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*Article*

# Anti-Spike Protein to Determine SARS-CoV-2 Antibody Levels: Is There a Specific Threshold Conferring Protection in Immunocompromised Patients?

**Philippe Halfon [1,2], Sylvie Jordana [1], Stéphane Blachier [3], Philippe Cartlamy [3], Laurent Kbaier [4], Guilhem Cavaille [2], Chloé Stavris [2], Frédérique Retornaz [2], Laurent Chiche [2] and Guillaume Penaranda [1,*]**

[1] Laboratoire Alphabio – Biogroup, Marseille, FRANCE
[2] Service de Médecine Interne, Hôpital Européen, Marseille, FRANCE
[3] Laboratoires Oriade Noviale – Biogroup, Grenoble, FRANCE
[4] Laboratoire Bioestérel – Biogroup, Mouans-Sartoux, France
* Correspondence: guillaume.penaranda@biogroup.fr; Tel. : +33 4 13 42 81 00;

**Abstract:** Background: Identifying a specific threshold level of SARS-CoV-2 antibodies that confers protection in immunocompromised patients has been very challenging. The aim was to assess the threshold of 264 binding antibody units (BAU)/ml using four different SARS-CoV-2 antibody assays (Abbott, Beckman, Roche, and Siemens) and to establish a new optimal threshold of protection for each of the four antibody assays. Methods: This study was performed on data retrieved from 69 individuals, who received at least one dose of the Pfizer/BioNTech BNT162b2 or Moderna COVID-19 vaccine (Spikevax) at the Alphabio Laboratory in Marseille, France (European Hospital, Alphabio – Biogroup). The results were compared to the percent inhibition calculated using a functional surrogate of a standardized virus neutralization test (Genscript). Results: Samples from 69 patients were analyzed. For a reference cutoff of 264 BAU/ml, assays showed moderate to good overall concordance with Genscript: 87% concordance for Abbott, 78% for Beckman, 75% for Roche, and 88% for Siemens. Overall concordance increased consistently after applying new thresholds, i.e., 148 BAU/ml (Abbott), 48 (Beckman), 559 (Roche), and 270 (Siemens). Conclusion: We suggest specific adjusted thresholds (BAU/ml) for the four commercial antibody assays that are used to assess pre-exposure prophylaxis in immunocompromised patients.

Keywords: SARS-CoV-2; Antibody binding assays; binding antibody units; Immunocompromised; Threshold

## 1. Introduction

As with many viral respiratory infections, knowledge of the immune response to SARS-CoV-2 after a natural infection or vaccination, that could be predictive of the protection conferred, is challenging and not well established [1–4]. To date, few studies have defined correlates of protection against SARS-CoV-2 infection that can be used by regulators and vaccine developers. Increasing evidence suggests that vaccination regimens for COVID-19, that are applied to the general population, do not adequately protect a significant proportion of immunocompromised patients [5,6].

A recent randomized efficacy trial of the ChAdOx1 nCoV-19 (AZD1222) vaccine conducted in more than 8,500 patients in the United Kingdom, analyzed the antibody levels associated with protection against SARS-CoV-2 [7]. They concluded that higher levels of all immune markers were correlated with a reduced risk of symptomatic infection. A vaccine efficacy of 80% against symptomatic infection caused by the majority alpha (B.1.1.7) variant of SARS-CoV-2 was achieved with 264 binding antibody units (BAU)/ml (95% confidence interval [CI]: 108, 806), and 506 BAU/ml (95% CI: 135, over limit) for anti-spike and anti-RBD antibodies, respectively. Recommendations based on

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only one study is not prudent. Indeed, the BAU/ml values were performed only on the B.1.1.7 variant in neutralization assays and not on different strains of the virus; hence, there may be no relation between immune markers and disease outcome [7].

Anti-SARS-CoV-2 antibody therapies have proven to be efficient in preventing hospitalization in unvaccinated high-risk patients, when administered early on after polymerase chain reaction (PCR) diagnosis or after contact with infected individuals [8]. Indeed, antibody therapy for pre-exposure prophylaxis (PrEP), may be efficient in preventing hospitalization in immunocompromised patients, regardless of the variant involved.

Based on these studies, a threshold of 264 BAU/ml antibody was used as a recommendation for the use of PrEP in SARS-CoV-2 in France, and extrapolated to immunocompromised patients [9].

Few studies have highlighted the lack of standardization of SARS-CoV-2 serology, despite the use of the international standards set by the World Health Organization (WHO) for SARS-CoV-2 immunoglobulin levels (BAU/ml) [10–13].

The objectives of the present study were to assess the threshold of 264 BAU/ml antibody, using four different SARS-CoV-2 antibody assays and further, to establish a new optimal threshold of protection for each of the four antibody assays [14].

## 2. Materials and Methods

### *2.1. Study design and participants.*

This study was performed using sera collected between October 2021 and December 2021 from 69 individuals, who received at least one dose of the Pfizer/BioNTech BNT162b2 or Moderna COVID-19 vaccine (Spikevax) from three to six months before sampling collection. All samples were collected at the Alphabio Laboratory in Marseille, France (European Hospital, Alphabio – Biogroup). All patients were immunocompromised and underwent chemotherapy and biotherapy (rituximab or immune checkpoint inhibitor).

According to French regulations, the study was approved by the French ethics committee (Health Data Hub, approval number: F20211217094518). The ethics committee waived the need for formal written informed consent from patients, as this study was performed on clinical data retrieved from routine tests; thus, no patient was specifically included in this study. As required by French regulations, patients attending clinical laboratories are informed that their biological results can be used for research purposes and that they are free to refuse to allow this (information annotated in the clinical laboratory report). All data were fully anonymized before the analysis. This study complied with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research involving human subjects.

### *2.2. Laboratory procedures.*

Four antibody binding assays were used for serological testing according to the instructions of the manufacturer. Two were quantitative: Abbott SARS-CoV-2 IgG II Quant-test (Abbott) (Abbott France, Rungis, France) with 50 arbitrary units (AU)/ml as a threshold for positivity, and Roche Elecsys anti-SARS-CoV-2 S (Roche Diagnostics France, Meylan, France) with 0.8 AU/ml used as a threshold for positivity. Two were semi-quantitative: Beckman Access SARS-CoV-2 IgG II (Beckman Coulter France SAS, Roissy CDG, France) with 30 AU/ml as a threshold for positivityand Siemens Atellica® IM SARS-CoV-2 IgG (Siemens Healthcare SAS, Saint-Denis, France) with 0.8 AU/ml used as a threshold for positivity.

BAU/ml proposed by the WHO, to standardize any assay to the WHO International Standard, were calculated by applying the following conversion factors as suggested by the manufacturers: Abbott, BAU/ml = (1/7) × AU/ml, Beckman, BAU/ml = 1 × AU/ml, Roche, BAU/ml = 1.029 × AU/ml, and Siemens, BAU/ml = 21.8 × AU/ml.

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The neutralizing capacity was estimated by performing a surrogate virus neutralization test (sVNT) assay (GenScript, Piscataway, NJ, USA) as previously described [10,15,16]. This assay detects antibodies that block the interaction of SARS-CoV-2 with its entry receptor angiotensin-converting enzyme 2. A threshold of 20% was used for positivity.

*2.3. Statistical Analyses.*

Quantitative data were reported using median and interquartile range (IQR), and qualitative data were reported using frequency and percentage. The nonparametric Kruskal–Wallis test for multiple comparisons was used to compare all assays. Pairwise comparisons were performed using the nonparametric Wilcoxon test. Agreements between antibody-binding assays and Genscript sVNT were performed using Cohen's kappa, crude concordance rate, and area under curve (AUC). Optimal cutoffs for distinguishing positivity were calculated using logistic regression on Genscript sVNT binary results (negative/positive), prior to the Youden index maximization approach on receiver operating characteristic curve results. The Youden index indicates the performance (the larger the better) at a given cutoff: Youden = sensitivity + specificity – 1 (the maximum value of the Youden index is 1) [17]. Statistical significance was set at $P < 0.05$. Calculations were performed using the SAS V9.4 software (SAS Institute Inc., Cary, NC, USA).

**3. Results**

Samples from 69 patients were included in this study. The female/male ratio was 67/33, and the median age was 47 years (IQR 34–63). All patients had received at least one dose of either Pfizer/BioNTech BNT162b2 or Moderna COVID-19 vaccine (Spikevax).

The median values observed for the antibody binding assays were 143 BAU/ml (IQR 39–748) for Abbott, 55 BAU/ml (IQR 19–217) for Beckman, 636 BAU/ml (IQR 98–2369) for Roche, and 161 BAU/ml (IQR 32–574) for Siemens, which demonstrated the variations between the assays (overall $P < 0.0001$). Beckman assay showed lower values as compared to all other assays ($P< 0.008$ for all paired comparisons); and lower values was observed for Siemens assay compared with Roche assay ($P = 0.0033$).

Comparisons were performed between Genscript sVNT positive and negative samples according to antibody binding assays, all of which were significant ($P < 0.0001$) (Figure 1). Agreement between the antibody binding assays and the Genscript sVNT assay is shown in Table 1. When considering a reference cutoff of 264 BAU/ml, the assays showed moderate to good agreement with Genscript sVNT, with strong variations of the kappa index from 0.52 for Beckman and Roche to 0.76 for Siemens (kappa = 0.72 for Abbott). The overall concordance between antibody binding assays and the Genscript sVNT varied from 75% for Roche to 88% for Siemens (87% for Abbott and 78% for Beckman). All assays showed a high AUC for prediction of positive and negative results of Genscript sVNT (AUC > 0.90 for all).

The optimal cutoff was analyzed for each antibody binding assay (Table 1). Using the Youden index maximization approach, optimal cutoffs were consistently lower than the reference cutoff of 264 BAU/ml for the Abbott and Beckman assays (148 and 48 BAU/ml, respectively). In contrast, the optimal cutoff was higher for the Roche assay (559 BAU/ml). For the Siemens assay, the optimal cutoff was within the same range as the reference cutoff (270 BAU/ml). When considering specific optimal cutoffs, agreement between each antibody binding assay and Genscript sVNT increased consistently from 0.03 units for the Siemens assay to 0.25 units for the Beckman assay (kappa = 0.79 and 0.77, respectively). Kappa increased to 0.76 for the Abbott assay (0.04 units increase) and to 0.71 for the Roche assay (0.19-unit increase). Overall, all assays showed good agreement with the Genscript sVNT. The overall concordance between the antibody binding assays and the Genscript sVNT also increased consistently i.e., 11% increase for Roche

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(86% concordance), 10% increase for Beckman (88% concordance), 2% increase for Siemens (90% concordance), and 1% increase for the Abbott assay (88% concordance).

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*3.2. Figures, Tables and Schemes*

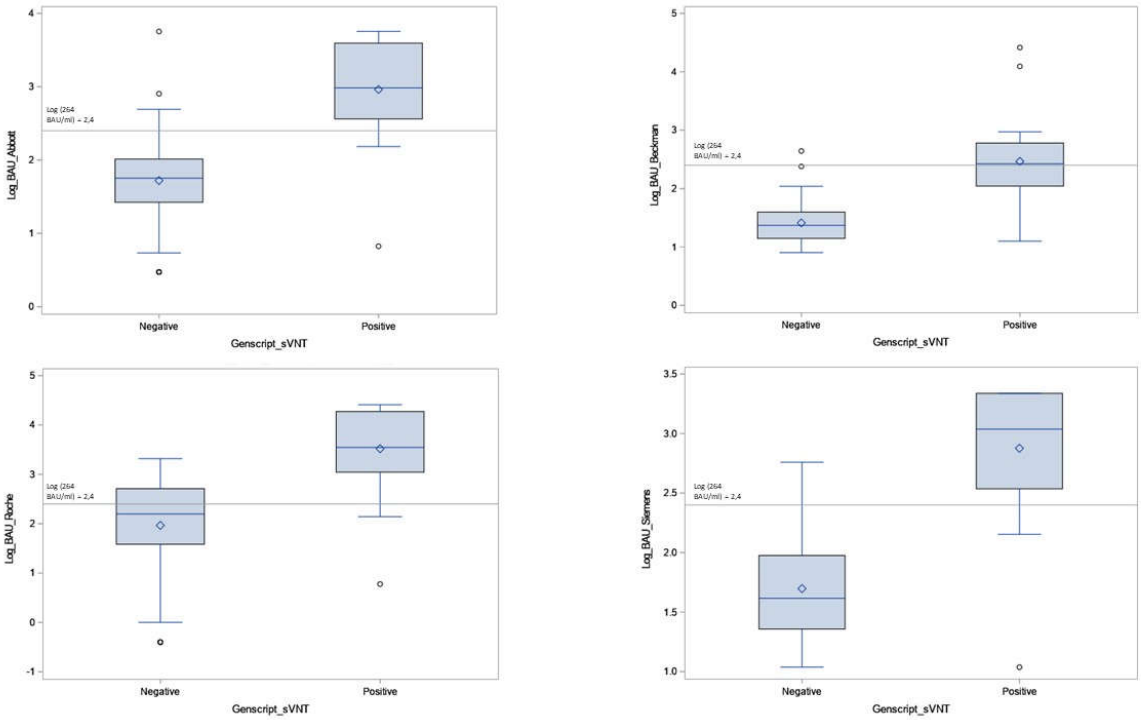


**Figure 1. Boxplots for each antibody binding assay according to Genscript sVNT positive and negative results.** Solid reference line represents 264 binding antibody units (BAU)/ml cutoff (2.4 Log). The Wilcoxon test for pairwise comparisons yielded P < 0.0001 for all comparisons.

**Table 1.** Agreement between antibody binding assays and Genscript sVNT positive and negative results according to the reference cutoff (264 BAU/ml) and to optimal cutoff values determined for each assay using logistic regression, ROC curve analysis, and the Youden index.

| Assay | Reference Cutoff (BAU/ml) | Genscript sVNT (n) | | Optimal Cutoff* (BAU/ml) | Genscript sVNT (n) | |
|---|---|---|---|---|---|---|
| | | Negative | Positive | | Negative | Positive |
| **Abbott**** | <264 | 36 | 5 | <148 | 33 | 1 |
| | ≥264 | 4 | 22 | ≥148 | 7 | 26 |
| **Beckman** | <264 | 39 | 14 | <48 | 33 | 1 |
| | ≥264 | 1 | 15 | ≥48 | 7 | 28 |
| **Roche** | <264 | 25 | 2 | <559 | 32 | 2 |
| | ≥264 | 15 | 27 | ≥559 | 8 | 27 |
| **Siemens** | <264 | 36 | 4 | <270 | 37 | 4 |
| | ≥264 | 4 | 25 | ≥270 | 3 | 25 |

BAU, binding antibody units; ROC, receiver operating characteristic; sVNT surrogate virus neutralization test. * Optimal cutoff determined using Youden index maximization; **n = 67, two results could not be assessed by the Abbott antibody binding assay.

## 4. Discussion

This study revealed the limitations of using a specific threshold for decision-making regarding PreP in immunocompromised patients. As previously observed by Perkmann et al. although all assays showed good agreement with the Genscript sVNT, they were not interchangeable, even when converted to BAU/ml using the WHO international standard for SARS-CoV-2 immunoglobulin levels [10]. The differences in the commercial

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assays used in this study are related to the components of the tests (the spike antigen epitopes used, the different isolates of the SARS-CoV-2, and the quantification of either total antibodies or only IgG) [18–20]. This implies that the cutoff values provided for the respective test systems are valid only for the diagnosis of a past infection and do not necessarily represent a threshold value for the presence of sufficient neutralizing activity. Therefore SARS-CoV-2 serology may be standardized.

For SARS-CoV-2, tests to neutralize live viruses are performed only in specialized laboratories and are not standardized, making it difficult to compare and justify the use of a well-characterized sVNT as a functional reference [21,22].

Additionally, neutralizing antibodies were not investigated, which could have helped in determining whether the anti-RBD or the anti-spike assays had the strongest correlation with virus neutralization. However, harmonization of neutralizing antibody titers is necessary to determine a common threshold using which vaccine protection can be predicted. This would allow for identification of the corresponding thresholds, using high-throughput binding antibody assays.

One of the limitations of this study was the low number of samples that were subjected to antibody quantification and the absence of an independent international standard (WHO in IU/ml). Another limitation was the lack of an external cohort to validate the suggested thresholds. There is also a limitation regarding the two semi-quantitative antibody binding assays as a saturation limit could be reached because of their limited measurement range.

In conclusion, there is no specific threshold conferring protection in immunocompromised patients. Therefore, we suggest specific BAU/ml adjusted thresholds for the four commercial antibody assays (Abbott, Beckman, Roche, and Siemens), which can be used to guide the use of PreP in immunocompromised patients.

**Author Contributions:** Study design: PH and GP. Data collection: SJ, SB, PC, LK, GC, CS, FR, and LC. Data analysis: GP. Data interpretation: PH and GP. Writing: PH and GP, with comments from all authors.

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**Institutional Review Board Statement:** According to French regulations, the study was approved by the French ethics committee (Health Data Hub, approval number: F20211217094518). The ethics committee waived the need for formal written informed consent from patients, as this study was performed on clinical data retrieved from routine tests; thus, no patient was specifically included in this study. As required by French regulations, patients attending clinical laboratories are informed that their biological results can be used for research purposes and that they are free to refuse to allow this (information annotated in the clinical laboratory report). All data were fully anonymized before the analysis. This study complied with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research involving human subjects.

**Informed Consent Statement:** Not Applicable, see Institutional Review Board Statement

**Data Availability Statement:** All requests for raw and analyzed data that underlie the results reported in this article should be addressed to (guillaume.penaranda@biogroup.fr) and will be reviewed by the study team to determine whether the request is subject to confidentiality and data protection obligations. Data that can be shared will be released via a material transfer agreement. Source data are provided with this paper.

**Conflicts of Interest:** The authors declare no conflict of interest

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