3561.9) in noninfected individuals, with declining percentages of 21.3% and 28.2%, respectively. These findings align with Vicenti *et al.,* (2021) [22], who noted faster antibody degradation in noninfected individuals. In this study, antibody decay in normal-weight individuals was not statistically significant. Obese participants showed a significant antibody decline, with serum IgG levels decreasing by 7.5% in normal-weight, 17.9% in overweight, and 25.7% in obese individuals over 3 months. Mishra *et al.,* (2021) [23] reported higher antibody titers in overweight and obese healthcare workers six months after two AstraZeneca doses. Albanesi *et al.,* (2022) [24] observed IgG levels decreasing in normal-weight, increasing in overweight, and declining again in obese individuals, aligning with our findings. In this study, 63 participants were aged 25-44, and 17 were aged 45-65. Six to eight months after a booster dose, median serum IgG levels were 2694.4 AU/ml for the 25-44 group (IQR: 1740.0-5897.7) and 2069.6 AU/ml for the 45-65 group (IQR: 1423.2-3659.1). After three months, IgG levels declined significantly to 2225.6 AU/ml (IQR: 1394.1-4868.2) for the younger group and 1625.1 AU/ml (IQR: 955.8-2229.1) for the older group, reflecting declines of 17.4% and 21.5%, respectively. Mishra *et al.,* (2021) [23] highlighted a faster IgG decline in older populations. Ciarambino *et al.,* (2021) [25] noted a progressive immune decline in older individuals. In the study, the study subjects having DM or HTN showed slightly lower antibody IgG levels than nondiabetic, normotensive participants. A study conducted by Soegiarto *et al.,* (2022) [26], with 101 healthcare workers who received two doses of vaccine reported that high blood pressure and a history of hypertension were associated with lower antibody titers. In this study, the decaying percentage of IgG at 3-month intervals was 25.6% for only DM having subjects, 31.0% for only HTN having subjects, and in both DM and HTN, it was 35.8%. Singh *et al.,* (2022) [27] found that the waning of anti-spike antibody titer over time was significantly lower in the hypertensive cohort compared to the normotensive cohort at 6 months. In this study, all 80 participants received Oxford AstraZeneca for their first two COVID-19 vaccine doses. As a booster, 8 received AstraZeneca, 49 received Pfizer, and 23 received Moderna. Six to eight month's post-booster, the median IgG levels were 2218.7 AU/ml (AstraZeneca), 2692.8 AU/ml (Pfizer), and 3014.5 AU/ml (Moderna). IgG levels were slightly higher with Pfizer and Moderna compared to AstraZeneca. Albanesi *et al.,* (2022) [24] also noted that mRNA vaccines (Pfizer and Moderna) were highly immunogenic after two doses, with Moderna producing slightly higher IgG levels than Pfizer. AstraZeneca followed by Moderna or Pfizer as a second dose is significantly more effective at inducing SARS-CoV-2 specific IgG than two doses of AstraZeneca. Sarker *et al.,* (2022) [28] reported higher antibody responses in mRNA vaccine (Pfizer and Moderna) recipients compared to AstraZeneca recipients in a Bangladeshi study. Similarly, Brunner *et al.,* (2022) [29] found that 8.4 month's post-vaccination, Moderna (mRNA-1273) induced higher antibody levels than Pfizer (BNT162b2), aligning with our findings. Antibody decay was observed across all three booster

vaccines over a three-month interval. The decline in AstraZeneca (29.2%) and Pfizer (20.8%) recipients was statistically significant, while the decrease in Moderna (16.9%) recipients was not. Mishra *et al.,* (2021) [23] reported a significant decline in antibody levels six months after two doses of the AZD1222 (AstraZeneca) vaccine in healthcare professionals. Similarly, Singh *et al.,* (2022) [27] observed waning humoral responses at six months, with a notable decrease in antibody titers for the Covishield AstraZeneca vaccine. Pareek *et al.,* (2022) [30] also documented a significant reduction in IgG titers seven months after a Pfizer (BNT162b2) booster, though neutralizing antibodies were not evaluated.

LIMITATION OF THE STUDY

This prospective observational study involved a relatively small sample size and was conducted over a limited period. Further follow-up at different time points would have been beneficial. As the study focused on a specific group from a single center, its findings are not representative of the entire population. Additionally, many SARS-CoV-2 infected individuals remained asymptomatic, introducing potential bias that could influence the results.

CONCLUSION & RECOMMENDATION

The antibody level decays significantly with time after taking the booster dose. The study observed a significant decrease in serum IgG levels at three months follow up interval among the same individuals who had taken COVID-19 booster dose six to eight months ago. This decrease was noted consistently across different demographics and health conditions, such as age, gender, infection status, vaccination status, BMI, and conditions like diabetes and hypertension. Interestingly, while all booster types led to reductions in IgG levels, the decline was insignificant with the Moderna booster, suggesting that while the effects of boosters diminish over time, the extent of this reduction can vary depending on the vaccine type used.

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Conflict of interest: None declared.

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