Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence

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After initially containing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), many European and Asian countries had a resurgence of COVID-19 consistent with a large proportion of the population remaining susceptible to the virus after the first epidemic wave.[1] By contrast, in Manaus, Brazil, a study of blood donors indicated that 76% (95% CI 67–98) of the population had been infected with SARS-CoV-2 by October, 2020.[2] High attack rates of SARS-CoV-2 were also estimated in population-based samples from other locations in the Amazon Basin—eg, Iquitos, Peru 70% (67–73).[3] The estimated SARS-CoV-2 attack rate in Manaus would be above the theoretical herd immunity threshold (67%), given a basic case reproduction number (R_0) of 3.[4]

In this context, the abrupt increase in the number of COVID-19 hospital admissions in Manaus during January, 2021 (3431 in Jan 1–19, 2021, *vs* 552 in Dec 1–19, 2020) is unexpected and of concern (figure).[5–10] After a large epidemic that peaked in late April, 2020, COVID-19 hospitalisations in Manaus remained stable and fairly low for 7 months from May to November, despite the relaxation of COVID-19 control measures during that period (figure).

There are at least four non-mutually exclusive possible explanations for the resurgence of COVID-19 in Manaus. First, the SARS-CoV-2 attack rate could have been overestimated during the first wave, and the population remained below the herd immunity threshold until the beginning of December, 2020. In this scenario, the resurgence could be explained by greater mixing of infected and susceptible individuals during December. The 76% estimate of past infection[2] might have been biased upwards due to adjustments to the observed 52·5% (95% CI 47·6–57·5) seroprevalence in June, 2020, to account for antibody waning. However, even this lower bound should confer important population immunity to avoid a larger outbreak. Furthermore, comparisons of blood donors with census data showed no major difference in a range of demographic variables,[2] and the mandatory exclusion of donors with symptoms of COVID-19 is expected to underestimate the true population exposure to the virus. Reanalysis and model comparison[11] by independent groups will help inform the best-fitting models for antibody waning and the representativeness of blood donors.

Second, immunity against infection might have already begun to wane by December, 2020, because of a general decrease in immune protection against SARS-CoV-2 after a first exposure. Waning of anti-nucleocapsid IgG antibody titres observed in blood donors[2] might reflect a loss of immune protection, although immunity to SARS-CoV-2 depends on a combination of B-cell and T-cell responses.[12] A study of UK health-care workers[13] showed that reinfection with SARS-CoV-2 is uncommon up to 6 months after the primary infection. However, most of the SARS-CoV-2 infections in Manaus occurred 7–8 months before the resurgence in January, 2021; this is longer than the period

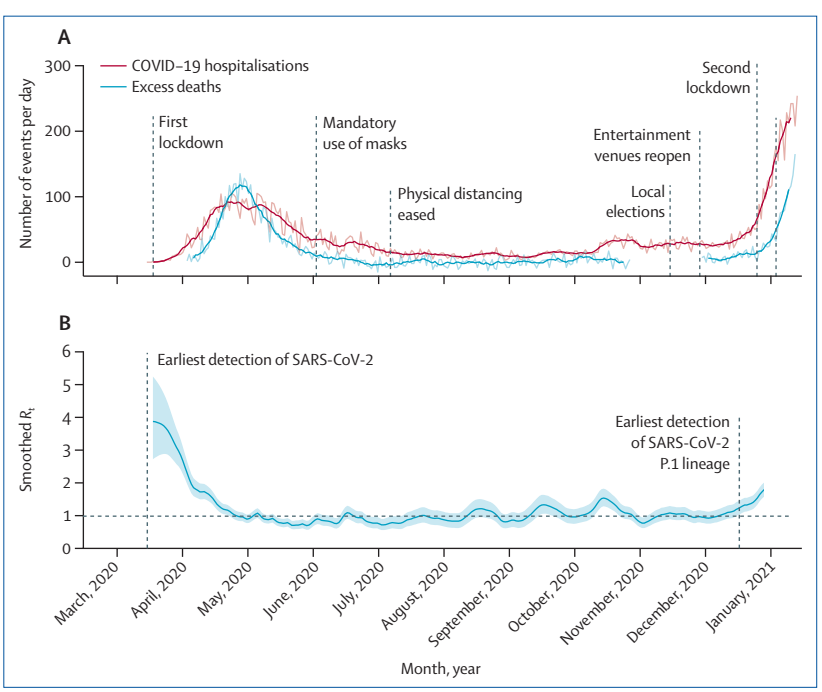

Figure: **COVID-19 hospitalisations, excess deaths, and R_t in Manaus, Brazil, 2020–21**
(A) Dark lines are the 7-day rolling averages and lighter lines are the daily time series of COVID-19 hospitalisations and excess deaths. Hospitalisation data are from the Fundação de Vigilância em Saúde do Amazonas.[5] Total all-cause deaths for 2020–21 were reported initially by the Prefeitura de Manaus[6] and subsequently in the daily COVID-19 bulletin of the Fundação de Vigilância em Saúde do Amazonas.[7] All-cause deaths from 2019 were from Arpen/AM (Associação dos Registradores Civis das Pessoas Naturais do Amazonas).[8] The compiled excess death data are from Bruce Nelson from the Instituto Nacional de Pesquisas da Amazônia.[9] (B) R_t was calculated using the time series of COVID-19 hospitalisations after removal of the past 14 days to account for delays in notification. R_t was calculated using the EpiFilter method.[10] Lines are median R_t estimates; shaded areas are the 95% CIs. R_t=Effective reproduction number. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

covered by the UK study,[13] but nonetheless suggests that waning immunity alone is unlikely to fully explain the recent resurgence. Moreover, population mobility in Manaus decreased from mid-November, 2020, with a sharp reduction in late December, 2020,[14] suggesting that behavioural change does not account for the resurgence of hospitalisations.

Third, SARS-CoV-2 lineages might evade immunity generated in response to previous infection.[15] Three recently detected SARS-CoV-2 lineages (B.1.1.7, B.1.351, and P.1), are unusually divergent and each possesses a unique constellation of mutations of potential biological importance.[16–18] Of these, two are circulating in Brazil (B.1.1.7 and P.1) and one (P.1) was detected in Manaus on Jan 12, 2021.[16] One case of SARS-CoV-2 reinfection has been associated with the P.1 lineage in Manaus[19] that accrued ten unique spike protein mutations, including E484K and N501K.[16] Moreover, the newly classified P.2 lineage (sublineage of B.1.128 that independently accrued the spike E484K mutation) has now been detected in several locations in Brazil, including Manaus.[20] P.2 variants with the E484K mutation have been detected in two people who have been reinfected with SARS-CoV-2 in Brazil,[21,22] and there is in-vitro evidence that the presence of the E484K mutation reduces neutralisation by polyclonal antibodies in convalescent sera.[15]

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Fourth, SARS-CoV-2 lineages circulating in the second wave might have higher inherent transmissibility than pre-existing lineages circulating in Manaus. The P.1 lineage was first discovered in Manaus.[16] In a preliminary study, this lineage reached a high frequency (42%, 13 of 31) among genome samples obtained from COVID-19 cases in December, 2020, but was absent in 26 samples collected in Manaus between March and November, 2020.[16] Thus far, little is known about the transmissibility of the P.1 lineage, but it shares several independently acquired mutations with the B.1.1.7 (N501Y) and the B.1.325 (K417N/T, E484K, N501Y) lineages circulating in the UK and South Africa, which seem to have increased transmissibility.[18] Contact tracing and outbreak investigation data are needed to better understand relative transmissibility of this lineage.

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The new SARS-CoV-2 lineages may drive a resurgence of cases in the places where they circulate if they have increased transmissibility compared with pre-existing circulating lineages and if they are associated with antigenic escape. For this reason, the genetic, immunological, clinical, and epidemiological characteristics of these SARS-CoV-2 variants need to be quickly investigated. Conversely, if resurgence in Manaus is due to waning of protective immunity, then similar resurgence scenarios should be expected in other locations. Sustained serological and genomic surveillance in Manaus and elsewhere is a priority, with simultaneous monitoring for SARS-CoV-2 reinfections and implementation of non-pharmaceutical interventions. Determining the efficacy of existing COVID-19 vaccines against variants in the P.1 lineage and other lineages with potential immune escape variants is also crucial. Genotyping viruses from COVID-19 patients who were not protected by vaccination in clinical trials would help us to understand if there are lineage-specific frequencies underlying reinfection. The protocols and findings of such studies should be coordinated and rapidly shared wherever such variants emerge and spread.

Since rapid data sharing is the basis for the development and implementation of actionable disease control measures during public health emergencies, we are openly sharing in real-time monthly curated serosurvey data from blood donors through the Brazil–UK Centre for Arbovirus Discovery, Diagnosis, Genomics and Epidemiology (CADDE) Centre GitHub website and will continue to share genetic sequence data and results from Manaus through openly accessible data platforms such as GISAID and Virological.

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**Ester C Sabino, Lewis F Buss, Maria P S Carvalho, Carlos A Prete Jr, Myuki A E Crispim, Nelson A Fraiji, Rafael H M Pereira, Kris V Parag, Pedro da Silva Peixoto, Moritz U G Kraemer, Marcio K Oikawa, Tassila Salomon, Zulma M Cucunuba, Márcia C Castro, Andreza Aruska de Souza Santos, Vítor H Nascimento, Henrique S Pereira, Neil M Ferguson, Oliver G Pybus, Adam Kucharski, Michael P Busch, Christopher Dye, Nuno R Faria*

sabinoec@usp.br

Departamento de Molestias Infecciosas e Parasitarias and Instituto de Medicina Tropical da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP 05403–000, Brazil (ECS, LFB, NRF); Fundação Hospitalar de Hematologia e Hemoterapia do Amazonas, Manaus, Brazil (MPSC, MAEC, NAF); Departamento

de Engenharia de Sistemas Eletrônicos, Escola Politécnica da Universidade de São Paulo, São Paulo, Brazil (CAP, VHN); Institute for Applied Economic Research–Ipea, Brasília, Brazil (RHMP); MRC Centre for Global Infectious Disease Analysis, J-IDEA, Imperial College London, London, UK (KVP, ZMC, NMF, NRF); Institute of Mathematics and Statistics, University of São Paulo, São Paulo, Brazil (PdSP); Department of Zoology, University of Oxford, Oxford, UK (MUGK, OGP, CD, NRF); Center of Mathematics, Computing and Cognition–Universidade Federal do ABC, São Paulo, Brazil (MKO); Fundação Hemominas–Fundação Centro de Hematologia e Hemoterapia de Minas Gerais, Belo Horizonte, Brazil (TS); Faculdade Ciências Médicas de Minas Gerais, Belo Horizonte, Brazil (TS); Department of Global Health and Population, Harvard T H Chan School of Public Health, Boston, MA, USA (MCC); Oxford School of Global and Area Studies, Latin American Centre, University of Oxford, Oxford, UK (AAdSS); Centro de Ciências Ambientais, Universidade Federal do Amazonas, Manaus, Brazil (HSP); Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, UK (AK); Vitalant Research Institute, San Francisco, CA, USA (MPB); University of California, San Francisco, CA, USA (MPB)

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