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Prior SARS-CoV-2 Infection and Risk of Subsequent COVID-19-Related Hospitalization: A Test Negative Design

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Background

- Previous evidence suggests that prior SARS-CoV-2 infection provides some protection against reinfection.[1-5]
- Extent of protection against severe outcomes, such as hospitalizations, afforded by prior infection is not certain.
- We used a test-negative design to evaluate the effectiveness of prior COVID-19 against acute respiratory infection-related (ARI) hospitalizations.

Methods

- Active surveillance at two hospitals in Atlanta, GA
- May 2021 – June 2022
- **Study Eligibility:**
  - Adults ≥18 years of age admitted with an acute respiratory infection (ARI)
  - Willing to participate in an interview regarding medical, social and vaccination history
  - Able to provide NP swabs at enrollment or from hospital testing
- Enrolled patients' medical records, past medical history, and vaccine documentation were reviewed and abstracted
- Prior SARS-CoV-2 infection defined as:
  - Self-reported prior SARS-CoV-2 infection
  - Positive SARS-CoV-2 test ≥90 days before ARI hospitalization.
- If individuals received ≥ 1 COVID-19 vaccine and symptom onset was ≥14 days after receipt of first dose, the individual was considered as vaccinated.
- **Analysis**
  - Molecular test negative design comparing COVID-19 positive and negative patients.
  - Characteristics compared with bivariate analysis (two-tailed p-value <0.05)
  - Generated a stepwise logistic regression model with inclusion in the model set at 0.05.
  - The final adjusted model included vaccination, comorbidities, and immunosuppression.
  - We also stratified our data to analyze the efficacy of prior infections without the influence of any COVID-19 vaccination.
  - Analysis performed using SAS v.9.4

Table 1: Baseline Demographics, Past Medical History, COVID-19 Vaccination Status and Distribution Among COVID-19 Positive and Negative Patients and Among Those With and Without Prior Infection

Demographic (n=1343)	COVID-19 Positive (n=684)	COVID-19 Negative (n=659)	P-value	Prior infection (n=66)	No prior infection (n=1277)	P-value
Age: Median, IQR	54 (41,65)	60 (47,70)	**<.0001**	60 (49, 67)	57 (44, 68)	0.5
Male	308 (45%)	303 (46%)		28 (42.4%)	583 (45.6%)	
Female	376 (55.0%)	356 (54.0%)	0.7	38 (57.6%)	694 (54.4%)	0.6
Race: White	153 (22.4%)	180 (27.3%)		15 (22.7%)	318 (24.9%)	
Black/African American	488 (71.4%)	433 (65.7%)	0.1	45 (68.2%)	876 (68.6%)	0.7
Multiracial	20 (2.9%)	18 (2.7%)		2 (3%)	36 (2.8%)	
Other/Unspecified	23 (3.4%)	28 (4.3%)		4 (6.1%)	47 (3.7%)	
Ethnicity: Hispanic/Latino	28 (4.1%)	26 (4.0%)	0.9	1 (1.5%)	53 (4.2%)	0.5
Non-Hispanic/Latino	628 (92.6%)	597 (92.3%)		61 (93.9%)	1164 (92.4%)	
Not Specified/ No response	28 (4.1%)	36 (5.5%)		4 (6.1%)	60 (4.7%)	
Comorbidities: Immunosuppression	148 (21.6%)	198 (30.1%)	**0.0004**	8 (12.1%)	338 (26.5%)	**0.009**
Respiratory Disease	149 (21.8%)	218 (33.1%)	**<0.0001**	25 (37.9%)	342 (26.8%)	0.05
Cardiac Disease	402 (58.8%)	453 (68.7%)	**0.0001**	53 (80.3%)	802 (62.8%)	**0.004**
Liver Disease	4 (0.6%)	11 (1.7%)	0.07	0 (0.0%)	15 (1.2%)	1.0
Severity: Admitted to ICU	158 (23.1%)	142 (21.6%)	0.5	10 (15.2%)	290 (22.7%)	0.2

Results

- Overall, 1343 patients enrolled in the study.
  - 684/1343 (50.9%) were SARS-CoV-2 positive.
  - 66/1343 (4.9%) had a prior SARS-CoV-2 infection.
- **Table 1** demonstrates the baseline differences between COVID-19 positive and negative patients and among those with and without prior COVID-19.
- COVID-19 positivity differed by:
  - Age, receipt of ≥ 1 COVID-19 vaccination, underlying immunosuppression, and respiratory and cardiac disease.
- Prior COVID-19 differed by:
  - Immunosuppression, cardiac disease
- **Table 2** demonstrates the effectiveness of prior SARS-CoV-2 infection against COVID-19-related hospitalization.
  - Crude odds ratio (OR) 0.27 (95% CI 0.15, 0.48)
  - Adjusted OR 0.26 (95% CI 0.14, 0.49).
- Reinfections represented 15/684 (2.2%) of COVID-19-related hospitalizations.

Table 2: Odds of COVID-19 Hospitalization Among Those With and Without Prior SARS-CoV-2 Infection

SARS-CoV-2 infection before ARI hospitalization	SARS-CoV-2 Positive (Cases)	SARS-CoV-2 Negative (test negative controls)	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio* (95% Confidence Interval)
Yes	15 (22.7%)	51 (77.3%)	0.27 (0.15, 0.48)	0.26 (0.14, 0.49)
No	669 (52.4%)	608 (47.6%)		

* Adjusted for co-morbidities and prior COVID-19 vaccination

Limitations

- Self selection bias due to voluntary enrollment in study
- Incomplete access to medical records (missing cases) and potential subject recall errors.
- Asymptomatic SARS-CoV-2 infections not included.
- Prior and ARI-related SARS-CoV-2 variant data not available (e.g., Delta, Omicron BA.1, BA.5)

Conclusions

- **Reinfections represented a small proportion (2.2%) of COVID-19-related hospitalizations.**
- **Prior SARS-CoV-2 infection provided short-term 74% (95% CI 51, 86) protection against COVID-19-related ARI hospitalizations.**
- **Data are needed about the duration of prior infection protection, variant-specific estimates, and the impact of vaccination by number of doses.**

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