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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 infection² 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 comparison¹¹ 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 donors² 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 workers¹³ 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 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 Manaus¹⁹ 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

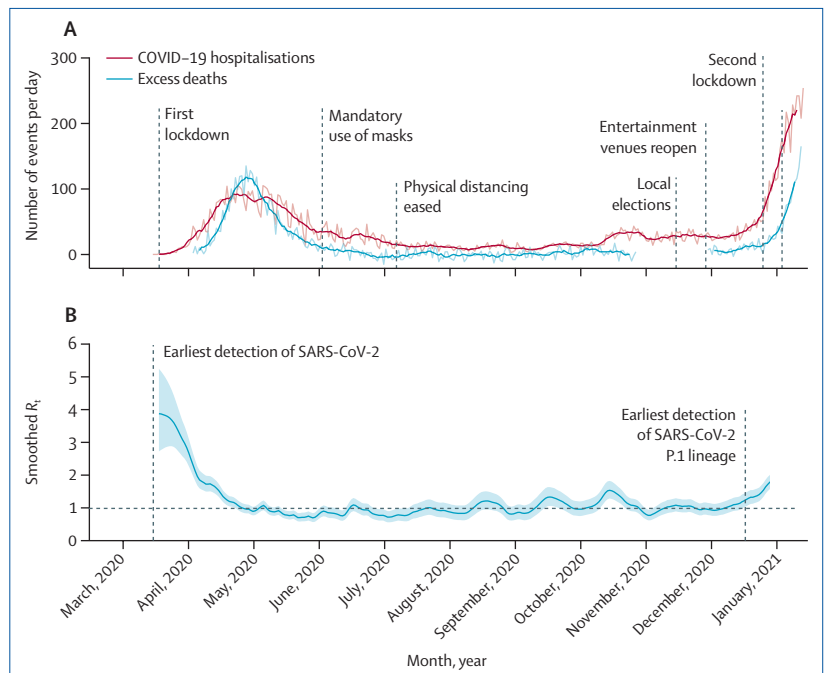


Figure: COVID-19 hospitalisations, excess deaths, and R_t in Manaus, Brazil, 2020–21
 (A) Dark lines are the 7-day rolling averages and lighter lines are the daily time series of COVID-19 hospitalisations and excess deaths. Hospitalisation data are from the Fundação de Vigilância em Saúde do Amazonas.⁵ Total all-cause deaths for 2020–21 were reported initially by the Prefeitura de Manaus⁶ 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 Cíveis 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.

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.

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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Long COVID guidelines need to reflect lived experience

Since May, 2020,¹ increasing attention has been given to the experiences of people with COVID-19 whose symptoms persist for 4 or more weeks. According to the Office for National Statistics (ONS), an estimated 186 000 people (95% CI 153 000–221 000) in private households in England currently have COVID-19 symptoms 5–12 weeks or longer after acute infection.² The ONS estimate that one in five people have symptoms that persist after 5 weeks, and one in ten have symptoms for 12 weeks or longer after acute COVID-19 infection.² Research on long COVID is growing, including into the underlying pathology, consequences, and sequelae, as well as rehabilitation for patients. Evidence suggests that a considerable proportion of people with long COVID have severe complications.^{3–5}

We have lived experiences of long COVID, with a range of symptoms lasting for more than 6 months. Staff in the UK National Health Service (NHS) have been variously supportive or disbelieving of our ongoing, often worsening, symptoms. Before our illness we were fit, healthy, and working in demanding roles, including as doctors, nurses, and other health professionals. Our symptoms of acute COVID-19 included dyspnoea, dry cough, fever, anosmia, and debilitating fatigue. Throughout 2020 we also experienced other symptoms and conditions, never experienced before our acute illnesses (panel). All of these conditions began during, or shortly after, acute COVID-19. We each are experiencing different patterns and varied severity of symptoms; we all share difficulties accessing adequate health-care services; some of us have received misguided assessment and treatment in some of the UK's recently established long COVID clinics and encountered dismissive behaviour from some health professionals.^{6–8} We share these experiences with thousands of people we engage with in rapidly growing online support groups.

We were encouraged by the announcement, on Oct 5, 2020, that the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP) were developing “a guideline on persistent effects of COVID-19 (long COVID) on patients”,⁹ consulting with a broad range of professional groups and some people with long COVID.

The final NICE–SIGN–RCGP guideline, published on Dec 18, 2020,¹⁰ should provide clear information on what is and is not known about the natural history of long COVID, provide guidance for health-care workers to identify cases, and inform clinical practice for the correct management of people with symptoms. Accurate assessment, diagnosis, treatment, and rehabilitation are especially important given the increasing evidence of organ pathology



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Panel: Conditions experienced by members of the UK doctors #longcovid group

- Myocarditis or pericarditis
- Microvascular angina
- Cardiac arrhythmias, including atrial flutter and atrial fibrillation
- Dysautonomia, including postural orthostatic tachycardia syndrome
- Mast cell activation syndrome
- Interstitial lung disease
- Thromboembolic disease (pulmonary emboli or cerebral venous thrombosis)
- Myelopathy, neuropathy, and neurocognitive disorders
- Renal impairment
- New-onset diabetes and thyroiditis
- Hepatitis and abnormal liver enzymes
- New-onset allergies and anaphylaxis
- Dysphonia