

**Barranquilla – Colombia, Junio 27 de 2025**

**To the Editorial Committee**

**Microbes, Infection and Chemotherapy**

**Dear Editors,**

We are writing to acknowledge and express our gratitude for the insightful comments and suggestions provided by the reviewers. In response, we have addressed each observation and correction in detail.

**Reviewer 1:**

**Recommendation: Accept this submission.**

**1. Relevance of the Title to the Article Content**

- **Rating:** Regular
- **Observations:** The title aligns with the introduction, providing conceptual information on Hybrid Immunity.
- **Authors' Response:** No suggestions or corrections were made on this point.

**2. Abstract: Presents the general idea of the topic, objectives, research methods, results, and conclusions, drafted objectively and concisely; and adheres to the maximum word count per section.**

- **Rating:** Regular
- **Observations:** Details regarding research methodology, ethics committee approval, as well as results and conclusions are provided.
- **Authors' Response:** No suggestions or corrections were made on this point.

**3. Introduction: Presentation of the topic, justification of the problem, objectives, hypothesis, and methodological foundation, exposing the topic in an organized and detailed manner.**

- **Rating:** Regular
- **Observations:**
  - Information on the definition of Hybrid Immunity is provided.
  - The type of methodology used for the study is detailed.

- **Authors' Response:** No suggestions or corrections were made on this point.
- 4. **Methodology: Describes the procedure, methods, and techniques used in data collection and analysis.**
  - **Rating:** Regular
  - **Observations:**
    - Population and sample data are detailed.
    - The antibody quantification process is detailed.
    - Ethics committee approval is mentioned.
    - The data analysis process and software used are detailed.
  - **Ethical Aspects: Does the manuscript include a paragraph on ethical aspects, mentioning ethics committee approval, informed consent, and strict adherence to research ethics?**
    - Yes, all these aspects are detailed.
  - **Authors' Response:** No suggestions or corrections were made on this point.
- 5. **Results: Are adequately presented and do not redundantly feature tables or graphs.**
  - **Rating:** Regular
  - **Observations:**
    - Sociodemographic data are detailed.
    - Statistical data, including p-value, are presented.
    - Correlation analysis is detailed.
  - **Authors' Response:** No suggestions or corrections were made on this point.
- 6. **Discussion: Presents a level of critical analysis in correspondence with the stated problem. Article purposes, scope, supporting theory, and proposed methodological design.**
  - **Rating:** Regular
  - **Observations:**

- It is specified that the study's results are similar to other national studies.
    - Participant recruitment in months post-pandemic is mentioned, contributing to the hybrid immunity proposal.
  - **Authors' Response:** No suggestions or corrections were made on this point.
7. **Conclusions: Presents the author's inferences and lessons learned regarding the researched topic, and should correspond to the study's objectives.**
- **Rating:** Good
  - **Observations:**
    - It is specified that immunity remains long-term (21 - 23 months).
    - Patients with risk factors should be prioritized, although these factors do not appear to influence the basal antibody concentration.
  - **Authors' Response:** The independent variables studied, associated with the host, were: Gender, age, baseline comorbidities (arterial hypertension, diabetes mellitus, overweight, obesity, metabolic syndrome), habits (tobacco and alcohol), type of vaccine received, number of booster doses, and type of immunization strategy received. Antibody IgG anti-S quantification (dependent variable) was measured taking into account each variable, adjusted to the condition of previous infection or not.
8. **References: Quality of bibliographic references and adherence to Vancouver format.**
- **Rating:** Good
  - **Observations:** Bibliographies not older than 5 years are presented in over 90% of citations.
  - **Authors' Response:** No suggestions or corrections were made on this point.
9. **Contributions: What are the main weaknesses of the manuscript and how can the author improve it?**
- **Observations:** Present more data on risk factors.
  - **Authors' Response:** The selected risk factors are those best characterized in the pathophysiology of COVID-19, with a higher risk of

death and severe disease. In our study, more than 12 variables were analyzed. However, we could consider other factors for future studies, given that the data collection instrument (structured survey questionnaire) was validated with the previously mentioned variables.

**Reviewer 2:**

**Recommendation: Publishable with modifications.**

**1. Relevance of the Title to the Article Content**

- **Rating:** Good
- **Observations:**
- **Authors' Response:** No suggestions or corrections were made on this point.

**2. Abstract: Presents the general idea of the topic, objectives, research methods, results, and conclusions, drafted objectively and concisely; and adheres to the maximum word count per section.**

- **Rating:** Regular
- **Observations:** Reduce and be concise in this section.
- **Authors' Response:** The suggested modifications were implemented, and the changes are reflected in the corrected manuscript.

**3. Introduction: Presentation of the topic, justification of the problem, objectives, hypothesis, and methodological foundation, exposing the topic in an organized and detailed manner.**

- **Rating:** Regular
- **Observations:** Scientific novelty is limited: Hybrid Immunity has already been extensively studied. This manuscript confirms previous findings rather than providing new ones. Discuss the added value of the study more deeply within the context of recent literature (2023-2024).
- **Authors' Response:** The suggested modifications were implemented, and the changes are reflected in the corrected manuscript. However, we believe that the detailed discussion should not be in the introduction, but rather in the discussion of the results.

**4. Methodology: Describes the procedure, methods, and techniques used in data collection and analysis.**

- **Rating:** Regular

- **Observations:**
  - The sample size is small for multivariate analysis or to detect small differences (n=51 per group).
  - The calculation of sample size or statistical power (power analysis) is not justified.
  - There is a high overlap in antibody titers between groups, which raises doubts about the reliability of the classification between previous infection or not (recall bias or underdiagnosis of asymptomatic infections).
  - "Simple linear regression" is used to project future responses to hypothetical boosters, without adjusting for confounding factors such as age or comorbidities. This may lead to speculative conclusions.
  - Mention at least an approval document number.
  - The cut-off point

≥105 BAU/mL is mentioned as “positive,” but it is not clinically justified why this threshold is chosen (is it protective? is it neutralizing?). Better justify the cut-off point used.

- **Ethical Aspects: Does the manuscript include a paragraph on ethical aspects, mentioning ethics committee approval, informed consent, and strict adherence to research ethics?**
  - Yes, but it is not very detailed.
- **Authors' Response:** The suggested modifications were implemented, and the changes are reflected in the corrected manuscript.

**5. Results: Are adequately presented and do not redundantly feature tables or graphs.**

- **Rating:** Regular
- **Observations:**
  - Remove (# - %) from rows and place them in columns.
  - Add confidence intervals to the analysis to strengthen estimates.
  - Table 2 is too confusing; improve presentation.
- **Authors' Response:** The suggested modifications were implemented, and the changes are reflected in the corrected manuscript.

6. **Discussion: Presents a level of critical analysis in correspondence with the stated problem. Article purposes, scope, supporting theory, and proposed methodological design.**
- **Rating:** Poor
  - **Observations:**
    - There is no adequate discussion; it is limited to repeating and interpreting results, with no adequate bibliographic evaluation.
    - There is a confirmation bias. Although no significant differences are found, it is stated that HI "positively" influences humoral immunity.
    - A critical reflection on the possibility of undiagnosed subclinical infections in group B (which would compromise comparison with group A) is omitted.
    - The assertion about the immunological equivalence of all vaccines lacks support, as numerically non-significant differences do not imply clinical or immunological equivalence.
    - Rewrite the discussion to reflect a more cautious interpretation of results.
    - Include a more robust limitations section (underreporting of infections, self-selection, lack of functional antibody measurement, statistical power).
    - Conduct an adequate bibliographic search.
  - **Authors' Response:** The suggested modifications were implemented, and the changes are reflected in the corrected manuscript.
7. **Conclusions: Presents the author's inferences and lessons learned regarding the researched topic, and should correspond to the study's objectives.**
- **Rating:** Poor
  - **Observations:**
  - **Authors' Response:** No suggestions or corrections were made on this point. However, we made changes considering the previous comments. All are reflected in the corrected manuscript.
8. **References: Quality of bibliographic references and adherence to Vancouver format.**

- **Rating:** Regular
- **Observations:**
  - Replace some general WHO references with peer-reviewed studies that offer more precise quantitative data.
  - Increase the number of studies for discussion, as it is too poor.
- **Authors' Response:** The suggested modifications were implemented, and the changes are reflected in the corrected manuscript.

9. **Contributions: What are the main weaknesses of the manuscript and how can the author improve it?**

- **Observations:**
  - Excessive repetition of some terms (e.g., “high reactivity,” “basal concentration,” “antibodies”).
  - Some paragraphs in the discussion are redundant or too long.
  - Avoid categorical statements not supported by evidence (“all vaccines are effective for prolonged immunity”).
- **Authors' Response:** The suggested modifications were implemented, and the changes are reflected in the corrected manuscript.