Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic

Lewis F. Buss[1]*, Carlos A. Prete Jr.[2]*, Claudia M. M. Abrahim[3]*, Alfredo Mendrone Jr.[4,5]*,
Tassila Salomon[6,7]*, Cesar de Almeida-Neto[4,5], Rafael F. O. França[8], Maria C. Belotti[2],
Maria P. S. S. Carvalho[3], Allyson G. Costa[3], Myuki A. E. Crispim[3], Suzete C. Ferreira[4,5],
Nelson A. Fraiji[3], Susie Gurzenda[9], Charles Whittaker[10], Leonardo T. Kamaura[11], Pedro L. Takecian[11],
Pedro da Silva Peixoto[11], Marcio K. Oikawa[12], Anna S. Nishiya[4,5], Vanderson Rocha[4,5],
Nanci A. Salles[4], Andreza Aruska de Souza Santos[13], Martirene A. da Silva[3], Brian Custer[14,15],
Kris V. Parag[16], Manoel Barral-Netto[17], Moritz U. G. Kraemer[18], Rafael H. M. Pereira[19],
Oliver G. Pybus[18], Michael P. Busch[14,15], Márcia C. Castro[9], Christopher Dye[18], Vitor H. Nascimento[2],
Nuno R. Faria[1,16,18]†, Ester C. Sabino[1]†

[1]Departamento de Molestias Infecciosas e Parasitarias and Instituto de Medicina Tropical da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil. [2]Departamento de Engenharia de Sistemas Eletrônicos, Escola Politécnica da Universidade de São Paulo, São Paulo, Brazil. [3]Fundação Hospitalar de Hematologia e Hemoterapia do Amazonas, Manaus, Brazil. [4]Fundação Pró-Sangue–Hemocentro de São Paulo, São Paulo, Brazil. [5]Laboratório de Investigação Médica em Patogênese e Terapia dirigida em Onco-Imuno-Hematologia (LIM-31), Departamento de Hematologia, Hospital das Clínicas HCFMUSP, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil. [6]Fundação Hemominas–Fundação Centro de Hematologia e Hemoterapia de Minas Gerais, Belo Horizonte, Brazil. [7]Faculdade Ciências Médicas de Minas Gerais, Belo Horizonte, Brazil. [8]Department of Virology and Experimental Therapy, Institute Aggeu Magalhaes, Oswaldo Cruz Foundation, Recife, Brazil. [9]Department of Global Health and Population, Harvard T. H. Chan School of Public Health, Boston, MA, USA. [10]Department of Infectious Disease Epidemiology, School of Public Health, Imperial College London, London, UK. [11]Institute of Mathematics and Statistics, University of São Paulo, São Paulo, Brazil. [12]Center of Mathematics, Computing and Cognition–Universidade Federal do ABC, São Paulo, Brazil. [13]Oxford School of Global and Area Studies, Latin American Centre, University of Oxford, Oxford, UK. [14]Vitalant Research Institute, San Francisco, CA, USA. [15]University of California, San Francisco, CA, USA. [16]MRC Centre for Global Infectious Disease Analysis, J-IDEA, Imperial College London, London, UK. [17]Instituto Gonçalo Moniz–Fundação Oswaldo Cruz (Fiocruz), Salvador, Brazil. [18]Department of Zoology, University of Oxford, Oxford, UK. [19]Institute for Applied Economic Research–Ipea, Brasília, Brazil.

*These authors contributed equally to this work.

†Corresponding author. Email: sabinoec@usp.br (E.C.S.); nfaria@ic.ac.uk (N.R.F.)

SARS-CoV-2 spread rapidly in the Brazilian Amazon and the attack rate there is an estimate of the final size of a largely unmitigated epidemic. We use a convenience sample of blood donors to show that by June, one month after the epidemic peak in Manaus, capital of Amazonas state, 44% of the population had detectable IgG antibodies. Correcting for cases without a detectable antibody response and antibody waning, we estimate a 66% attack rate in June, rising to 76% in October. This is higher than in São Paulo, in southeastern Brazil, where the estimated attack rate in October is 29%. These results confirm that, when poorly controlled, COVID-19 can infect a high fraction of the population causing high mortality.

Brazil has experienced one of the world's most rapidly-growing COVID-19 epidemics, with the Amazon being the worst hit region (*1*). Manaus is the capital and largest metropolis in the Amazon, with a population of over two million and population density of 158 inhabitants/km². The first SARS-CoV-2 case in Manaus was confirmed on 13th March 2020 (*2*) and was followed by an explosive epidemic, peaking in early May with 4.5-fold excess mortality (*3*). This was followed by a sustained drop in new cases despite relaxation of non-pharmaceutical interventions (NPIs). The prevalence of antibodies against SARS-CoV-2 is an estimate of the attack rate in Manaus and provides a data-based estimate of

the extent of COVID-19 spread in the absence of effective mitigation.

Given a basic reproduction number (R_0) of 2.5–3.0 for Amazonas state, (see (*4*)), the expected attack rate during an unmitigated epidemic in a homogeneously mixed population is 89–94% (*5*). When the percentage of infected people exceeds the herd immunity threshold of 60–67% [$100 \times (1 - 1/R_0)$], each infection generates fewer than one secondary case (case reproduction number, $R_t < 1$) and incidence declines. The goal of this study was to measure the SARS-CoV-2 attack rate in Manaus and to explore whether the epidemic was contained ($R_t < 1$) because infection reached the herd

immunity threshold, or because of other factors such as behavioral changes and NPIs. We compare data from Manaus with findings from Sao Paulo, where the first Brazilian COVID-19 cases were detected (*2*, *6*) and the rise and fall in mortality were slower and more protracted.

We used a chemiluminescence assay (CIMA) that detects IgG antibody against the SARS-CoV-2 nucleocapsid (N) protein (Abbott, Chicago, USA). To infer the attack rate from antibody test positivity we need to account for the sensitivity and specificity of the test (*7*). The specificity of the CIMA is high (>99.0%) (*8*–*10*), but previous high (>90.0%) sensitivity estimates (*8*, *10*)) may not apply to blood donor screening (*11*, *12*) for two reasons. First, most SARS-CoV-2 infections in blood donors are asymptomatic and weaker antibody responses in asymptomatic disease (*13*) may lead to a lower initial seroconversion rate (i.e., more "serosilent" infections). Second, due to antibody waning, sensitivity falls over time (*14*), such that test positivity increasingly underestimates the true attack rate.

We used a variety of clinical samples at different time points to gain insight into the dynamics of the anti-N IgG detected by the Abbott CIMA (Fig. 1). In samples from COVID-19 hospitalized patients collected at 20-33 days post symptom onset, reflecting high disease severity and optimal timing of blood collection, sensitivity was 91.8% (*95*% confidence interval, CI, 80.8% to 96.8%), suggesting that ~8% of severe convalescent cases do not develop detectable antibodies. Among a cohort of symptomatic cases with mild disease also tested in the early convalescent period, sensitivity fell to 84.5% (*95*% CI 78.7% to 88.9%) – indicating initial seroconversion is lower in milder cases. In samples drawn later (50 to 131 days) from the same mild disease cohort, sensitivity was lower still (80.4%, *95*% CI 71.8% to 86.8%), reflecting antibody waning. Indeed, in a subset of 104 patients with two consecutive blood draws, the signal-to-cutoff (S/C) declined over the period observed (Fig. 1B) and among 88 individuals with a positive reading at the first time point, the mean rate of decay was $-0.9 \log_2$ S/C units every 100 days (*95*% CI -1.1 to -0.75), equating to a half-life of 106 days (*95*% CI 89 to 132 days) (Fig. 1C).

Finally, we tested 1,000 blood donations given in São Paulo in July 2020 in parallel using a second high-specificity (>99.0% (*15*)) immunoassay less prone to antibody waning (*14*). (Roche Elecsys, Rotkreuz, Switzerland). One-hundred and three samples were positive using the Abbott CIMA and an additional 30 were positive using the Roche assay. Assuming all 133 samples were true positives the sensitivity of the Abbott N IgG assay was 77.4% (*95*% CI 69.6% to 83.7%) on asymptomatic blood donor samples. As samples in July were donated four months into the ongoing epidemic in São Paulo, the false negatives using the Abbott assay include both cases that did not initially seroconvert, as well as past

infections that had subsequently seroreverted.

Because specificity was high, with only one false-positive result in 821 pre-epidemic donations from Manaus (Fig. 1A), we also attempted to improve assay performance by reducing the threshold for a positive result from 1.4 S/C (as per the manufacturer) to 0.4 S/C. This resulted in 27 false-positives and a specificity of 96.7%, but substantially improved sensitivities at this threshold as shown in Fig. 1A and table S1.

In order to estimate the proportion of the population with IgG antibodies against SARS-CoV-2, we used a convenience sample of routine blood donations made at the Fundação Pró-Sangue blood bank in São Paulo and the Fundação Hospitalar de Hematologia e Hemoterapia do Amazonas (HEMOAM) in Manaus. The monthly sample size and sampling dates, spanning February to October, are shown in table S2.

The prevalence of SARS-CoV-2 antibodies in February and March was low (<1%) in both São Paulo and Manaus. This is consistent with the timing of the first confirmed cases that were diagnosed on 13th March in Manaus, and on the 25th of February in São Paulo (*2*). In Manaus, after adjustment for the sensitivity and specificity of the test (but not antibody waning), and re-weighting for age and sex, the prevalence of SARS-CoV-2 IgG antibodies was 4.8% (*95*% CI 3.3% to 6.8%) in April, 44.5% (*95*% CI 39.2% to 50.0%) in May, reaching a peak of 52.5% (47.6% to 57.5%) in June (Fig. 2 and table S2). The increasing seroprevalence closely followed the curve of cumulative deaths. In São Paulo the prevalence of SARS-CoV-2 IgG in blood donors also increased steadily, reaching 13.6% (*95*% CI 12.0% to 8.1%) in June.

Between June and October, the effect of seroreversion became apparent in both cities. In Manaus, following the peak antibody prevalence in June, the proportion of blood donors that tested positive fell steadily to 25.8% in October. Excluding extreme negative samples (<0.4 S/C), the median assay signal fell steadily from May: 3.9 (May), 3.5 (June), 2.3 (July), 1.7 (August), 1.4 (September), and 1.3 (October) (Fig. 2B). Similarly, in São Paulo antibody prevalence remained stable between June and October, while the number of daily COVID-19 deaths also remained relatively stable, reflecting a balance between antibody waning from infections earlier in the outbreak and seroconversions following recent infections (Fig. 2C).

In Manaus, the effect of antibody waning on apparent prevalence was partially ameliorated by reducing the threshold for a positive result from 1.4 S/C to 0.4 S/C and correcting for the resulting increased false-positive rate. However, the results in São Paulo were largely unchanged by this correction (Fig. 2 and table S2).

We further correct for seroreversion with a model-based

approach (see supplementary materials). Briefly, we assume that the probability of remaining seropositive decays exponentially from the time of recovery. We estimate the decay rate and the proportion of patients that serorevert using the seroprevalence data from Manaus to find the minimum decay rate that minimizes the number of new cases in July and August while avoiding decreases in prevalence – i.e., assuming there were few cases in Manaus in July and August and changes in seroprevalence were due mainly to waning antibodies. The results of these corrections are shown in Fig. 2 and table S2. After adjusting for seroreversion, we find that cumulative incidence in Manaus may have reached as high as 66.2% (95% CI 61.5% to 80.1%) in July and 76.0% (95% CI 66.6% to 97.9%) in October. Although this is the minimum prevalence estimate allowed by the exponential decay model, and should therefore be conservative, in the absence of an accepted approach to account for seroreversion, these results should be interpreted with caution. The reliability of this estimate depends on the validity of the exponential decay assumption.

To calculate infection fatality ratios (IFRs) we used the age-sex and sensitivity-specificity adjusted prevalence in June, as this was following the epidemic peak in Manaus, but before significant seroreversion. In Manaus, the IFRs were 0.17% and 0.28%, considering PCR confirmed COVID-19 deaths and probable COVID-19 deaths based on syndromic identification, respectively; whereas in São Paulo, the global IFRs were 0.46% and 0.72%, respectively. The difference may be explained by an older population structure in São Paulo (fig. S1A). Supporting this inference, the age-specific IFRs were similar in the two cities, and similar to estimates based on data from China (16) (fig. S1B) and a recent systematic review (17). We also obtained similar age-specific IFRs using the seroreversion-corrected prevalence estimates from October (fig. S1).

Blood donors may not be representative of the wider population. The eligible age range for blood donation in Brazil (16 - 69yr), as well as sex distributions in donors, are different from the underlying populations in both cities (fig. S2). Re-weighting our estimates for age and sex (Fig. 2 and table S2) resulted in a slight reduction in prevalence, particularly in Manaus, where men were overrepresented among donors and also had a higher seroprevalence (fig. S3). Self-reported ethnicity was similar in donors to the census populations (fig. S2). The median income in blood donors' census tracts of residence was marginally higher than a population-weighted average for both cities (fig. S4). Regarding the spatial distribution of donors, there was a similar antibody prevalence across different regions sampled in both cities (fig. S5), and we achieved good geographic coverage in both cities (see supplementary materials and fig. S5).

Because potential donors are deferred if they have a positive SARS-CoV-2 PCR or clinical diagnosis of COVID-19, increasing access to testing might have reduced the pool of eligible donors through time. However, only 2.7% of residents in Manaus and 8.5% in São Paulo reported having a PCR test performed by September (fig. S6). As such, changing access to testing is unlikely to have been important. Considering these factors together, we suggest that our results can be cautiously extrapolated to the population aged 16-69yr in Manaus and São Paulo. Within this group, blood donors may underestimate the true exposure to SARS-CoV-2 due to a potentially higher socioeconomic profile, deferral of symptomatic donors, and the possibility of greater health awareness and engagement among those that donate blood. However, it is likely that seroprevalence in children and older adults is lower.

Our results show that between 44% and 66% of the population of Manaus was infected with SARS-CoV-2 by July, following the epidemic peak there. The lower estimate does not account for false-negative cases or antibody waning; the upper estimate accounts for both. R_t fell < 1 (fig. S7) in late April when cumulative infections were between 5% and 46% of the population. NPIs (table S3) were implemented in mid to late March when physical distancing also increased (fig. S8). It is likely that these factors worked in tandem with growing population immunity to contain the epidemic. Transmission has since continued in Manaus, albeit at a lower level than in April-May (Fig. 2 and fig. S7). From the second week of August there has been a small increase in the number of cases (18) which, at the time of writing, has begun to decline. Consequently, the attack rate rose to 76% in October. This remains lower than predicted in a homogeneously-mixed population with no mitigation strategies (~90%). Homogeneous mixing is unlikely to be a valid assumption (19) and behavioral change and NPIs may explain why the estimated final epidemic size has not yet reached 89–94% as expected for R_0 values between 2.5–3.0 (4).

By 1st October, Manaus recorded 2,642 (1,193/million inhabitants [mil]) COVID-19 confirmed deaths and 3,789 (1,710/mil) severe acute respiratory syndrome deaths; São Paulo recorded 12,988 (1,070/mil) and 20,063 (1,652/mil), respectively. The cumulative mortality proportions were similar in both cities and high compared to other locations – e.g., United Kingdom (620/mil), France (490/mil) or the United States (625/mil), as of Oct 1st (20). The different attack rates in Manaus and São Paulo (76% versus 29% of people infected), despite similar overall mortality rates, are due to the higher IFR in São Paulo. The age-standardized mortality ratio was 2.0 comparing observed deaths in Manaus to those expected projecting the age-specific mortality in São Paulo on the age structure of Manaus. The R_0 was similar in the two cities (fig. S7) but cases and deaths in-

creased then decreased more slowly in São Paulo than Manaus where the rise and fall was more abrupt (fig. S7). The lower attack rate in São Paulo is partly explained by the larger population size (2.2 versus 12.2 million inhabitants). As population size increases, the time to reach a given attack rate also increases (*21*).

The attack rate in Manaus is higher than estimates based on seroprevalence studies conducted in Europe and North America (*8, 22, 23*), and recent results from Kenyan blood donors (*24*). A similarly high seroprevalence (~50%) was observed in slums in Mumbai, India (*25*). In Brazil, one population-based serosurvey in São Paulo (*26*) found a similar prevalence to our study (26.2% versus 28.8% in blood donors, in October). In Manaus, a lower seroprevalence (14%, in June) was found in a random household sample of 250 people (*1*). But this study was not powered at the city level and used the lower sensitivity Wondfo (*27*) rapid test. As such, the results are not be directly comparable.

Future investigations should be conducted to investigate what accounted for such extensive transmission of SARS-CoV-2 in Manaus. Possible explanations include socioeconomic conditions, household crowding (*28*), limited access to clean water, and reliance on high-transmission risk boat travel (*1*) in which over-crowding results in accelerated contagion, similar to that seen on cruise ships (*29*). The young mobile population with potentially low pre-existing immunity to SARS-CoV-2 (*30*), as well as the early circulation of multiple virus lineages introduced from multiple locations may have contributed to the large scale of the outbreak.

In conclusion, our data show that >70% of the population has been infected in Manaus approximately seven months after the virus first arrived in the city. This is above the theoretical herd immunity threshold. However, prior infection may not confer long-lasting immunity (*30, 31*). Indeed, we observed rapid antibody waning in Manaus, consistent with other reports that have shown signal waning on the Abbott IgG assay (*14, 32*). However, other commercial assays, with different designs or targeting different antigens, have more stable signal (*14*), and there is evidence for a robust neutralizing antibody response several months out from infection (*33*). Rare reports of reinfection have been confirmed (*34*), but the frequency of its occurrence remains an open question (*35*). Manaus represents a "sentinel" population, giving us a data-based indication of what may happen if SARS-CoV-2 is allowed to spread largely unmitigated. Further seroepidemiological, molecular and genomic surveillance studies in the region are required urgently to determine the longevity of population immunity, the correlation with the observed antibody waning and the diversity of circulating lineages. Monitoring of new cases and the ratio of local versus imported cases will also be vital to understand the extent to which population immunity might prevent future transmission, and the potential need for booster vaccinations to bolster protective immunity.

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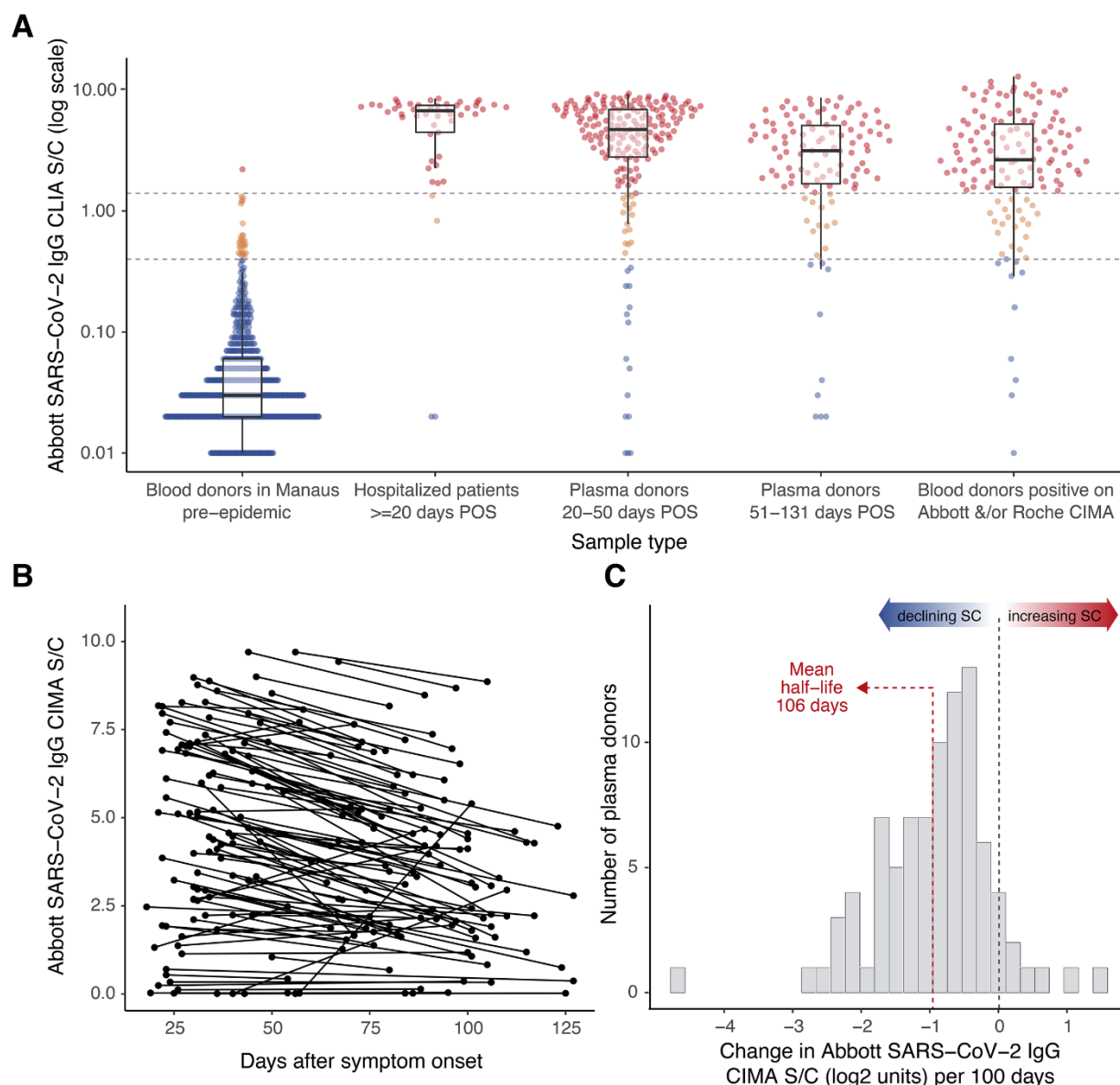
Fig. 1. Abbott SARS-CoV-2 N IgG chemiluminescence assay performance and antibody dynamics in different clinical samples. (**A**) Signal-to-cutoff (S/C) values using the Abbott chemiluminescence assay (CIMA) in the following clinical samples (from left to right): 821 routine blood donation samples from Manaus in February 2020, > 1 month prior to the first notified case in the city; 49 samples collected at 20-33 days after symptom onset from SARS-CoV-2-PCR positive patients in São Paulo requiring hospital care; 193 patients in São Paulo with PCR-confirmed symptomatic COVID-19 not requiring hospital care, with plasma donation samples taken in the early convalescent period; 107 samples from the same non-hospitalized plasma donor cohort from the late convalescent period; 133 samples that tested positive on either the Abbott CIMA or the Roche Elecsys assay out of 1,000 routine blood donations collected in July 2020 and tested in parallel from the Fundação Pró-Sangue blood center (São Paulo). Upper dashed line - manufacturer's threshold for positive result of 1.4 S/C; lower dashed line - alternative threshold of 0.4 S/C. Box plots of Abbott IgG CIMA S/C central line is the median; upper and lower hinges are the 25th and 75th centiles, respectively; whiskers show the range, extending to a maximum of 1.5 times interquartile range from hinge. (**B**) S/C values of the Abbott CIMA for 104 convalescent plasma donors who were sampled at two different times. (**C**) Histogram of the slopes among 88 individuals shown in (B) that tested positive (>1.4 S/C) at the first time point. POS = post onset of symptoms.
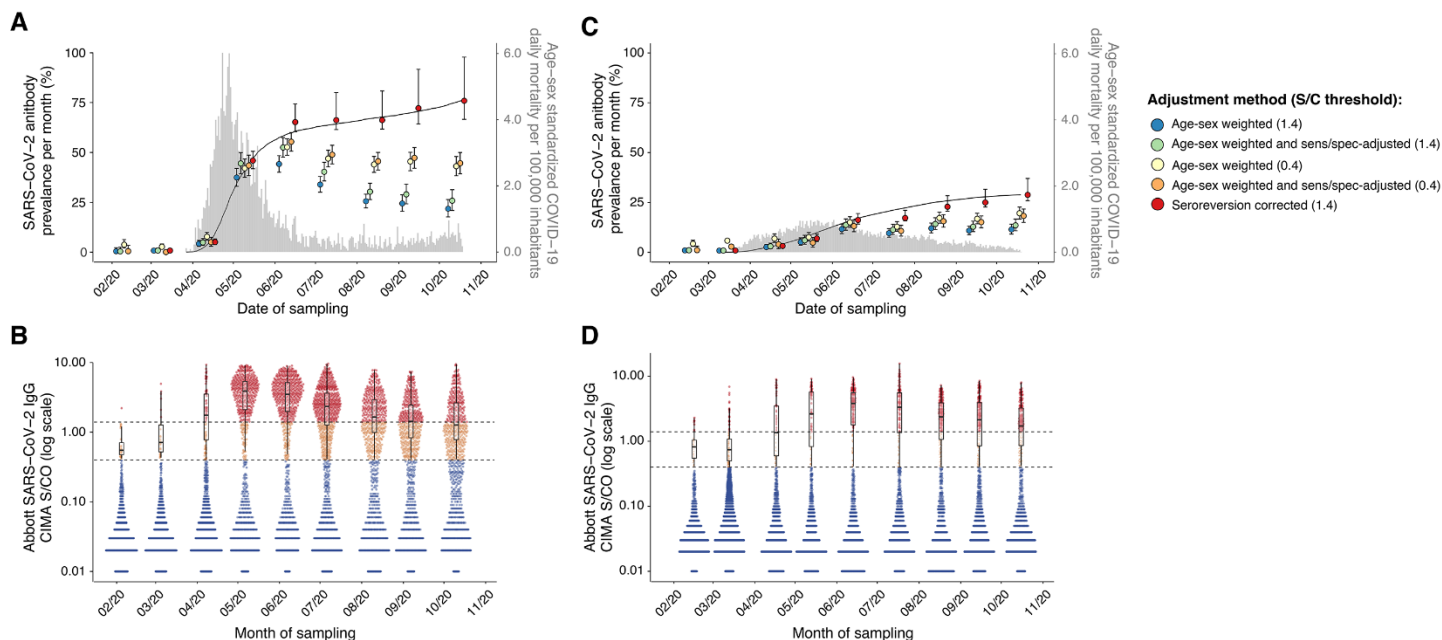
Fig. 2. Monthly antibody prevalence and signal-to-cutoff (S/C) reading in Manaus and São Paulo. (A and C) SARS-CoV-2 antibody prevalence estimates in Manaus (A) and São Paulo (C) with a range of corrections, from left to right: re-weighting positive tests, at positivity threshold of 1.4 S/C, to the age-sex distribution of each city; further correcting for sensitivity and specificity at this assay threshold; re-weighting positive tests at for age and sex at a reduced threshold of 0.4 S/C; correcting for sensitivity and specificity at this threshold; finally correcting for seroreversion. Error bars are 95% confidence intervals. Grey bars are standardized daily mortality using confirmed COVID-19 deaths from the SIVEP-Gripe (https://covid.saude.gov.br/) notification system and standardized by the direct method using the total projected Brazilian population for 2020 as reference. Black lines are rescaled cumulative deaths, such that the maximum is set to the maximum seroprevalence estimate for each city. Mortality data are plotted according to the date of death. (B and D) Distribution of S/C values over the seven monthly samples are shown for Manaus (B) and São Paulo (D). Each point represents the S/C reading for a single donation sample. Upper dashed line - manufacturer's threshold (1.4 S/C units); lower dashed line - alternative threshold (0.4 S/C units); black boxplots show the median (central lines), interquartile range (hinges) and range extending to 1.5 times the interquartile range from each hinge (whiskers) of S/C values above 0.4 (i.e., excluding very low and likely true-negative values).

Science

Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic

Lewis F. Buss, Carlos A. Prete Jr, Claudia M. M. Abrahim, Alfredo Mendrone Jr, Tassila Salomon, Cesar de Almeida-Neto, Rafael F. O. França, Maria C. Belotti, Maria P. S. S. Carvalho, Allyson G. Costa, Myuki A. E. Crispim, Suzete C. Ferreira, Nelson A. Fraiji, Susie Gurzenda, Charles Whittaker, Leonardo T. Kamaura, Pedro L. Takecian, Pedro da Silva Peixoto, Marcio K. Oikawa, Anna S. Nishiya, Vanderson Rocha, Nanci A. Salles, Andreza Aruska de Souza Santos, Martirene A. da Silva, Brian Custer, Kris V. Parag, Manoel Barral-Netto, Moritz U. G. Kraemer, Rafael H. M. Pereira, Oliver G. Pybus, Michael P. Busch, Márcia C. Castro, Christopher Dye, Vitor H. Nascimento, Nuno R. Faria and Ester C. Sabino

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