Interacting Epidemics in Amazonian Brazil: Prior Dengue Infection Associated with Increased COVID-19 Risk in a Population-Based Cohort Study

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Summary

Serologically proven prior dengue infection is associated with increased subsequent risk of clinically apparent COVID-19 in Amazonians, implying that sequential dengue and COVID-19 epidemics may impose an extra burden of disease to affected communities in the tropical and subtropical world.

Abstract

Background Immunity after dengue virus (DENV) infection has been suggested to cross-protect from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and mortality.

Methods We tested whether serologically proven prior DENV infection diagnosed in September-October 2019, before the coronavirus 2019 (COVID-19) pandemic, reduced the risk of SARS-CoV-2 infection and clinically apparent COVID-19 over the next 13 months in a population-based cohort in Amazonian Brazil. Mixed-effects multiple logistic regression analysis was used to identify predictors of infection and disease, adjusting for potential individual and household-level confounders. Virus genomes from 14 local SARS-CoV-2 isolates were obtained using whole-genome sequencing.

Results Anti-DENV IgG was found in 37.0% of 1,285 cohort participants (95% confidence interval [CI], 34.3% to 39.7%) in 2019, with 10.4 (95% CI, 6.7 to 15.5) seroconversion events per 100 person-years during the follow-up. In 2020, 35.2% of the participants (95% CI, 32.6% to 37.8%) had anti-SARS-CoV-2 IgG and 57.1% of the 448 SARS-CoV-2 seropositives (95% CI, 52.4% to 61.8%) reported clinical manifestations at the time of infection. Participants aged >60 y were twice more likely to have symptomatic COVID-19 than under-five children. Locally circulating SARS-CoV-2 isolates were assigned to the B.1.1.33 lineage. Contrary to the cross-protection hypothesis, prior DENV infection was associated with twice the risk of clinically apparent COVID-19 upon SARS-CoV-2 infection, with *P* values between 0.025 and 0.039 after adjustment for identified confounders.

Conclusion Higher risk of clinically apparent COVID-19 among individuals with prior dengue has important public health implications for communities sequentially exposed to DENV and SARS-CoV-2 epidemics.

Keywords: SARS-CoV-2; COVID-19; dengue; serology; genome sequencing; Amazon

Dengue virus (DENV) is widespread in the tropical and subtropical world, with 3.9 billion people exposed to infection [1]. Approximately 390 million infections occur each year worldwide [2], with over 2 million dengue cases and 872 deaths in the Americas until the epidemiological week 47 of 2020 [3].

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected 115 million people worldwide [4]. Nearly 51 million COVID-19 cases have been reported in the Americas [4], where DENV and other arboviruses cause periodic outbreaks in several countries [3]. The COVID-19 crisis in Brazil is particularly severe in the Amazon, where the stretched health infrastructure was rapidly overwhelmed by severe cases and the more transmissible SARS-CoV-2 P.1 lineage has recently emerged [5,6].

There are growing concerns that dengue and COVID-19 epidemics may interact synergistically, with disproportionately greater morbidity and mortality in vulnerable populations [3,7], but prior DENV immunity has also been suggested to cross-protect from SARS-CoV-2 infection and death [8-10]. Here we examine the interactions between dengue and COVID-19 in Amazonian Brazil. Contrary to the cross-protection hypothesis, we report an increased risk of clinically apparent COVID-19 among Amazonians with prior DENV infection, with important public health implications.

METHODS

Study site

DENV was reintroduced in Brazil in 1981 and has since spread countrywide [11], with 661 cases per 100,000 population in 2020 [3]. The study site, Mâncio Lima (urban population, 9,000), is situated in the upper Juruá Valley region of Acre State, next to the border with Peru (Supplementary Fig. 1), where the first dengue outbreak was recorded in 2014 [12]. Mâncio Lima experiences most DENV transmission during the rainy season, between November and April (Supplementary Fig. 2). The first local COVID-19 case was notified on April 29, 2020, with a total of 1,766 laboratory-confirmed cases recorded as of 28 February 2021 (Supplementary Fig. 2).

Study design and population

Cohort participants are members of randomly drawn (approximately 20%) urban households in Mâncio Lima (ClinicalTrials.gov, NCT03689036). Five assessments were made since the cohort onset in March 2018 and new residents joining the households were enrolled over time (Supplementary Methods online). The Institutional Review Board of the Institute of Biomedical Sciences, University of São Paulo, and the National Committee of Ethics in Research, Ministry of Health of Brazil (CAAE numbers 64767416.6.0000.5467 and 30481820.3.0000.5467) approved the study protocols. Written informed consent was obtained from study participants or their parents/guardians.

We analyzed sociodemographic and morbidity data and plasma samples from 1,285 individuals aged <1 to 92 y (mean, 29.9 y). Plasmas obtained in September-October 2019 (“2019 survey”) were tested for anti-DENV IgG and those obtained in October-November 2020 (“2020 survey”) were tested for anti-SARS-CoV-2 IgG (Figure 1). Information on housing quality and assets was used to derive a

household-level wealth index [13] as a proxy of socioeconomic status. To characterize SARS-CoV-2 lineages circulating at the peak of the current epidemic, we obtained two nasopharyngeal swab samples from 49 consecutive symptomatic patients (age range, 3-77 y) seeking COVID-19 testing in Mâncio Lima in August 2020. One swab was used for point-of-care antigen-based diagnosis (ECO F COVID-19 Ag test FA0054; Ecodiagnostica, Corinto, Brazil) and the other was preserved in RNA/DNA Shield (Zymo Research, Irvine, CA) for RNA extraction.

< Figure 1 >

Antibody assays

We tested plasmas from the 2019 survey for anti-DENV IgG, which persists for life following an infection [14], using an ELISA with DENV serotype 2 viral particles (EI 266b-9601 G; Euroimmun, Lübeck, Germany) with 98.5% sensitivity and 95.7% specificity, according to the manufacturer. During the 2020 survey, we tested plasmas from the same individuals for anti-SARS-CoV-2 IgG with an ELISA that uses the recombinant subdomain S1 of the Spike protein as antibody-capture antigen (EI 2606-9601 G; Euroimmun) [15], with a sensitivity of 82.5% to 93.3% and specificity of 98.0% to 98.5% [16,17]. To identify DENV seroconversion events between surveys, we tested 186 randomly chosen samples collected in 2020 from donors who were DENV seronegative in 2019. To determine whether antibodies cross-reactive to SARS-CoV-2 existed before the COVID-19 epidemic, we tested for anti-SARS-CoV-2 IgG in 105 randomly chosen plasmas obtained in 2019 from donors found to be seropositive in 2020.

SARS-CoV-2 genome sequencing

Template RNA was prepared using QIAamp Viral RNA mini kits (Qiagen, Hilden, Germany). We detected SARS-CoV-2 RNA in all 15 antigen-positive samples using a 2-plex TaqMan assay that targets the RdRP and E genes (GenScript, Piscataway, NJ) and selected 14 samples with cycle threshold <30 for whole-genome sequencing as part of a countrywide SARS-CoV-2 genomic surveillance project [18]. Nanopore sequencing on the MinION platform (Oxford Nanopore, Oxford, UK) was carried out using the ARTIC V3 multiplexed amplicon protocol [19] (Supplementary Methods online). Assembled sequences yielded at least 75% coverage of the SARS-CoV-2 genome, with at least 20-fold depth. Lineages were classified using the Pangolin software [20] and maximum likelihood phylogenetic analysis with complete reference genomes. New genome sequences were deposited in the GISAID platform (https://www.gisaid.org/; accession numbers, EPI_ISL_1251212 to EPI_ISL_1251225).

Outcome definitions

Four primary outcomes were considered (Figure 1). (1) Presence of anti-DENV IgG in the 2019 survey, regardless of any clinical signs and symptoms, as a proxy of dengue infection prior to the COVID-19 epidemic. (2) Presence of anti-SARS-CoV-2 IgG in the 2020 survey, regardless of clinical signs and symptoms, as a proxy of SARS-CoV-2 infection during the follow-up. (3) Presence of anti-SARS-CoV-2 IgG combined with at least one new or increased sign or symptom (fever, cough, shortness of breath, chills, muscle pain, loss of taste or smell, sore throat, diarrhea, or vomiting [21]) experienced since March 2020, as a proxy of clinically apparent COVID-19 during the follow-up. (4) Clinically apparent COVID-19 (as defined above) in study participants with SARS-CoV-2 infection retrospectively diagnosed on the basis of anti-SARS-CoV-2 IgG detected in 2020. A secondary

outcome was DENV seroconversion, defined as a negative ELISA result (reactivity index [RI] < 0.8) in 2019 followed by a positive ELISA result (RI ≥ 1.1) in 2020 in the same study participant.

Data analysis

Data were transferred from tablets programmed with REDCap [22] to STATA 15.1 (StataCorp, College Station, TX) for analysis. Separate multiple logistic regression models were built to identify factors associated with each binary outcome: (a) prior dengue infection, (b) SARS-CoV-2 infection; (c) clinically apparent COVID-19, and (d) clinically apparent COVID-19 upon serologically documented SARS-CoV-2 infection. Preliminary unadjusted analysis is termed here "model 0". Because study subjects are nested into households, which introduces dependency among observations, for each outcome we built three mixed-effects logistic regression models with random effects at the household level and robust variance. We used the following STATA syntax: (a) models 1 and 3, *melogit outcome indvar1 indvar2 || household: housevar1 housevar2*, *vce(robust) or* and (b) model 2, *melogit outcome indvar1 indvar2 housevar1 housevar2 || household: , vce(robust) or*. In the models, "indvar1" and "indvar2" are individual-level covariates and "housevar1" and "housevar2" are household-level covariates. Individual covariates were age in 2019 (categorical variable in models 1 and 2 and continuous in model 3), sex (female vs. male), laboratory-confirmed malaria within the past 12 months (no vs. yes; only for COVID-19 models), overnight stay(s) away from Mâncio Lima within the past 12 months (no vs. yes; only for COVID-19 models), and DENV seropositivity in 2019 (no vs. yes; only for COVID-19 models). Household covariates were wealth index quintiles and household size. Age, sex, and covariates associated with the outcome at a significance level <20% in unadjusted analysis were retained in multiple logistic regression models, from which the few participants with missing values (n ≤ 5 per model) were excluded. Statistical significance was defined at the 5% level; odds ratio (OR) estimates are provided along with 95% confidence intervals (CIs) to quantify the influence of each predictor on the outcome, while

controlling for all other covariates. Models 1 and 3 do not provide OR estimates for household-level covariates. We also computed the intraclass correlation coefficient (ICC), the proportion of the variability in the outcome attributable to differences between versus within households.

RESULTS

Baseline dengue seropositivity and seroconversion

Altogether, 37.0% (95% CI, 34.3% to 39.7%) of the study participants had serological evidence of DENV infection prior to the current SARS-CoV-2 pandemic. Seropositivity rates increased with age (Figure 2A), which is not unexpected, as the number of infections accumulates over time [23]. However, all participants who were born in Mâncio Lima and neighboring municipalities (95.5% of the study population), except under-five children, had exactly 5 y of exposure (assuming that they did not leave the region) to DENV since dengue outbreaks started in the region [12]. However, only 24.7% of the 6-15-y old individuals had anti-DENV IgG detected in 2019, compared with 58.3% in the ≥60-y old individuals, suggesting that the cumulative exposure to DENV (e.g., due to human mobility) has varied significantly across age strata since 2014.

< Figure 2 >

Mixed-effects multiple logistic regression analysis identified older age to be significantly associated with DENV seropositivity (Table 1). Subjects in the intermediate wealth strata (quintiles 3 and 4) were also at increased risk of infection, possibly because of greater mobility. Model 1 showed a

moderate clustering of DENV infections at the household level, after adjustment for individual covariates (ICC = 33.9%, 95% CI, 20.2 to 50.9%).

Of 186 initially seronegatives retested for DENV IgG in 2020, 13 months later, 22 (11.8%) developed specific antibodies (Supplementary Fig. 3), with 10.4 (95% CI, 6.7 to 15.5) seroconversion events per 100 person-years at risk. Seroconverters were 12.6 y older than their seronegative counterparts (mean, 36.4 vs. 23.8 y; *P* = 0.007, *t*-test), but this observation should not be overinterpreted given the small sample size. Of note, recent cohort studies have associated older age with greater probability of disease upon DENV infection [24,25].

< Table 1 >

SARS-CoV-2 infection and clinically apparent COVID-19 during the follow-up

Serological evidence of SARS-Cov-2 infection was found for 452 individuals tested in 2020 (35.2%; 95% CI, 32.6 to 37.8%), with similar antibody positivity rates across age groups (Figure 2B). Seropositivity was not predicted in multiple logistic regression analysis by age, sex, overnight stays out of the town, or socioeconomic status; prior DENV infection did not emerge as a risk factor for SARS-Cov-2 infection either (Table 2). Crowding was marginally associated with an increased risk of SARS-CoV-2 infection, which was moderately clustered at the household level (model 1 ICC = 49.4%, 95% CI, 24.7% to 76.4%). DENV seroconverters were as likely as non-seroconverters to have SARS-CoV-2 antibodies (12.1% vs. 11.7%; *P* = 1.000, Fisher exact test, n = 186), consistent with no false-positive SARS-CoV-2 serology due to DENV exposure in this population. Moreover, of 105 pre-

epidemic plasmas from donors who tested positive for SARS-CoV-2 IgG in the following year, only 1 (0.9%) was weakly positive (RI = 1.15) (Supplementary Fig. 4).

< Table 2 >

Genome sequences from 14 SARS-CoV-2 isolates circulating in Mâncio Lima in August 2020 were assigned to the B.1.1.33 lineage, defined by two nonsynonymous mutations in ORF6 (T27299C; numbering relative to GenBank sequence NC_045512.2) and the nucleocapsid protein gene (T29148C) [18]. Originally termed "clade 2", B.1.1.33 is one of the two SARS-CoV-2 lineages that dominated the first epidemic wave in Brazil [18]. The lineage emerged in February 2020 and spread through community transmission to reach all regions of this country by mid-March [26].

Clinical data were available for 1,281 study participants. Of them, 256 (20.0%; 95% CI, 17.8 to 22.3%) met the definition of clinically apparent COVID-19. Specific IgG levels measured by our semiquantitative protocol were similar between individuals with symptomatic vs. asymptomatic SARS-CoV infections during the follow-up (mean RI, 4.92 vs. 4.67; $P = 0.303$, *t*-test). Although all age groups were uniformly exposed to SARS-CoV-2 (Figure 2B), individuals >15 y were twice more likely to develop COVID-19 than their younger counterparts (Figure 2C). Of note, 6.5% of the study participants had laboratory-confirmed malaria during the follow-up. Because the clinical manifestations of COVID-19 and malaria partially overlap, malaria episodes in SARS-CoV-2 seropositive individuals might have been misclassified as COVID-19. Reassuringly, however, malaria and symptomatic COVID-19 were not significantly associated to each other in our population during the study period (Table 3). Older age, prior dengue infection, wealth and crowding emerged as predictors of clinically apparent COVID-19 identified by multiple logistic regression analysis after

adjusting for potential confounders. We found relatively little COVID-19 clustering at the household level (model 1 ICC = 64.8%, 95% CI, 23.9% to 91.5%).

< Table 3 >

Of the 448 SARS-CoV-2 seropositive participants with complete clinical data, 57.1% (95% CI, 52.% to 61.8%) reported clinical manifestations upon infection. Older individuals were more likely to report symptoms (Figure 2D). Indeed, older age, prior DENV infection, and (marginally) wealth were positively associated with the risk of disease following SARS-CoV-2 infection (Table 4).

< Table 4 >

Prior dengue infection and subsequent COVID-19 risk

Age is likely to confound the association between prior DENV infection and COVID-19 risk, because it is strongly associated with COVID-19 outcomes and the exposure of interest. We tested whether adjusting for age as a continuous variable (model 3) would reduce residual confounding and attenuate the magnitude of association observed in models 1 and 2 (with age as a categorical variable) and model 0 (unadjusted analysis). We obtained similar OR estimates, regardless of the age variable used, for the association between dengue and COVID-19 analyzed with different multiple logistic regression models (Figure 3). OR estimates were slightly larger in adjusted analyses, but the corresponding 95% CIs were wider than in model 0.

< Figure 3 >

DISCUSSION

The association between prior DENV infection and increased risk of clinically apparent COVID-19 is a novel finding with significant public health implications. Two previous studies have found evidence of an opposite association. First, an ecological analysis showed a negative correlation between COVID-19 cases and deaths during the first pandemic wave in Brazil and the number of clinical dengue cases recorded at the municipal level [8]. Second, self-reported prior dengue was associated with reduced mortality in hospitalized COVID-19 patients [9]. We argue that both studies may have severely underestimated DENV exposure, because few infections cause clinical symptoms [24] and <10% of infections are diagnosed on clinical grounds as dengue cases in Brazil [27,28]. DENV seroconversion studies also indicate that the clinical diagnosis of dengue in the Amazon is poorly specific [28,29]. Importantly, there was no association between self-reported history of dengue and DENV seropositivity in a large cross-sectional survey in Rio de Janeiro [30].

Cross-reactive DENV antibodies have been suggested to cause false-positive COVID-19 serology [31,32] and, in theory, could either neutralize SARS-CoV-2 or increase the risk of disease due to antibody-dependent enhancement [10]. Cross-protection conferred by related viruses may be surprisingly complex. For example, prior DENV infection partially protects against Zika, but prior Zika virus infection increases the risk of severe dengue [33]. Other coronaviruses, such as OC43, offer some protection against subsequent severe COVID-19 in children [34]. Contrary to the notion of extensive DENV and SARS-CoV-2 antibody cross-reactivity, all but one pre-pandemic plasmas tested

negative for SARS-CoV-2 although one third of them had anti-DENV IgG antibodies. Moreover, DENV seroconversion events during our study did not result in SARS-CoV-2 seropositivity.

There has been little temporal overlap between dengue and COVID-19 epidemics in South America [3]. Dengue cases peaked during the 2019-20 summer season in the Southern Hemisphere, rainy season in our study site, when COVID-19 transmission was at its nadir. However, the sequential epidemics have affected populations potentially exposed to nutritional deficiencies and other pathogens that can increase the susceptibility to both dengue and COVID-19 [7], in communities with disrupted vector control and surveillance activities due to the COVID-19 pandemic [35]. The elderly are particularly vulnerable to the interacting endemics. Although severe COVID-19 predominates in older persons, while DENV infections are mostly found in children and young adults worldwide [35], DENV appears to infect preferentially older adults in our study population. Indeed, dengue emerged as a major cause of morbidity and mortality in the elderly in some endemic settings [24,25]. Older age groups with chronic comorbidities are more likely to develop severe disease once infected with SARS-CoV-2 or DENV [35].

Our study has many strengths. First, the longitudinal design enables us to discern temporal associations between DENV exposure and the outcomes of interest. Second, serology allows to objectively identify a prior DENV infection, regardless of symptoms. Third, we applied standardized clinical criteria [21] to define clinically apparent COVID-19 upon serologically proven SARS-CoV-2 infection.

The study also has some limitations. First, false-positive DENV serology may arise from yellow fever (YF) vaccination, which is near universal in the Amazon, but we have previously found similar DENV

IgG positivity rates in Amazonians who have or have not received a YF vaccine booster within the past 10 y [29]. Zika, another flavivirus known to circulate in Brazil, is a further source of cross-reactive antibodies. Second, DENV seronegatives at the baseline may have seroconverted during the 2019-20 rainy season, prior to the COVID-19 epidemic, being misclassified as DENV unexposed. Third, retrospective COVID-19 diagnosis is affected by SARS-CoV-2 antibody decay, especially in asymptomatic and mildly symptomatic individuals. Six months after a laboratory-confirmed SARS-CoV-2 infection, antibody detection sensitivity ranges from 33% to 98% [36]. Fourth, RIs do not provide a precise measurement of antibody concentration, for which validated antibody controls would be required. Finally, self-reported COVID-19 symptoms are prone to recall bias and may overlap with those of other common infections, such as malaria. Nevertheless, we provide evidence that individuals with incident malaria are not more likely to have COVID-19 diagnosed at the end of the follow-up.

We characterized clinically apparent COVID-19 and associated risk factors at the time B.1.1.33 was the dominant SARS-CoV-2 lineage in our study site. However, B.1.1.33 is expected to be overtaken by more transmissible variants, such as P.1 [5], with dire clinical and public health consequences [6]. Whether infection with novel variants causes more severe disease, especially in younger patients, remains to be determined by continued clinical and laboratory monitoring.

We conclude that sequential dengue and COVID-19 epidemics impose an extra burden of disease to Amazonian populations, with no evidence that DENV infections cross-protect from SARS-CoV-2 infection and clinical COVID-19.

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Figure legends

Figure 1. **Study flowchart.** Numbers of individuals analyzed for each outcome are indicated, but less observations were included in final multiple logistic regression models (Tables 1, 2 and 3) due to additional missing information.

Figure 2. **Dengue virus (DENV) and SARS-Cov-2 infection and clinically apparent COVID-19 across age groups in Amazonians.** Top panels: (*A*) age-related prevalence (%) of anti-DENV IgG in 2019 and (*B*) age-related prevalence (%) of anti-SARS-CoV2 IgG in 2020 (n = 1,285 for both). Lower panels: (*C*) age-related proportion (%) of study participants had a retrospective diagnosis of clinically apparent COVID-19 during the follow-up (n = 1,281) and (*D*) age-related proportion (%) of SARS-CoV-2-seropositive individuals in 2020 who reported COVID-19-related clinical signs or symptoms (n = 448).

Figure 3. Prior dengue virus (DENV) infection and risk of SARS-CoV-2 infection and clinically apparent COVID-19 in Amazonians. Odds ratios (OR) indicate the magnitude of association between serologically defined DENV infection and each of three outcomes: SARS-CoV-2 infection; clinically apparent COVID-19; and clinically apparent COVID-19 upon serologically documented SARS-CoV-2 infection. OR estimates and their respective 95% confidence intervals (95% CIs) and *P* values were derived from unadjusted analysis ("model 0") and separate mixed-effects multiple logistic regression models in which household-level covariates are entered in the random-effects compartment (models 1 and 3) or fixed-effects compartment (model 2) and age is adjusted as a categorical (models 1 and 2) or continuous variable (model 3). See the main text for further details.

Table 1. Factors associated with dengue virus seropositivity during the 2019 survey, a proxy of past dengue infection in Amazonians.

Covariates		**Model 0 (n = 1285)[a]**			**Model 1 (n = 1281)[b]**			**Model 2 (n = 1281)[c]**		
Individual-level	*n*	OR[d]	(95% CI[e])	*P*	OR[d]	(95% CI[e])	*P*	OR[d]	(95% CI[e])	*P*
Age group										
0-5 y	102	1.00	Reference		1.00	Reference		1.00	Reference	
6-15 y	300	1.90	(1.03, 3.49)	0.039	2.55	(1.25, 5.20)	0.010	2.53	(1.24, 5.15)	0.008
16-30 y	302	3.42	(1.88, 6.20)	<0.0001	5.40	(2.70, 10.83)	<0.0001	5.38	(2.67, 10.86)	<0.0001
31-45 y	299	4.52	(2.50, 8.19)	<0.0001	7.48	(3.68, 15.19)	<0.0001	7.41	(3.63, 15.09)	<0.0001
46-60 y	150	4.56	(2.41, 8.61)	<0.0001	8.19	(3.62, 18.54)	<0.0001	9.87	(4.23, 23.04)	<0.0001

>60 y	132	8.12	(4.25, 15.52)	<0.0001	18.24	(7.67, 43.39)	<0.0001	17.44	(7.29, 41.73)	<0.0001
			P for trend < 0.0001			*P* for trend < 0.0001			*P* for trend < 0.0001	
Sex										
Female	696	1.00	Reference		1.00	Reference		1.00	Reference	
Male	589	1.13	(0.90, 1.42)	0.282	1.26	(0.95, 1.67)	0.107	1.25	(0.94, 1.65)	0.123
Household-level										
Wealth index quintile										
1 (poorest)	258	1.00	Reference			-		1.00	Reference	
2	256	1.22	(0.83, 1.79)	0.303		-		1.21	(0.60, 2.42)	0.592
3	259	2.36	(1.64, 3.42)	<0.0001		-		2.41	(1.20, 4.83)	0.013

4	258	2.24	(1.55, 3.24)	<0.0001		-	2.11	(1.07, 4.14)	0.031
5 (most affluent)	254	1.53	(1.05, 2.23)	0.027		-	1.16	(0.57, 2.38)	0.683
			P for trend < 0.0001			-		*P* for trend = 0.597	
Household size									
1-4 people	783	1.00	Reference			-	1.00	Reference	
6-8 people	415	0.96	(0.75, 1.23)	0.740		-	1.59	(0.99, 2.53)	0.052
9+ people	83	0.41	(0.24, 0.71)	0.002		-	0.85	(0.35, 2.06)	0.714
			P for trend = 0.017			-		*P* for trend = 0.612	

[a]Results for unadjusted analysis are presented under “model 0”. Totals may vary for some covariates due to missing data.

[b]Model 1 corresponds to the following STATA syntax: *melogit outcome indvar1 indvar2 || household: housevar1 housevar2, vce(robust) or.* Note that odds ratios are not calculated for the household-level covariates included in the random-effects component.

[c]Model 2 corresponds to the following STATA syntax: *melogit outcome indvar1 indvar2 housevar1 housevar2 || household:, vce(robust) or.* Odds ratios are calculated for both individual and household-level covariates included in the fixed-effects component.

Table 2. Factors associated with SARS-CoV-2 seropositivity during the 2020 survey, a proxy of recent SARS-CoV-2 infection in Amazonians.

Covariates		**Model 0 (n = 1285)[a]**			**Model 1 (n = 1281)[b]**			**Model 2 (n = 1281)[c]**		
Individual-level	*n*	OR[d]	(95% CI[e])	*P*	OR[d]	(95% CI[e])	*P*	OR[d]	(95% CI[e])	*P*
Age group										
0-5 y	102	1.00	Reference		1.00	Reference		1.00	Reference	
6-15 y	300	1.09	(0.68, 1.74)	0.711	0.86	(0.40, 1.83)	0.695	0.82	(0.39, 1.72)	0.596
16-30 y	302	1.03	(0.65, 1.65)	0.881	0.96	(0.47, 1.99)	0.919	0.96	(0.46, 1.99)	0.915
31-45 y	299	0.92	(0.58, 1.547	0.738	0.62	(0.28, 1.36)	0.235	0.65	(0.30, 1.41)	0.274
46-60 y	150	0.68	(0.40, 1.17)	0.166	0.43	(0.17, 1.11)	0.080	0.41	(0.16, 1.05)	0.063
>60 y	132	0.85	(0.49, 1.46)	0.554	0.91	(0.37, 2.25)	0.844	0.96	(0.39, 2.39)	0.937
			P for trend = 0.061			*P* for trend = 0.139			*P* for trend = 0.243	
Sex										
Female	696	1.00	Reference		1.00	Reference		1.00	Reference	

Male	589	0.92	(0.73, 1.16)	0.469	0.78	(0.55, 1.12)	0.179	0.78	(0.55, 1.12)	0.181
Past dengue										
No	829	1.00	Reference		1.00	Reference		1.00	Reference	
Yes	456	1.17	(0.93, 1.48)	0.187	1.33	(0.85, 2.08)	0.210	1.28	(0.82, 2.00)	0.283
Overnight out of town										
No	928	1.00	Reference		1.00	Reference		1.00	Reference	
Yes	349	1.39	(1.08, 1.80)	0.010	1.27	(0.74, 2.18)	0.392	1.46	(0.84, 2.53)	0.184
Recent malaria										
No	1194	1.00	Reference			-			-	
Yes	83	0.99	(0.62, 1.58)	0.978		-			-	
Household-level										
Wealth index quintile										
1 (poorest)	258	1.00	Reference			-		1.00	Reference	
2	256	1.06	(0.74, 1.52)	0.733		-		1.51	(0.54, 4.19)	0.433
3	259	1.06	(0.74, 1.52)	0.740		-		1.79	(0.62, 5.12)	0.279

4	258	0.68	(0.47, 0.99)	0.047		-	0.75	(0.27, 2.14)	0.595
5 (most affluent)	254	1.13	(0.79, 1.62)	0.494		-	1.83	(0.64, 5.25)	0.261
			P for trend = 0.682			-		*P* for trend = 0.777	
Household size									
1-4 people	783	1.00	Reference			-	1.00	Reference	
6-8 people	415	1.36	(1.06, 1.74)	0.015		-	1.95	(0.93, 4.07)	0.077
9+ people	83	1.90	(1.20, 3.00)	0.006		-	4.27	(0.84, 21.76)	0.081
			P for trend = 0.001			-		*P* for trend = 0.046	

[a]Results for unadjusted analysis are presented under "model 0". Totals may vary for some covariates due to missing data.

[b]Model 1 corresponds to the following STATA syntax: *melogit outcome indvar1 indvar2 || household: housevar1 housevar2, vce(robust) or.* Note that odds ratios are not calculated for household-level covariates included in the random-effects component.

[c]Model 2 corresponds to the following STATA syntax: *melogit outcome indvar1 indvar2 housevar1 housevar2 || household:, vce(robust) or.* Odds ratios are calculated for both individual and household-level covariates included in the fixed-effects component.

Table 3 Factors associated with clinically apparent COVID-19 retrospectively diagnosed during the 2020 survey in Amazonians.

Covariates		**Model 0 (n = 1281)[a]**			**Model 1 (n = 1276)[b]**			**Model 2 (n = 1276)[c]**		
Individual-level	*n*	OR[d]	(95% CI[e])	*P*	OR[d]	(95% CI[e])	*P*	OR[d]	(95% CI[e])	*P*
Age										
0-5 y	102	1.00	Reference		1.00	Reference		1.00	Reference	
6-15 y	298	1.16	(0.58, 2.31)	0.668	1.20	(0.37, 3.88)	0.761	1.23	(0.38, 4.00)	0.735
16-30 y	301	2.23	(1.15, 4.31)	0.017	3.40	(0.98, 11.84)	0.054	3.65	(1.03, 12.96)	0.045
31-45 y	299	2.37	(1.23, 4.59)	0.010	3.05	(0.95, 9.78)	0.060	3.43	(1.05, 11.23)	0.042
46-60 y	149	2.05	(1.00, 4.21)	0.050	3.16	(0.88, 11.38)	0.078	3.45	(0.95, 12.49)	0.059
>60 y	132	2.30	(1.11, 4.75)	0.024	6.52	(1.77, 24.03)	0.005	7.82	(2.13, 28.67)	0.002
			P for trend = 0.001			*P* for trend < 0.0001			*P* for trend < 0.0001	
Sex										
Female	692	1.00	Reference		1.00	Reference		1.00	Reference	

Male	588	0.95	(0.72, 1.25)	0.725	0.85	(0.55, 1.32)	0.474	0.86	(0.56, 1.32)	0.489
Past dengue										
No	825	1.00	Reference		1.00	Reference		1.00	Reference	
Yes	456	1.54	(1.16, 2.03)	0.002	1.86	(1.05, 3.29)	0.033	1.81	(1.06, 3.08)	0.029
Overnight out of town										
No	927	1.00	Reference		1.00	Reference		1.00	Reference	
Yes	349	1.30	(0.96, 1.75)	0.086	1.27	(0.67, 2.38)	0.462	1.22	(0.66, 2.27)	0.518
Recent malaria										
No	1193	1.00	Reference			-			-	
Yes	83	1.20	(0.71, 2.05)	0.494		-			-	
Household-level										
Wealth index quintile										
1 (poorest)	258	1.00	Reference			-		1.00	Reference	
2	253	1.17	(0.74, 1.85)	0.494		-		1.38	(0.48, 4.01)	0.550
3	259	1.58	(1.02, 2.45)	0.039		-		2.72	(0.91, 8.19)	0.074

4	257	0.84	(0.52, 1.35)	0.473		-	0.75	(0.25, 2.28)	0.611
5 (most affluent)	254	1.96	(1.27, 3.01)	0.002		-	3.20	(1.05, 9.81)	0.041
			P for trend = 0.024			-		*P* for trend = 0.259	
Household size									
1-4 people	782	1.00	Reference			-	1.00	Reference	
6-8 people	415	1.26	(0.94, 1.69)	0.121		-	2.63	(1.22, 5.64)	0.016
9+ people	83	1.40	(0.82, 2.40)	0.211		-	5.04	(1.25, 20.27)	0.023
			P for trend = 0.073			-		*P* for trend < 0.0001	

[a]Results for unadjusted analysis are presented under "model 0". Totals may vary for some covariates due to missing data.

[b]Model 1 corresponds to the following STATA syntax: *melogit outcome indvar1 indvar2 || household: housevar1 housevar2*, *vce(robust) or.* Note that odds ratios are not calculated for the the household-level covariates included in the random-effects component.

[c]Model 2 corresponds to the following STATA syntax: *melogit outcome indvar1 indvar2 housevar1 housevar2 || household:*, *vce(robust) or.* Odds ratios are calculated for individual and household-level covariates included in the fixed-effects component.

Table 4. Factors associated with clinically apparent COVID-19 in Amazonians with serological evidence of SARS-CoV-2 infection during the 2020 survey

Covariates		**Model 0 (n = 448)[a]**			**Model 1 (n = 448)[b]**			**Model 2 (n = 448)[c]**		
Individual-level	*n*	OR[d]	(95% CI[e])	*P*	OR[d]	(95% CI[e])	*P*	OR[d]	(95% CI[e])	*P*
Age										
0-5 y	37	1.00	Reference		1.00	Reference		1.00	Reference	
6-15 y	113	1.14	(0.52, 2.51)	0.742	1.49	(0.47, 4.76)	0.498	1.44	(0.47, 4.43)	0.520
16-30 y	111	3.42	(1.56, 7.53)	0.002	5.68	(1.47, 21.99)	0.012	5.52	(1.47, 20.64)	0.011
31-45 y	103	4.84	(2.16, 10.84)	<0.0001	7.39	(2.10, 26.01)	0.002	7.24	(2.16, 24.33)	0.001
46-60 y	41	7.41	(2.70, 20.34)	<0.0001	20.81	(3.76, 115.30)	0.001	13.20	(2.77, 63.00)	0.001
>60 y	43	5.38	(2.06, 14.02)	0.001	14.69	(2.86, 75.49)	0.001	10.12	(2.21, 46.11)	0.003
			P for trend < 0.0001			*P* for trend <0.0001			*P* for trend < 0.0001	
Sex										
Female	248	1.00	Reference		1.00	Reference		1.00	Reference	

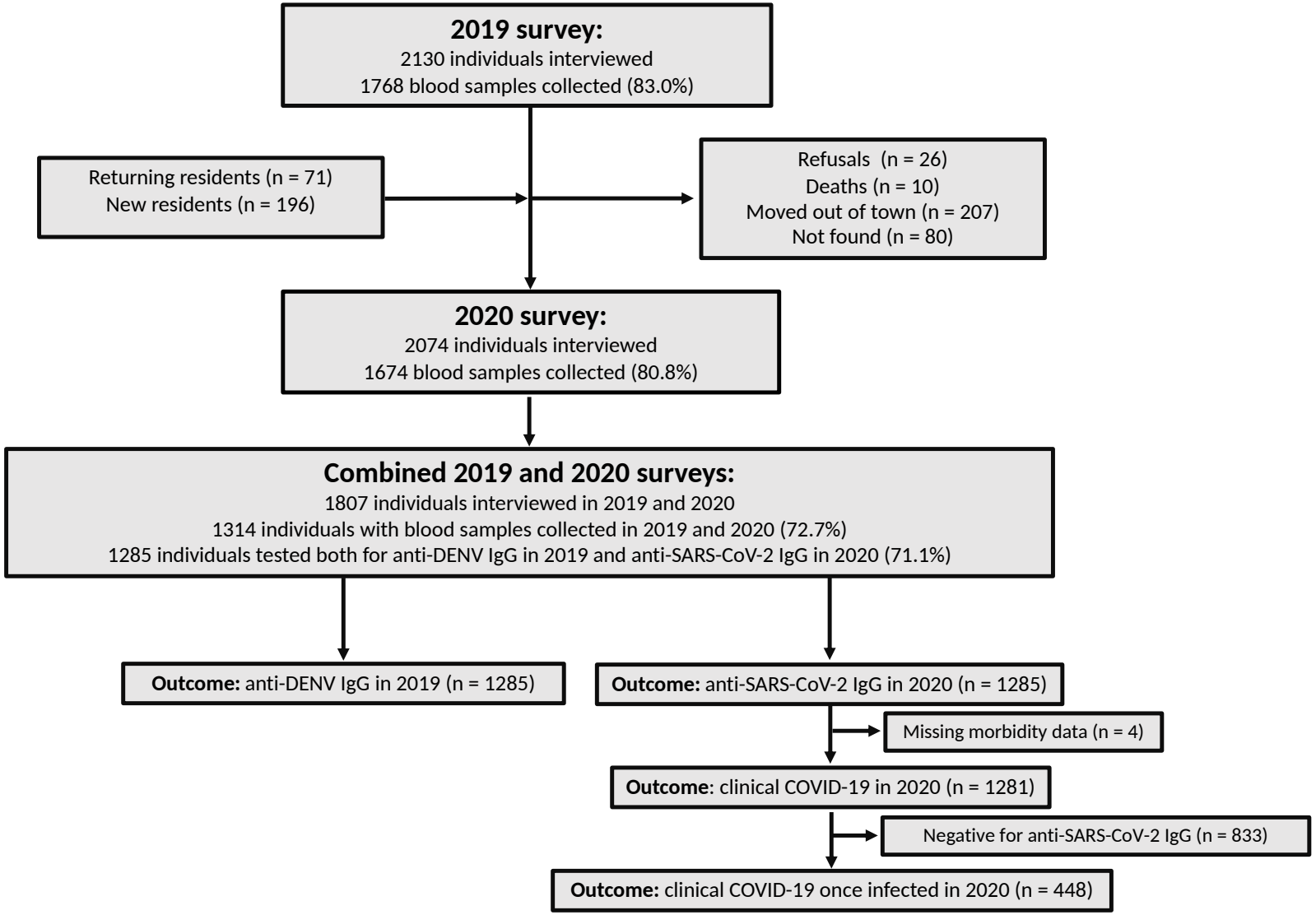
Male	200	1.03	(0.70, 1.50)	0.891	0.98	(0.56, 1.82)	0.976	1.07	(0.61, 1.87)	0.809
Past dengue										
No	270	1.00	Reference		1.00	Reference		1.00	Reference	
Yes	178	1.74	(1.18, 2.57)	0.006	2.04	(1.08, 3.87)	0.028	1.98	(1.05, 3.74)	0.035
Overnight out of town										
No	305	1.00	Reference			-			-	
Yes	142	0.99	(0.66, 1.47)	0.947		-			-	
Recent malaria										
No	418	1.00	Reference			-			-	
Yes	29	1.47	(0.66, 3.23)	0.343		-			-	
Household-level										
Wealth index quintile										
1 (poorest)	92	1.00	Reference			-		1.00	Reference	
2	92	1.24	(0.70, 2.22)	0.461		-		1.04	(0.36, 3.02)	0.947
3	96	2.07	(1.16, 3.72)	0.014		-		1.79	(0.64, 5.01)	0.265

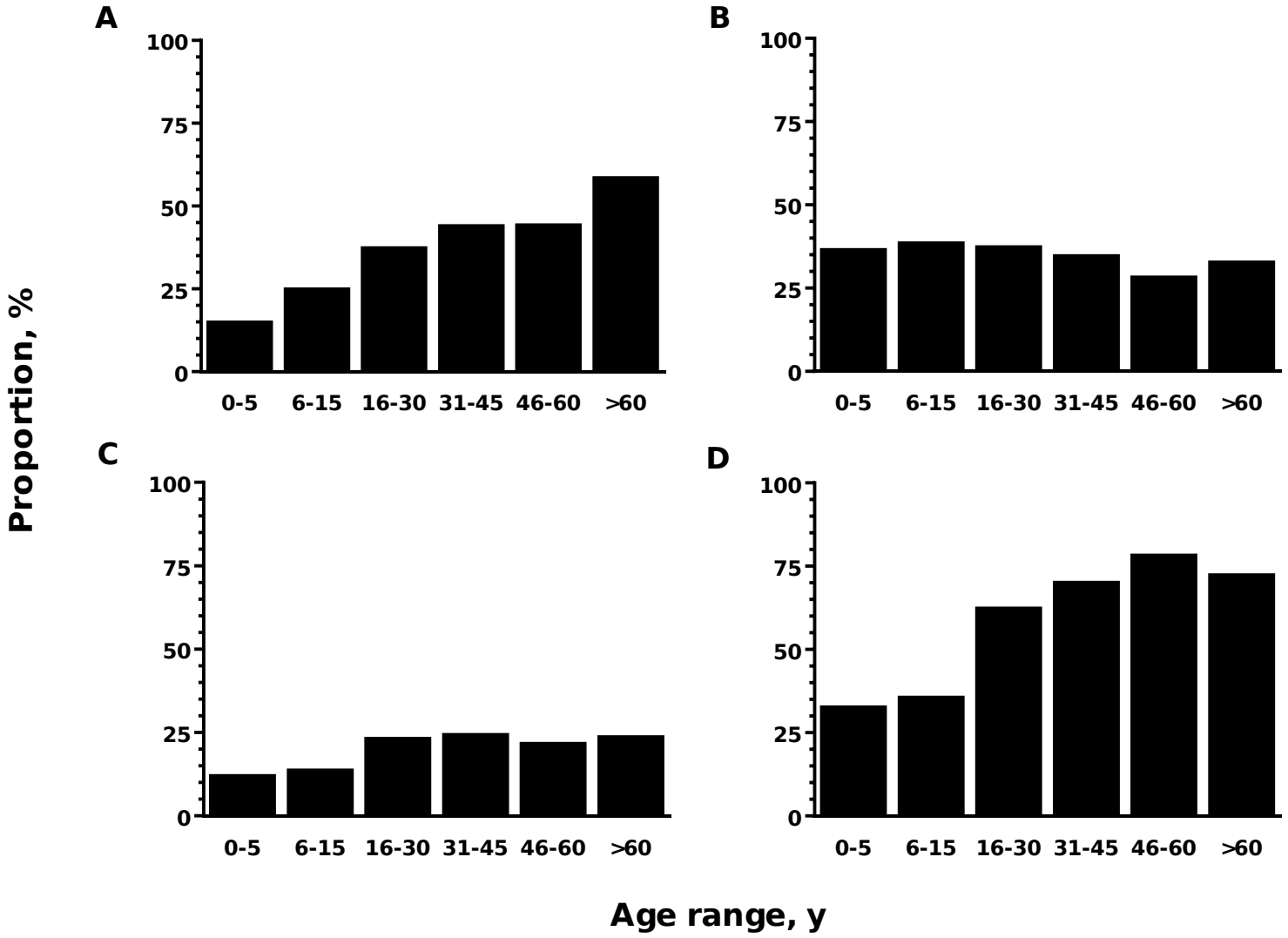
4	70	1.26	(0.68, 2.35)	0.466		-	0.92	(0.30, 2.88)	0.844
5 (most affluent)	98	2.98	(1.63, 5.42)	<0.0001		-	3.06	(0.97, 9.63)	0.056
			P for trend < 0.0001			-		*P* for trend = 0.081	
Household size									
1-4 people	248	1.00	Reference			-		-	
6-8 people	161	0.96	(0.64, 1.43)	0.854		-		-	
9+ people	39	0.76	(0.37, 1.49)	0.427		-		-	
			P for trend = 0.502			-		-	

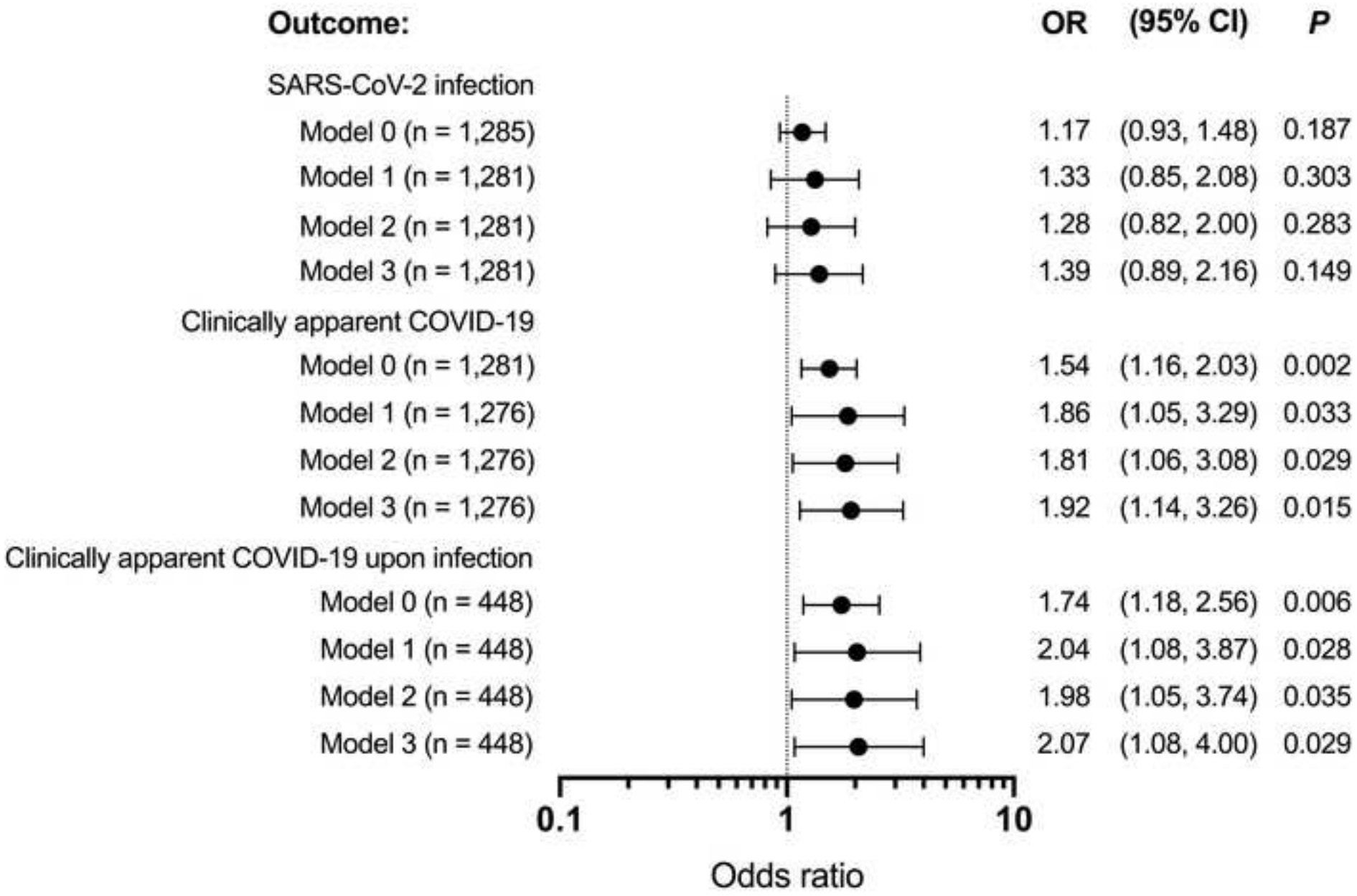
[a]Results for unadjusted analysis are presented under "model 0". Totals may vary for some covariates due to missing data.

[b]Model 1 corresponds to the following STATA syntax: *melogit outcome indvar1 indvar2 || household: housevar1 housevar2, vce(robust) or.* Note that odds ratios are not calculated for the random-effects component.

[c]Model 2 corresponds to the following STATA syntax: *melogit outcome indvar1 indvar2 housevar1 housevar2 || household:, vce(robust) or.* Odds ratios are calculated for individual and household-level covariates included in the fixed-effects component.


2019 survey:
2130 individuals interviewed
1768 blood samples collected (83.0%)
Returning residents (n = 71)
New residents (n = 196)
Refusals (n = 26)
Deaths (n = 10)
Moved out of town (n = 207)
Not found (n = 80)
2020 survey:
2074 individuals interviewed
1674 blood samples collected (80.8%)
Combined 2019 and 2020 surveys:
1807 individuals interviewed in 2019 and 2020
1314 individuals with blood samples collected in 2019 and 2020 (72.7%)
1285 individuals tested both for anti-DENV IgG in 2019 and anti-SARS-CoV-2 IgG in 2020 (71.1%)
Outcome: anti-DENV IgG in 2019 (n = 1285)
Outcome: anti-SARS-CoV-2 IgG in 2020 (n = 1285)
Missing morbidity data (n = 4)
Outcome: clinical COVID-19 in 2020 (n = 1281)
Negative for anti-SARS-CoV-2 IgG (n = 833)
Outcome: clinical COVID-19 once infected in 2020 (n = 448)


A
B
C
D
100
75
50
25
0
0-5
6-15
16-30
31-45
46-60
>60
Proportion, %
Age range, y


Outcome:
OR
(95% CI)
P
SARS-CoV-2 infection
Model 0 (n = 1,285)
1.17
(0.93, 1.48)
0.187
Model 1 (n = 1,281)
1.33
(0.85, 2.08)
0.303
Model 2 (n = 1,281)
1.28
(0.82, 2.00)
0.283
Model 3 (n = 1,281)
1.39
(0.89, 2.16)
0.149
Clinically apparent COVID-19
Model 0 (n = 1,281)
1.54
(1.16, 2.03)
0.002
Model 1 (n = 1,276)
1.86
(1.05, 3.29)
0.033
Model 2 (n = 1,276)
1.81
(1.06, 3.08)
0.029
Model 3 (n = 1,276)
1.92
(1.14, 3.26)
0.015
Clinically apparent COVID-19 upon infection
Model 0 (n = 448)
1.74
(1.18, 2.56)
0.006
Model 1 (n = 448)
2.04
(1.08, 3.87)
0.028
Model 2 (n = 448)
1.98
(1.05, 3.74)
0.035
Model 3 (n = 448)
2.07
(1.08, 4.00)
0.029
0.1
1
10
Odds ratio