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Clinical Spectrum of Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Protection From Symptomatic Reinfection

Hannah E. Maier,[1,a] Guillermina Kuan,[2,3,a] Saira Saborio,[2,4,a] Fausto Andres Bustos Carrillo,[5] Miguel Plazaola,[2] Carlos Barilla,[2] Nery Sanchez,[2] Roger Lopez,[2,4] Matt Smith,[1] John Kubale,[1] Sergio Ojeda,[2,3] Julio C. Zuniga-Moya,[1] Bradley Carlson,[1] Brenda Lopez,[2] Anna M. Gajewski,[2] Mahboob Chowdhury,[1] Eva Harris,[5] Angel Balmaseda,[2,4] and Aubree Gordon[1]

[1]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA; [2]Sustainable Sciences Institute, Managua, Nicaragua; [3]Centro de Salud Sócrates Flores Vivas, Ministry of Health, Managua, Nicaragua; [4]Centro Nacional de Diagnóstico y Referencia, Ministry of Health, Managua, Nicaragua; and [5]Division of Infectious Diseases and Vaccinology, School of Public Health, University of California, Berkeley, California, USA

Background. There are few data on the full spectrum of disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection across the lifespan from community-based or nonclinical settings.

Methods. We followed 2338 people in Managua, Nicaragua, aged <94 years from March 2020 through March 2021. SARS-CoV-2 infection was identified through real-time reverse transcription polymerase chain reaction (RT-PCR) or through enzyme-linked immunosorbent assay. Disease presentation was assessed at the time of infection or retrospectively by survey at the time of blood collection.

Results. There was a large epidemic that peaked between March and August 2020. In total, 129 RT-PCR–positive infections were detected, for an overall incidence rate of 5.3 infections per 100 person-years (95% confidence interval [CI], 4.4–6.3). Seroprevalence was 56.7% (95% CI, 53.5%–60.1%) and was consistent from age 11 through adulthood but was lower in children aged ≤10 years. Overall, 31.0% of the infections were symptomatic, with 54.7% mild, 41.6% moderate, and 3.7% severe. There were 2 deaths that were likely due to SARS-CoV-2 infection, yielding an infection fatality rate of 0.2%. Antibody titers exhibited a J-shaped curve with respect to age, with the lowest titers observed among older children and young adults and the highest among older adults. When compared to SARS-CoV-2–seronegative individuals, SARS-CoV-2 seropositivity at the midyear sample was associated with 93.6% protection from symptomatic reinfection (95% CI, 51.1%–99.2%).

Conclusions. This population exhibited a very high SARS-CoV-2 seropositivity with lower-than-expected severity, and immunity from natural infection was protective against symptomatic reinfection.

Keywords. SARS-CoV-2; community-based; cohort; seropositive; reinfection.

More than a year into the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, which has caused hundreds of millions of infections and millions of deaths [1], the full burden due to coronavirus disease 2019 (COVID-19) remains unknown. This is particularly evident in low- and middle-income countries (LMICs). Many studies have reported common COVID-19 manifestations [2] and severity [3–5] worldwide and some specifically in Latin American countries [6]. However, the majority of studies have reported on cases identified in clinics and hospitals. These often represent more severe cases and leave the full picture of COVID-19 as yet unclear. Studies in the United States (US) and Europe have shown that SARS-CoV-2 infection induced approximately 80%–90% [7–9] protection from repeat symptomatic infection, but it is critical to know whether similar levels of protection exist in LMICs, which generally have younger populations. However, due to limited testing and the broad clinical spectrum of COVID-19, the true extent of the coronavirus pandemic in LMICs such as Nicaragua remains unknown [10].

We performed a community-based prospective cohort study of families to assess the incidence of SARS-CoV-2 infection and disease across the life course, characterize the spectrum of COVID-19, and examine the degree of protection from repeat SARS-CoV-2 infection among seropositive individuals.

METHODS

Ethics Statement

This study was approved by the institutional review boards at the Nicaraguan Ministry of Health and the University of Michigan (HUM00119145 and HUM00178355). Informed consent or parental permission was obtained for all participants. Assent was obtained from children aged ≥6 years.

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[a]H. E. M., G. K., and S. S. contributed equally to this work.

Correspondence: A. Gordon, Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, 5622 SPH I, 1415 Washington Heights, Ann Arbor, MI 48109-2029 (gordonal@umich.edu).

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Study Design

The Household Influenza Cohort Study (HICS) began in 2017 and is an ongoing study in Managua, Nicaragua. HICS is a community-based cohort in which participants are provided with their primary care, are encouraged to report to the study health center at the first indication of any illness, and are followed for influenza infection and illness. The study was expanded in February 2020 to include testing respiratory and blood samples for SARS-CoV-2. Data on COVID-19 signs and symptoms were systematically collected at each medical visit. At enrollment and in March–April of every year thereafter, an annual blood sample was collected. In October–November 2020, a second consent was sought to collect midyear blood samples after the first wave of COVID-19, to administer a COVID-19 questionnaire to the entire cohort, and, for those households with a confirmed acute COVID-19 case, to conduct an embedded SARS-CoV-2 transmission study (see Supplementary Data).

If a participant died, a University of Michigan study physician determined whether the death was related to COVID-19 based on their death certificate, medical records, and a verbal autopsy from a visit with the family. For analysis of case severity, COVID-19–related deaths that occurred prior to the midyear sample were included and categorized as seropositive.

This analysis uses data collected in the ongoing cohort from 1 March 2020, through 31 March 2021. Annual blood samples were collected in March 2020 or at enrollment, and midyear samples were collected during October–November 2020. SARS-CoV-2 infections confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) were reported for the entire study period, and seropositive infections were reported for the period between blood samples. Respiratory samples were collected when participants reported to the study health clinic and either met testing criteria or participated in the transmission substudy. Throughout February–June 2020, the testing criteria were (1) fever or feverishness with cough, sore throat, or runny nose or (2) lower respiratory illness with or without fever. In addition, for children aged <2 years, the criteria included fever/feverishness without a defined focus. In June 2020, we expanded the criteria to include loss of taste or smell, rash or conjunctivitis, and fever without a defined focus for all participants.

Laboratory Assays

RT-PCR was run according to the protocols developed by the Poon lab [11]. Enzyme-linked immunosorbent assays (ELISAs) were run on paired midyear and annual serum samples following the Krammer laboratory protocol [12], and constructs of the SARS-CoV-2 spike protein receptor binding domain for ELISAs were produced in a single batch at the Life Sciences Institute at the University of Michigan. All RT-PCR and most ELISAs were performed at the Nicaraguan National Virology Laboratory, with a minority of 2020 and 2019 annual samples processed at the University of Michigan due to lack of available sample in Nicaragua. We classified samples based on ELISA as shown in Supplementary Figure 1. Participants with indeterminate ELISA results were counted as missing, as were those with positive midyear and annual samples who did not have a ≥4-fold rise in titer because their antibody responses could not be distinguished from cross-reactive antibodies. While we primarily measured seroconversion, we use the term seropositivity due to a small subset of participants not having baseline samples.

Illness Definitions

Cases were defined as seropositive participants who reported a COVID-19–related illness: (1) during the first epidemic (March–August 2020) as determined by RT-PCR results; (2) associated with a positive RT-PCR test; or (3) had an epidemiological connection; namely, someone in their household tested positive by RT-PCR (Supplementary Figure 1). To be considered associated, the illness and RT-PCR test or epidemiologic connection had to occur within 30 days of each other. Disease severity levels were defined as asymptomatic, mild, moderate, and severe (Supplementary Figure 1). Mild cases reported loss of smell or taste or exhibited ≥2 COVID-19–related manifestations. Moderate cases reported rapid or difficulty breathing, shortness of breath, chest pain or tightness in the chest, had an outpatient hospital visit, or self-reported their disease severity as moderate or severe. Severe cases were admitted to the hospital or self-reported their disease severity as very severe.

Analysis

Person-time was calculated as the amount of time between 1 March 2020 or enrollment and 31 March 2021 or withdrawal from the study. For participants lost to follow-up, the withdrawal date was recorded as the midpoint of the date of their last contact with study personnel and the date they were recorded as withdrawn. A Poisson distribution was used to calculate 95% confidence intervals (CIs) for incidence and attack rates. Participant age was calculated on 31 October 2020, near the midyear sample collection. Illness onset or death dates were used to calculate incidence for seropositive cases. Trends in antibody titers by severity were assessed using linear models of $\log_2$-transformed titer values and numerically coded severity values (subclinical = 0, severe = 3). Protection was calculated for individuals who were seropositive at the midyear from symptomatic reinfection (see Supplementary Data). Rates of seropositivity and severity from our study population were age-standardized to other countries for comparison using data from the United Nations [13].

RESULTS

Between 1 March 2020, and 31 March 2021, HICS followed 2338 participants in 435 households for 2449 person-years

(PY). During that period, 57 people enrolled in and 133 left the study. The cohort consisted of 1154 children aged <18 years (49.4%) and 1184 adults aged ≥18 years (50.6%), with a mean age of 24 years. Sex was approximately equally distributed in children, but adult male participation was lower (Table 1). COVID-19–related illness peaked in May–June 2020 (Figure 1A and 1B). In October–November 2020, we obtained consent from 2025 people (87% of the cohort) to collect an additional (midyear) blood sample and survey on COVID-19. Thirty households with 150 household contacts participated in the transmission substudy. Eleven individuals died during the study period. Two deaths in June were considered COVID-19–related due to timing, illness presentation, causes of death, and the presence of additional household COVID-19 cases around the time of death. Three other deaths where timing occurred outside the peak SARS-CoV-2 transmission period with no epidemiologic link were considered possibly COVID-19 related, with respiratory signs and symptoms noted in the medical records, but not listed as causes of death.

RT-PCR–Confirmed Infections

During the study period, 129 people tested positive by RT-PCR for SARS-CoV-2 (Figure 1B), yielding an overall incidence of 5.3 RT-PCR–confirmed infections per 100 PY (95% CI, 4.4–6.3). RT-PCR positivity peaked in May 2020, with 27.3 infections per 100 PY (95% CI, 21.1–35.2; Figure 1C), and increased with age to a high of 10.0% of adults aged 60–96 years (Figure 1D).

ELISA-Confirmed Infections

A diagram of ELISA results is presented in Supplementary Figure 2. Of the 2025 midyear ELISAs, 863 were negative, 27 were indeterminate, and 1135 were positive; of the corresponding paired 2020 annual ELISAs for the positive midyear ELISAs, 1070 were negative, 26 were positive with ≥4-fold rise in titer, 5 were positive with <4-fold rise in titer, and 34 did not have annual ELISAs (3 of whom were born in 2020); of the 5 positive 2020 annual ELISAs, 1 was still positive in 2019 and 1 had an indeterminate ELISA, the others did not have results. Of the remaining 1995 people with ELISA results (98.4% of those who consented to the blood draw), after excluding indeterminate ELISAs and those previously positive without seroconversion and adding 2 COVID-19–related deaths, 1132 were positive, giving an overall seroprevalence of 56.7% (95% CI, 53.5%–60.1%; Figure 2A). Seropositivity was significantly lower in children aged ≤10 years (χ^2 test, $P < .001$) but was similar from 11–17 years (60.4%) to 60–96 (61.9%) years. The lowest seropositivity was in children aged 3–4 years (39.4%), while children ≤2 years had somewhat higher seropositivity (47.2%; Figure 2A). The overall seroprevalence was 57.5% when age-standardized to Nicaragua's population and 58.7% when age-standardized to the US population (Supplementary Figure

Table 1. Household Influenza Cohort Study Participant Characteristics, 1 March 2020–31 March 2021

Characteristic	Age, y							Total (N = 2338)
	0–2 (n = 103)	3–4 (n = 117)	5–10 (n = 470)	11–17 (n = 464)	18–29 (n = 375)	30–59 (n = 679)	60–96 (n = 130)	
Age, y, mean (SD)	1 (1)	4 (0)	7 (2)	14 (2)	23 (4)	41 (8)	69 (7)	24 (18)
Sex								
Female	48 (47)	60 (51)	236 (50)	231 (50)	252 (67)	492 (72)	93 (72)	1412 (60)
Male	55 (53)	57 (49)	234 (50)	233 (50)	123 (33)	187 (28)	37 (28)	926 (40)
No COVID-19 survey	4	12	19	26	46	55	10	172
Preexisting health condition								
Obesity[a]	0 (0)	4 (4)	52 (11)	56 (12)	95 (28)	356 (57)	51 (41)	614 (28)
≥1 condition[b]	6 (6)	7 (7)	38 (8)	40 (9)	53 (16)	213 (34)	86 (72)	443 (20)
≥3 conditions[b]	0 (0)	0 (0)	0 (0)	1 (0)	4 (1)	24 (4)	18 (15)	47 (2)
High BP	0 (0)	0 (0)	1 (0)	2 (0)	14 (4)	111 (18)	58 (48)	186 (9)
Diabetes	0 (0)	0 (0)	2 (0)	0 (0)	6 (2)	59 (9)	47 (39)	114 (5)
Asthma	2 (2)	3 (3)	25 (6)	24 (5)	17 (5)	26 (4)	6 (5)	103 (5)
Kidney disease	2 (2)	0 (0)	2 (0)	5 (1)	13 (4)	42 (7)	14 (12)	78 (4)
Smoking[c]								
Ever smoked	…	…	…	6 (3)	75 (23)	143 (23)	42 (35)	266 (21)
Never smoked	…	…	…	214 (97)	253 (77)	481 (77)	78 (65)	1026 (79)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BP, blood pressure; COVID-19, coronavirus disease 2019; SD, standard deviation.

[a]Height and weight were measured at the 2020 annual survey in and around March.

[b]Excluding obesity.

[c]Questions about smoking were asked to participants aged 14 and older; 1 person aged 18–29 years and 5 people aged 60–96 years who answered the COVID-19 questionnaire did not answer smoking questions.

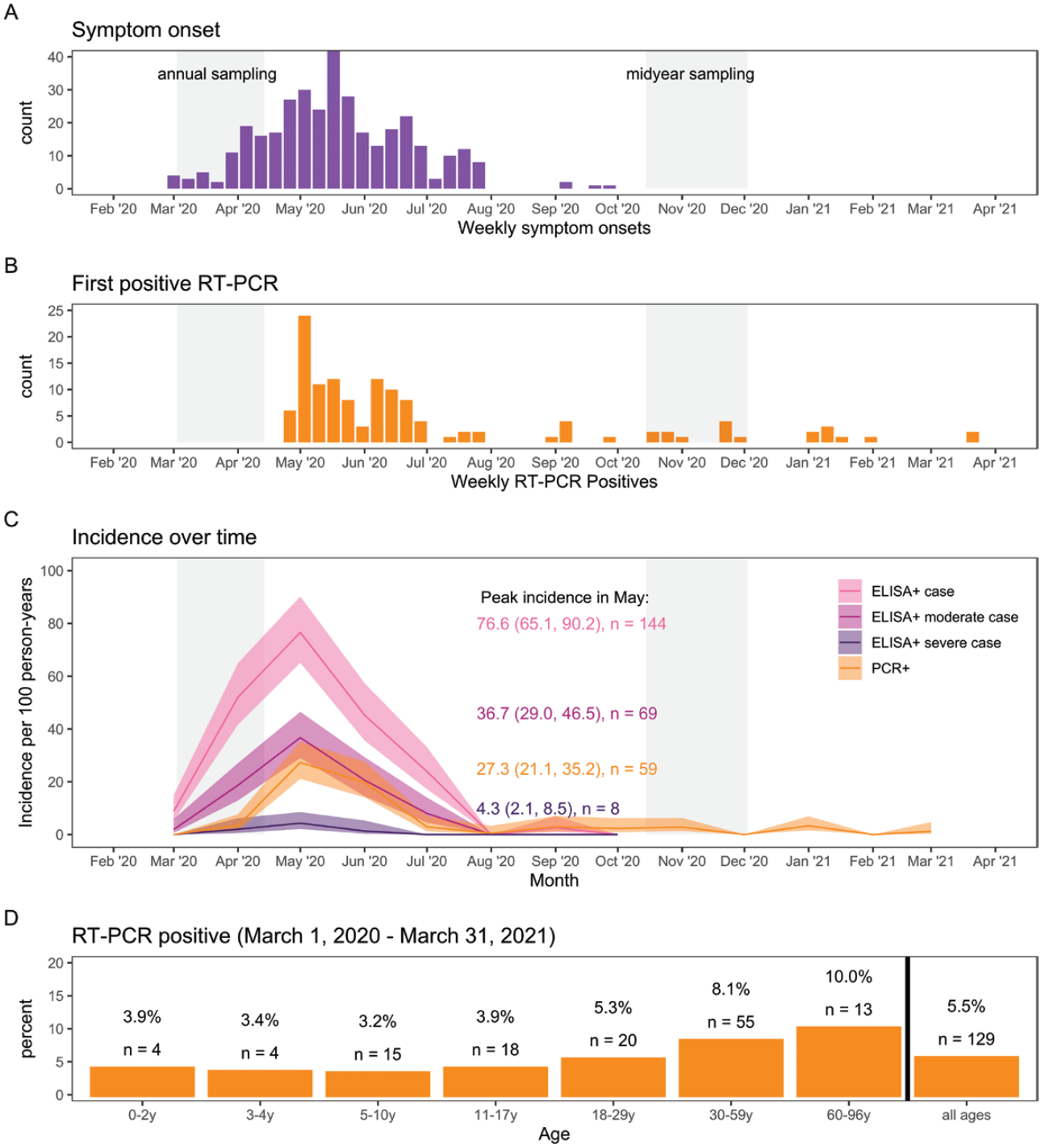

Figure 1. Epidemic timing and reverse-transcription polymerase chain reaction (RT-PCR) positivity. Gray-shaded regions indicate the timing of annual and midyear blood sample collections. *A*, Illness onsets among enzyme-linked immunosorbent assay (ELISA)–positive cases. *B*, Dates of individuals' first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–positive RT-PCR. *C*, Incidence per 100 person-years of SARS-CoV-2 infection outcomes over time. Outcomes are indicated by color: ELISA-positive cases of all severities are pink, moderate cases are magenta, severe cases purple; RT-PCR–confirmed infections are orange. Peak incidence rates for infection during May 2020 with 95% confidence intervals and the number of observations for each outcome are printed to the right of the peak. *D*, SARS-CoV-2 RT-PCR positivity by age.

3*A*). Among RT-PCR–confirmed infections occurring before the midyear blood collection, 86% seroconverted by ELISA and had detectable titers approximately 6 months after the SARS-CoV-2 peak.

Severity Among ELISA-Confirmed Infections

All seropositive participants answered a COVID-19 questionnaire. Of the seropositive, 351 (31.0% [95% CI, 27.9%–34.4%]) were cases and 781 (69.0% [95% CI, 64.3%–74.0%]) were

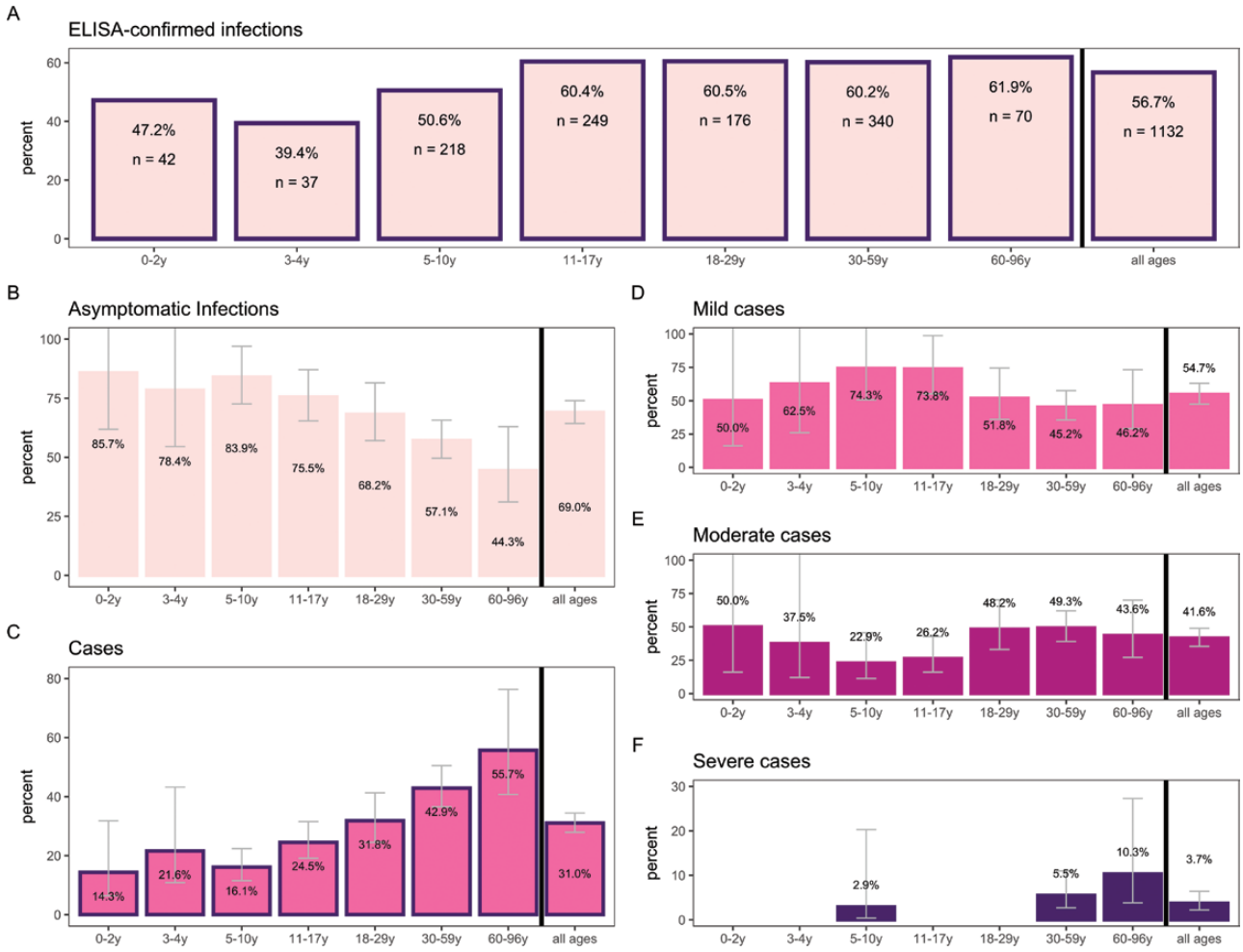

Figure 2. Enzyme-linked immunosorbent assay (ELISA)–confirmed infections and severity, by age. *A*, ELISA-confirmed infections, by age. *B*, Percentage of ELISA-confirmed infections that were subclinical. *C*, Percentage of ELISA-confirmed infections that were cases. The proportions of cases of each severity level are shown on the right: mild [pink, (*D*)], moderate [magenta, (*E*)], and severe [purple, (*F*)]. Error bars represent 95% confidence intervals.

subclinical (Figure 2B and 2C, Supplementary Table 1). Among cases, 192 (54.7%) were mild, 146 (41.6%) were moderate, and 13 (3.7%) were severe (17.0%, 12.9%, and 1.1% of infections, respectively), with more moderate and severe cases among older participants (Figure 2D–F). Age-adjusted rates for Nicaragua were 33.8% symptomatic infections, with 55.9% mild, 41.2% moderate, and 3.1% severe, and for the US, 39.0% symptomatic infections, with 52.8% mild, 43.2% moderate, and 4.6% severe (Supplementary Figure 3*B*–*D*). Females had a higher seropositivity than males (59.3% vs 52.6%, Supplementary Figure 6*A*), and their infections were more often symptomatic: 20.2% (95% CI, 17.9%–22.9%) vs 13.4% (95% CI, 11.0%–16.2%) (Supplementary Table 1); RT-PCR positivity was similar overall by sex, although older males had higher RT-PCR positivity (among participants aged 60–96 years, 13.5% of males vs 5.6% of females were RT-PCR positive; Supplementary Figure 6*B*).

Participants with symptomatic ELISA-confirmed infections who thought they had COVID-19 (n = 165 [47.3%]; Figure 3A) closely mirrored moderate and severe cases (n = 159 [45.3%]; Figure 2E and 2F). Cases reported an average of 7 COVID-19–related signs and symptoms (range, 1–21). The average case recovery time was 20 days (standard deviation, 25 days [range, 2–150]). Long recovery times (≥28 days) were reported by 61 cases (17.4% of cases, 5.4% of seropositives), with a high of 27.4% among cases aged 30–59 years (Figure 3C). The proportion of cases who thought they had COVID-19, the number of symptoms, and recovery times all increased with age (Figure 3A–C).

The 5 most commonly reported disease manifestations among cases (Supplementary Figure 4*A*) were, for children: runny nose, cough, sore throat, headache, and loss of smell or taste; and for adults: loss of smell or taste, headache, sore throat, cough, and muscle aches (Supplementary Figure 4*B*). The "classic" COVID-19 manifestations of feverishness, cough, and difficulty breathing were reported by 36 people (10.3% of cases; Supplementary Figure 9*A*), 6 children and

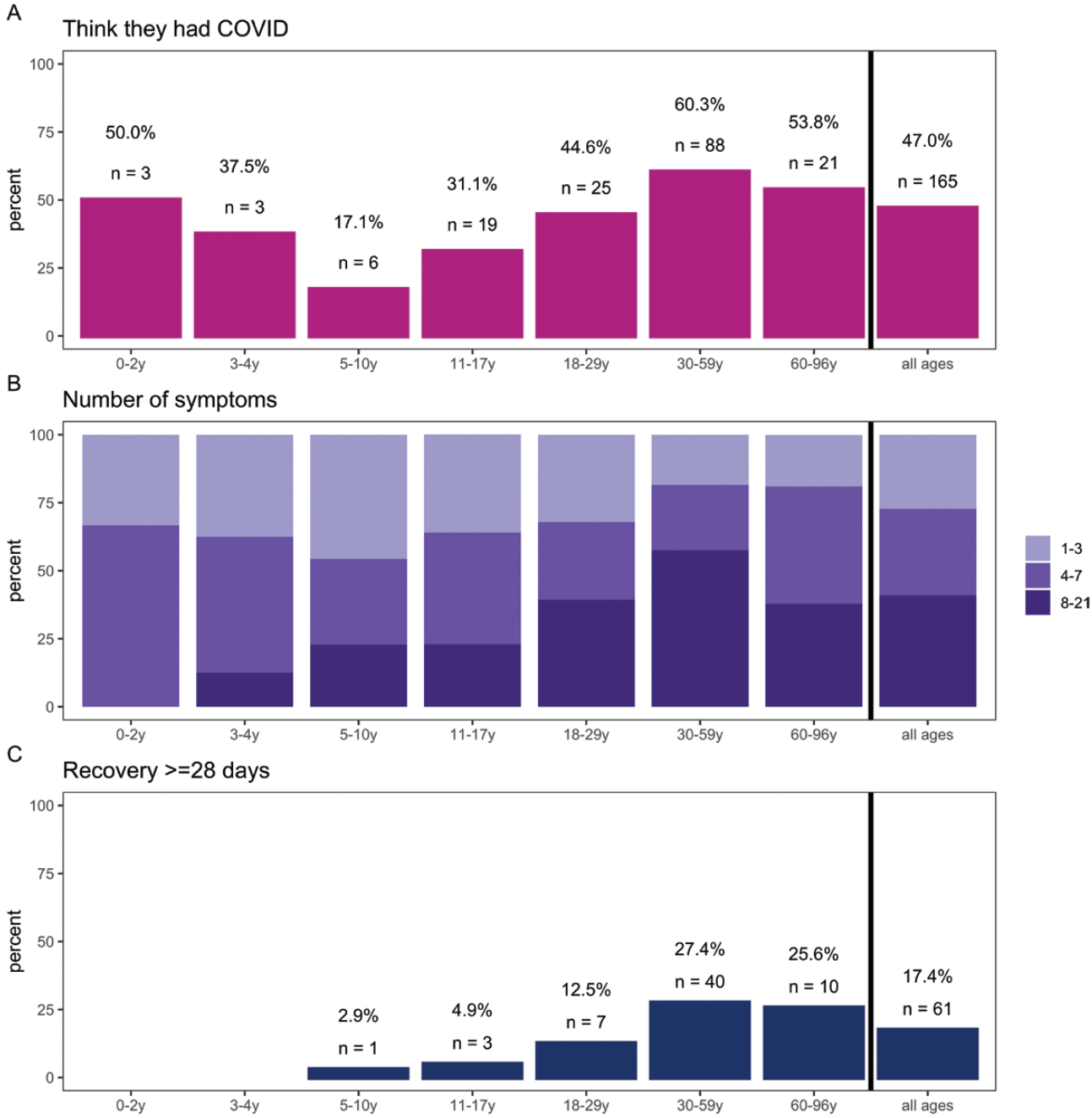

Figure 3. Coronavirus disease 2019 (COVID-19) severity measures among enzyme-linked immunosorbent assay (ELISA)–confirmed cases, by age. *A*, Percentage of participants who thought they had COVID-19. *B*, Number of symptoms. *C*, Percentage who had recovery times of ≥28 days.

30 adults (Supplementary Figure 9*B*), while 82 people (23.4% of cases) reported all 5 of loss of smell or taste, cough, headache, sore throat, and runny nose (Supplementary Figure 10*A*). Nineteen children and 73 adults reported each of their top symptom clusters (Supplementary Figure 10*B*). There were 29 people (8.3% of cases) who had experienced illness for ≥28 days who still reported being sick in October 2020 or later; headache, joint pain, fatigue, lightheadedness/dizziness, cough, and trouble sleeping were their most common lingering signs and symptoms (Supplementary Figure 5*A*); only 3 children aged 0–17 years reported any lingering symptoms (Supplementary Figure 5*B*).

The overall infection fatality rate and case fatality rate were 0.2% (95% CI, .0–.7%) and 0.6% (95% CI, .1%–2.3%), respectively, and among adults aged ≥60 years, they were 2.9% (95% CI, .7%–11.4%) and 5.1% (95% CI, 1.3%–20.5%), respectively. Including the 3 possibly COVID-19–related deaths would give rates of 0.4% (95% CI, .2%–1.1%) and 1.4% (95% CI, .6%–3.4%).

Disease in the Transmission Substudy

To investigate disease occurrence from household SARS-CoV-2 transmission, we examined infection rates and disease severity in the transmission substudy. Seropositivity was similar in the transmission (50.4%) and cohort (56.7%) studies (Supplementary Figure 7*A*), and RT-PCR positivity was higher in the transmission study by design (28.0% vs 5.5%; Supplementary Figure 7*B*), but seropositive household contacts were 2.3 times more likely (95% CI, 1.7–3.1) to report symptoms. Severity was also very similar in both studies (Supplementary Figure 8*A*–*E* and Figure 3A–C).

Antibody Response and Protection

To further examine population-level immunity, midyear antibody titer levels were examined (Figure 4A–C). Antibody titers by age had a J-shaped curve—they were lowest among older children/young adults, higher in younger children, and highest among older adults. Titers were higher for older males than older females (Figure 4A). Interestingly, titers were only higher for symptomatic compared to subclinical infections among young and middle-aged adults, but there was no difference in children or older adults (Figure 4B); likewise, titers only increased significantly with severity for adults (Figure 4C); however, we only had 1 child with a severe case and thus our ability to examine the relationship was limited. Of note, in subclinical adult cases, titer increased with increasing age.

To examine the protection from symptomatic reinfection provided by anti–SARS-CoV-2 antibodies, we compared the number of symptomatic RT-PCR–confirmed infections by serostatus (see Supplementary Methods). Between the midyear sample and 31 March 2021, there were 12 cases among 863 seronegatives (1.4%) and 1 symptomatic reinfection among 1132

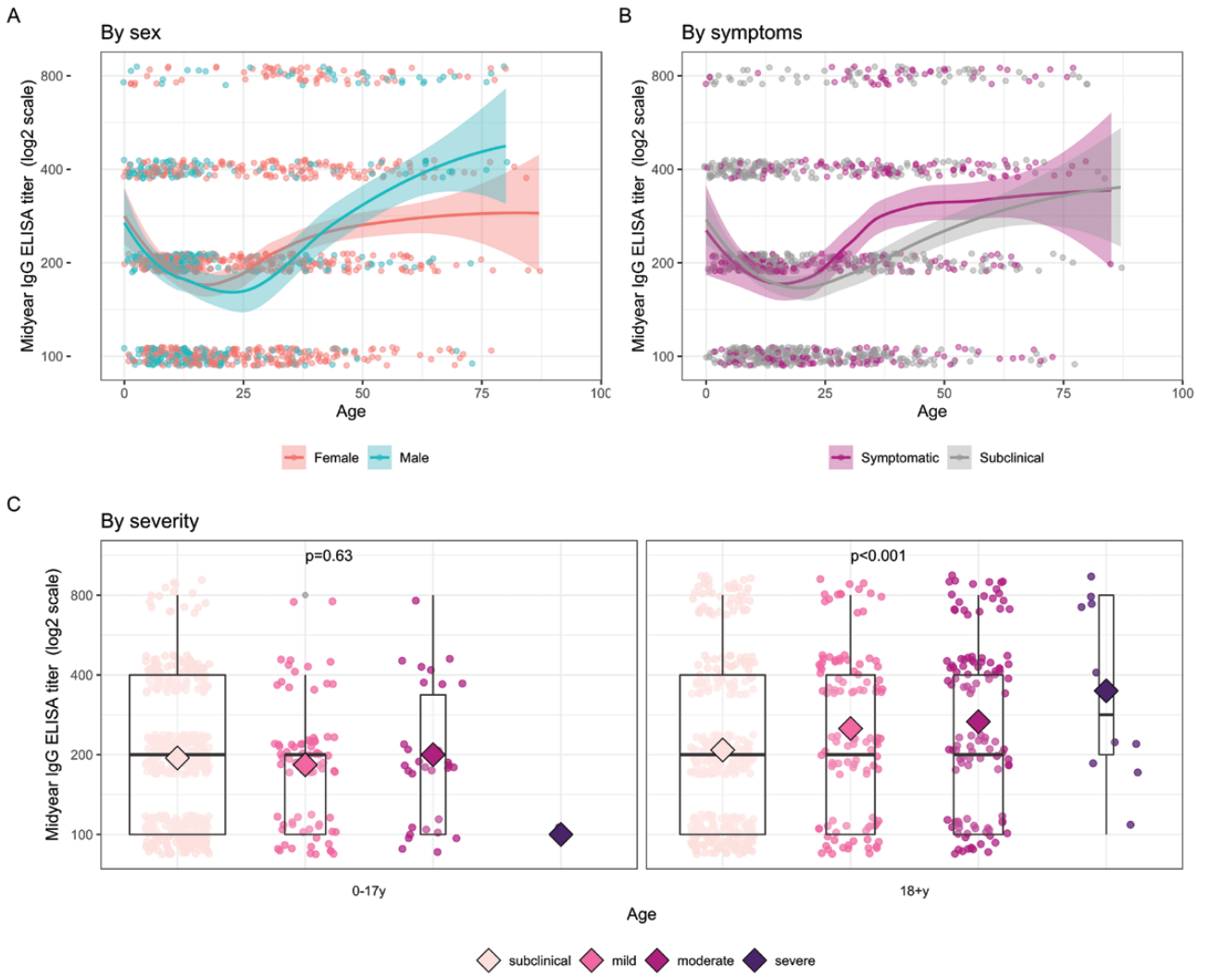

Figure 4. Midyear immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) antibody titers to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), by age. Titers are also shown by sex (*A*), symptoms (*B*), and severity (*C*). Midyear samples were collected in October–November 2020. Locally estimated scatterplot smoothing lines were fit to the $\log_2$-transformed data and shaded regions show 95% confidence intervals (*A* and *B*). Boxplots show the 25th and 75th percentiles and median; diamonds represent mean titer values, and *P* values shown are for trends, from linear models (*C*).

seropositives (0.1%; Supplementary Table 2). Seropositivity at the midyear was associated with 93.6% protection from symptomatic reinfection (95% CI, 51.1%–99.2%) through March 2021 (Supplementary Table 3).

DISCUSSION

We found that approximately 57% of the household cohort was infected by SARS-CoV-2 within the first wave of the COVID-19 epidemic in Managua, which lasted approximately 5 months and occurred before the emergence of SARS-CoV-2 variants late in 2020 [14]. More than half of infections were subclinical, and among symptomatic COVID-19 infections 3.7% were severe cases. In addition, recovery times were long, and a substantial number of cases still reported signs and symptoms in October 2020, 5 months after the epidemic peak. Immunity derived from natural infection with SARS-CoV-2 was highly protective against symptomatic reinfection through March 2021.

Overall, SARS-CoV-2 infections in our study setting were less frequently symptomatic and cases less frequently severe than reported in temperate settings. Importantly, even with the lower severity in our study setting compared to other settings, COVID-19 severity was still high.

Fever was also less common among cases than reported elsewhere. Subclinical infections have been estimated to make up at least a third of SARS-CoV-2 infections, with a higher proportion among children [15–17]. We found a substantially higher proportion (69%) of subclinical infections; even standardized to the US age structure, the proportion of subclinical infection remained >50%. Nicaraguan healthcare workers also had a higher subclinical proportion (55%) [10] than in studies of healthcare workers in China (0–47%) [18], the US (29%) [19], and Italy (29%) [20]. The higher proportion of symptomatic infections in the transmission study (64%) compared to the cohort study (28%) may be due to closer contact among family members, which may lead to higher infectious doses and thus infections more likely to be symptomatic [21, 22]. Alternatively, there may have been underreporting in the cohort where participants recalled their symptoms often months later.

The proportion of severe cases among infections, from studies where enrollment was independent of hospital admission, has ranged between 9% and 15% in China, France, Norway, and Brazil [3–5, 18]. These values are higher than in the HICS (1%), even after age-standardizing to the US with its older age distribution. In our transmission substudy, severity was still much lower than reported elsewhere. Prior to the emergence of SARS-CoV-2 variants [14], other tropical locations such as Africa and India also reported lower case counts [23, 24]. In Nicaragua, as in many tropical settings, people spend more time outdoors, and indoor locations have higher levels of ventilation, as typically there is no glass in the windows or they are left open; these practices may lower the infectious dose, and thereby severity.

High SARS-CoV-2 positivity has been noted in other Nicaraguan studies, though lower than in our study population: 34% seroprevalence in León and 30% positive for SARS-CoV-2 by loop-mediated isothermal amplification detection in Nicaraguan health workers [10, 25]. Seroprevalence in other settings has varied widely but was generally lower, ranging from 4.6% in Spain to 40.4% in Brazil [26, 27].

In our study, loss of smell or taste, cough, and sore throat were among the most commonly reported COVID-19 manifestations for both pediatric and adult cases. Notably, fever was only reported by 41% of our cases. Conversely, a systematic review of 9 countries from Asia, Europe, and the US showed that COVID-19 most commonly presents with fever (78%), cough (57%), fatigue (31%), and sore throat (12%) [2]. Symptom clusters in our study also differed from the "classic" triad of COVID-19 symptoms [28], with only 10% reporting feverishness, cough, and difficulty breathing, compared to 23% who reported loss of smell or taste, cough, headache, sore throat, and runny nose. Other studies have reported 15%–20% of infections have "long COVID" [29–31], similar to our study (17.4% of cases).

Protection against symptomatic reinfection generated from natural SARS-CoV-2 infection was comparable to vaccine-derived protection [32]. Anti–SARS-CoV-2 antibody levels were lowest among older children and young adults, suggesting that such age groups have the weakest antibody responses and hence the weakest antibody-based protection against reinfection. Therefore, these age groups, which are large in LMICs like Nicaragua, may continue to play a significant role in transmission if not vaccinated. Interestingly, the trend in antibody titers by age did not closely match the trends in severity by age, suggesting that other important factors besides disease severity contribute to the antibody response. As observed in other studies, higher antibody levels were associated with increased disease severity in adults [33, 34], but severity was not associated with antibody levels in children. In subclinical adult infections, antibody levels increased with increasing age, contrary to the decrease that would be expected given that younger adults have stronger immune systems. One possibility that would explain this increase would be that even in subclinical infections, adults may take longer to clear the virus as they age, resulting in a stronger immune response as has been seen in influenza [35]. In children antibody levels decreased with increasing age regardless of symptom status; this decrease in titer with increasing age has been observed in other studies when examining neutralizing antibody titers and total antibody levels [36, 37]. It is possible that factors such as prior or recent exposure to seasonal coronaviruses may affect the immune response, and others have also suggested that original antigenic sin may impair the immune response in adults [36].

Most previous studies have enrolled individuals through methods susceptible to significant biases. Cohorts arising from voluntary testing, for example, likely underestimate the

prevalence of subclinical infections and overestimate severity [17, 18]. Nonlongitudinal studies are often unable to distinguish between subclinical and presymptomatic infections [17]. Study populations representing high-risk patient groups recruited in hospitals or upon illness onset likely overestimate disease severity [38, 39]. Our prospective community-based cohort study permitted a more accurate description of the spectrum of SARS-CoV-2 infection and disease outcomes. This study population in Managua, Nicaragua, experienced a high level of SARS-CoV-2 infections within a short timeframe, but fortunately—and surprisingly—disease occurrence and severity were relatively mild compared to other settings.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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