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Short communication

# COVID-19 vaccine – Long term immune decline and breakthrough infections

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ABSTRACT

*Background:* Since the introduction of BNT162b2 mRNA COVID-19 vaccine by Pfizer in late 2020, efficacy and immunogenicity waning of COVID-19 vaccines was reported, and decision making regarding a booster remains a top priority worldwide, a decision that should be made based on breakthrough infection rate and antibody titer decline overtime.
*Methods:* We conducted a 5-month longitudinal prospective study involving vaccinated healthcare personnel, who were tested monthly for antibody titer, and sampled biweekly and on clinical indication for SARS-COV-2 polymerase chain reaction (PCR), to determine antibody decline and breakthrough infection.
*Results:* 100 participants were recruited to the study. Antibody titer reached the climate after one month of the second dose of the vaccine, and declined rapidly thereafter: the median antibody levels were 895; 22,266; 9,682; 2,554 and 1,401 AU/ml in the day of the second dose, and in one month interval thereafter, respectively. In other words, four months after vaccination, the mean antibody level was 6% of the peak levels. During the study period, 4 breakthrough infections were diagnosed, 2 of which were asymptomatic, and the remaining two were mild cases; sharp elevation of antibody titer was seen after infection.
*Conclusion:* Antibody titer drops rapidly one month after the second dose of the vaccine. All infections within the study period were mild or asymptomatic, after which titer elevations were seen.


## 1. Background

Since the introduction of Anti COVID-19 vaccines, Immunogenicity has been studied intensively [1,2]. Phase III trials have shown about 95% efficacy in preventing symptomatic disease, and real life data shows similar effect [3–5]. Furthermore, long-term efficacy, immunogenicity and safety are being heavily investigated [6]. After COVID-19 vaccination, the immune system produce immunoglobulin G (IgG) which may neutralize SARS-CoV-2 by binding to the receptor binding domain (RBD) of the S1 subunit of the spike protein of SARS-CoV-2 in serum. Recent studies showed that antibody levels drop rapidly after vaccination [6]; moreover, protection against infection also drops overtime after the second dose of the vaccine [7].

Data of previous studies discussed antibody titer decline over time, and effectiveness of vaccine in disease prevention based on polymerase chain reaction (PCR) tests taken on clinical indications (e.g. suggestive symptoms or close contact with infected person), but may disregard asymptomatic infections and undocumented infections [6,7].

Our study aims to discuss the change in the titer of anti Covid-19 antibody overtime, and to address symptomatic and asymptomatic breakthrough infection through routine PCR tests on biweekly basis, and thus, a possible relationship between titers and breakthrough infections. Secondary aims are titers among different demographic groups, categorizing vaccine's side-effects, and the relationship between side-effects and immunogenicity.

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## 2. Patients and methods

A prospective longitudinal cohort study between January and July 2021 included personnel working at EMMS Nazareth hospital in Israel. The hospital is located in high COVID-19 prevalence area and operates three COVID departments.

All participants are health care workers who were invited to volunteer for the study and the first 100 volunteers, from different sectors, were recruited. All participants were fully vaccinated with BNT162b2 mRNA Covid-19 Vaccine, by Pfizer © with two doses, and 3 weeks interval in between

Inclusion criteria included no known previous SARS-COV-infection before the second dose of the vaccine and age of 18 years or older.

Serum was collected at the day of the second dose, and then once a month for consecutive four months. Blood was drawn by the study physicians, immediately before the second dose of the vaccine, and once a month for the study period. At each time point, the whole cohort was sampled within up to 48 h. Samples were transferred to the lab within 30 min. Serum for anti COVID-19 antibody titers was processed by Abbot's © SARS-CoV-2 IgG II Quant assay using the ARCHITECT system, designed to detect IgG antibodies.

Breakthrough infections were detected by nasopharyngeal swabs, obtained in two weeks interval as a screening method, starting one week after the second dose, and at any point if a participant declared a close contact with SARS-Cov-2 patient or had suggestive symptoms (e,g. fever, sore throat, headache, fatigue, cough, nasal congestion, agosia or anosmia). The swabs were obtained by the study physicians and were transferred to the laboratory within 30 min PCR tests for COVID-19 detection was done using STARlet, Hamilton kit ©.

Demographic data, chronic medical conditions, regular medications and vaccination side effects were recorded. The study was approved by the local IRB and informed consents were signed by the participants.

### 2.1. Statistical analysis

The non-parametric local regression (LOWESS smoothing) was used for presentation of the titers levels throughout the days post the second vaccine, with 95% confidence intervals (95% CI). The trends were also displayed by age and gender.

Comparison between patients with and without side effects post vaccinations regarding antibody titer levels, was performed using Wilcoxon rank-sum test.

The statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ was considered statistically significant.

## 3. Results

One hundred volunteers were included, 55 males, mean age was 40.7 ± 13.7 years. All participants were health care personnel: 38 physicians, 31 nurses, 18 *para*-medical staff and 13 administrative personnel. On the day of the second dose of the vaccine median titers were 885 (33–13827) AU/ml. Recruitment, drop-out, and infection rates are described in Fig. 1.

The median titers during the following four months (excluding infected subjects) were 22,266 (571–80000), 9,682 (2,157–62,491) and 2,554 (615–49,653) and 1,410 (277–6,103) AU/ml, respectively. In other words, after one month of the second dose, the titer raised in 24 folds as compared to the day of second dose. However; during the four consecutive months, the median titers dropped by 57%, 74% and 45% respectively. In other words, titer after four months from the second dose was only 6.3% of the maximal titer (Fig. 2).

Furthermore, it was noticed that participants older than 50 years, had lower antibody titers than in patients younger than 30: mean titer 33660 ± 20771 and 14786 ± 15471 IU/ml for younger than 30 and over 50 years, respectively, 95% CI 1.58–5.01. However; no clear difference was seen between these two groups and 30–50 years of age group (Fig. 3). Moreover, in partic-

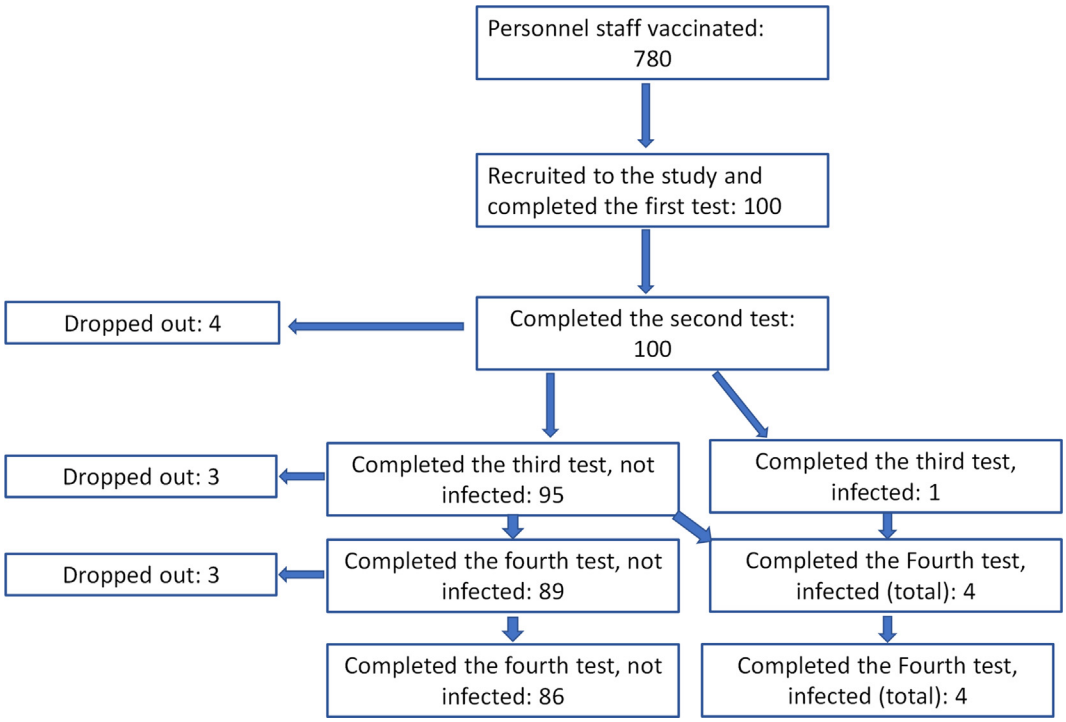


**Fig. 1.** Flow chart of study design and follow-up.

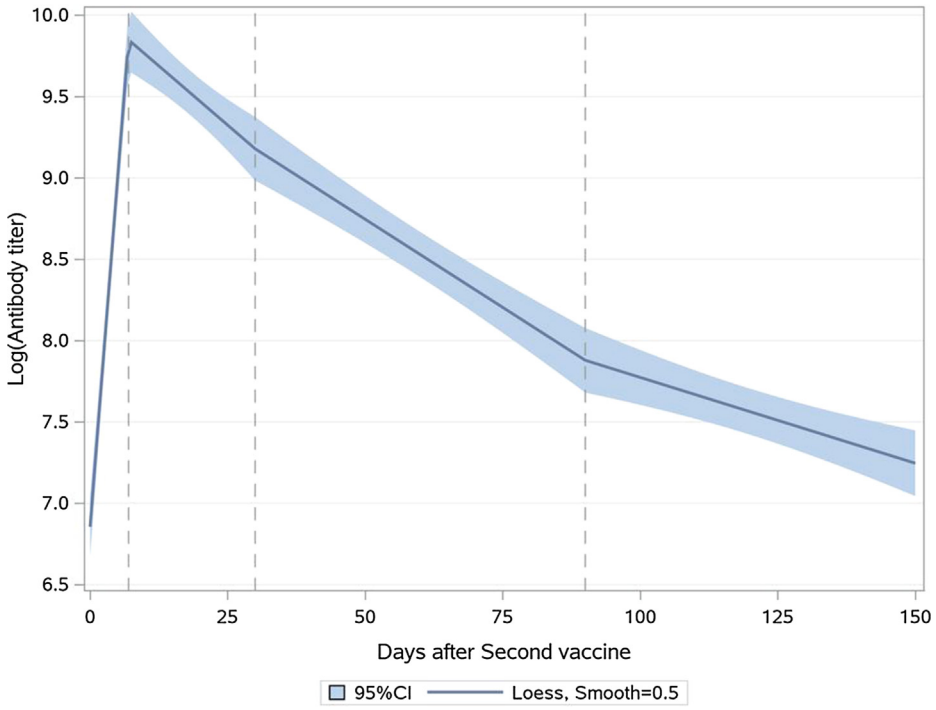


**Fig. 2.** Antibody titer overtime.

ipants older than 50, higher titers were seen in females than in males: mean titer 24013 ± 16684 and 8909 ± 7674 IU/ml in females and males, respectively, 95% CI 1.8–12.5 (Fig. 4).

In our cohort, four participants were tested positive for COVID-19 during the study period. All positive participants were sampled twice with naso-pharyngeal swabs for PCR, and were positive in both tests, all of whom were immunocompetent and infected with B.1.1.7 variant. It is remarkable that two participants were asymptomatic and diagnosed by the biweekly screening, and two had mild symptoms. The first participant was diagnosed 3 weeks after the second dose (while complaining of cough and myalgia), although his antibody titer was highly positive (8,089 IU/ml) three weeks before. The other three were diagnosed 5 weeks after the second dose, their antibody titers one week before being infected were 21,000 (asymptomatic), 5,267 (complaining of cough and myalgia), and 7,015 IU/ml (asymptomatic). It is noteworthy that two weeks after the infection, antibody titers of all these 4 participants elevated to 44,000, 32,370, 19,485, and 19,108 respectively.

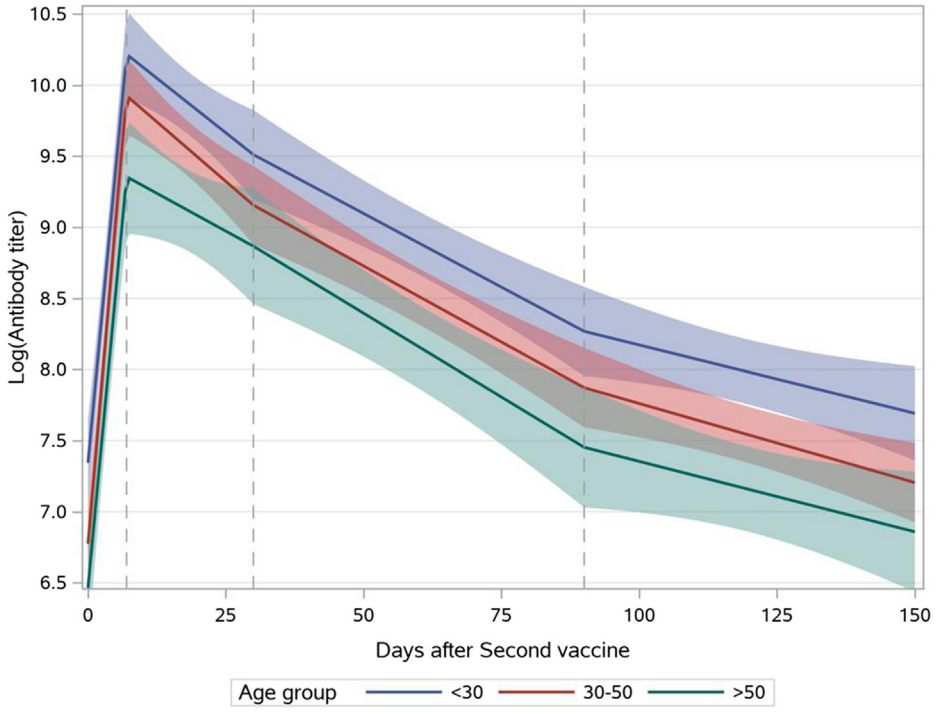


**Fig. 3.** Antibody titer in 3 ages groups: under 30, 30–50 and above 50 years.

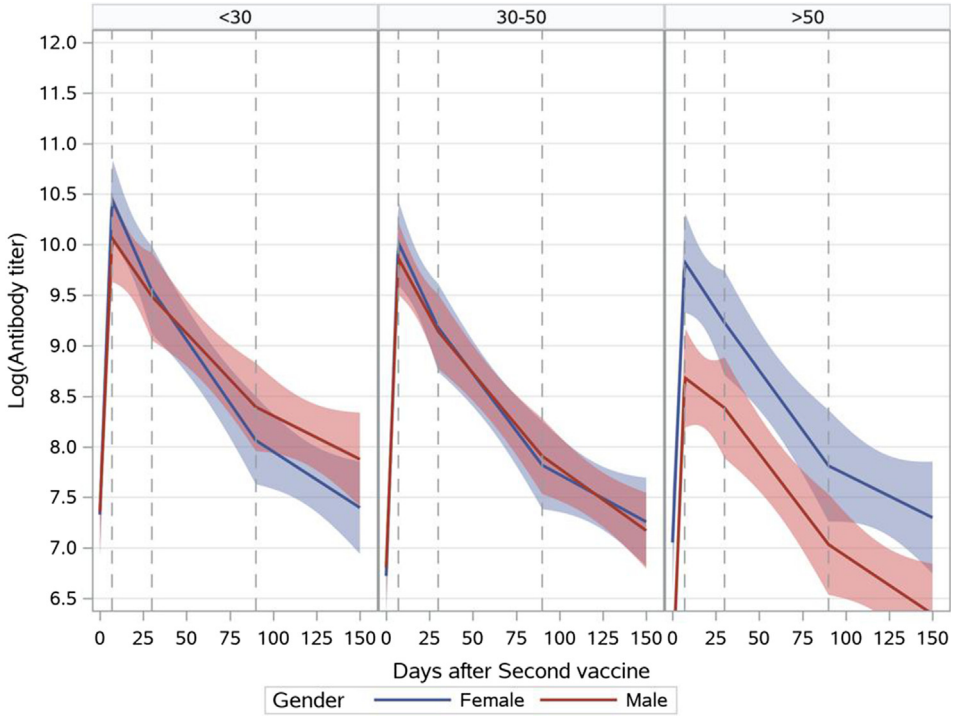


**Fig. 4.** Antibody titer in males and females in different age groups.

**Table 1**
Side effects after the first and second dose. The number of patients is the same as the percentage.

| Side effect | First Dose | Second dose |
|---|---|---|
| Injection site pain | 75 | 75 |
| Fever | 2 | 4 |
| Headache | 4 | 20 |
| Chills | 1 | 14 |
| Numbness | 1 | 5 |
| Hypertension | 1 | 1 |
| Fatigue | 5 | 10 |
| Myalgia | 3 | 16 |
| Other | 2 | 8 |
| None | 26 | 25 |
| Total | 92 | 153 |

None of these four patients needed hospitalization; all were quarantined for ten days, and their household members were all tested negative. It is also noteworthy that all the other participants' titers declined except one participant, who had a titer elevation between the second and the third month; he denied any symptoms, and his PCR tests were negative.

The most common side effect was injection site pain (75%), after each dose. Mean visual analog scale (VAS) was similar for the first and the second dose (2.9 ± 2.7 and (2.85 ± 2.4, respectively). All other side effects including headache, fever, chills, numbness, fatigue and myalgia were more common after the second dose as compared to the first one (Table 1). Patients with side effects after the second dose had significtally higher antibody titer levels ($p = 0.02$). However, patients with side effects after the first dose did not have higher titer levels as compared to patients without side effects ($p = 0.95$). (Fig. 5).

## 4. Discussion

Our study is unique for combining long term immunologic response after COVID-19 vaccine, side effects and clinical symptoms monitoring throughout the study, alongside with continuous virologic sampling with nasopharyngeal swabs for PCR, thus, minimizes the opportunity for disregarding asymptomatic and undocumented infections.

Our data show that one month after the second dose of the vaccine, antibody titer reached a climate, and dropped rapidly after that. Moreover, it is evident that four months after the second dose, the median titer level was as low as 6% of the maximal median titer. This data raise a question about the timing of any possible booster in the near future even in immune-competent healthy population. Doria-Rose et al. showed a detectable antibody titer with slight titer decline in 33 patients 6 months after mRNA-1273 vaccine [9], however, our results may differ because of fundamental differences, such as different vaccine, different serologic assay and study group. Recently published studies show similar results of titer and immunity decline throughout the first till the sixth month after the second dose of BNT162b2 Covid-19 Vaccine [6,7]. Moreover, similar to Levi *et al* study, we show lower titers among older age group and among males as compared to females [6]. Bergwerk *et al* reported lower neutralizing antibody titers in the *peri*-infection period in infected group as compared with uninfected controls [8], however; in our group the total antibody titers were comparable to the rest of the group. This might be related to methods (sampling, antibody type), and cohort dissimilarity.

Importantly, four cases (4%) of breakthrough infection were diagnosed even with positive high titers without a noted cutoff. Our study shows a significant increase in the antibody titer levels after COVID-19 infection in vaccinated personnel. We also observed one participant that had an unexplained elevation in antibody titer, which can be explained by a breakthrough infection, however he remained asymptomatic, and his PCR tests were negative.

Likewise, side effects of the second dose had the same correlation with titer levels. It is noteworthy that COVID-19 vaccine correlates with higher incidence of myocarditis in adolescents and young adults [10]. That raises another question whether the vaccine dose should by modified by age among other factors such as immunosuppression.

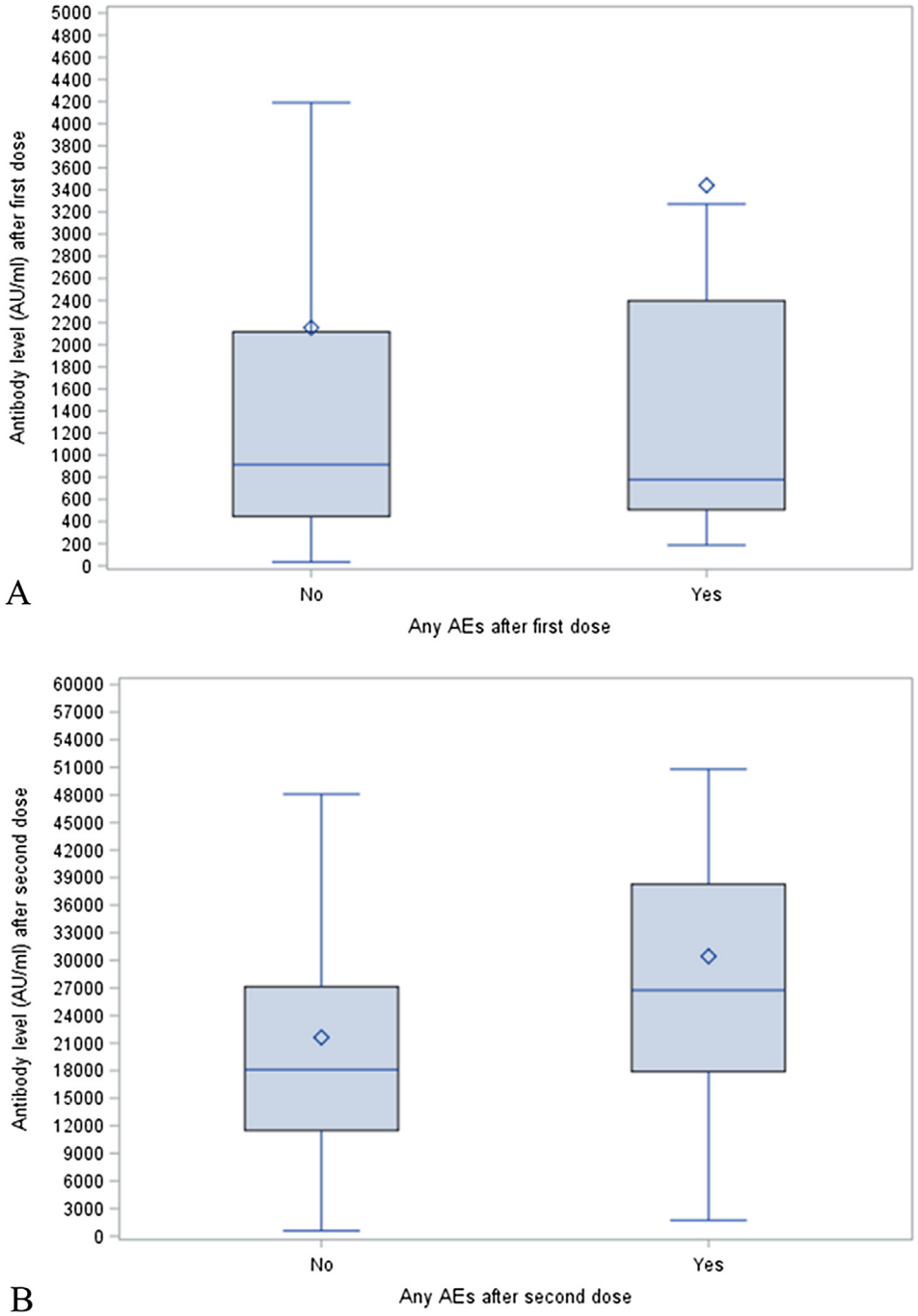


**Fig. 5.** Antibody level after first dose (5A) and second dose (5B) of vaccine, in participants who had or had not any adverse events after vaccination.

For summary: our data shows a rapid drop in antibody titers starting one month after vaccination. Break through infection after vaccination can be totally asymptomatic, and is accompanied by natural boost of the antibody titer. Further studies are needed, in order to decide when is the most appropriate time for a vaccine booster, and if dose adjustment should be considered, taking into account immune-suppression, age and gender.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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