CORRESPONDENCE

Protection Associated with Previous SARS-CoV-2 Infection in Nicaragua

TO THE EDITOR: The course of the current pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will be determined in part by the quality and durability of protective immunity induced by previous infection, vaccination, or both, as well as by the severity of illness in persons with some level of immunity.[1,2] From March 2020 through October 2021 in the Household Influenza Cohort Study (HICS) study, we followed 2353 participants, ranging in age from newborn infants to elderly persons up to 94 years of age, in 437 households in Nicaragua for the presence of SARS-CoV-2 infection (Fig. 1A). The study was approved by the institutional review boards at the Nicaraguan Ministry of Health, the University of Michigan, and the University of California, Berkeley. All the participants (or their parents or guardians if they were under the age of 18 years) provided written informed consent; children who were 6 years of age or older also provided assent.

Here, we report on immunity levels in the second wave of the pandemic (from April through October 2021), during which the P.1 (gamma) and B.1.617.2 (delta) variants predominated, to evaluate protection induced by previous SARS-CoV-2 infection against coronavirus disease 2019 (Covid-19) (Fig. S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Starting in March 2021, vaccines against Covid-19 became available in the community, so in this analysis we excluded participants who had received one or more vaccine doses in order to assess protection associated only with previous infection.

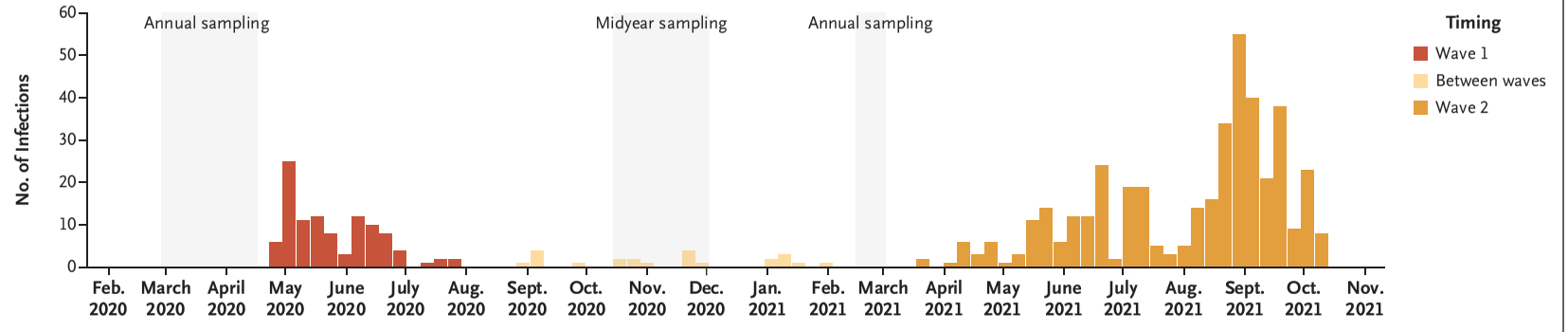
During this period, we identified 378 participants with Covid-19 as determined by reverse-transcriptase–polymerase-chain-reaction assay in our cohort. We analyzed paired serum samples (current vs. baseline) by means of enzyme-linked immunosorbent assay (ELISA). The SARS-CoV-2 spike receptor-binding domain and spike proteins for ELISA were produced in single batches at the Life Sciences Institute at the University of Michigan. Genetic sequencing was performed by the Pathogen Surveillance Program (PSP) Study Group at the Icahn School of Medicine at Mount Sinai and by the Nicaraguan National Virology Laboratory.

We compared the incidence of infection that occurred during the second wave among participants who were seropositive (1284 participants [62.2% of the cohort]) and those who were seronegative (780 participants [37.8% of the cohort]) in March 2021 (Fig. 1B and Table S1). We calculated the percent protection as 1−the risk ratio for SARS-CoV-2 infection among participants who were seropositive as compared with those who were seronegative.

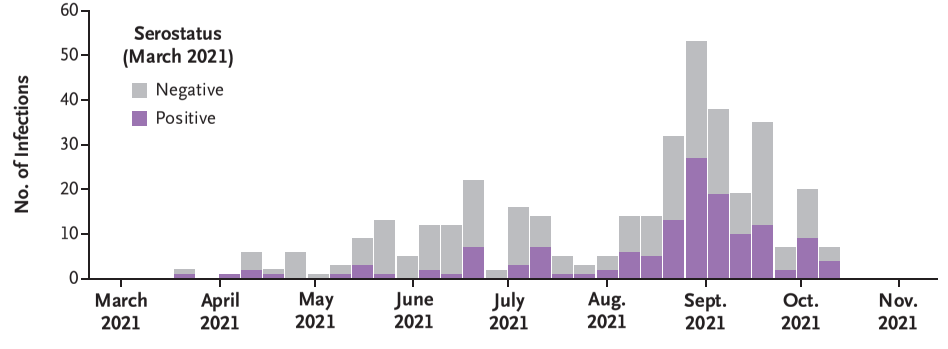
Infection-induced immunity provided some protection against infection during the second wave approximately 1 year after the first wave. Protection was higher against more severe outcomes, with 78.9% protection (95% confidence interval [CI], 63.4 to 87.9) against moderate or severe infection (in 17 of 1284 seropositive participants as compared with 49 of 780 seronegative participants), 68.1% protection (95% CI, 59.2 to 75.1) against symptomatic infection (in 96 of 1284 seropositive participants as compared with 183 of 780 seronegative participants), and 63.9% protection (95% CI, 55.5 to 70.7) against any detectable infection (in 141 of 1284 seropositive participants as compared with 237 of 780 seronegative participants) (Fig. 1C and 1D).

According to age group, protection against symptomatic infection was 51.0% (95% CI, 17.4 to 70.9) among participants 9 years of age or younger (in 21 of 276 seropositive participants as compared with 43 of 277 seronegative participants), 73.3% (95% CI, 63.7 to 80.4) among participants between 10 and 49 years of age (in 63 of 880 seropositive participants as compared with 115 of 429 seronegative participants), and 72.3% (95% CI, 44.8 to 86.1) among participants who were 50 years of age or older (in 12 of 128

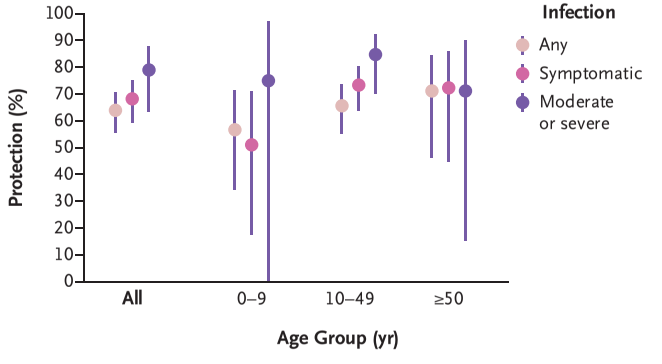
A Pandemic Waves and Timing of ELISA Sampling



B SARS-CoV-2 Infection after March 1, 2021, on RT-PCR, According to Serostatus



C Protection against SARS-CoV-2 Infection



D Protection from Previous Infection, According to RT-PCR Seropositivity and Age Group

	Age	All	Seropositive	RT-PCR (all)	RT-PCR (symptomatic)	RT-PCR (moderate or severe disease)	Seropositive RT-PCR (all)	Seropositive RT-PCR (symptomatic)	Seropositive RT-PCR (moderate or severe disease)	Protection (all)	Protection (symptomatic)	Protection (moderate or severe disease)
	yr					*no.*					*percent*	
1	All	2064	1284	378	279	66	141	96	17	63.9 (55.5 to 70.7)	68.1 (59.2 to 75.1)	78.9 (63.4 to 87.9)
2	0–9	553	276	106	64	5	32	21	1	56.6 (34.3 to 71.3)	51.0 (17.4 to 70.9)	74.9 (–124.4 to 97.2)
3	10–49	1309	880	227	178	46	94	63	11	65.6 (55.1 to 73.5)	73.3 (63.7 to 80.4)	84.7 (69.8 to 92.2)
4	≥50	202	128	45	37	15	15	12	5	71.1 (46.3 to 84.4)	72.3 (44.8 to 86.1)	71.1 (15.4 to 90.1)

Figure 1 (facing page). Protection against Covid-19 Associated with SARS-CoV-2 Seropositivity.

Panel A shows the pandemic waves of coronavirus disease 2019 (Covid-19) from February 2020 through November 2021 and the timing of sampling for analysis on enzyme-linked immunosorbent assay (ELISA). Panel B shows the curve of positive infections on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay after March 1, 2021, according to serostatus. Panel C shows the percent protection against Covid-19 (any infection, symptomatic, or moderate or severe) from previous infection overall and according to age group. Table D shows the percent protection against Covid-19 according to RT-PCR serostatus and age group.

seropositive participants as compared with 25 of 74 seronegative participants). Protection against any detectable infection was 56.6% (95% CI, 34.3 to 71.3) among participants 9 years of age or younger (in 32 of 276 seropositive participants as compared with 74 of 277 seronegative participants), 65.6% (95% CI, 55.1 to 73.5) among those between 10 and 49 years of age (in 94 of 880 seropositive participants as compared with 133 of 429 seronegative participants), and 71.1% (95% CI, 46.3 to 84.4) among those who were 50 years of age or older (in 15 of 128 seropositive participants as compared with 30 of 74 seronegative participants).

Our current overall estimate of 68.1% protection against symptomatic infection through October 2021 was lower than our previous observation of 93.6% protection before March 2021,[3] a difference that was probably due to longer follow-up time to observe infections (and for immunity to wane) and the predominance of variants that differed from the original strains against which immunity had been generated. A limitation of these findings is that they may differ from protection during the current era of the omicron variant.

Given waning protection against Covid-19, high levels of community infection will affect future transmission and severity of disease, yet communities that have already had high infection rates will still benefit from immune augmentation through vaccination.[4,5]

Hannah E. Maier, Ph.D.
University of Michigan
Ann Arbor, MI

Angel Balmaseda, M.D.
Sustainable Sciences Institute
Managua, Nicaragua

Saira Saborio, M.S.
Ministry of Health
Managua, Nicaragua

Sergio Ojeda, M.D.
Carlos Barilla, B.A.
Nery Sanchez, M.D.
Sustainable Sciences Institute
Managua, Nicaragua

Roger Lopez, M.P.H.
Ministry of Health
Managua, Nicaragua

Miguel Plazaola, M.D.
Sustainable Sciences Institute
Managua, Nicaragua

Cristhiam Cerpas, B.S.
Ministry of Health
Managua, Nicaragua

Harm van Bakel, Ph.D.
Icahn School of Medicine at Mount Sinai
New York, NY

John Kubale, Ph.D.
University of Michigan
Ann Arbor, MI

Eva Harris, Ph.D.
University of California, Berkeley
Berkeley, CA

Guillermina Kuan, M.D.
Sustainable Sciences Institute
Managua, Nicaragua

Aubree Gordon, Ph.D.
University of Michigan
Ann Arbor, MI
gordonal@umich.edu

Supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (award no. R01 AI120997 and contract no. HHSN272201400006C, to Dr. Gordon) and a grant from Open Philanthropy.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on July 20, 2022, at NEJM.org.

1. Milne G, Hames T, Scotton C, et al. Does infection with or vaccination against SARS-CoV-2 lead to lasting immunity? Lancet Respir Med 2021;9:1450-66.
2. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science 2020;368:860-8.
3. Maier HE, Kuan G, Saborio S, et al. Clinical spectrum of SARS-CoV-2 infection and protection from symptomatic re-infection. Clin Infect Dis 2021 August 19 (Epub ahead of print).
4. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. Association of prior SARS-CoV-2 infection with risk of breakthrough infection following mRNA vaccination in Qatar. JAMA 2021;326:1930-9.
5. Gazit S, Shlezinger R, Perez G, et al. Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections. August 25, 2021 (https://www.medrxiv.org/content/10.1101/2021.08.24.21262415v1). preprint.

DOI: 10.1056/NEJMc2203985