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Brazil's COVID-19 epicenter in Manaus: How much of the population has already been exposed and are vulnerable to SARS-CoV-2?

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Abstract: Is Brazil's COVID-19 epicenter really approaching herd immunity? A recent study estimated that in October 2020 three-quarters of the population of Manaus (the capital of the largest state in the Brazilian Amazon) had had contact with SARS-CoV-2. We show that 46% of the Manaus population having had contact with SARS-CoV-2 at that time is a more plausible estimate, and that Amazonia is still far from herd immunity. The second wave of COVID-19 is now evident in Manaus. We predict that and the pandemic of COVID-19 will continue throughout 2021, given the duration of naturally acquired immunity of only 270 days and the slow pace of vaccination. Manaus has a large percentage of the population that is susceptible (35% to 45% as of May 17, 2021). Against this backdrop, measures to restrict urban mobility and social isolation are still necessary, such as the closure of schools and universities, since the resumption of these activities in 2020 due to the low attack rates of SARS-CoV-2 were the main trigger for the second wave in Manaus.

Keywords: Coronavirus, Amazon, Manaus, herd immunity, immunity loss, reinfection, SEIR, SEIRS

Introduction

Manaus, the capital of the largest state in Brazil's Amazon region, gained significant world attention when non-scientific media reported that the city could be the first place in the world to have achieved herd immunity [1]. In local media and political discourse this misinformation was reinforced based on a preprint by Buss and coworkers [2] (which was later published after significant modifications) in which the authors argued that three-quarters of the population had already been exposed to SARS-CoV-2 by October 2020 [3]. In August 2020 the possibility of a second wave of COVID-19 had been predicted to be the likely due to the negligence of decision-makers [4]. The situation in Manaus in January and February 2021 corroborates the occurrence of a second wave with a surge of confirmed cases, hospitalizations, and deaths [5], contradicting the hypothesis of herd immunity.

The same authors who had raised the hypothesis of herd immunity published a second paper putting forward an alternative hypothesis, suggesting that their calculations could have been mistaken and that the attack rates of SARS-CoV-2 in Manaus may have been overestimated [6]. Here we test the hypothesis that the attack rates of SARS-CoV-2 were overestimated, in addition to presenting a more plausible model for the first and second waves in Manaus using the real attack rates of SARS-CoV- 2 on the population. These data are particularly important for guiding decision making on strategies to contain the pandemic in Manaus, in addition to their relevance to the ongoing congressional investigation of the decisions that generated the second COVID-19 wave in the region.

Methods

The SEIR, SEIRS, and multi-strain models

The SEIR (Susceptible – Exposed – Infected – Removed) model for simulating the time evolution of epidemics is the primary tool for analyzing the epidemiological curves of the COVID-19 pandemic [7-10]. Individuals susceptible to infection in a population come into contact at random with the SARS-CoV-2 virus, becoming exposed. After the incubation period, they become infected and can transmit the virus randomly to other susceptible individuals. Infected individuals can be either asymptomatic (have few or no symptoms) or symptomatic. Over time, infected individuals are removed (they either recover or die and no longer can infect susceptible individuals). The SEIRS (Susceptible – Exposed – Infected – Removed- Susceptible) model [11, 12] is an extension of the SEIR model, allowing individuals who have been removed and are still surviving to become susceptible again after a given average period for loss of immunity. Adding individuals' capability to return to the infected pool drastically changes the epidemiological regime, creating the possibility of recurring waves of infection and a persistent, non-vanishing flux of COVID-19 hospitalizations and deaths. The multi-strain [13, 14] SEIR model allows two or more strains of the SARS-CoV-2 virus to co-exist, with different outbreak dates and transmission rates.

Our multi-strain SEIRS model combines the features of the SEIRS and multi-strain SEIR models; this setup allows testing the hypotheses of the presence of a new SARS-CoV-2 variant with a higher-than-usual transmission rate, along with a potential loss of immunity. We studied a scenario under the multi-strain SEIRS model that was based on a daily data series of social distancing in Manaus obtained from the COVID-19 Community Mobility Reports [15], including public transportation usage from February 15, 2020 to May 15, 2021, average immunity loss periods, new strain outbreak dates, and transmission rates. Our model also assumes immunization of 15% of the population by vaccine by May 15, 2021, this being the percentage of the population that had received at least one dose of a vaccine by that date. Because we assume that all persons with one dose of a vaccine are immunized, our model can be considered conservative. We argue that the December 2020 surge of severe acute respiratory illness (SARI) hospitalizations in Manaus cannot be fully explained by a multi-strain SEIR model alone. However, it easily fits a multi-strain SEIRS model, assuming the emergence of a new SARS-CoV-2 strain that is twice as contagious as the previous one beginning on November 15, 2020 [16].

Perspective

Buss et al. reached their conclusion that three-quarters of the population had been exposed based on blood-donor samples, a source with well-known selection bias (as pointed out by the authors themselves) [3]. The study indicates a prevalence of SARS-CoV-2 infection in the population as being between 4.1% and 5.5% [3] during the period from April 6 to 17, 2020, immediately prior to the first collapse of the hospital network and the explosive peak of deaths in epidemiological week 17 (April 19-25, 2020) [18]. Because the mortality indicator is a delayed sign of viral circulation, the peak of community transmission occurred weeks earlier and not in early May, as suggested by Buss et al. [3], contradicting Figure 7B of their Supplementary Material, which shows that the peak of mortality (according to the occurrence date) was at the end of April [3].

Buss et al. also estimated a high seroprevalence of 44.1 to 65.2% of the population Manaus for the June 5-15, 2020 period [3]. This estimate differs radically from data from another study that estimated seroprevalence at 14.6% in early June [19]. Buss et al. [3] attributed the discrepancy between these studies to sampling power, the low sensitivity of rapid tests, and the decline in the humoral response. However, although the study that estimated lower seroprevalence than the study by Buss et al. did not make a correction for the decline of the humoral response, a correction for the sensitivity of the rapid test was carried out, confirming the values in the study [19]. Thus, it does not seem plausible to attribute the difference in results to the factors mentioned.

Buss et al. also suggested that the epidemic was ending in early August [3]. However, beginning in the second epidemiological week in August (epidemiological week 33), severe acute respiratory illness (SARI) cases increased steadily, doubling in the following months [20] and confirming a new acceleration of the epidemic in Manaus [5], leading ICU occupancy in the public health system to grow from 36 beds on August 19 [21] to 136 beds on December 20 [22]. Also, in the month between July 18 and August 17, 132 deaths due to COVID-19 were recorded, while in the month between October 18 and November 17 there were 219 recorded deaths, an increase of 65.9% [23].

Epidemiological analyses show that the high (76%) infection prevalence estimate of Buss et al. [3] is incompatible with their own assumed low value of 0.257% for the infection fatality ratio (IFR), which would also imply an unrealistically high efficiency of COVID-19 treatment per age group in Manaus's hospitals, as compared to São Paulo's better-equipped hospitals (see Buss et al. [3], SM Figure 1). However, hospitals in the Northern Region of Brazil, including the city of Manaus, had a mortality rate of 50% for patients admitted for COVID-19, whereas in Brazil’s Southeast Region, where the city of São Paulo is located, there was only 34% mortality in patients hospitalized for COVID-19 [24], which corroborates the incompatibility of the infection prevalence estimated by Buss et al. with the IFR they estimated.

Results and discussion

Susceptible – Exposed – Infected – Removed (SEIR) and Susceptible – Exposed – Infected – Removed – Susceptible (SEIRS) models are the primary tools for analyzing the epidemiological curves of the COVID-19 pandemic [10]. Here we use a fully stochastic, compartmental SEIR model to perform an analysis on data on reported deaths and cases of SARI – the same data on which Buss et al. based their analyses. Figure 1 depicts two no-intervention COVID-19 scenarios generated with the SEIR model for observed (until October) and projected (November and December) numbers of infected individuals and hospitalized patients in Manaus, assuming a (relatively high) population-mixing value of 0.85 to fit the observed data.

The epidemiological curves are sensitive to the IFR value adopted. The first scenario (Figure 1A) uses the 0.257% IFR value assumed by Buss et al. [3]. The second scenario (Figure 1B) uses the more-realistic IFR value of 0.300%. The COVID-19 infection prevalence by October 15 predicted by the SEIR model is 54.7% for the first scenario and 47.4% for the second scenario. The first scenario shows that Buss et al.'s assumptions project a vanishing number of deaths from November onwards, which is incompatible with the observed increasing trend in Manaus's hospitalizations in October and November (Figure 1A). The second scenario matches the observed trend much more closely (Figure 2B). We stress that these computed proportions of infected individuals are, in both cases, upper limits, stretching the allowed population mixing value significantly upwards to 85%. Another scenario with even more reasonable lower population mixing and higher IFR values (e.g., 74% and 0.350%, respectively) produces a smaller infection prevalence of 41.0%. In conclusion, the 76% infection prevalence of COVID-19 as of October suggested by Buss et al. [3] is not supported by analyses using SEIR compartment models. Moreover, given a significant reduction of mobility in Manaus during the period from late March through May (Figure 2C), our models adequately explain the reduction in transmission rates from June onwards (Figure 2B). This is more plausible than the high infection rate defended by Buss et al. [3].

Based on the model that best fits the data from Manaus (Figure 2), it can be concluded that the second wave of COVID-19 in Manaus was caused by the early resumption of activities, with the main trigger being schools returning to face-to-face classes when the proportion of susceptible people in Manaus was still high. The SEIRS model suggests that there is a loss of immunity from natural contact with the virus in around 270 days, which is corroborated by the literature [17]. The increase in cases, hospitalizations and deaths due to relaxation of social distancing indicated by the SEIRS model shows that this resulted from the return to face-to-face classes on September 24, which swelled the volume of public transport in the following weeks when parents felt safe to send their children to school. Schools were the main trigger initiating the second wave. The return to face-to-face classes had a greater impact on the increase in cases and hospitalizations than either the elections held on November 15 and 29 or the end-of-year holidays. Our model also indicates that the second wave was already underway before the emergence of the P.1 variant and that the variant originated only in the middle of November when viral circulation increased due to the return to face-to-face classes (Figure 2).

As a result, our updated multi-strain SEIRS model, shown in Figure 2, indicates a substantial increase in COVID-19 hospitalizations by the second half of October, followed by a sharp rise by the end of December 2020 (Figure 2B). As shown in Figure 2B, this second wave was not started by the new P.1 SARS-CoV-2 variant (blue line) but rather by the older variant (green line). However, the P.1 variant boosted the second wave, becoming prevalent by the end of 2020. The two variants combined produced a second wave of hospitalizations and deaths even more significant than the first wave of April-June 2020. Awareness of the sudden rise of hospitalizations in the last week of December caused a substantial reduction in circulation (Figure 2C), which lasted through January. Circulation increased again steadily from February until May 2021, reaching levels above those at the beginning of the epidemic in March 2020. Assuming no substantial acceleration of the vaccination program in Manaus, our model projects a plateau of more than thirty COVID-19 daily hospitalizations and seven daily deaths in this city.

Given the current levels of susceptible people in the population of Manaus (35% until 45% of the entire population as of May 17, 2021), the increase in urban mobility generated by the return of classroom or hybrid classes tends to lead to a third wave of COVID-19 and to the emergence of new variants. Due to loss of the immunity acquired from natural contact with SARS-CoV-2 and the low percentage of vaccination, it is estimated through the SEIRS model that the safe resumption of either fully face-to-face or hybrid classes in Manaus will only be possible when vaccination reaches at least 70% of the city's population. A study published by FioCruz found that children are more likely to be infected with SARS-CoV-2 than to be transmitting it, but the children in the evaluated community remained in isolation and did not return to face-to-face classes [25]. Children are known to have viral loads equivalent to those of adults, and they can contaminate others even when they are themselves asymptomatic [26]. SARS-CoV-2 transmission occurs through the air, and cloth masks in Brazil only reduce transmission by 15-70% [27], which casts doubt on the biosafety protocols used in Manaus and in Brazil as a whole. The increase in viral circulation due to the return of face-to-face and hybrid classes is associated with the increase in urban mobility caused by this return (mainly in public transport), as was observed in October 2020.

The federal government's actions had the effect of disrupting state-level responses, undermining emergency aid, delaying the purchase of vaccines and even refusing to make drinking water available to affected Indigenous people [28]. Brazil's Federal Court of Accounts (TCU) characterized this set of actions not as an unfortunate sequence of mistakes and examples of bureaucratic incompetence, but rather as "a political choice at the center of the presidential administration to prioritize protecting the economy" [28]. A study of federal actions during the pandemic by the Center for Research and Studies on Sanitary Law (CEPEDISA) of the Faculty of Public Health (FSP) at the University of São Paulo (USP) concluded that: "By dismissing the thesis of incompetence or neglect on the part of the federal government, this study reveals the existence of an institutional strategy to spread of the virus, promoted by the federal government under the leadership of the President" [28]. Supporters of President Jair Bolsonaro defended the lifting of social isolation based on herd immunity [29], and leading Bolsonaro supporters in the state of Amazonas engaged in anti-vaccination lobbying [30]. Suggestions of stricter social isolation to contain the advance of the pandemic and the possibility of a second wave were denied by representatives in the Amazonas State legislature who support the president [31].

The governor of the state of Amazonas, Wilson Lima, refused to take measures to stop the spread of the virus in Manaus as an "explicit strategy" to curry favor with President Bolsonaro, according to vice-governor Carlos Almeida Filho, who broke with the governor following the January 2021 Manaus oxygen crisis [32]. The vice-governor stated in an interview that "the strategy was to show alignment [with Bolsonaro]. One thing was clear, the policy was to claim that there was herd immunity" [32]. In Brazil's National Congress a parliamentary commission of inquiry is investigating the actions of the executive branch of government during the COVID-19 crisis (especially in Manaus) [33]. On 25 May 2021 this commission heard the sworn testimony of Mayra Pinheiro (executive secretary of the Ministry of Health) [33], where she defended an earlier statement criticizing isolation measures that were taken for the whole population rather than only for high-risk groups. She had stated "We hindered the natural evolution of the disease in those people who would be asymptomatic, such as children, and we would have had a herd immunity effect" [34]. The admission that the federal government defended the return to face-to-face classes in order to stimulate SARS-CoV-2 viral spread so that the population could reach herd immunity is significant (e.g. [35]), since President Bolsonaro has official responsibility for the government's having promoted this strategy through the health ministry's "Brazil cannot stop" campaign [36]. This means that, in order to achieve herd immunity, the President was taking responsibility for a 1% mortality risk for the entire population of the country as a result of community spread of SARS-CoV-2, which implies more than 1.4 million deaths [36]. The testimony of Mayra Pinheiro shows that the Ministry of Health was engaged in deliberate action by to stimulate COVID-19 infections, which culminated in the emergence of the second wave and the appearance of the P1 variant.

The results of the present study confirm that Manaus never reached herd immunity, and that herd immunity would be impossible to achieve solely by natural contact with the virus. Our results also indicate that the second wave of COVID-19 in Manaus started in October 2020, being triggered by the return to face-to-face classes on September 24 and not by the P.1 variant, which appeared only in November according to the SEIRS model. The proportions of infection by the P.1 variant in Manaus estimated by the SEIRS model for the months of November, December and January were corroborated by genomic data from Naveca and Costa, 2021 [16].

In addition, data on restrictive measures in 41 countries show that closing schools and universities is one of the most effective the measures for curbing community transmission of SARS-CoV-2, second only to restricting all encounters between people to 10 persons or less [37].Thus, the absence of social isolation and the early resumption of activities based on the assumption that Manaus had reached herd immunity caused the second wave of COVID-19 in the city of Manaus and the peak of the wave was augmented by the P.1 variant.

It is vital to measure the true proportion of the population of Manaus that has had contact with SARS-CoV-2 because results such as those of Buss et al. are being used by politicians as an argument to justify the claim that the second wave of COVID-19 in Manaus could not have been predicted. Instead, these politicians claim that the second wave is entirely explained by the emergence of a new virus strain in the region [38], and the surge of new cases has nothing to do with the lifting of social-distancing measures by the health authorities and regional politicians, such as the return to face-to-face classes. We had warned of the likely second wave of COVID-19 and collapse of the health system in Manaus several months before these events took place, but politicians neglected our warnings [4, 31]. The results here make it even more evident that the second wave of COVID-19 in Manaus was due to negligence and not to the emergence of a new virus strain in the region.

The Amazonas state government scheduled a new return to face-to-face classes on 31 May 2021 [39]. This is of great concern given the population's low vaccination rates and low immunity. Unfortunately, recent data show that the number of new cases is already increasing [40-41], suggesting that the return of face-to-face classes will trigger another crisis in the Manaus public health system.

Conclusion

Less than 50% of the city of Manaus had contact with SARS-CoV-2 by mid-October 2020. The herd immunity theory was used extensively by politicians to defend the lifting of social isolation, which significantly aggravated the current second wave in Manaus. Given that the loss of immunity due to natural contact with SARS-CoV-2 in Manaus is estimated at 270 days and that vaccination percentages are still very low, we estimate that at the beginning of May 2021 just over 55% of the population of Manaus had some immunity to SARS-CoV-2. This implies that the pandemic will continue during 2021 and puts Manaus at eminent risk of a third wave of COVID-19 in the face of new relaxations of restrictions, such as the return to face-to-face classes.

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Author contributions LF, WAS and LHD conceived of the idea; LHD, LF, WAS and ACLA designed the research; WAS, LHD, LF, JL and ACLA conducted statistical analyses; LF, WAS, ACLA, JL, RCV, UT, PMF and LHD wrote the manuscript; LF, WAS, ACLA, JL, RCV, UT, PMF and LHD revised the manuscript.

Compliance with Ethical Standards

Conflict of Interest. The authors declare that they have no conflict of interest.

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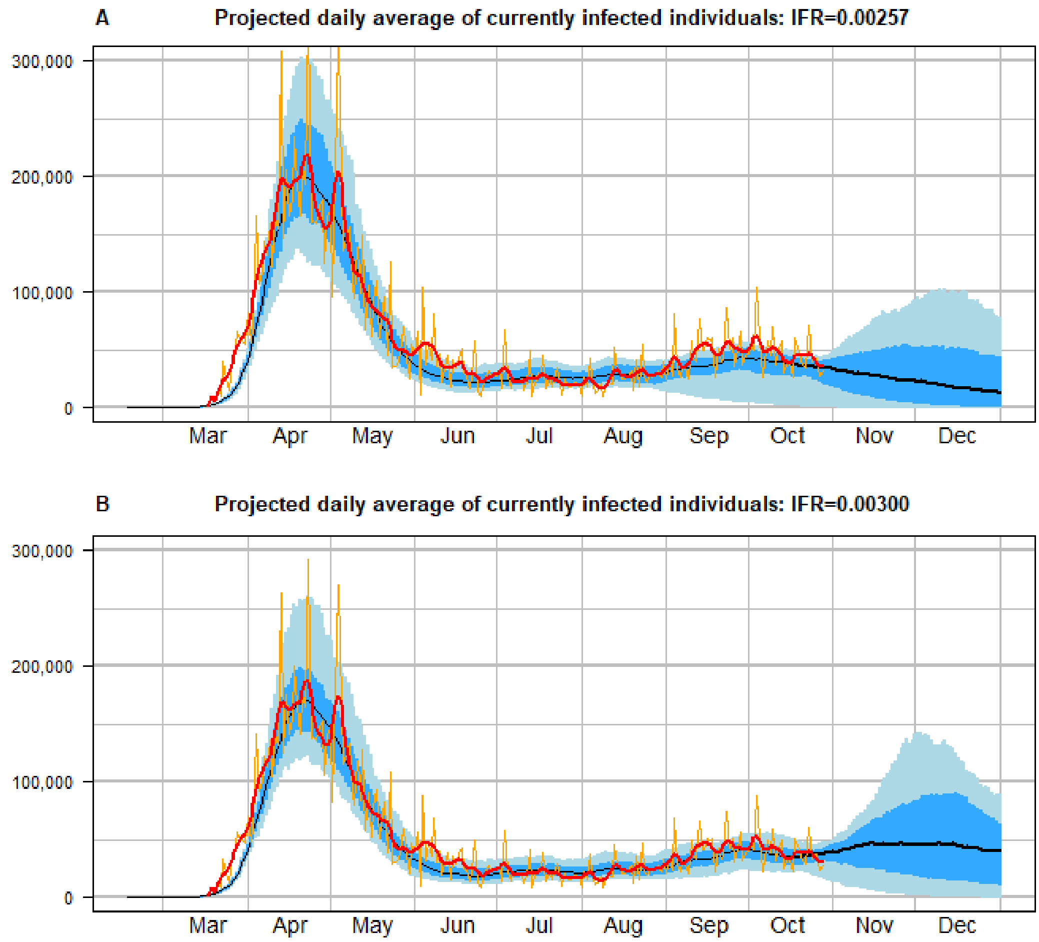

Figure 1. Simulation of COVID-19 in Manaus using (A) the infection fatality ratio (IFR) value from Buss et al. [3] and (B) a more-realistic IFR value. Infected individuals are shown by the black curve, while hospitalized patients are scaled to fit the black curve (daily counts in orange and moving window of averaged daily counts in red). Blue shading indicates 95% and 68% confidence intervals. The more-realistic scenario in (B) indicates substantial continued infections (and consequently deaths).

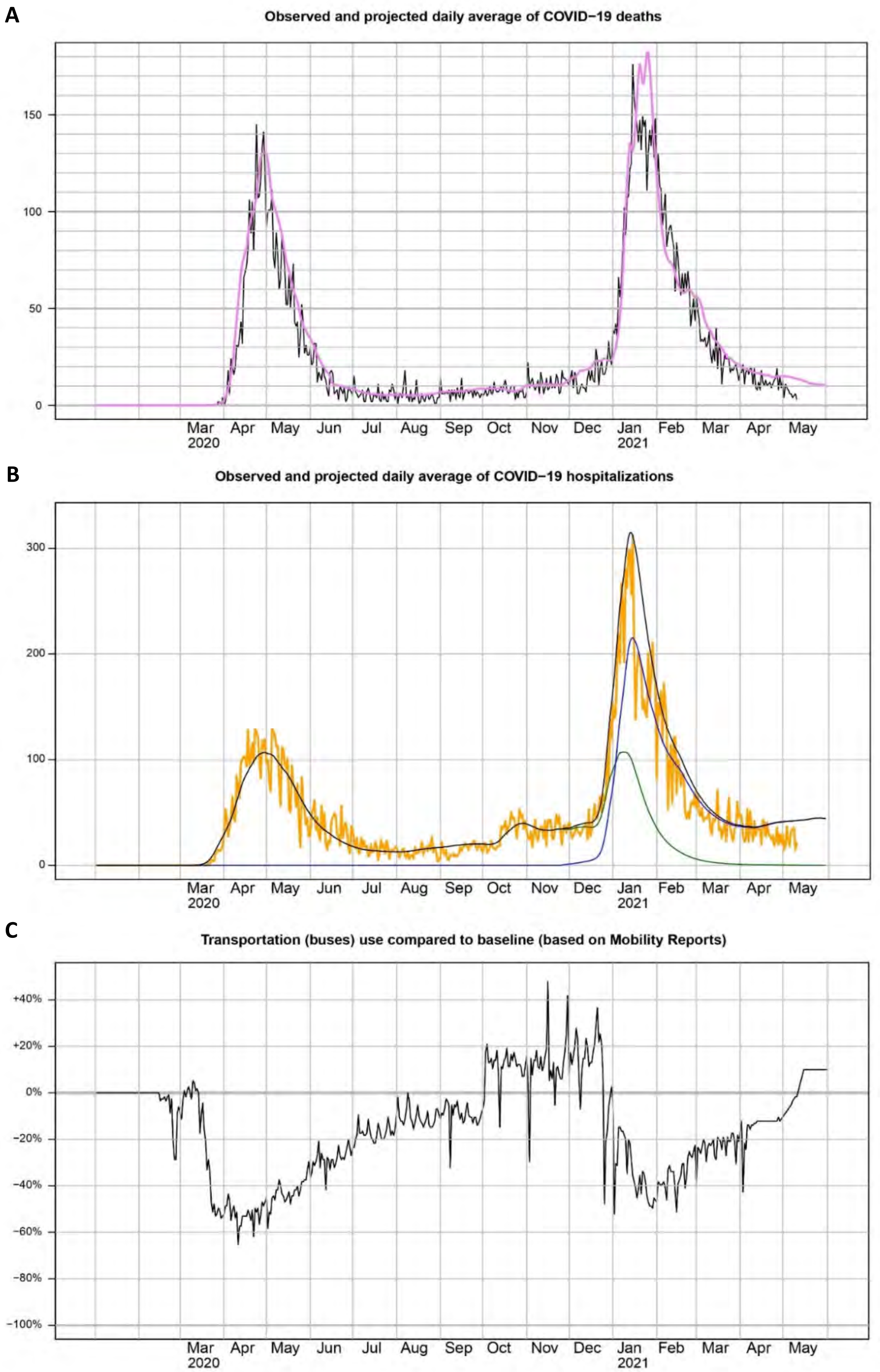

Figure 2. Model with best fit and that best explains the first and second COVID-19 waves in Manaus. In **A**, violet (dark green) indicates the projected (observed) deaths. In **B**, orange indicates daily observed hospitalizations; the projected hospitalizations due to

the two SARS-CoV-2 variants are indicated in green (original), blue (P.1) and black (total). **C** shows the community use of public transport (busses), compared to the February 2020 baseline.