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Longitudinal analysis of anti-SARS-CoV-2 neutralizing antibody (NAb) titers in vaccinees using a novel giant magnetoresistive (GMR) assay

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ARTICLE INFO

Keywords:

Neutralizing antibodies
COVID-19
Patient plasma/serum
Longitudinal study
Vaccine efficacy
Magnetoe-nanosensors

ABSTRACT

The COVID-19 pandemic has highlighted the need to monitor important correlates of immunity on a population-wide level. To this end, we have developed a competitive assay to assess neutralizing antibody (NAb) titer on the giant magnetoresistive (GMR) biosensor platform. We compared the clinical performance of our biosensor with established techniques such as Ortho's VITROS Anti-SARS-CoV-2 IgG Quantitative Antibody test. Results obtained between the VITROS test and the GMR assay showed correlation ($r = -0.93$). We then validated the assay with patient plasma samples that had been tested using focus reduction neutralization testing (FRNT). The results obtained from our GMR assay exhibit a previously identified trend of increased NAb titers 2 weeks post-vaccination. We further evaluated NAb titers 6 months post-vaccination and observed waning neutralizing antibody titers over that time in vaccinated patients. In addition, we calibrated our assay to an arbitrary unit (IU/mL) using World Health Organization (WHO) reference plasma provided by the National Institute of Biological Standards and Control (NIBSC). Our biosensor provides highly specific and sensitive results in serum and plasma with analytical, clinical, and point-of-care (POC) applications due to quick turnaround times on samples and the cost-effectiveness of the platform.

1. Background

With over 102 million confirmed cases and 1 million deaths in the United States alone by the time of writing [1], the onset of COVID-19 has necessitated a new approach to healthcare, one in which patient health can be easily and cheaply evaluated. Even as case numbers and fatalities have fallen from their respective peaks in recent months, COVID-19 remains a potent public health challenge [2], requiring new tools and careful monitoring to counter future outbreaks and manage vulnerable populations [3]. Over 662 million vaccine doses have been administered in the US to meet this challenge [1] and discussions about the need for further "booster shots" following primary vaccinations hinge upon a faithful representation of the population's immune defenses over time. Unfortunately, vaccine-induced humoral immunity tends to wane in the months after vaccination and the rate of this change varies from individual to individual [4–7]. Thus, to maintain an accurate picture of a population's immunity toward SARS-CoV-2, the time-dependent protection imparted by the vaccine must be regularly evaluated on a per-patient basis.

Neutralizing antibody (NAb) titer has been found to be a valuable indicator of immunity and health status as well as a predictor for likely outcomes in patients infected with SARS-CoV-2 [8–14]. As such, several means of evaluating neutralizing antibody titers in patients have been utilized for the purpose of determining vaccine efficacy. Live virus neutralization tests (VNTs) like the plaque reduction neutralization test (PRNT) or the focus reduction neutralization test (FRNT) are considered to be "gold standard" in accuracy when evaluating NAb content. However, these tests suffer from several weaknesses. VNTs are time-consuming, low throughput, and require highly trained personnel to operate [15,16]. There are also safety concerns associated with tests that utilize live SARS-CoV-2, which must be conducted in biosafety level 3 (BSL-3) rated facilities.

Giant magnetoresistive (GMR) biosensors have been utilized to great effect in the past for biomarker detection [17–23]. This technology converts the presence of an antigen in a sample into a detectable change in magnetoresistance due to the proximity of magnetic nanoparticles (MNPs) to the sensors. GMR biosensors are multiplexable, highly versatile, and are compatible with a wide variety of biomolecules.

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Below, we describe a GMR-based SARS-CoV-2 assay for the detection of NAb levels in serum and plasma. Our assay can provide actionable results within hours as opposed to virus neutralization techniques which have turnaround times on the order of days. In addition, our assay only requires BSL-2 facilities as it utilizes the SARS-CoV-2 spike receptor binding domain (RBD) rather than live virus, increasing its accessibility.

We believe that our GMR-based assay fills the need for a COVID-19 neutralizing antibody assay that improves upon VNTs, with reduced time-to-results and increased accessibility. These factors, plus the previously demonstrated cost-effectiveness of the platform [23], lend GMR biosensors to point-of-care applications and effective scalability; technologies that fill this niche will be needed to manage future outbreaks [24].

2. Materials and methods

2.1. Patient selection and plasma sample collection

Our vaccination cohort was comprised of samples from 24 patients who had received primary vaccination, either via Pfizer/BioNTech (BNT162b2) or Moderna (mRNA-1273). Both are mRNA vaccines that are administered in two doses with a month-long intermediate period. A portion of our plasma samples ($n = 28$ samples) were obtained courtesy of Drs. Prabhu Arunachalam and Bali Pulendran. The samples were collected from volunteers who were pre-screened for vaccination status, previous exposure to COVID-19, and current health status. Only healthy patients with no prior or current known exposure to COVID-19 were included. We collected samples at three different timepoints: pre-vaccination baseline; 2 weeks post-vaccination; and 6 months post-vaccination. Blood samples (~ 50 – 150 μ L) were obtained from volunteers via finger-prick using a SurgiLance safety lancet (MediPurpose) and Minivette POCT capillary tubes (Sarstedt). After collection, the blood sample was centrifuged at 1000 g for 12 min. The resulting plasma supernatant was pipetted into a separate tube. The plasma was stored at -80 °C prior to testing. Research protocols involving the screening of volunteers and collection and testing of human samples were approved by the Stanford University Institutional Review Board (Protocol #: IRB-61649). For demographic information on our patient cohort, refer to the [supplementary material \(Table S1\)](#).

2.2. Reagents

A list of the reagents used in this assay can be found in [Table 1](#).

2.3. Surface functionalization of GMR sensor arrays

The GMR sensors were cleaned, pretreated, and functionalized prior

to performing the assays. Sensor surfaces were washed with acetone, followed by methanol, and finally isopropanol to remove any organic residue on the surface. The surfaces were air dried with a nitrogen (N_2) air gun. The sensor surfaces were then treated with a 15% solution of hydrogen peroxide (H_2O_2) in deionized water (DI H_2O). After 15 min in the H_2O_2 solution at room temperature, the sensor surfaces were washed with DI H_2O and then dried with N_2 . The chips were then immersed in a 10% (3-aminopropyl) triethoxysilane (APTES)-acetone solution at room temperature for 30 min. This silanization step allows for the covalent grafting of proteins during spotting. After this period, the chips were washed with acetone and DI H_2O and finally dried with N_2 .

Three probes were spotted onto the sensor chips using the Scienion sciFlexarrayer S5: biotinylated BSA (biotin-BSA; positive control) at a concentration of 1 mg/mL (6 sensors per chip); ovalbumin (OVA; negative control) at 200 μ g/mL (10 sensors per chip); and angiotensin converting enzyme 2 (ACE2) at 250 μ g/mL (12 sensors per chip).

2.4. SARS-CoV-2 neutralizing antibody assay

The chip surface was washed with a buffer solution (0.1% BSA in 0.05% Tween-20 in PBS), blocked using casein solution for 1 h at room temperature to prevent non-specific binding, and then washed again. Separately, biotinylated spike RBD protein (biotin-RBD) was mixed with the plasma or serum sample in a 1:1 ratio by volume. This solution was allowed to incubate at room temperature for 1 h. During this incubation period, any NABs present in the sample bound to the biotin-RBD ([Fig. 1](#)). After the blocking and incubation steps, the biotin-RBD-sample solution was added to the chip and left at room temperature for 1 h again. At this point, the ACE2 receptors which were previously spotted onto the GMR sensors were able to bind to any un-neutralized biotin-RBD. After 1 h, the chip was again treated with wash buffer solution, cleaning off excess biotin-RBD and antibodies and leaving behind the ACE2-bound biotin-RBD complexes attached to the sensor surface. The cartridge was loaded into the GMR reading stations and streptavidin-labeled MNPs were pipetted into the sensor well. The streptavidin-biotin bond formed between the biotin-RBD and the streptavidin-MNPs tethers the MNPs to the sensor surface. The assay was allowed to run for 15 min until signals had all reached saturation ([Fig. S1](#)).

2.5. FRNT and Ortho VITROS IgG assays

A pilot set of COVID-19 convalescent plasma (CCP) samples was analyzed by personnel at the Stanford Blood Center using Ortho's VITROS IgG Assay in accordance with the manufacturer's instructions. Samples received from Drs. Arunachalam and Pulendran had previously been characterized via focus reduction neutralization testing (FRNT) [25].

2.6. Statistical analysis

Statistical analysis was performed using GraphPad Prism 9.3.1. Individual sample data are reported as the median $\pm$ standard deviation. Signals from all other sensors were normalized to the background of the sample using the signals from the negative control sensors. Curve equations were generated using either Deming regression or a sigmoidal 4-parameter logistic regression ([Tables S2, S3 and S4](#)). Goodness of fit was determined using the coefficient of determination (R^2) and correlation was measured using the Pearson correlation coefficient (r). P-values were calculated using mixed-effects analysis with Tukey's multiple comparisons test. Receiver operating characteristic (ROC) analysis was performed to establish the signal threshold for our assay using FRNT as the comparator standard; the resulting curve can be found in the [supplementary material \(Fig. S2\)](#). Those sensors reporting a signal greater than or less than 2 standard deviations from the median were defined as outliers and ignored in the calculation of the endpoint signal for a sample.

Table 1

List of reagents necessary for the assay including manufacturers and catalog numbers.

Item Description	Manufacturer	Catalog Number
Biotinylated BSA (Biotin-BSA)	Sigma-Aldrich	A8549
Ovalbumin (OVA)	Sigma-Aldrich	A5503
Angiotensin converting enzyme 2 (ACE2) receptors	Sino Biological	10108-H05H
Phosphate-buffered saline (PBS, 1X, pH 7.2)	Gibco	20012-027
Tween 20	Fisher Scientific	BP337-500
Bovine serum albumin (BSA)	Sigma-Aldrich	A9418-10G
Blocker casein solution	Thermo Fisher	37582
Biotinylated SARS-CoV-2 spike RBD	Sino Biological	40592-V08H-B
Anti-SARS-CoV-2 neutralizing antibodies (NAB)	Active Motif	91361
Pre-pandemic pooled human plasma samples	Lee Biosolutions	
Streptavidin MicroBeads	Miltenyi Biotec	130-048-101

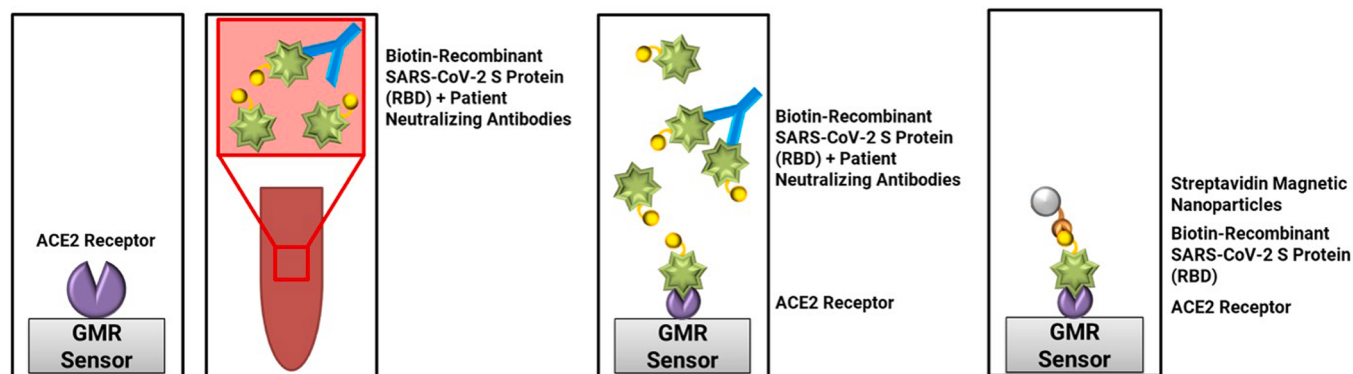


Fig. 1. Schematic of the GMR-based NAB assay. ACE2 receptors are functionalized on the sensor surface. Biotin-RBD is mixed with the sample to bind NABs in the sample, if present. Un-neutralized biotin-RBD binds to ACE2 receptors on the sensor surface and then binds to streptavidin-labeled MNPs to generate a GMR signal. GMR signal and the concentration of NABs are inversely correlated.

3. Results

3.1. Characterization of the GMR SARS-CoV-2 neutralizing antibody assay

SARS-CoV-2 virions infiltrate human somatic cells when the spike RBD proteins of the virus bind to the ACE2 receptors present on the cell membrane. Antibodies in plasma can neutralize the virus by binding to the viral RBD, thereby preventing infiltration. Given the design of this assay, where signal is generated by the binding of free biotin-RBD to ACE2 receptors on the sensor surface, lower titers of NABs will yield higher GMR signals (change in resistance, ppm) while higher levels of NABs will yield lower GMR signals.

The optimal biotin-RBD concentration was first determined. Biotin-RBD was diluted in wash buffer to the following concentrations: 1000, 500, 200, 100, and 50 ng/mL. These dilutions were tested using the assay as described above with pre-pandemic (collected prior to 2019) pooled human plasma. The optimal biotin-RBD concentration (500 ng/mL) was chosen as the point where the curve reaches saturation (Fig. 2A). At this saturation point, there is a sufficient amount of biotin-RBD such that a majority of the ACE2 capture probes on the sensors are bound. This concentration was used in all subsequent testing. Standard curves were generated using contrived samples where commercially available NABs were spiked into pre-pandemic pooled human plasma samples at varying dilutions (Fig. 2B).

To validate the performance of our assay, we tested a small pilot set of CCP samples. These samples had been previously tested by the Stanford Blood Center using Ortho's VITROS IgG assay. This test received an emergency use authorization (EUA) from the Food and Drug Administration (FDA) as one of the first high throughput assays for identifying CCP samples as high- or low- antibody titer [26]. With this pilot set, we see correlation between the results of the two assays (Fig. 3).

3.2. Temporal changes in neutralizing antibody levels pre- and post-vaccination

We demonstrated the ability of our GMR assay to trace NAB levels over time in a cohort of plasma samples from 24 patients, pre- and post-vaccination. This cohort included patients who were immunized with vaccines from BioNTech/Pfizer (BNT162b2) and Moderna (mRNA-1273). Samples were collected at three different timepoints: pre-vaccination baseline; 2 weeks post-vaccination; and 6 months post-vaccination. As shown in Fig. 4, our assay can detect the change in NAB titers that is expected to accompany vaccination. Patients exhibited a sharp increase in NAB titer at 2 weeks post-vaccination ($p < 0.0001$). From these peak values, patient NAB levels began to wane 6 months

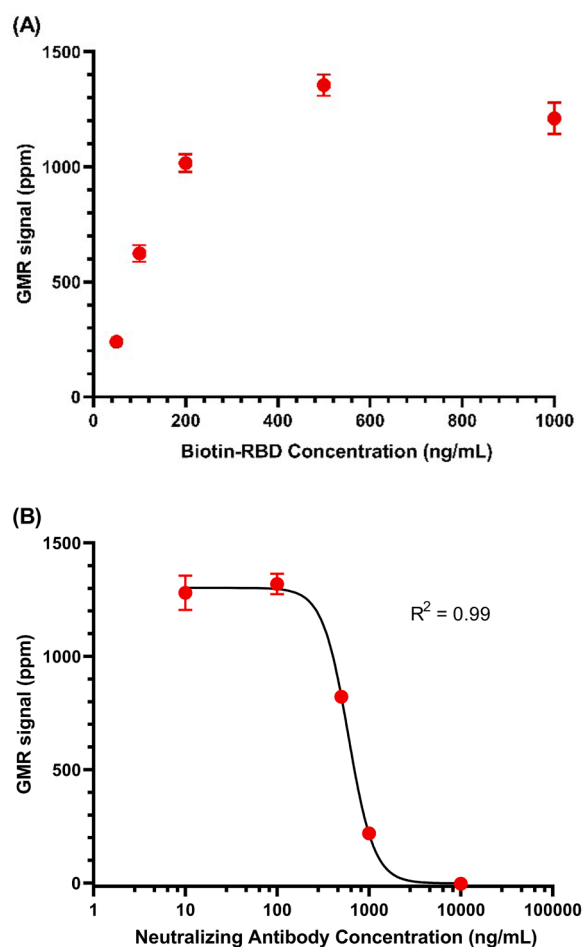


Fig. 2. (A) Biotin-RBD optimization was performed to decide the concentration to be used in the NAB assay. Optimal concentration can be determined as the point at which the curve saturates. (B) NAB standard curve in ng/mL.

post-vaccination ($p = 0.0005$). Despite this, NAB levels at this timepoint tended to be higher than pre-vaccination levels ($p = 0.0242$). This finding indicates that within our patient cohort, vaccination imparted significant humoral protection for months after receiving the second dose. Our work agrees with findings elsewhere that mRNA vaccine efficacy with respect to neutralizing antibody titers tended to wane 6 months post-vaccination from peak values [4–7] yet remain elevated compared to pre-vaccination levels [4,5].

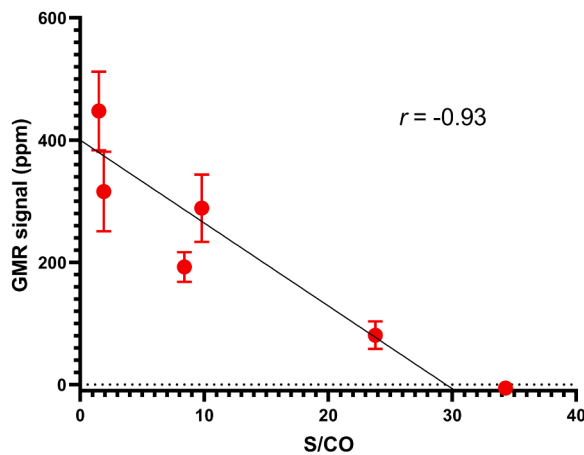


Fig. 3. Convalescent plasma samples tested using Ortho's VITROS IgG assay and our GMR assay. S/CO: signal-cutoff ratio.

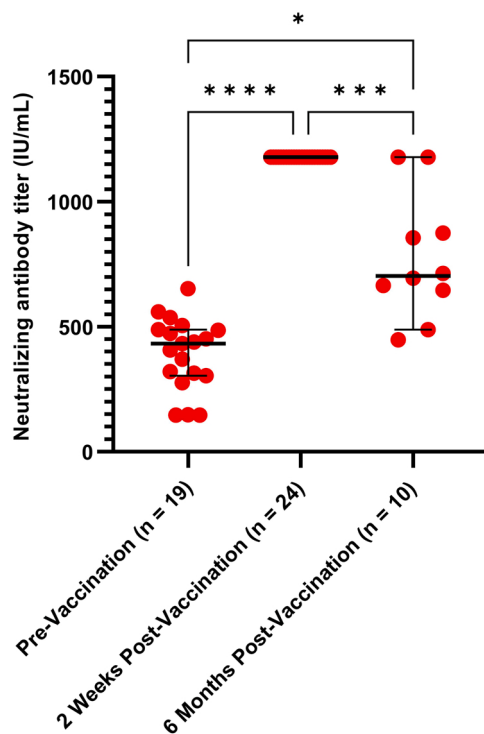


Fig. 4. Summary of all longitudinal vaccinated patient samples tested using the GMR assay. *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$. Bars represent median $\pm$ 95% CI. Values outside of the range of the assay were placed at either the ULOQ or the LLOQ.

A subgroup ($n = 28$ samples) of our cohort's samples were previously characterized using FRNT [21]. FRNT is a member of the same family of virus neutralization tests as PRNT and provides commensurate results [27,28]. These samples were collected from 14 volunteers at pre-vaccination baseline (Day 0) and 2 weeks post-vaccination. FRNT analysis indicated a sharp increase in patient NAb concentration 2 weeks after full vaccination (Fig. 5). We tested the same samples using the GMR assay and found high agreement between the results of the two tests. Using the FRNT results as a comparator standard, we found our test had a sensitivity of 100% (95% CI: 78.5–100%) and a specificity of 100% (95% CI: 78.5–100%) with a GMR signal threshold of 292.9 ppm (Fig. S2).

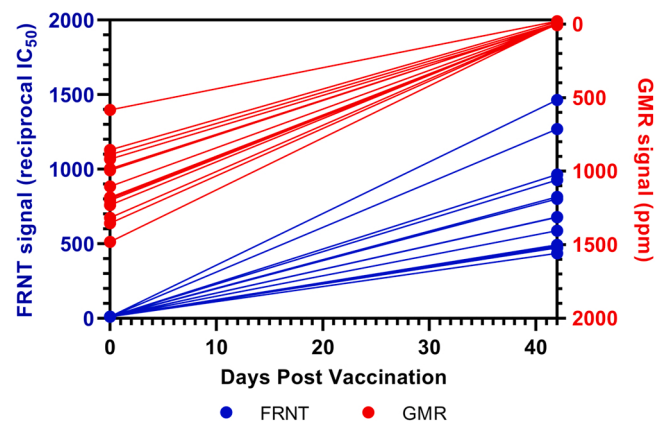


Fig. 5. Results from FRNT and our GMR assay with a subgroup of our plasma samples, at pre-vaccination baseline (Day 0; $n = 14$) and 2 weeks post-vaccination (Day 42; $n = 14$).

4. Discussion

Neutralizing antibody titers in patients are of great interest as the presence of NAb in the peri-infection period has been identified as an important component of immune protection against SARS-CoV-2 [11–13]. Breakthrough infections in vaccinated patients tended to occur in individuals with lower NAb titers compared to controls [13]. Higher neutralizing antibody titers in the peri-infection period are associated with increased likelihoods of survival and decreased likelihoods that a patient will suffer severe symptomatic infection [11,12]; alleviating the severity of disease for patients is especially important given the relationship between patient outcomes and the stress on US health systems [29]. Because of this, information on NAb levels is crucial to understanding patient immunity and prognosis when confronted with SARS-CoV-2 infection.

In this study, we demonstrated that the GMR platform is compatible with a SARS-CoV-2 NAb assay. This is a competitive assay, where the biotin-RBD can bind to either the NAb present in the sample or the ACE2 receptors on the sensor surface. The amount of un-neutralized RBD in the sample is inversely correlated to the change in resistance detected by the GMR chip. Higher signal indicates lower NAb levels and lower signal indicates higher NAb levels.

We compared our GMR assay to several established techniques, the first of which was Ortho's VITROS IgG assay. Our results indicated correlation between the latter and the GMR NAb assay ($r = -0.93$). The correlation between the two tests implies that our assay can be used as a tool for determining recent SARS-CoV-2 infection, which was one of the intended purposes for Ortho's VITROS test as outlined in its EUA [30].

FRNT and similar VNTs (like PRNT) have a high degree of accuracy and reproducibility and are considered the gold standard for quantifying neutralizing antibody titer within a sample [15]. However, these techniques suffer from long turnaround times, taking on the order of days to deliver results on samples [25,27,28]. In addition, these tests require working with live SARS-CoV-2 virions and cell culture which in turn necessitates special training for laboratory personnel and BSL-3 certified facilities [15,16]. In contrast, the GMR assay can deliver quick results (~ 3 h) on samples and requires only a BSL-2 laboratory. Our assay was also found to give similar qualitative results to FRNT; the sensitivity and specificity of our assay relative to FRNT is 100% and 100%, respectively. Baseline samples of the test group fell below the LOD of the FRNT performed; the signals of samples collected 2 weeks post-vaccination were above the ULOQ of the GMR assay. In order to quantify the correlation between the two techniques, further work collecting and testing patient samples that fall within the dynamic ranges of both assays will be necessary.

In compliance with recommendations from the WHO on the

development of novel SARS-CoV-2 serological assays [31], we have calibrated the assay using reference plasma provided by the NIBSC (Fig. S3). We define the limit of detection (LOD) as 74 IU/mL (1328 ppm). The lower limit of quantitation (LLOQ) was determined to be 147 IU/mL (1315 ppm) and the upper limit of quantitation (ULOQ) was determined to be 1178 IU/mL (118 ppm).

As new variants of SARS-CoV-2 emerge on the global stage, the assay presented here can be amended to evaluate antibody response to other SARS-CoV-2 virions. This versatility is particularly salient to variants that will emerge in the future, as Omicron (B.1.1.529) did in the early months of 2022. Mutations to the spike protein associated with Omicron result in greater antigenic escape from antibodies compared to previous variants [32,33]. By modifying the mutations present on the recombinant spike protein employed, the assay described above can be used to study NAb response to Omicron or other variants. Such work could be conducted by integrating a microfluidic device with the GMR biosensor – as in [34] – which channels different solutions to separate sensors on the same chip. By changing the mutation of spike RBD protein used for each microfluidic channel, we could analyze the neutralizing ability of a single patient's plasma/serum against multiple variants simultaneously.

In addition to vaccine efficacy, our tool can be employed to distinguish high titer convalescent plasma that is suitable for use in CCP treatments. Such therapies have been demonstrated to have utility for treating certain patients, including the elderly, immunosuppressed, and non-intubated [35,36].

The assay proposed above analyzes the NAb content of serum or plasma obtained by finger-prick. Useful future work could include investigating the applicability of this assay to other media. Working with analytes that do not require venipuncture collection or centrifugation such as saliva and mucus would improve the standard of care associated with this test. We also consider further reduction of assay times to be feasible given past work on similar tests that saw turnaround times of ~15 min [37]. Finally, we believe that this assay is a prime candidate for deployment as a point-of-care tool, as has been done with other GMR assays [23,37,38]. In the future, this neutralizing antibody test could be conducted in a self-contained, single-use cartridge on which all sample and fluid handling would be automated. This would allow for minimal user interaction and quick results on a lightweight device with a small footprint, for use at the point-of-care. Any additional work conducted towards these ends would be a highly valuable contribution in combatting and monitoring COVID-19 outbreaks.

5. Conclusion

We have described an assay that utilizes the giant magnetoresistive (GMR) biosensor platform to assess neutralizing antibody (NAb) titers in patient serum or plasma. This assay is specific, sensitive, and has a sufficient range to examine the typical NAb titers seen in plasma samples. Our test has potential for a number of different analytical and clinical applications, including vaccine efficacy monitoring and detection of recent illness at the point-of-care. We employed this test to analyze the NAb levels of a cohort of volunteers following vaccination and found that humoral immunity tended to wane 6 months post-vaccination from peak yet remain elevated compared to pre-vaccination levels. These findings are in agreement with results reported by other studies. We believe that this assay has significant advantages over – and is a viable alternative to – traditional methods like the gold standard virus neutralization tests.

CRediT authorship contribution statement

Elaine Ng: Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. **Christopher Choi:** Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Shan X. Wang:** Supervision.

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.

Data availability

Data will be made available on request.

Acknowledgments

We would like to thank Drs. Prabhu Arunachalam, Bali Pulendran, Suchitra Pandey, and Tho Pham for their generosity in providing samples for our study. The authors were supported in part by the National Cancer Institute (NCI; R01 CA257843) and the National Institute of Allergy and Infectious Diseases (NIAID; R01 AI125197) of the National Institutes of Health (NIH). E.N. acknowledges support from the Stanford Cancer-Translational Nanotechnology Training (Cancer-TNT) T32 Fellowship Program. C.C. acknowledges support from the National Science Foundation (NSF) Graduate Research Fellowship Program (GRFP).

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.snb.2023.133773](https://doi.org/10.1016/j.snb.2023.133773).

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