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

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After initially containing the newly-emerged SARS-CoV-2 virus, many European and Asian countries experienced a recrudescence of cases as control measures were relaxed. This is consistent with the view that only a small fraction the populations of these countries were infected during the first epidemic wave, and many people remained susceptible to COVID-19[1]. By contrast, in Manaus, Brazil, a study of blood donors indicated that 76% of the population had been infected by October 2020,[2] with high attack rates also estimated in population-based samples from other Latin American locations (e.g., Iquitos, Peru 71%[3], Monteria, Colombia 55.3%[4], Maranhão, Brazil 40.4%[5]). The attack rate of 76% in Manaus would be above the herd immunity threshold (66%), given an estimated basic case reproduction number of $R_0 = 3$.

In this context, the abrupt increase in the number of COVID-19 patients admitted to hospitals and deaths in Manaus since mid-December 2020 is unexpected and of great concern (Fig S1.A). After a large epidemic peak that turned over in late April, mortality and hospitalizations in Manaus remained stable at a comparatively low level for seven months (May-November), despite the relaxation of control measures during that period (Fig S1) and the easing of physical isolation (Fig S1.C). There are broadly two possible explanations for this. The first is that the attack rate in Manaus was overestimated during the first wave, and that the percentage of people infected was still below the herd immunity threshold. In this case, the resurgence might be explained by greater mixing during December among an unexpectedly large number of susceptible people. Although it is conceivable that estimates of infection made from blood donors are biased upwards, there is no definitive evidence to support or refute this[2]. Indeed, sampling blood donors is likely to have underestimated exposure to infection in Manaus because potential donors with symptoms of COVID-19 were

excluded from giving blood. Furthermore, physical isolation, as measured from mobile phone data, increased in November and December (Fig S1C), suggesting that recent behavior change does not account for the resurgence of patients admitted to hospitals (Fig S1A).

The second possible explanation is that immunity to reinfection, while high just after the initial outbreak, had already begun to wane by December, either because human immune protection lasts no longer than a few months or because the SARS-CoV-2 viral population now contains genetic variants that can escape immunity. The waning of 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[6]. The longevity of immunity to SARS-CoV-2 infection is still unclear. However, two recent studies of UK health-care workers [7,8] showed that reinfection with SARS-CoV-2 is uncommon up to five months after the primary infection. Most infections in Manaus occurred seven to eight months prior to the recent resurgence; this is beyond the period covered by these two studies, but suggests that waning immunity alone is unlikely to explain the recent resurgence.

The alternative is that new genetic variants of SARS-CoV-2 are able to circumvent immunity to a previous infection. Although the mutation rate of SARS-Cov-2 is relatively slow compared with other RNA viruses, there are now hundreds of lineages containing thousands of variants in circulation around the world. Of these lineages, three are considered important because they contain constellations of mutations associated with higher transmissibility and reduced neutralization by antibodies.

In December, a new lineage named P1, with spike protein mutations including E484K and N501K, was discovered in Manaus[9]. This lineage had already reached a high frequency (42%, 13/31) among genomes isolated from cases in December 2020, but was absent in 26 samples collected in Manaus between March to November 2020[9]. Little is known yet about the P1 lineage, but it shares several independently acquired mutations with the B.1.1.7 and the B.1.325 lineages discovered in the United Kingdom and South Africa, which appear to have increased transmissibility[10-12]. Variants carrying the E484K mutation have also been found in people who have been reinfected with SARS-CoV-2[13-14], and there is strong *in vitro* evidence that that the presence of the E484K mutation reduces binding by polyclonal antibodies in convalescent sera[15].

None of the plausible explanations for the resurgence of COVID-19 in Manaus can yet be ruled out. It is clear, however, that if novel SARS-CoV-2 variants are more transmissible than their progenitors, and if they can escape natural or vaccine-induced immunity, they will be extremely dangerous. For this reason, the genetic, immunological and epidemiological characteristics of these variants need quickly to be investigated. Continuing genomic surveillance in Manaus and elsewhere in Brazil is a high priority, with simultaneous monitoring for re-infections. Determining the efficacy of existing vaccines against variants in the P1 lineage, and other potential immune escape variants, is also critical. Genotyping viruses from COVID-19 patients that were not protected by vaccination in clinical trials would help to address this question. The protocols and findings of such studies should be coordinated and shared wherever such variants emerge and spread ─ Brazil, South Africa, the United Kingdom, and worldwide.

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