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Prevalence and predictors of anti-SARS-CoV-2 serology in a highly vulnerable population of Rio de Janeiro: A population-based serosurvey

Lara E. Coelho,[a]* Paula M. Luz,[a] Débora C. Pires,[a] Emilia M. Jalil,[a] Hugo Perazzo,[a] Thiago S. Torres,[a] Sandra W. Cardoso,[a] Eduardo M. Peixoto,[a] Sandro Nazer,[a] Eduardo Massad,[b] Mariângela F. Silveira,[c] Fernando C. Barros,[d] Ana T.R. Vasconcelos,[e] Carlos A.M. Costa,[f] Rodrigo T. Amancio,[g] Daniel A.M. Villela,[h] Tiago Pereira,[i] Guilherme T. Goedert,[j,k,l] Cleber V.B.D. Santos,[m] Nadia C.P. Rodrigues,[f,m] Beatriz Grinsztejn,[a] Valdilea G. Veloso,[a] and Claudio J. Struchiner [b,m]

[a]Instituto Nacional de Infectologia Evandro Chagas, FIOCRUZ, Rio de Janeiro, Brasil
[b]Escola de Matemática Aplicada, Fundação Getúlio Vargas, Rio de Janeiro, Brasil
[c]Programa de Pós-Graduação em Epidemiologia, Universidade Federal de Pelotas, Rio Grande do Sul, Brasil
[d]Universidade Católica de Pelotas, Rio Grande do Sul, Brasil
[e]Laboratório Nacional de Computação Científica (LNCC), Petrópolis, Brasil
[f]Escola Nacional de Saúde Pública, FIOCRUZ, Rio de Janeiro, Brasil
[g]Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brasil
[h]Programa de Computação Científica (PROCC), FIOCRUZ, Rio de Janeiro, Brasil
[i]Instituto de Ciências Matemáticas e Computação, Universidade de São Paulo, Brasil
[j]Università degli Studi di Roma Tor Vergata and INFN, Rome, Italy
[k]RWTH Aachen University, Aachen, Germany
[l]The Cyprus Institute, Nicosia, Cyprus
[m]Instituto de Medicina Social Hesio Cordeiro, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brasil

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Summary

Background COVID-19 serosurveys allow for the monitoring of the level of SARS-CoV-2 transmission and support data-driven decisions. We estimated the seroprevalence of anti-SARS-CoV-2 antibodies in a large *favela* complex in Rio de Janeiro, Brazil.

Methods A population-based panel study was conducted in Complexo de Manguinhos (16 *favelas*) with a probabilistic sampling of participants aged ≥1 year who were randomly selected from a census of individuals registered in primary health care clinics that serve the area. Participants answered a structured interview and provided blood samples for serology. Multilevel regression models (with random intercepts to account for participants' *favela* of residence) were used to assess factors associated with having anti-S IgG antibodies. Secondary analyses estimated seroprevalence using an additional anti-N IgG assay.

Findings 4,033 participants were included (from Sep/2020 to Feb/2021, 22 epidemic weeks), the median age was 39·8 years (IQR:21·8-57·7), 61% were female, 41% were mixed-race (*Pardo*) and 23% Black. Overall prevalence was 49·0% (95%CI:46·8%-51·2%) which varied across favelas (from 68·3% to 31·4%). Lower prevalence estimates were found when using the anti-N IgG assay. Odds of having anti-S IgG antibodies were highest for young adults, and those reporting larger household size, poor adherence to social distancing and use of public transportation.

Interpretation We found a significantly higher prevalence of anti-S IgG antibodies than initially anticipated. Disparities in estimates obtained using different serological assays highlight the need for cautious interpretation of serosurveys estimates given the heterogeneity of exposure in communities, loss of immunological biomarkers, serological antigen target, and variant-specific test affinity.

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*Corresponding author at: Av. Brasil 4365, Manguinhos, Rio de Janeiro, RJ Zipcode: 21040-900, Brazil.
E-mail address: lara.coelho@ini.fiocruz.br (L.E. Coelho).

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Research in context

Evidence before this study

COVID-19 serosurveys allow for the monitoring of the level of SARS-CoV-2 transmission and support data-driven decisions, which can be particularly useful in low-income settings with limited testing capacity. We reviewed the evidence for the seroprevalence of SARS-CoV-2 in Brazil available as of Mar 17, 2022, by searching the Medline and the Virtual Health Library (*Biblioteca Virtual em Saúde* of the Pan American Health Organization) databases for articles and preprints, published in English or Portuguese, using the terms ["serosurveillance" OR "seroepidemiology" OR "seroprevalence"] AND ["SARS-CoV-2" OR "COVID-19"] AND ["Brazil"]. Few studies described the seroprevalence of SARS-CoV-2 in urban slums and *favelas*, using different sampling and recruitment strategies, various serological assays, and periods of the COVID-19 pandemic. Most studies included small samples that were not representative of the entire community/area. Other national or regional population-based studies have limited representativity of individuals living in *favelas* or slums.

Added value of this study

Brazil has become a hotspot for COVID-19 globally and the magnitude of the COVID-19 epidemic in Brazil can be, at least partially, explained by the country's massive socioeconomic inequality. *Favelas* represent a combination of concentrated poverty, insecure and inadequate housing conditions, and lack of access to essential services, such as clean water, sanitation, and healthcare. We conducted a population-based study in one of the poorest areas in Rio de Janeiro, Complexo de Manguinhos, which comprises 16 different *favelas*. We found COVID-19 seroprevalence (anti-S IgG antibodies) estimates were much higher than anticipated, and spatially varied largely across different *favelas*. Our analyses showed that young adults, males, and those reporting a large household size and use of public transportation had the highest probability of having a reactive serology. A secondary analysis shows that seroprevalence estimates of anti-N IgG antibodies were lower than of anti-S IgG antibodies.

Implications of all the available evidence

Our results reinforce the remarkable inequality in COVID-19 burden, with people living in *favelas* presenting a much higher prevalence than previously documented for Rio de Janeiro state and municipality. Poverty and inadequate housing conditions are drivers of COVID-19 transmission in vulnerable urban communities. Despite high levels of seroprevalence, we documented the unfolding of a new transmission wave. This pattern was possibly driven by the combined effect of loss of immunity, the emergence of new a variant, and the lack of variants' cross-immunity, all of which were documented in our study. Finally, our results highlight the need for cautious interpretation of estimates of serosurveys given the heterogeneity of exposure in communities, loss of immunological biomarkers, and variant-specific test affinity.

Introduction

Serological surveys serve the important purpose of describing the population's immune profile against specific pathogens.[1] For COVID-19, serological studies are foundational as they allow the monitoring of transmission levels and thus support data-driven decisions on how to tackle the pandemic without completely shutting down economies.[2] When the proper assumptions are met, serological studies provide the most direct estimate of how close a particular population is to the herd immunity threshold.[3] However, the herd immunity threshold is influenced by various sources of heterogeneities, including population demography, social structure, contact rates (within and between age groups), the degree and duration of immunity elicited by pathogen and vaccine, as well as the stochastic nature of an epidemic process.[4–7] Moreover, the serosurveys conducted in low-income countries or neighbourhoods have important limitations in their study design and procedures.[8] This is particularly problematic since serosurveys can be of great value in low-income settings with limited testing capacity where COVID-19 surveillance cannot rely on routine care and contact tracing.

Brazil has become one of the epicentres of the COVID-19 pandemic, and as of July 12th, 2022, over 32.8 million cases were confirmed, and 673,000 deaths due to COVID-19 were registered.[9] The magnitude and impacts of the COVID-19 pandemic in Brazil can be, at least partially, explained by the country's massive socioeconomic inequity. Brazil is the largest country in Latin America, the 5th most populous country in the world and, despite being one of the largest economies in the world, is one of the most unequal countries globally, where currently 27·6 million people are estimated to be living below the poverty line.[10]

Contrasting with most countries globally, Brazilian poverty is predominantly urban, with 72% of the poor living in urban areas.[11,12] Poverty and rapid and unplanned urbanization resulted in housing deficits and inadequate housing conditions in large metropolitan areas. Rio de Janeiro is the 16th largest metropolitan area in the world,[13] with over 13 million inhabitants, of whom 22% are estimated to live in informal settlements, or slums (known as *favelas* or *comunidades*).[12,14]

Favelas are characterized (in different degrees) by a combination of concentrated poverty, insecure and inadequate housing conditions, and lack of access to essential services such as clean water, sanitation, and healthcare.[12,14] In addition, most of their inhabitants are low-paid workers or informal workers, particularly those working in the service sector (e.g., food, cleaning, or delivery services).[15] Consequently, and of relevance to the present study, these individuals are more likely to be designated as essential workers and thereby still required to go to work and rely on public transportation for doing so.

Here, we estimated the weekly seroprevalence of anti-SARS-CoV-2 antibodies in a probabilistic sample of individuals living in one of the largest and poorest favela complexes in Rio de Janeiro — Complexo de Manguinhos. Meanwhile, the population in the state of Rio de Janeiro experienced a lineage replacement captured by the genomic surveillance system in place in the state. Thus, to situate the observed prevalence within the epidemic scenario of the state of Rio de Janeiro, we present our results alongside the state's surveillance data. Furthermore, we used an automated commercially available assay to detect anti-Spike (anti-S) SARS-CoV-2 IgG antibodies.

Methods

Study area

Manguinhos is a neighbourhood located in the Northern area of Rio de Janeiro city. It is mainly comprised of *favelas* (slums) and has the 5th worse Human Development Index (HDI) in the city. This area started to be populated in 1901 with its first favela known as Parque Oswaldo Cruz, and over the years, new *favelas* were settled. In 2010, when the last population census was conducted in Brazil, it was estimated that over 36,000 individuals were living in Manguinhos.

Two primary health care clinics, *Clínica da Família Victor Valla* (CFVV) and *Centro de Saúde Escola Germano Sinval Faria* (CSEGSF), provide public primary health care to Manguinhos' population through the Family Health Program (*Programa de Saúde da Família*), within the Brazilian Public Health System (*Sistema Único de Saúde, SUS*). These clinics actively monitor and maintain a routinely updated registry of the population living in the area aided by Community Health Agents (*Agente Comunitário de Saúde*).[16] These agents are part of the multidisciplinary team that provides primary health care services, who reside in the community and are responsible for home visits and population registries, among other health promotion strategies and educational duties.

Study design and participants

"Comvida-1" is a population-based panel study conducted in Manguinhos. Individuals aged 1 year or older, registered in one of the two primary health care clinics (CFVV or CSEGSF) composed the sampling unit that was taken as eligible for the study.

To calculate the sample size, we considered our main operational limitation, the weekly capacity for interviews and sample collection in the field, estimated at 750 per week.[17–19] We assigned to the prevalence (θ) of individuals carrying anti-SARS-CoV-2 antibodies in a given week the value of 5% which, together with the sensitivity (100%) and specificity (99·6%) of the serological test and the weekly capacity, yielded the posterior estimate of the mean of 4·82% (90% confidence interval [CI] 3·58-6·22%).

As of July 2020, 38,883 individuals were registered at one of the two above-mentioned primary health clinics. We aimed to enrol 6000 individuals aged ≥ 1 year old to be enrolled over 8 weeks, assuming an enrollment rate of 750 individuals per week.

Recruitment process

A list containing the names and addresses of 16,000 potential volunteers, randomly sampled without replacement, was generated. A total of 12,574 individuals were searched and offered participation in the study of which 4033 were included in the study and 8541 were deemed inclusion failure. The most common reasons for inclusion failure were "No one answered the door after 2 attempts (including one attempt over the weekend)"; "Individuals moved/changed address" and "Individuals or their representative declined participation" (*Supplementary Material* 1 Figure 1). Demographic characteristics (age and sex) were available in the list provided by the primary health clinics and were compared for those included in the study versus those deemed as inclusion failure (*Supplementary Material* 1 Table 1).

The number of attempts needed to successfully enrol a participant coupled with the high inclusion failure (67%) resulted in a very time-consuming process that was much longer than previously anticipated. These difficulties together with other challenges that were experienced in the field (i.e., interruption of the activities due to heavy rain or due to armed conflict between the police and the criminal faction that controls the area) prolonged the study far beyond the initially planned 8

weeks to a total of 22 weeks, with a per week number of enrollments varying from 17 (at Week 22) to 311 (at Week 11) and a median of 202 enrollments/week.

All participants gave written informed consent before participation in the Comvida-1 study. For individuals younger than 18 years, parents or a legal representative provided consent. Local ethics committees approved the study (*Instituto Nacional de Infectologia Evandro Chagas* (INI)/Fiocruz, *Escola Nacional de Saúde Pública* (ENSP)/Fiocruz, and *Instituto* Oswaldo Cruz (IOC)/Fiocruz).

Study procedures

A study team comprising two interviewers and one laboratory technician (phlebotomist) visited the address and invited the individuals to participate. After informed consent, participants underwent a structured interview and venipuncture for blood collection. Samples were transported in refrigerated containers to INI/Fiocruz clinical research laboratory. Samples' transport and temperature were monitored to follow the assay manufacturer's instructions.

To facilitate the transit of the study team in the area, at least one interviewer of each team lived in Manguinhos. This was also a safeguard measure since residents have free access to all *favelas*, and Manguinhos, like other areas in Rio de Janeiro city, hosts paramilitary groups and drug dealers that may prevent the transit of non-residents in the area. All addresses were visited at least twice, including one attempt over the weekend. Potential participants were allowed to reschedule the visit to a more convenient day/time. If the team identified the residence of a potential participant but he/she was not present by the time of the visit attempt, the team requested a phone number and scheduled a visit. For the potential participants not found at the provided home address, the study team tried to identify the new address by talking to neighbours, local traders and other community leaders.

To promote the study and engage community participation, we conducted meetings with local stakeholders, religious leaders, and community associations to inform them about the procedures and to explain the risks and benefits of participating in the study. In addition, the study team also engaged in local radio shows and meetings (churches, community associations) to explain the study and to address questions and concerns raised by the community members. Posters and flyers advertising the study were distributed in Manguinhos busiest places (i.e., churches, local trade stores, and community associations).

Laboratory analysis

Serum samples were processed and analyzed for the presence of anti-SARS-CoV-2 antibodies. The assay used for the main analyses was the SARS-CoV-2 IgG II Quant assay on ARCHITECT analyzer (Abbott Ireland, Sligo, Ireland; reference 6S60-22), a chemiluminescent microparticle immunoassay (CMIA) that quantifies IgG antibodies against the spike protein receptor-binding domain (RBD) of SARS-CoV-2 with a 50AU/ml as a positive cut-off and upper limit of quantification of 40,000 AU/mL (80,000 AU/mL at 1:2 dilution). The sensitivity and specificity of the test are 99·37% and 99·55%, according to the manufacturer.[20]

In addition, all participants had their serum tested for anti-SARS-CoV-2 Nucleocapsid (anti-N) IgG antibodies (Abbott Ireland, Sligo, Ireland; reference 6R86-22 & 6R86-32; on ARCHITECT analyser), a CMIA designed to detect IgG antibodies to the nucleocapsid protein of SARS-CoV-2 with a cut-off of 1·40 Index (S/C). According to the manufacturer, the sensitivity and specificity of the test are 100% and 99·63%, respectively.[21]

Data collection

Data from study participants were gathered through structured interviews programmed using REDCap software on mobile phones. Data included sociodemographic information (sex, age, education level, self-reported race/skin colour [White, Black, *Pardo (Mixed-Black)*, Asian, Indigenous], household size (number of people co-living in the same house), and family income (measured in number of minimum wages; monthly minimum wage was 1,045 Brazilian Reais [BRL] in 2020 which corresponds to 199 United States Dollars [USD]).[22] We also inquired about COVID-19 symptoms and level of adherence to social distancing measures and face mask use in the two weeks prior to the interview; adherence responses were categorized as poor, moderate, and intense. Participants were questioned about the main means of transportation used during the COVID-19 pandemic (responses categorized as "walk or bike", "drive own car or motorcycle", "cab/ride-sharing apps/*mototaxi*", or "public transport [bus, subway, train]"). The presence of chronic comorbidities (i.e., arterial hypertension, diabetes, cancer, asthma) was assessed with the question "has a health professional ever said you have:". Participants were then asked how frequently any household member including themselves left the house and how often they received visits from people not living at their home over the past two weeks. Finally, participants were asked if any household member was a beneficiary of the *Bolsa Familia* or *Auxilío Financeiro Emergencial* cash transfer programs. *Bolsa Familia* is a nationwide conditional cash transfer program for families in extreme poverty conditions.[23] Publications addressing the program's impact have shown that it reduced poverty and hunger, child mortality and improved access to elementary education.[24–26] *Auxilío Financeiro Emergencial*, was an emergency financial

assistance program implemented during the COVID-19 pandemic (Apr 2020 through Oct 2021) targeting low-income informal workers, the self-employed, and those already registered in *Bolsa Familia* (who are eligible to receive this transfer in place of their regular Bolsa Familia transfer).[27] Compared to *Bolsa Familia*, *Auxilío Financeiro Emergencial* eligibility criteria was broader and in 2020, 294 billion BRL were transferred to approximately 67 million beneficiaries (72% of them were not previously beneficiaries of the *Bolsa Familia* program).[28]

Statistical analysis

The study population was grouped according to the *favela* they resided in. Between-group comparisons were performed using the Chi-square test for categorical variables and the Kruskal Wallis test for continuous variables. Prevalence of IgG antibodies and 95% CI were calculated using Poisson regression models with robust variance.[29] Titers of anti-S IgG of the positive samples were described over time and by age group. We obtained data on the prevalence of SARS-CoV-2 variants for the study period from the Corona-ômica-RJ Network (available at http://www.corona-omica.rj.lncc.br/).

Multilevel logistic regression models[30] were used to assess factors associated with reactive anti-S IgG serology. To account for the spatial clustering of participants in each of the 16 *favelas*, we assumed a random intercept, meaning that each of the 16 *favelas* had its unique intercept. In contrast, we assumed fixed effects for all other covariates (meaning an estimated mean effect for the 16 favelas). The following covariates were assumed as potentially associated with anti-S IgG serology: study period (divided into epidemic weeks 1 to 22 with participants classified according to the epidemic week they were included), age, sex, race/skin colour, education, household size, family income, *Bolsa Família, Auxílio Financeiro Emergencial*, self-reported adherence to social distancing, self-reported adherence to face mask use, if left home, if received visits, if any household member left home, and main means of transportation used during the pandemic. Age, household size, and epidemic week were included in the models using cubic splines with 3-knots to relax the assumption of linear association. Furthermore, propensity score weights were also included, these are described below.

Bivariate multilevel logistic models were used to test the significance of the association between the covariates and anti-S IgG antibodies reactivity. The final multilevel model included all covariates with a p-value <0·05. Moreover, the final model was restricted to participants aged five years or older due to the inclusion of the covariate adherence to face masks which were recommended only for those aged five years or older.[31]

As described above, we used a random sampling of the source population to generate a list of potential study participants. However, study participation was influenced by the challenges experienced during the study, which ultimately impacted the representativeness of the study participants. *Supplementary Material* 1 Table 1 compares the study population to those who were deemed as inclusion failures. We used propensity score weights to account for an individual's likelihood of inclusion in the study. We first used logistic regression models to estimate the probability of study inclusion[32] among those who were sampled and sought participation, age and sex were used as predictors (*Supplementary Material* 1 Table 2). The propensity score weights were defined as the inverse of the predicted conditional probability as estimated by the logistic regression model. Probability of study inclusion varied between 0.18 and 0.59 (mean 0.32, median 0.31) and weights varied between 1.23 and 5.33 (mean 2.00, median 1.55).

Average marginal predicted probabilities and interquartile ranges (IQR) were estimated from the final adjusted multilevel logistic regression model.[33,34] Analyses were performed in R version 4.1.2, using package lme4 for multilevel regression analyses. Maps were created with QGIS version 3.22.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All the authors had full access to the data in the study and had final responsibility for the decision to submit it for publication.

Results

Study population characteristics

A total of 4,033 participants were included from September 15th, 2020 through February 10th, 2021 (Table 1). The median age was 39·8 years (IQR 21·8-57·7), 21·7% were aged 60 years or older, 60·7% were female, 40·7% were *Pardo*, 22·7% were Black and 44% had less than 10 years of formal education. Household size was three or more persons for 65·7% of the participants, 40·4% reported family monthly income of up to one minimum wage, and 12·6% reported no income. 22·4% of the participants were beneficiaries of *Bolsa Família* program and 47·5% received *Auxílio Financeiro Emergencial*. Public transport (bus, train, and subway) was the main mode of transportation used during the COVID-19 pandemic (43·6%). For the two weeks before the study inclusion, 25·6% of the participants reported poor adherence to social distancing measures, 74·4% reported intense use of face masks, and 34·0% said they had left home often/every day.

Table 1 also shows the breakdown of the study participants according to anti-S IgG antibodies reactivity. The median age for those with anti-S IgG antibodies was lower (37·1 *versus* 42·2 years) compared to those without anti-S IgG antibodies. Household size was

	Non-reactive	Reactive	Total	*P*-value[d]
N	2058	1975	4033	
Age, median (IQR)	42·2 (22·3-60·2)	37·1 (21·5-55)	39·8 (21·8-57·7)	< 0·001[e]
Age, categorical (%)				< 0·001
1—4	74 (3·6)	39 (2·0)	113 (2·8)	
5—9	107 (5·2)	87 (4·4)	194 (4·8)	
10—19	273 (13·3)	309 (15·6)	582 (14·4)	
20—29	259 (12·6)	341 (17·3)	600 (14·9)	
30—39	253 (12·3)	294 (14·9)	547 (13·6)	
40—49	275 (13·4)	282 (14·3)	557 (13·8)	
50—59	299 (14·5)	267 (13·5)	566 (14)	
60—69	300 (14·6)	231 (11·7)	531 (13·2)	
70—79	164 (8·0)	94 (4·8)	258 (6·4)	
80+	54 (2·6)	31 (1·6)	85 (2·1)	
Gender				0·293
Female	1266 (61·5)	1183 (59·9)	2449 (60·7)	
Male	792 (38·5)	792 (40·1)	1584 (39·3)	
Race/Skin colour (%)				0·260
White	621 (30·2)	570 (28·9)	1191 (29·5)	
Black	470 (22·8)	444 (22·5)	914 (22·7)	
Pardo (mixed)	809 (39·3)	834 (42·2)	1643 (40·7)	
Indigenous	21 (1·0)	20 (1·0)	41 (1·0)	
Asian	13 (0·6)	15 (0·8)	28 (0·7)	
Missing	124 (6)	92 (4·7)	216 (5·4)	
Education, Years[a]				0·751
0—4	111 (6·9)	98 (6·4)	209 (6·6)	
5—9	614 (38·3)	563 (36·6)	1177 (37·4)	
10—12	602 (37·5)	610 (39·6)	1212 (38·5)	
13+	135 (8·4)	129 (8·4)	264 (8·4)	
Missing	142 (8·9)	140 (9·1)	282 (9·0)	
Household size (# persons)				<0·001
1	212 (10·3)	139 (7)	351 (8·7)	
2	414 (20·1)	358 (18·1)	772 (19·1)	
3	507 (24·6)	494 (25)	1001 (24·8)	
4	401 (19·5)	426 (21·6)	827 (20·5)	
5	221 (10·7)	244 (12·4)	465 (11·5)	
6+	159 (7·7)	199 (10·1)	358 (8·9)	
Missing	144 (7)	115 (5·8)	259 (6·4)	
Family income				0·401
No income	259 (12·6)	248 (12·6)	507 (12·6)	
≤1 MW	812 (39·5)	818 (41·4)	1630 (40·4)	
(1—2] MW	506 (24·6)	465 (23·5)	971 (24·1)	
(2—3] MW	175 (8·5)	159 (8·1)	334 (8·3)	
≥3 MW	83 (4)	97 (4·9)	180 (4·5)	
Missing	223 (10·8)	188 (9·5)	411 (10·2)	
Bolsa família				0·329
No	1494 (72·6)	1406 (71·2)	2900 (71·9)	
Yes	443 (21·5)	462 (23·4)	905 (22·4)	
Missing	121 (5·9)	107 (5·4)	228 (5·7)	
Auxílio Financeiro Emergencial				0·344
No	978 (47·5)	913 (46·2)	1891 (46·9)	
Yes	958 (46·6)	959 (48·6)	1917 (47·5)	
Missing	122 (5·9)	103 (5·2)	225 (5·6)	

Table 1 *(Continued)*

	Non-reactive	Reactive	Total	*P*-value[d]
Self-reported adherence to social distancing (past 2wks)				< 0·001
Poor	488 (23·7)	544 (27·5)	1032 (25·6)	
Moderate	448 (21·8)	532 (26·9)	980 (24·3)	
Intense	995 (48·3)	792 (40·1)	1787 (44·3)	
Missing	127 (6·2)	107 (5·4)	234 (5·8)	
Self-reported adherence to face masks (past 2 wks)[b]				0·077
Poor	179 (9)	197 (10·2)	376 (9·6)	
Moderate	179 (9)	206 (10·6)	385 (9·8)	
Usually/always	1491 (75·2)	1426 (73·7)	2917 (74·4)	
Missing	135 (6·8)	107 (5·5)	242 (6·2)	
Left the house (past 2wks)				< 0·001
Never	364 (17·7)	282 (14·3)	646 (16·0)	
Essentials/sometimes	929 (45·1)	841 (42·6)	1770 (43·9)	
Often/everyday	628 (30·5)	742 (37·6)	1370 (34·0)	
Missing	137 (6·7)	110 (5·6)	247 (6·1)	
Received visits at home (past 2wks)				< 0·001
Never	1129 (54·9)	1038 (52·6)	2167 (53·7)	
1−2 times/week	575 (27·9)	597 (30·2)	1172 (29·1)	
Almost everyday	193 (9·4)	209 (10·6)	402 (10·0)	
Missing	161 (7·8)	131 (6·6)	292 (7·2)	
Did any household member leave the house (past 2wks)				0·005
No	287 (13·9)	247 (12·5)	534 (13·2)	
Yes, but only sometimes	596 (29)	537 (27·2)	1133 (28·1)	
Yes, often/everyday	993 (48·3)	1055 (53·4)	2048 (50·8)	
Missing	182 (8·8)	136 (6·9)	318 (7·9)	
Main means of transportation used during pandemic				
Walk/bike	448 (21·8)	399 (20·2)	847 (21·0)	0·101
Own car/motorcycle	343 (16·7)	299 (15·1)	642 (15·9)	
Cab/ridesharing apps/mototaxi	266 (12·9)	250 (12·7)	516 (12·8)	
Public transport (bus, subway, train)	855 (41·5)	903 (45·7)	1758 (43·6)	
Missing	146 (7·1)	124 (6·3)	270 (6·7)	
COVID-19 related symptoms (past 2 weeks)[c]				
Cough	163 (8·4)	183 (9·7)	346 (9·0)	0·156
Sore throat	116 (6·0)	117 (6·2)	233 (6·1)	0·757
Anosmia/ageusia	57 (2·9)	123 (6·5)	180 (4·7)	< 0·001
Diarrhea	87 (4·5)	72 (3·8)	159 (4·1)	0·312
Shortness of breath	71 (3·6)	77 (4·1)	148 (3·9)	0·488
Fever	52 (2·7)	58 (3·1)	110 (2·9)	0·462
Vomiting	35 (1·8)	26 (1·4)	61 (1·6)	0·298

***Table 1*: Characteristics of the study population according to anti-SARS-CoV-2 serology (anti-S IgG) result.**

[a] Restricted to a subset of participants aged ≥20 years-old.

[b] Restricted to a subset of participants aged ≥5 years-old.

[c] Missing data for cough (n = 200), sore throat (n = 196), anosmia/ageusia (n =197), diarrhea (n =200) shortness of breath (n =200), fever (n =205), vomiting (n =202).

[d] Chi-square test p-value.

[e] Kruskal-Wallis test p-value.

significantly different between the two groups with a higher proportion of participants reporting a household size greater than three persons among those with anti-S IgG antibodies. Poor adherence to social distancing, to face masks and to variables that are proxies for risk exposure (i.e., "Left the house", "Received visits at home", "Did any household member leave the house") was more frequent among participants with anti-S IgG antibodies compared to those without. The proportion of participants reporting COVID-19-related symptoms was not different between those with anti-S IgG antibodies and those without, except for anosmia/ageusia, reported by 6·5% of those with anti-S IgG antibodies and by 2·9% of the participants without anti-S IgG antibodies (Table 1, p<0·001).

Dynamics of anti-S IgG antibodies in Manguinhos

The overall prevalence of anti-S IgG antibodies carriers during the study period was 49·0% (95%CI 46·8%-51·2%). The prevalence of anti-S IgG antibody carriers varied spatially and over the study period (Figures 1, 2, and 3). Spatially, the prevalence was highest in Bonsucesso (Perereca) *favela* (68·3%, 95%CI 55·7-82·6%) and lowest in Ex-combatentes *favela* (31·4%, 95%CI 0·23%-0·41%). It is important to note that Bonsucesso (Perereca) is likely one of the poorest favelas in Manguinhos. At the same time, Ex-combatentes is an older settlement in the area, purposely built to be a housing complex, and, therefore it is much more structured and organized than other areas in Manguinhos.

The SARS-CoV-2 dynamics of Gamma (P1) and Zeta (P2) variants in the state of Rio de Janeiro according to data from the Corona-ômica-RJ Network (available at http://www.corona-omica.rj.lncc.br/) is shown in Figure 3. The prevalence of anti-S IgG antibodies in our study population was relatively stable over the first 15 weeks and increased slightly after epidemic week 15 when the Gamma (P1) variant emerged in Rio de Janeiro state (Figure 3).

Factors associated with reactive anti-SARS-CoV-2 serology (Anti-S IgG antibodies)

Supplementary Material 1 Table 3 provides crude and adjusted Odds Ratios (aORs) estimated from multilevel regression models and Figure 4 shows the predicted probabilities of having anti-S IgG antibodies according to the model's estimates. Young adults had the greatest probability of having anti-S IgG antibodies. Females had a borderline significant lower probability of having anti-S IgG antibodies compared to males (aOR 0·94, 95%CI 0·87-1·01). Probability increased almost linearly according to household size and was greatest among individuals with family income ≥three minimum wages (aOR 1·44, 95%CI 1·17-1·77). Probabilities of having anti-S IgG antibodies were highest among participants that reported public transport as their main mode of transportation (aOR 1·26, 95%CI 1·14-1·38) and among those reporting leaving the house often/every day (aOR 1·38, 95%CI 1·22-1·55) and lowest among those reporting intense adherence to social distancing measures (aOR 0·90, 95%CI 0·84-0·99).

Finally, to further explore the relationship between face mask use and the prevalence of anti-S IgG antibodies, *Supplementary Material* 1 Table 4 depicts study

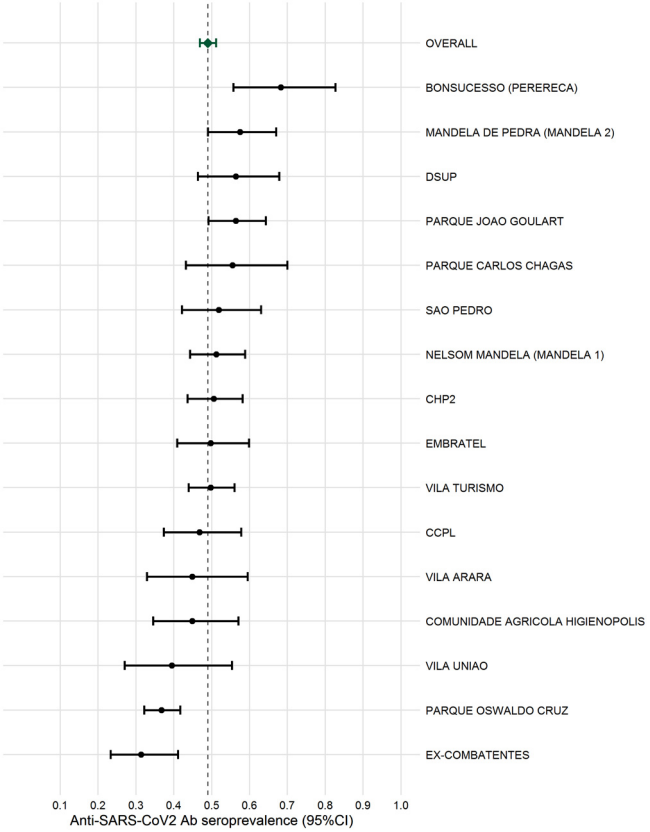

Figure 1. Prevalence of reactive anti-SARS-CoV2 serology (anti-S IgG) by *favela*.

Figure 2. Space and time dynamics of anti-SARS-CoV 2 prevalence (anti-S IgG antibodies) in Manguinhos.
Source: Data provided by Manguinhos COmVIDa populational-based serosurvey. Background image from Google Earth.

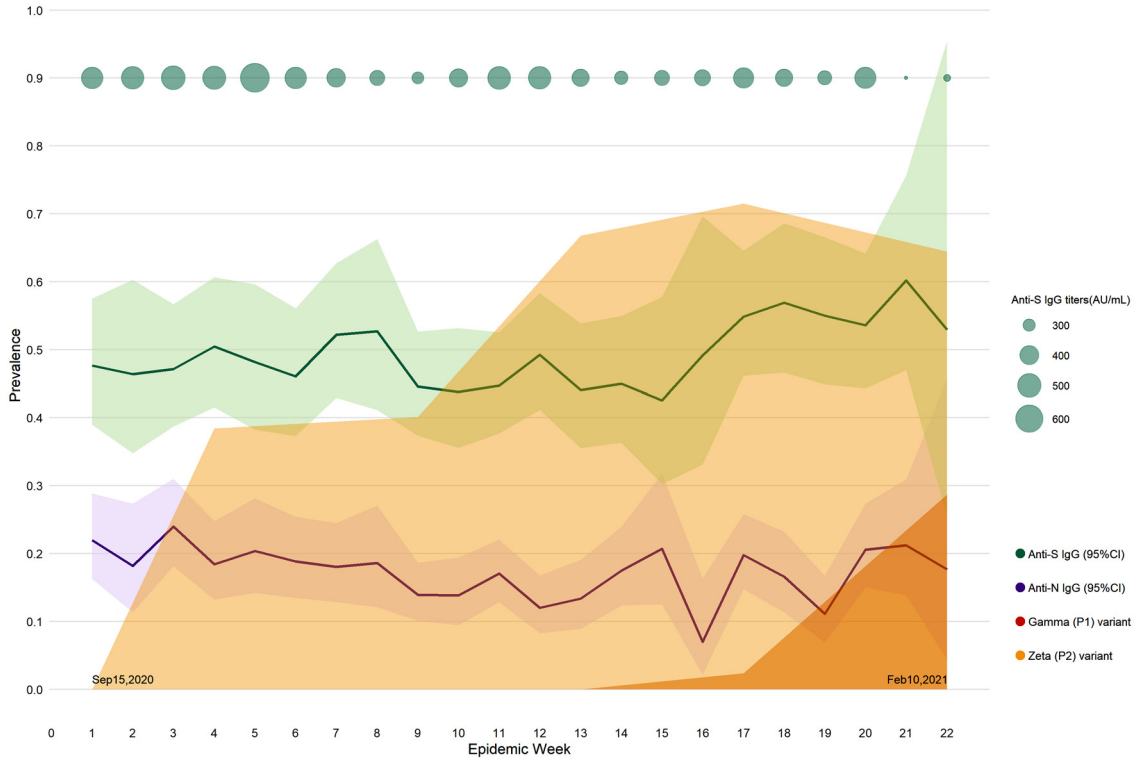

Figure 3. Prevalence of Anti-S IgG antibodies and median titers of serologic results among study participants over the study period.

Anti-S IgG antibodies titers are median values of reactive results each week. Prevalence of SARS-CoV-2 Zeta (P2) and Gamma (P1) variants in Rio de Janeiro state over the study period, source: Corona-ômica-RJ Network (http://www.corona-omica.rj.lncc.br/).

population characteristics (particularly social distancing and proxy variables) according to face mask use. Participants who reported intense adherence to face mask use ("Usually/Always") were more likely to be older (median age 43·8, IQR 25·7,60·2) and female (62·9%) than the other groups ("Poor" and "Moderate"). They also reported better adherence to social distancing and proxy variables in the past 2 weeks; 55% reported intense adherence to social distancing, 18·9% reported they didn't leave the house, and 59·2% reported they didn't receive external visits. In contrast, participants who reported high adherence to face masks were more likely to use public transportation.

Corroborating patterns depicted in Figure 3, the probability of having anti-S IgG antibodies remained relatively stable up to epidemic week 15 and increased thereafter (Figure 4). These patterns can be better visualized in *Supplementary Material* 2 Figures 1–3.

Kinetics of anti-SARS-CoV-2 IgG antibodies

In a secondary analysis, we estimated the prevalence of anti-N IgG antibody carriers overall and across age groups. The overall prevalence of anti-N IgG antibodies was 17·4% (95%CI 16·1%-18·7%), which is much lower than that for anti-S IgG antibodies (49·0%, 95%CI 46·8%-51·2%). Among participants with positive anti-S IgG, 34·2% were also anti-N IgG positive. On the other hand, among those with negative anti-S IgG, 98·8% were also anti-N IgG negative (*Supplementary Material* 1 Table 5). Moreover, among those with positive anti-N IgG (n=700), 96·4% had also a positive anti-S IgG (with a median anti-S IgG antibodies titer of 830 [IQR 404,1506]). Contrastingly, among those with negative anti-N IgG (n=3,333), 39·0% (n=1,300) had positive anti-S serology (with a median anti-S IgG antibodies titer of 294 [IQR 150,580]). Further, although prevalence estimates were lower using anti-N IgG assay than anti-S IgG assay across all ages, estimates were closer for age groups 1-9, 60-79, and 80+ years (Figure 5). Interestingly, quantitative anti-S IgG antibody titers were higher among individuals in the same age strata (1-9, 60-79, and 80+ years; Figure 6).

Discussion

This study highlighted a high prevalence of anti-S IgG antibody carriers in over 4000 individuals living in one

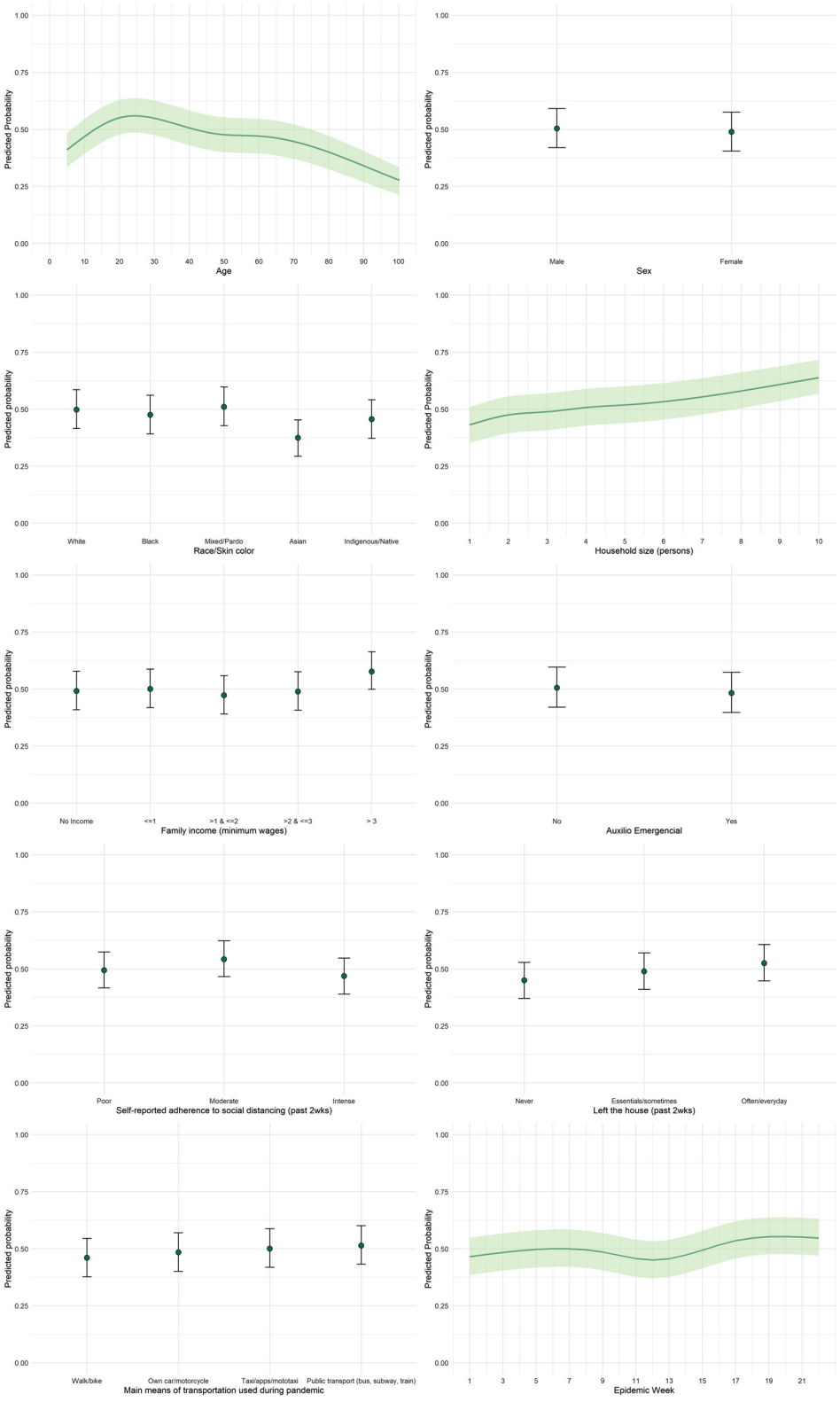

Figure 4. Predicted probabilities of reactive Anti-SARS-CoV 2 serology (Anti-S IgG) as estimated from adjusted logistic multi-level regression models.

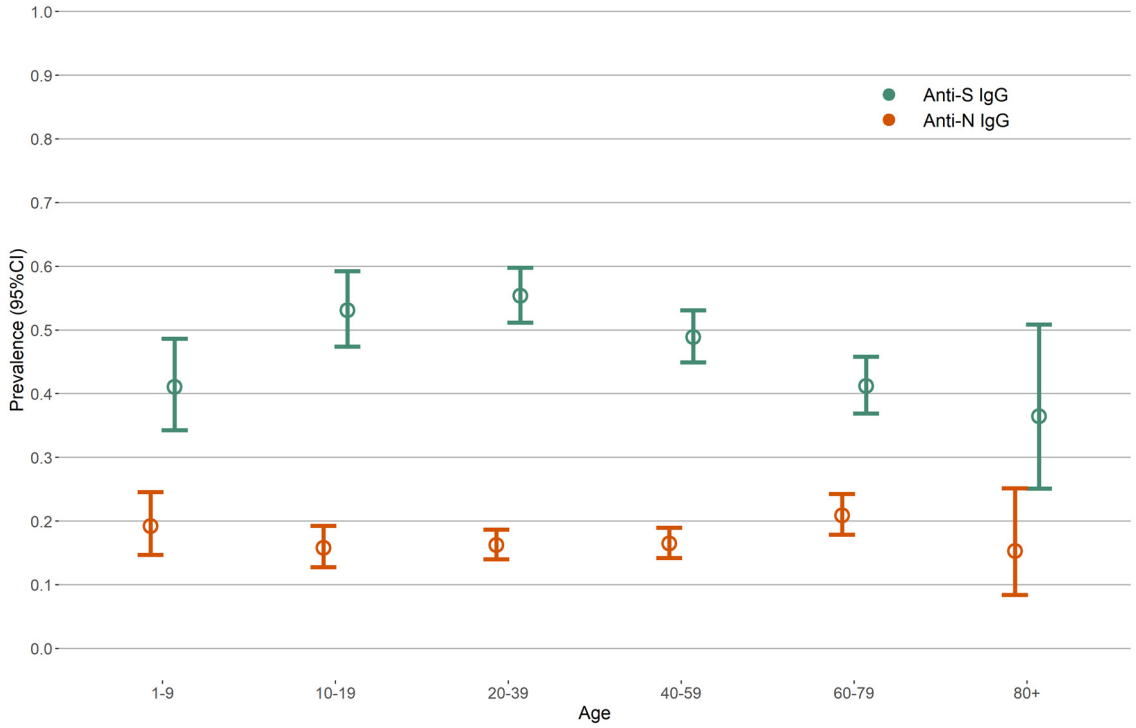

Figure 5. Prevalence estimates of Anti-N IgG carriers and Anti-S IgG carriers by age.

of the most vulnerable neighbourhoods in Rio de Janeiro city, Brazil, spanning from September 2020 through February 2021. In Brazil, COVID-19 vaccination started on January 19th, 2021 and was initially restricted to front-line health professionals, the elderly (80 years or older), people with disabilities living in long-term care facilities, and Indigenous peoples. Accordingly, at the end of our study period (February 10th, 2021), only 2·2% of the Brazilian population had received the first dose of the COVID-19 vaccine and less than 0·1% were fully vaccinated.[35] Thus, the prevalence estimates found in our study reflect the COVID-19 burden (naturally acquired antibodies) before the expansion of vaccine eligibility to the general adult population.

The first important finding from our study is the significant burden of COVID-19 in this community, as reflected by the antibody prevalence (49·0%) which was much higher than previous estimates for Rio de Janeiro city. In June 2020, the estimated adjusted seroprevalence was 7·5% in a populational based study of individuals aged one-year or older in Rio de Janeiro city,[36] while in Rio de Janeiro state, an adjusted prevalence of 3·8% was found among 2,857 blood donors aged 18–69 years (April 2020).[37] Our estimates are closer to those found in studies including people living in vulnerable areas of other cities in Brazil. In the metropolitan area of Vitória (also in the Southeast region of Brazil), in June 2020, the estimated prevalence among individuals aged two years or older living in slums was 12·1% (n=714)[38]; while a study that included 2,035 urban slum residents Salvador city (Northeast region of Brazil) observed a 46·4% prevalence (from November 2020 to February 2021).[39] Additionally, a survey conducted with homeless persons in a large day-shelter in São Paulo city (Southeast region of Brazil) found a 54·7% prevalence in August 2020.[40] In a vulnerable area in Sao Paulo city (Paraisópolis), a 43·8% prevalence was found among individuals aged 18 years or older (n = 272) (from September to December 2020).[41] Moreover, a prospective cohort study conducted in the same neighbourhood as our study estimated the incidence of COVID-19 during four waves (from May 2020 to Nov 2021) and found that the incidence was much higher than previously reported by similar studies in the US and that the incidence was the highest in the first wave (May through November 2020).[42] These results suggest that the burden of COVID-19 is highly unequal, impacting to a much higher degree vulnerable and marginalized populations. We hypothesize that the reasons for the disparities in COVID-19 burden stem from precarious living conditions (densely populated *favelas* and large household sizes), poverty (limited access to clean water and cleaning supplies), employment and income insecurity (people working in low-paid and informal jobs who are at risk of losing their income partially or completely), and the lack of economic support from the government, thus hindering the adoption of social distancing measures.

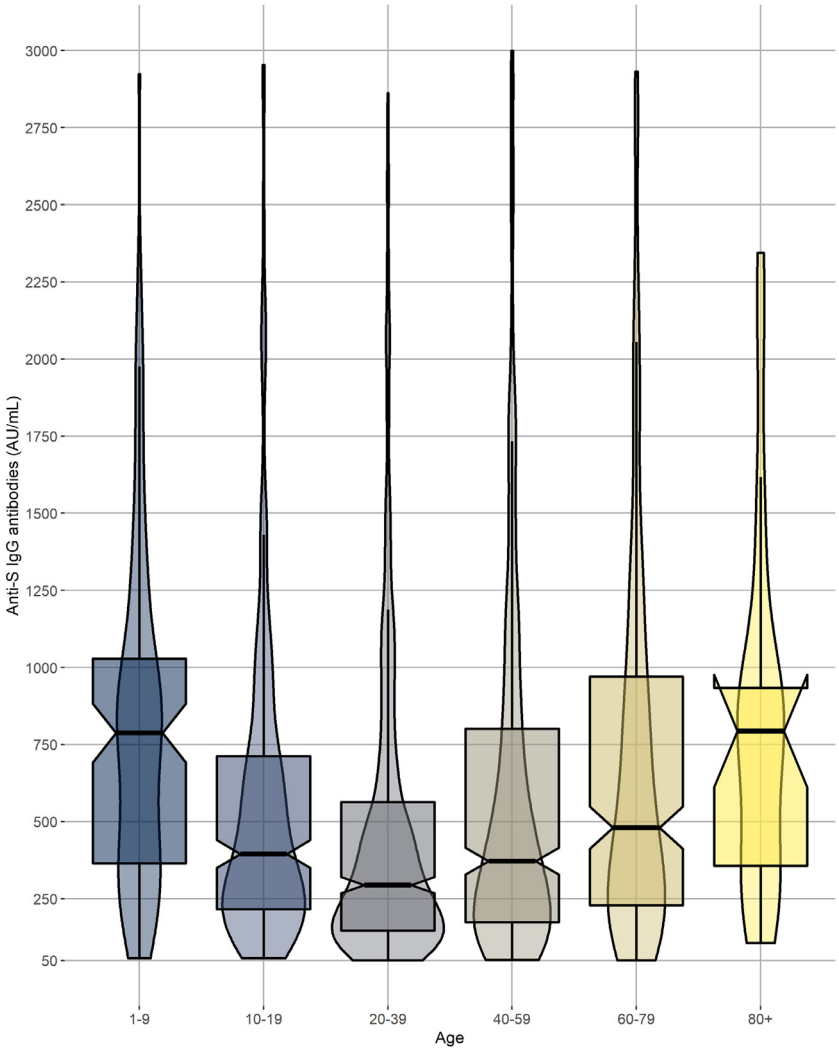

Figure 6. Quantitative Anti-S IgG antibodies level among individuals with reactive serology by age strata.
Violin plot and box plot showing the density distribution, median, first and third quartiles of Anti-S IgG antibodies titers by age strata.

Indeed, these hypotheses are corroborated by our results. First, prevalence estimates varied spatially across different favelas in Manguinhos: they were higher in the poorest areas such as Bonsucesso (Pereca) and Mandela de Pedra (*favelas* characterized by unplanned streets and multiple shacks with a small distance between them) and lowest in better structured and planned areas (such as Ex-Combatentes and Parque Oswaldo Cruz, that were settled as planned housing complexes). Second, our adjusted models showed a linear association between household size and the odds of having anti-S IgG antibodies. Similarly to other infectious diseases (i.e., dengue and tuberculosis), SARS-CoV-2 spread is significantly higher in densely populated areas and overcrowded houses.[43–45] Third, we found that family income ≥ three minimum wages was associated with greater odds of having anti-S IgG antibodies while receiving *Auxilio Financeiro Emergencial* was associated with lower odds. These results corroborate the hypothesis that economically active adults ("young adults with jobs") did not stop (or were unable to stop) working during the COVID-19 pandemic and were, therefore, the most at-risk group in our study population.[46] In contrast, it became feasible for those receiving *Auxilio Financeiro Emergencial* to stay at home and thus adhere to social distancing measures. Job and income insecurity are intrinsically linked to food insecurity in most vulnerable populations. A study evaluating food insecurity in two *favelas* in São Paulo during the early weeks of social distancing measures adoption in Brazil[47] found that almost 10% of the population experienced hunger and almost half experienced moderate or severe food insecurity. This study also found that families with children were less likely to experience severe

or moderate food insecurity, likely because they were protected by the *Bolsa Familia* program, which benefits mostly families with children. Finally, we found a complex association between adherence to non-biomedical preventive measures (i.e., social distancing and its proxies and face mask use) and the odds of having anti-S IgG antibodies. In both crude and adjusted models, adherence to social distancing was associated with lower odds of having anti-S IgG antibodies, whereas those that reported they "left the house often/every day" had higher odds of having anti-S IgG antibodies. Contrastingly, in the adjusted model, adherence to face masks had a non-significant effect on increasing the odds of having anti-S IgG antibodies. Several studies have shown that social distancing and face mask use are associated with a lower risk of COVID-19.[48–50] However, it is important to highlight that a randomized cluster study in Bangladesh didn't find a protective effect of the use of cloth masks on the risk of COVID-19 (though a clear protective effect was observed for surgical masks).[49] Cloth masks were largely used in Brazil and their protection is not well known and can vary according to the material and layers used.[51] We speculate that although 75% of the study population reported intense adherence to face masks, its protective effect might have been confounded by other risk factors not evaluated in the study, such as close-contact rates, potential differences between groups (those who adhered to face masks use *versus* those who haven't), face mask quality, appropriate use, storage and cleaning, all factors that impact masks' effectiveness. Interestingly, our participants reported a higher level of intense face mask use (74 ·4%) than other studies in Brazil[52,53] and our assessment of face masks' use through a face-to-face interview might have influenced these results. In a study conducted in the streets of a commercial centre of a city in São Paulo State, in a period of mandatory use of face masks in this state, observation of over a thousand individuals on the street showed that 38·4% did not wear a face mask and that 12% were inappropriately using it.[52] Also, an online survey conducted in April 2020 with 23,896 respondents found that only 45·5% of the participants reported using face masks when going outside.[53] Finally, risk compensation behaviour has been associated with the use of face masks or mandates in the United States[50]; but this association was not observed in the randomized cluster trial from Bangladesh.[49]

The Brazilian response to COVID-19 was insufficient. Federal leadership actively jeopardized non-biomedical preventive measures, the pandemic aggravated socioeconomic inequities and vaccine availability had important delays.[54–57] Consequently, Brazil has become one of the hotspots of COVID-19, with an unequal distribution of the burden of infection and unfavourable outcomes across the country. National data has shown substantial racial disparities in COVID-19-associated mortality, with Black and *Pardos* having higher in-hospital mortality than White individuals.[54] In addition, the spatial distribution of the epidemic in the country was mostly driven by socioeconomic disparities.[56,58] The highest death rates occurred in states with greater socioeconomic vulnerabilities, mostly in the North and Northeast regions of the country.[56] Notwithstanding, a study that evaluated in-hospital mortality found that Rio de Janeiro state's mortality hazard was one of the highest in the country, surpassed only by Amazonas and Pernambuco (states in North and Northeast regions, respectively, and with worse socioeconomic and health system indicators).[54] The authors also found the mortality risk was two-fold higher in Rio de Janeiro metropolitan area compared to the rest of the state. Another study observed that the Rio de Janeiro municipality had the second-highest excess mortality and standardised mortality ratio among Brazilian cities.[59] Altogether, these data suggest that vulnerable communities in Rio de Janeiro were deeply impacted by COVID-19.

In a secondary analysis, we showed how the COVID-19 prevalence estimates varied significantly according to the serological assay used. Prevalence estimates using the anti-N IgG assay were much lower than those based on the anti-S IgG assay. Both assays are automated and commercially available and have high sensitivity and specificity according to the manufacturer, suggesting that the discrepancies derive from antibody kinetics after natural infection and affinity to specific variants.[60–64] Antibodies targeting different components of the SARS-CoV-2 (i.e., nucleocapsid or spike proteins) have different dynamics. Anti-N IgG antibodies are detected earlier in the course of the infection and wane fastest (half-life of 63-85 days), followed by anti-RBD (half-life 83-126 days) and lastly by anti-S IgG (half-life 126-229 days).[65–68] At 6-8 months after symptoms onset, the proportion of individuals seropositive for anti-RBD IgG was 88% and for anti-S IgG was 90%.[66] A study from the United States using a large COVID-19 data registry coupled with laboratory data (Labcorp) of 39,086 individuals with confirmed SARS-CoV-2 infection (positive PCR test) between March 2020 and January 2021 found that 68% of the individuals remained seropositive for anti-N antibodies and 88% for anti-S antibodies at ~10 months after infection.[65] An Italian study evaluated the persistence of anti-SARS-CoV-2 antibodies (anti-N and anti-S) by repeating serological assays in seropositive individuals that were previously enrolled in a large serosurvey study conducted 4 months before.[69] They found that over 40% of the participants that had a previous positive anti-N result had a negative anti-N result in the second evaluation; however, 78% of those with a negative anti-N result at the second evaluation, had a positive anti-S result. A large Canadian study of blood donors (*N*=17,428 samples collected between Apr 2020 and Mar 2021) qualitatively compared the agreement of four serological assays including the two used in our analyses (Abbott anti-S, Abbott anti-N, Sinai anti-RBD and Sinai anti-N).[70] They found that the highest agreement of

positive Abbott anti-S results was with Sinai anti-RDB results (72·6%) while the lowest agreement was with Abbott anti-N (28·7%). For negative Abbott anti-S results, the agreement was high (>97%) with all assays (being 99·7% for Abbott anti-N negative results). Notably, in our study, we observed similar positive (34·2%) and negative agreement (98·8%) between Abbott's anti-S and Anti-N results. Relative to the discrepancies found in our study and current scientific evidence, we speculate that most of our anti-S IgG carriers, particularly those included up to week 14, were not recently infected and that anti-N antibody levels have probably waned overtime after natural infection in a large proportion of our study population. This finding is also supported by the lack of difference in the proportion of participants reporting COVID-19 symptoms in the past two weeks among those with and without anti-S IgG antibodies, except for anosmia/ageusia (more frequent among those with anti-S antibodies), symptoms known to last longer after COVID-19 onset. Additionally, the gaps between anti-S and anti-N estimates were narrower among the youngest and eldest and wider among young adults in our study population, suggesting a possible transmission dynamic in Manguinhos, with young adults infected earlier in the pandemic period and acting as index/source cases for the other members of the community. Finally, our results reinforce the need for a cautious interpretation of COVID-19 seroprevalence surveys as estimates are prone to variation due to heterogeneities in the study population, antibodies waning over time, and serological assay's affinity to specific circulating variants.

Notably, we found a lower prevalence of COVID-19 symptoms among participants with anti-S IgG antibodies (i.e. cough 10%, anosmia/ageusia 6.5%, sore throat 6.2%) compared to previous studies. A multicity study in Brazil found that participants with reactive serology reported headache (58%), changes in smell/taste (56%), fever (52%), and cough (48%).[71] Whereas in Vitória city among those with reactive serology, 45%, 40% and 38% reported anosmia, cough, and myalgia, respectively.[38] These differences may be attributed to a shorter period of symptoms observation in our study compared to the first-mentioned study (past two weeks *versus* past two-to-three months), but not different from the second study. Another potential reason could be related to the performance of serological assays used. We used a CLIA quantitative anti-S IgG assay while other studies used lateral flow IgM/IgG anti-S rapid tests (Wondfo test, Wondfo Biotech Co., Guangzhou, China[71] and IgM/IgG test from Celer Technologies Inc.[38]). Lateral flow serological tests have lower sensitivity than chemiluminescence immune assays and ELISA assays.[72,73] Irrespective of the test method, serological tests show a general pattern: a low sensitivity in the first week after symptoms onset, rising in the second week and peaking at week three after symptoms onset; beyond week five sensitivity tends to decline for all methods, being lowest for lateral flow tests.[72] The two studies that used IgM/IgG lateral flow tests might have detected participants with more recent SARS-CoV-2 infection, which would explain their high symptoms prevalence.

Our study has several limitations that are common to other observational studies conducted in marginalized communities. First, a high proportion of the individuals initially sampled were not included in the study, potentially imposing a selection bias. Indeed, we found that individuals sampled but not included in the study were more likely to be male and younger than those included. To address this limitation, individuals' likelihood of inclusion in the study was estimated and incorporated into the regression models as propensity score weights. Second, our study target sample size (n=6,000) was not reached, and the study period was longer than initially planned. Nonetheless, the number of participants per epidemic week allowed the estimation of the prevalence of anti-SARS-CoV2 carriers within reasonable confidence bounds. Third, outcomes and exposure variables (including adherence to non-biomedical measures [i.e., social distancing and face mask use]) were collected at the same point in time and as such the precise temporality among variables cannot be established, thus the associations should be interpreted with caution. Fourth, we found a lack of protective association between the use of face masks and the odds of having anti-S IgG antibodies. This association could be confounded by several unmeasured factors including the type of face mask (i.e., cloth, surgical, N95/respirators)[49,51] and its appropriate use, manipulation and storage. Moreover, compared to prior studies,[52,53] we found a higher prevalence of intense face mask use that may reflect some reporting bias given the face-to-face format of our interviews.[74] A strength of our analysis was the use of multiple statistical frameworks (e.g., exploratory, frequentist, and Bayesian) that argue for our results' robustness. Another strength of our study was the use of two automated commercially available assays to detect anti-S and anti-N SARS-COV-2 IgG antibodies. Finally, it is worth mentioning that although we have not performed internal validation tests of the performance of the anti-S IgG assay used in our analysis, several studies[42,69,75,76] used this assay to estimate seroprevalence and a large study with over 17,000 well-characterized blood samples (Canadian blood donors study) has estimated Abbott anti-S IgG sensitivity to be 95·96% (95% CI, 93·27 to 97·63%) and the specificity as 99·35% (95% CI, 99·21 to 99·46%).[70]

Conclusions

Our results show a significantly higher prevalence of anti-S IgG antibodies than initially anticipated in an extremely socioeconomic vulnerable population before

vaccine implementation in Rio de Janeiro, Brazil. Young adults and those reporting large household size, poor adherence to social distancing and use of public transportation had the highest probability of having anti-S IgG antibodies. Moreover, despite high seroprevalence levels, we documented an increase in seroprevalence that is temporarily linked to a new transmission wave that occurred in Rio de Janeiro state. This pattern was possibly driven by the combined effect of loss of immunity, the emergence of new a variant, and the lack of variants' cross-immunity, all of which were documented in our study. This dynamic challenges the possible role of herd immunity in mitigating the community transmission of SARS-COV-2 and the consequential burden of COVID-19. Finally, disparities in prevalence estimate obtained using different serological assays (Anti-S and Anti-N) reinforce the need for cautious interpretation of serosurveys estimates given the heterogeneity of exposure in communities, loss of immunological biomarkers, serological assay method and antigen target, and variant-specific test affinity.

Contributors

CJS, LEC, VGV, BG, PML, TST, HP, EMJ conceived and designed the study. DCP, EMP, SN, LEC, EMJ, RTA worked on the study implementation, data collection and data management. LEC, CJS and PML performed the analysis and wrote the manuscript. SWC, EM, MFS, FCB, ATRV, CAMC, DAMV, TP, GTG, CVS, NCPR revised the manuscript. All authors discussed the results and contributed to the final manuscript.

Data sharing statement

Data supporting this manuscript may be available upon reasonable request to the corresponding author.

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Editor note

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Declaration of interests

DAMV is an Ad-hoc member of the *Committee on COVID-19 Immunization* from the Ministry of Health; CJS participates I PAHO and WHO advisory Boards (unpaid). All authors declare no competing interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100338.

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