PROTECTION AGAINST SARS-COV-2 REINFECTIONS IN CHILDREN UNDER FIVE YEARS OF AGE WHO EXPERIENCED A MILD COVID-19: RESULTS FROM A SURVEY STUDY

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Introduction

Previous studies have shown that antibody titers elicited by infection or vaccination are associated with protection in adults [1, 2]. However, limited data exists on the protective role of antibodies in children. With the recent approval of COVID-19 vaccines for young children, it is important to understand the humoral correlates of protection in this population. Our previous research indicated an inverse correlation between humoral responses and age, with children aged <5 years exhibiting higher levels of antigen-specific antibody titers compared to older individuals up to 12 months after COVID-19 [3].

Objectives

This study aims to investigate whether <5-year-old children who experienced a mild COVID-19 are more protected against reinfections compared to older individuals.

Methods

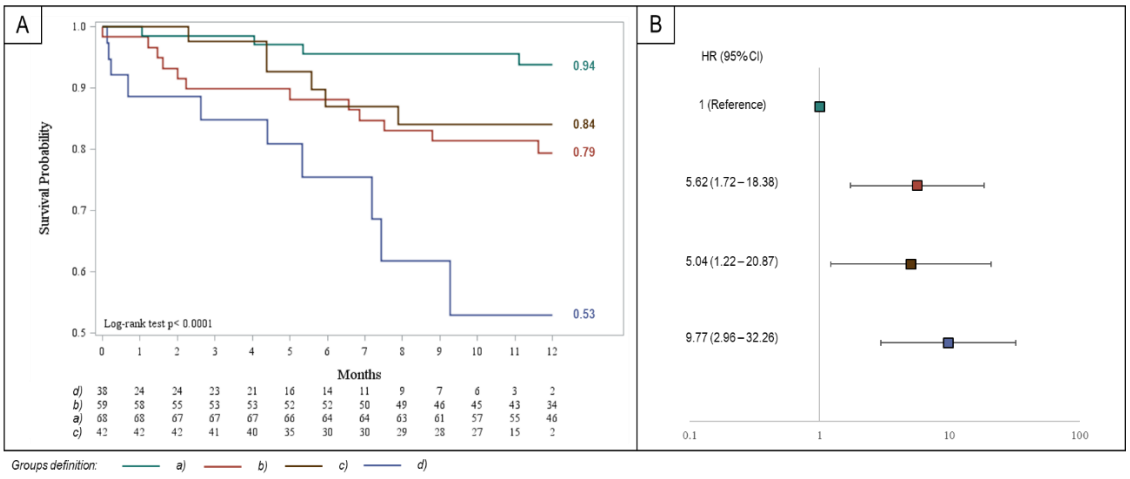
A survey study was conducted from January to April 2023, involving 393 families attending the COVID-19 family cluster clinic [3]. Questionnaires were completed by parents to gather information on their children's close contact with confirmed COVID-19 cases, occurrences of SARS-CoV-2 reinfections, and vaccination history up to 12 months from the index date, defined as the date of the first SARS-CoV-2 infection or COVID-19 vaccination. Children were categorized based on age and immunization status in four exposure groups: a) SARS-CoV-2-recovered participants aged <5 years (reference group), b) SARS- CoV-2-recovered participants aged ≥5-22 years, c) naïve-vaccinated aged ≥5-22 years, and d) participants aged ≥5-22 years with hybrid immunity defined as one-dose vaccination within 12 months after a previous SARS-CoV-2 infection. Sociodemographic and clinical characteristics were summarized as frequencies and percentages. Survival probability was calculated using Kaplan-Meier estimator. Cox proportional hazard regression was used to analyze the association between exposure groups and reinfection.

Results

A total of 156 families participated in the study (response rate=40%), with 208 children included. No severe reinfections requiring hospitalisation were reported in any group. The cumulative 1-year reinfection survival was significantly higher in children <5 years (94%) compared to older SARS-CoV-2-recovered (79%), older naïve-vaccinated (84%), and older children with hybrid immunity (53%) ($p<0.0001$) (Figure A). Reinfection

survival was low in individuals with hybrid immunity achieved through a single dose of vaccination. Cox model analysis confirmed the increased reinfection risk in children aged five and above compared with those SARS-CoV-2-recovered aged <5 years, regardless of the exposure group (Figure B).

Figure. Cumulative reinfection survival probability at 1-year among the exposure groups (A). Adjusted hazard ratio and 95% CI for 1-year reinfection, according to exposure groups. The adjustment was based on sex, the presence of at least one comorbidity, and SARS-CoV-2 circulating variants (pre-omicron and/or omicron subvariants) during follow-up (B).



a) SARS-CoV-2-recovered participants aged 0-<5 years (reference group), b) SARS-CoV-2-recovered participants aged ≥5-22 years, c) naïve-vaccinated aged ≥5-22 years, and d) participants aged ≥5-22 years with hybrid immunity defined as one-dose vaccination within 12 months after previous SARS-CoV-2 infection.

Conclusions

We found that children aged <5 years who had experienced mild COVID-19 had a significantly lower risk of subsequent reinfections compared to older infected and/or vaccinated individuals up to 12 months after infection or vaccination. This suggests that higher humoral responses in young children may provide robust protection against reinfections, consistent with observations in adults [1,2,4]. However, the protective role of IgG anti-RBD antibodies was correlated with a reduced risk of symptomatic but not asymptomatic infection, leading to a possible underestimation of the outcomes.

Furthermore, a 1-dose vaccination regimen in previously infected children demonstrated low correlates of protection, suggesting the importance of taking 2-dose primary series of vaccination, regardless of a previous infection. The higher efficacy of a complete hybrid immunity has already been proved in adults [5].

The waning of IgG S-RBD titers [3] and the observed reduction in protection against infection have raised the importance of longitudinal serological studies for defining a protective threshold of anti-RBD antibody titers that would trigger revaccination. Further studies with larger sample sizes are necessary to confirm our findings and to assess the protective role of memory B cells against SARS-CoV-2 infection in young children. Understanding the relationship between immune responses and protection from COVID-19 will be instrumental in predicting the effectiveness of vaccines in the pediatric population and guiding the development of optimized vaccination strategies for children.

References

1. Khoury D.S., Schlub T.E., Cromer D., et al. Correlates of Protection, Thresholds of Protection, and Immunobridging among Persons with SARS-CoV-2 Infection. Emerging Infectious Diseases. 2023 Feb;29(2):381-388..

2. Perry J., Osman S., Wright J., et al. Does a humoral correlate of protection exist for SARS- CoV-2? A systematic review. PLoS One. 2022 Apr;17(4):e0266852.

3. Di Chiara C., Cantarutti A., Costenaro P., et al. Long-term Immune Response to SARS- CoV-2 Infection Among Children and Adults After Mild Infection. JAMA Netw Open. 2022 Jul;5(7):e2221616.

4. Goldblatt D, Alter G, Crotty S, Plotkin SA. Correlates of protection against SARS-CoV-2 infection and COVID-19 disease. Immunol Rev. 2022 Jun; 310(1):6-26.

5. Carazo S, Skowronski DM, Brisson M, et al. Protection against omicron (B.1.1.529) BA.2 reinfection conferred by primary omicron BA.1 or pre-omicron SARS-CoV-2 infection among health-care workers with and without mRNA vaccination: a test- negative case-control study. Lancet Infect Dis. 2023 Jan; 23(1):45-55.