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Dynamics of COVID-19 in Amazonia: A history of government denialism and the risk of a third wave

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ABSTRACT

The city of Manaus (the capital of Brazil's state of Amazonas) has become a key location for understanding the dynamics of the global pandemic of COVID-19. Different groups of scientists have foreseen different scenarios, such as the second wave or that Manaus could escape such a wave by having reached herd immunity. Here we test five hypotheses that explain the second wave of COVID-19 in Manaus: 1) The greater transmissibility of the Amazonian (gamma or P.1) variant is responsible for the second wave; 2) SARS-CoV-2 infection levels during the first wave were overestimated by those foreseeing herd immunity, and the population remained below this threshold when the second wave began at the beginning of December 2020; 3) Antibodies acquired from infection by one lineage do not confer immunity against other lineages; 4) Loss of immunity has generated a feedback phenomenon among infected people, which could generate future waves, and 5) A combination of the foregoing hypotheses. We also evaluated the possibility of a third wave in Manaus despite advances in vaccination, the new wave being due to the introduction of the delta variant in the region and the loss of immunity from natural contact with the virus. We developed a multi-strain SEIRS (Susceptible-Exposed-Infected-Removed-Susceptible) model and fed it with data for Manaus on mobility, COVID-19 hospitalizations, numbers of cases and deaths. Our model contemplated the current vaccination rates for all vaccines applied in Manaus and the individual protection rates already known for each vaccine. Our results indicate that the SARS-CoV-2 gamma (P.1) strain that originated in the Amazon region is not the cause of the second wave of COVID-19 in Manaus, but rather this strain originated during the second wave and became predominant in January 2021. Our multi-strain SEIRS model indicates that neither the doubled transmission rate of the gamma variant nor the loss of immunity alone is sufficient to explain the sudden rise of hospitalizations in late December 2020. Our results also indicate that the most plausible explanation for the current second wave is a SARS-CoV-2 infection level at around 50% of the population in early December 2020, together with loss of population immunity and early relaxation of restrictive measures. The most-plausible model indicates that contact with one strain does not provide protection against other strains and that the gamma variant has a transmissibility rate twice that of the original SARS-CoV-2 strain. Our model also shows that, despite the advance of vaccination, and even if future vaccination advances at a steady pace, the introduction of the delta variant or other new variants could cause a new wave of COVID-19.

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1. Introduction

The SARS-CoV-2 virus, which causes coronavirus disease 2019 (COVID-19), is responsible for the biggest pandemic of the 21st century. Decision makers have tried to identify the most effective strategies to overcome the pandemic and avoid as many deaths as possible, but there appears to be an exception in the case of Manaus, the capital of Brazil's state of Amazonas and the largest city in the Amazon region. In order to favor the economy in the short term, local politicians refused to take measures to stop the pandemic and prevent a second wave of COVID-19, even when official government data did not indicate a decline in the number of cases or deaths (Ferrante et al., 2020). In January 2021 Manaus experienced a second wave of cases, hospitalizations and deaths that surpassed the first peak of the pandemic that occurred in April and May 2020 (FVS, 2021a). Hardly any other city in the world has undergone a natural experiment with the pandemic like the current one in Manaus.

The population's high rate of contact with SARS-CoV-2 (Buss et al., 2021) raises the questions of which hypotheses are the most plausible to explain the second COVID-19 wave that Manaus is experiencing, and whether seroprevalence was overestimated (Sabino et al., 2021). Several studies have suggested that natural immunity is temporary and would tend to fade within a few months (Brett and Rohani, 2020; Edridge et al., 2020; Yang and Ibarrondo, 2020; Ferrante et al., 2021a), and this is also a plausible explanation for the second wave in Manaus (Ferrante et al., 2021a; 2021b). On January 10, 2021, the Japanese government announced that it had identified a new variant of SARS-CoV-2 in people who had traveled to Japan from Manaus (Naveca et al., 2021).

Genomic evidence indicates that the Amazonian (gamma or P.1) variant was not yet in circulation in Manaus in November 2020 and that it became almost predominant in January 2021 (Naveca et al., 2021). Although politicians have been quick to blame the advent of the second wave on the new variant (thus avoiding the conclusion that their own refusal to take recommended control measures was to blame), the data make clear that the hypothesis that the second wave was initiated by the gamma variant is less plausible than other hypotheses. However, the gamma-variant hypothesis also needs to be tested. Here we test five hypotheses to explain the second wave of COVID-19 in Manaus: 1) The greater transmissibility of the gamma variant is responsible for the second wave. 2) SARS-CoV-2 infection levels were overestimated during the first wave, and the population remained below the limit for herd immunity when the second wave began in December 2020; 3) Antibodies acquired from infection by one lineage do not confer immunity against other lineages; 4) Loss of immunity has generated a feedback phenomenon among infected people, which could generate future waves, and 5) A combination of the foregoing hypotheses and rapid lifting of social-distancing restrictions.

We also evaluated the possibility of a third wave in Manaus. Despite advances in vaccination, a new wave would be likely due to the introduction of the delta variant in the region and the loss of immunity from natural contact with the virus. The arrival of the omicron variant now makes a third wave virtually certain.

2. Methods

2.1. The SEIR, SEIRS, and multi-strain models

The SEIR (Susceptible – Exposed – Infected – Removed) model is the primary tool for analyzing the epidemiological curves of the COVID-19 pandemic (Adam, 2020; Bakker et al., 2020; Li et al., 2020; Prem et al., 2020). 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 (Trawicki, 2017; Bjørnstad et al., 2020) 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 the capability of individuals to return to the infected pool drastically changes the epidemiological regime, creating the possibility of recurring infection waves and a persistent, non-vanishing flux of COVID-19 hospitalizations and deaths. The SEIRS model equations are:

$$
\begin{aligned}
\frac{dS(t)}{dt} &= -[\beta_\gamma S_\gamma(t) I_\gamma(t) + \beta_\delta S_\delta(t) I_\delta(t)] \times M_t - \alpha S(t)(C_s) + \omega R_\gamma(t) + \omega R_\delta(t) \\
\frac{dE_\gamma(t)}{dt} &= \beta_\gamma S(t) I_\gamma(t) \times M_t - \gamma_\gamma E_\gamma(t) \\
\frac{dE_\delta(t)}{dt} &= \beta_\gamma S(t) I_\delta(t) \times M_t - \gamma_\delta E_\delta(t) \\
\frac{dI_\gamma(t)}{dt} &= \gamma_\gamma E_\gamma(t) - \xi I_\gamma(t) \\
\frac{dI_\delta(t)}{dt} &= \gamma_\delta E_\delta(t) - \xi I_\delta(t) + \beta_\delta R_\gamma(t) I_\delta(t) \\
\frac{dHI_\gamma(t)}{dt} &= \xi_\gamma I_\gamma - (1-\kappa)\lambda H_\gamma(t) - \kappa\rho H_\gamma(t) \\
\frac{dHI_\delta(t)}{dt} &= \xi_\delta I_\delta - (1-\kappa)\lambda \mathrm{H}(t) - \kappa\rho H_\delta(t) \\
\frac{dR_\gamma(t)}{dt} &= (1-\kappa)\lambda H_\gamma(t) - \beta_\delta R_\gamma(t) I_\delta(t) - \omega R_\gamma(t) \\
\frac{dR_\delta(t)}{dt} &= (1-\kappa)\lambda \mathrm{H}(t) - \omega R_\delta(t) \\
\frac{dD_\delta(t)}{dt} &= \kappa\rho H_\gamma(t) \\
\frac{dD_\delta(t)}{dt} &= \kappa\rho H_\delta(t) \\
\frac{dV(t)}{dt} &= \alpha S(t)(C_s)
\end{aligned}
$$

with the compartments indicated by:

- S: Susceptible
- E: Exposed
- I: Infected
- H: Hospitalized (due to COVID-19 infection)
- R: Recovered
- D: Deceased
- V: Vaccinated

We draw attention to the fact that all variables (S, E, I, H, R, D, V) are 3-dimensional vectors (corresponding to the three age ranges of the population of Manaus – see below).

The model's parameters are:

- β_γ and β_δ are the transmission rates for the two SARS-CoV-2 strains considered
- α is the vaccination rate, obtained via linear regression
- γ_γ^{-1} and γ_δ^{-1} are the incubation periods for the two SARS-CoV-2 strains considered
- σ is the vaccine overall inefficacy, weighted for 1st and 2nd doses of Astra-Zeneca, Pfizer, CoronaVac (SinoVac) and Janssen vaccines
- ξ^{-1} is the infection time
- κ is the infection fatality rate
- λ^{-1} is the recovery time
- ω is the rate of re-susceptibility (changeover between Recovered and Susceptible).

- C_s is the sum of the compartments $S(t) + E_\gamma(t) + E_\delta(t) + I_\gamma(t) + I_\delta(t) + \mathrm{H}(t) + H_\delta(t) + R_\gamma(t) + R_\delta(t)$.

$M_t = \begin{bmatrix} P_{(a,a)} & P_{(b,a)} & P_{(c,a)} \\ P_{(a,b)} & P_{(b,b)} & P_{(c,b)} \\ P_{(a,c)} & P_{(b,c)} & P_{(c,c)} \end{bmatrix}$ is a transition matrix of the three age groups considered: (a) below 18 yrs. (b) 18–59 yrs. and (c) 60 + yr.

The multi-strain (Fudolig et al., 2020; Khyar and Allali, 2020) SEIR model allows two or more strains of the SARS-CoV-2 virus to co-exist, with different outbreak dates and transmission rates. Finally, 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 used this model for the following two purposes: (1) to test above-mentioned five hypotheses regarding the second wave of COVID-19 that Manaus experienced in January 2021 and (2) to estimate the impact of the delta variant. To test our hypotheses regarding the second wave, we studied several scenarios generated by the multi-strain SEIRS model, with different values for social distancing, average immunity loss period, new strain outbreak date, and transmission rate. 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 can be easily fit into a multi-strain SEIRS model, assuming the emergence of a new SARS-CoV-2 strain that is twice as contagious as the previous one and an average period for loss of immunity of about eight months.

As a second application, we included data on vaccination rates up to August 2021 and a projection of vaccination progress to the end of 2021 to simulate the effect of introducing the delta variant into the susceptible population in Manaus over this period (Fig. 1). We considered all vaccines applied in accord with information by age group (based on bulletins released by the Health Secretariat of the State of Amazonas) (FVS, 2021b; 2021c) and the levels of protection provided by the first and second vaccine doses according to the most recent literature (Bernal et al., 2021; Kang et al., 2021).

Given the rapid dissemination of the delta strain, our analysis showed that the number of infections by the gamma strain after a previous infection by the delta strain must have been negligible. This possibility was thus disregarded in the model.

The multi-strain SEIRS algorithm described in this section was implemented in Python 3.8.10 and R version 3.6.3 programming languages, using the deSolve package, with GNU/Linux Mint 20.2.

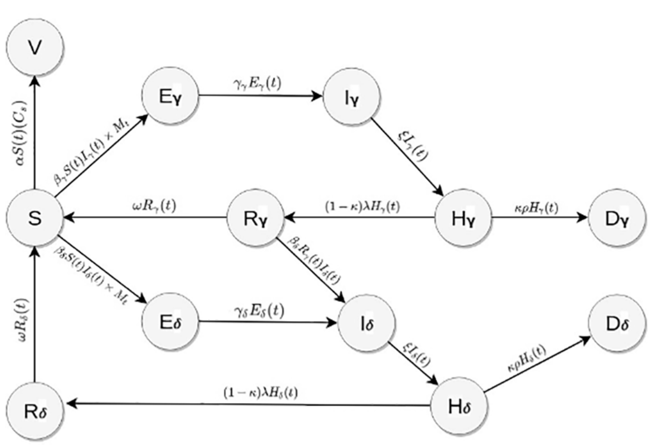

Fig. 1. State-transition diagram for the compartments of the COVID-19 epidemiological model.

2.2. Model parameters and data structure for Manaus

Amazonas, the largest state in Brazil's Amazon region, was the first to have its health system collapse due to the COVID-19 pandemic. Manaus (the capital of Amazonas) has a population of 2.2 million and is home to all of the state's intensive-care units (ICUs). Due to insufficient community testing for COVID-19 in Brazil, most of the tests are used for health and security personnel and hospitalized patients. This leads to a lack of periodic and randomized testing of the general population and makes it difficult to model the epidemic based on data on confirmed cases. Thus, in the present analysis of the Manaus epidemic, we base our model mostly on data on reported deaths and cases of SARI. We do not work with the number of officially registered (confirmed) cases of COVID-19 to estimate the number of unreported cases. The under-reporting of deaths due to COVID-19 in Brazil is well-known and has been the subject of scientific publications (França et al., 2020). It is also important to note that our model assumes that individuals' contacts follow a uniformly random pattern of interaction. There is no spatial (geographic) restriction on social contact; this is embedded in the transmission parameter, which is determined empirically from the observed data at the beginning of the epidemic.

In our model, the population can be partitioned into different groups according to age, income level, or occupation, allowing calculations to be based on a social-contact matrix that specifies the intensity of contact between such groups (Bakker et al., 2020; Duczmal et al., 2020; França et al., 2020; Li et al., 2020; Prem et al., 2020). In age-structured models, the population is stratified into two or more age groups, and the models reflect the different intensities of social contact among them. This is particularly important for the elderly, who are more vulnerable to COVID-19. For Brazil in general, and for Manaus in particular, elderly people usually live in the same households as their younger family members, if not in the same rooms, as is often the case in lower-income homes. Thus, in these neighborhoods, we assume high population mixing, in line with Bitar and Steinmetz (2020). In this situation, it is much more challenging to model social-contact networks based on age-structured models.

In the application of our model to test the hypotheses regarding the second wave of COVID-19 in Manaus, the population is partitioned into two sub-compartments with distinct social-contact rates. The compartment model employs the contact matrix

$C = [Cij]$

where C_{ij} indicates the social-contact intensity of virus transmission from an individual in group i to an individual in group j, where $0 \le C_{ij} \le 1$. If $C_{ij} = 1$, then the contact is not restricted, and if $C_{\mathrm{ij}} = 0$ no individual in group i can transmit the virus to any individual in group j (França et al., 2020; Prem et al., 2020).

On the other hand, in the application of our model to the estimation of the impact of the delta variant we employed a transition matrix ($\mathrm{M_t}$) dividing the population in the three sub-compartments according to age groups as the vaccination schedule is age-dependent, with older and more-vulnerable persons being vaccinated first. COVID-19 parameters are different for each age group.

In applying the model to test the hypotheses regarding the second wave, the multi-strain SEIRS simulation runs were conducted with a full ensemble of stochastic parameters, reflecting as precisely as possible the variation in the clinically observed parameters in accord with recent COVID-19 literature (Lauer et al., 2020; Prem et al., 2020; Sanche et al., 2020; Verity et al., 2020). Each full simulation consists of 1000 Monte Carlo replications of the epidemiological curves for susceptible, exposed, infected, and removed individuals. For the set of epidemiological solutions to the system from each Monte Carlo replication, all of the COVID-19 epidemiological parameters and scenario parameters are randomized following their statistical distributions in accordance with the latest estimates from the literature. We used a fourth-order Runge-

Kutta method to solve the system of differential equations numerically. The initial condition assumes the value of 0.001 for the compartment of exposed individuals at a time (day) t = 1 (where day one is January 1, 2020).

The parameters of interest in the model are described as follows:

- We assume the population of Manaus to be N = 2.2 million inhabitants and consider scenarios with a population mixing value of 0.85 (Bitar and Steinmetz, 2020).
- COVID-19′s infection fatality rate (IFR) for the population of Manaus is based on estimates of the infection fatality rate for each age group and on the age structure of the population of the Manaus city according to the Brazilian census (IBGE, 2010; Ioannidis, 2020). We consider IFR to be a normally distributed random variable (σ = 0.0005). We assumed an average IFR value of 0.30% until May 31, 2020, linearly decreasing until June 30 to 0.20%, and remaining constant at that level from then onwards; this modeling follows empirically from fitting the COVID-19 hospitalization and death curves in Manaus and reflects the overall improvement of patient care following the first wave during March and April 2020. The initial March-April IFR value of 0.30% was estimated through a semi-Bayesian procedure to adjust the SEIRS computed curve for infected individuals to the observed curve for hospitalizations. This value is close to the 0.27% median IFR value (Ioannidis, 2020) and the 0.26% IFR value estimated for Manaus by Buss et al. (2021).
- The average infectious period is normally distributed (μ = 10.0 days, σ = 2.0 days) (Verity et al., 2020).
- The number of days from symptom onset to death is Gamma distributed (μ = 20 days, sd = 7.9 days) (CDC, 2021), age-adjusted for the population of Manaus (IBGE, 2010).
- The incubation period is normally distributed (μ = 5.5 days, σ = 1.0 days) (Lauer et al., 2020).
- The inverse of the average period for loss of immunity parameter ω (Trawicki, 2017; Bjørnstad et al. 2020) is set to the values of zero, 1/150, 1/180, 1/240, 1/300 and 1/720 (measured in days^{-1}).
- The gamma (P.1) strain outbreak date was set as November 15, 2020, consistent with the census of different SARS-CoV-2 strains in Amazonas state, from November 2020 to January 2021, performed through genomic characterization (Naveca and Costa, 2021).

In applying the model to simulate to impact of the delta variant, the above parameters were adjusted and calibrated to observed data on hospitalizations and deaths in the period from November 2020 until mid-August 2021 and to vaccination numbers from January 2021 until July 2021. Daily counts of COVID-19-related deaths in the municipality of Manaus were estimated (according to the date of occurrence) from data obtained from official records of deaths due to severe acute respiratory illness (SARI) by the Municipal Health Department (Open Data SUS, 2020; Prefeitura de Manaus, 2020) from April 2020 to January 2021. Due to underreporting of deaths from COVID-19 in Manaus (Felizardo, 2020; Silva et al., 2020), especially during the peak in mortality in the first epidemic phase in April 2020, we considered data on unspecified SARI (the etiological agent of SARI is still being investigated) and confirmed deaths due to COVID-19. In our model we assume that all of these deaths are due to COVID-19. During the years 2016–2019 only 8, 13, 2, and 18 deaths due to SARI were recorded in the months of April to July, respectively, in the city of Manaus (Open Data SUS, 2020).

2.3. Immunity-loss test

The Amazonas Health Surveillance Foundation (FVS) bulletin shows a rapid increase in COVID-19 hospitalizations in Manaus in the last two weeks of December 2020 (FVS, 2021a), as seen in Fig. 1a. This probably reflects the exposure to SARS-CoV-2 during all the months of October, November and December with return of in-person classes and the loosening of commerce restrictions, a substantial increase in general circulation, and less adherence to mask use.

Using the multi-strain SEIRS model, we ran scenarios where the parameter ω (the inverse of the average period for loss of immunity) was set to zero (indicating no immunity loss), 1/720, 1/300, 1/240, 1/180, and 1/150, measured in days^{-1} units (Fig. 1d-e). The first graph shows the recorded COVID-19 daily deaths until December 2020, followed by the projected SEIRS death curves from January 2021 onwards. From March 2020 to January 9, 2021, the second graph showed the observed raw (in orange) and smoothed (in red) daily SARI hospitalizations, superimposed on the curve for the number of infected individuals computed by the multi-strain SEIRS system. The red/orange curve is drawn out-of-scale with a 6-day delay from infection to hospitalization (in order to fit the black curve). According to different values of the average period for loss of immunity, the six curves from December 2020 onwards project the number of infected individuals at each point in time (under the first graph).

During the last weeks of December 2020 and the first week of January 2021, the sharp increase in COVID-19 hospitalizations (orange/red curve) cannot be matched with the SEIRS curves for the number of infected individuals when the ω value is zero, 1/720, 1/300, 1/180, or 1/150. However, a tighter match is achieved when ω is set to 1/240, suggesting that the average period for the loss of immunity is about 240 days. Scenarios that do not consider the loss of immunity, and consequently COVID-19 reinfection, cannot fully explain the surge of hospitalizations in December 2020.

3. Results and discussion

3.1. The second wave and the gamma variant

In January 2021, Manaus experienced a second wave of cases, hospitalizations and deaths that surpassed the first peak of the pandemic that occurred in April and May 2020 (Fig. 2a). The gamma variant, which is of Amazonian origin, is believed to have arisen between November and December 2020 (Naveca et al., 2021), with an estimated 51% of the infections in Manaus being due to this variant between December 17th and 31st, 2020, rising to 60% of infections by the end of January 2021 (Naveca et al., 2021). We simulated an exaggerated scenario to test the hypothesis that the second wave was solely caused by the gamma variant, where we assumed that this variant had been in circulation since November 1, 2020 (i.e., before it is believed to have appeared) and has a transmission rate five times higher than the original strain that gave rise to the pandemic (i.e., much higher than the estimated doubling of the transmission rate). Our SEIRS model indicates that under this exaggerated scenario the number of cases and deaths during the second wave in Manaus would be only one-third of the number that has in fact been observed, thus refuting the hypothesis that the new variant caused the onset of the second wave (Fig. 2b). This hypothesis test is corroborated the genomic analyses and by the estimated numbers of gamma-variant infections between November and January (Naveca et al., 2021), ruling out the possibility that the gamma variant generated the second wave of COVID-19 in Manaus.

We assessed the pandemic scenario in Manaus using a SEIRS model that was fit to observed data on deaths and hospitalizations from the first case recorded in Manaus in March 2020 up to March 2021. The model showed that the second wave was potentially greater than the first wave, both in terms of the number of infections and the number of deaths. In this scenario, the best model indicates that the only plausible hypothesis is a combination of factors, such as a population with a much lower percentage of infection than is currently estimated for Manaus, together with a high rate of immunity loss and a high rate of reinfection, in addition to a smaller proportion contaminated by the gamma variant (See Fig. 2c). This scenario is corroborated by a census of infections in Manaus with genomic identification (Naveca et al., 2021) and by models that corrected the SARS-CoV-2 attack rates that were previously

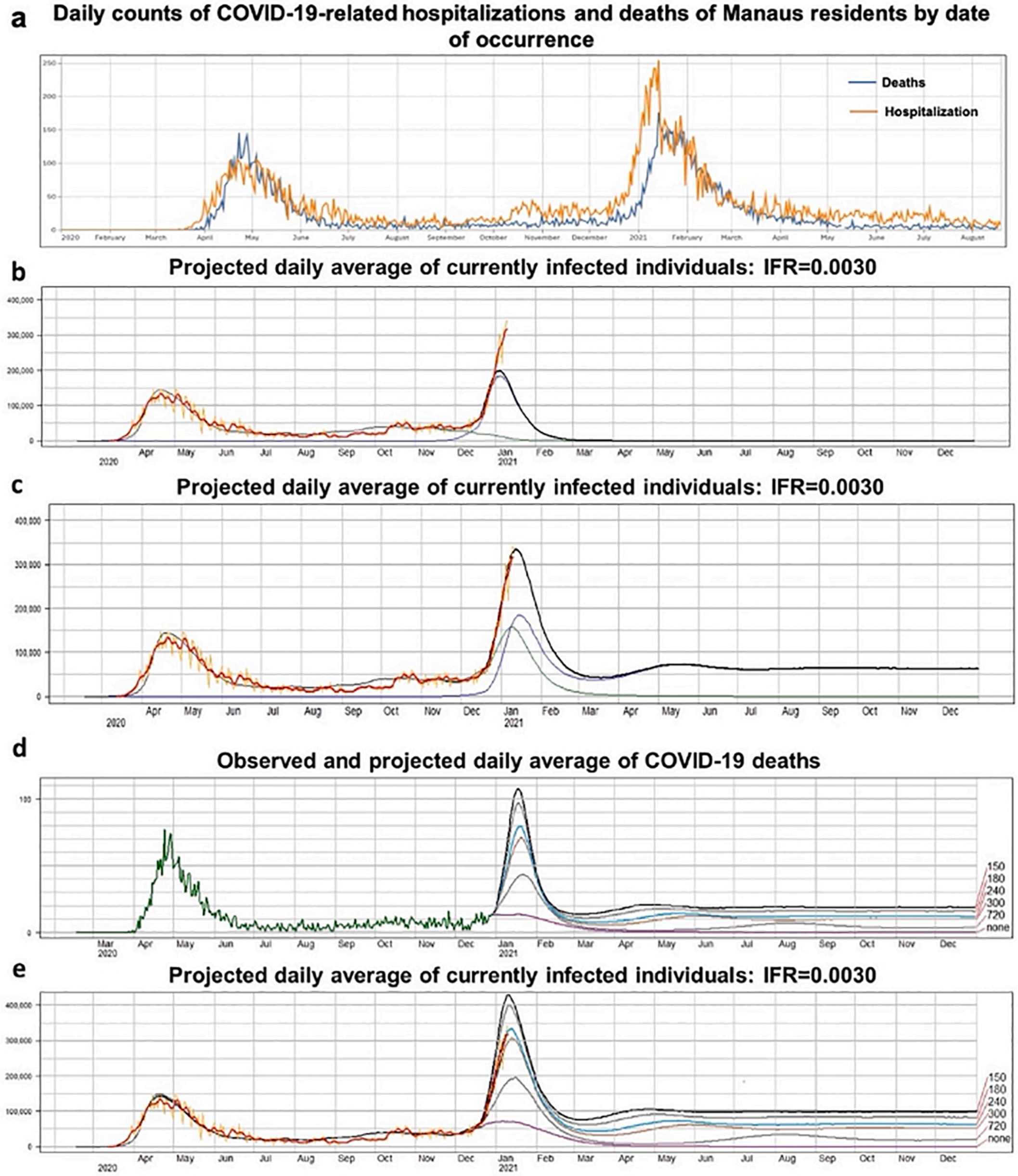

Fig. 2. **a** Daily counts of COVID-19-related hospitalizations and deaths of Manaus residents by date of occurrence (source: FVS Bulletin). **b** Without immunity loss, even a hypothetical new strain that is five times more transmissible cannot explain the sudden rise of COVID-19-related hospitalizations in December 2020 (the thin blue (green) line indicates the new (old) strain). **c** Assuming an average period of immunity loss of 240 days and a new strain with twice the usual transmission rate (thin blue line), the computed daily counts of COVID-19-related hospitalizations fit the observed data well. **d-e** Six non-intervention scenarios of the COVID-19 pandemic in Manaus from March 2020 to December 2021. Scenarios are shown with average periods for loss of immunity from 150 to 720 days, plus a non-immunity-loss scenario (none). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

overestimated in the city (Ferrante et al., 2021b).

The most plausible model also indicates that contact with SARS-CoV-2 did not confer immunity to the gamma variant. Serological tests in patients in Manaus attest to the loss of immunity due to natural contact with the virus and demonstrate the absence of any immunity to the gamma variant being present from immunity that had been acquired conferred by contact with the original strain of SARS-CoV-2 (Ferrante et al., 2021a). These findings confirm the results of our model.

According to our model, the only plausible projected scenarios based on the observed data for Manaus have naturally acquired immunity to the original lineage of SARS-CoV-2 being lost after an average of 240 days (Fig. 2c-e). A longer period of natural immunity would not be consistent with the scale of the current wave of COVID-19 in the city, in line with evidence of a recent study (Hall et al., 2021). Based on the most-plausible model (Fig. 2c), the gamma variant is estimated to be two (2.0) times more transmissible than the SARS-CoV-2 strain that gave rise to the pandemic. This transmission rate is lower than a previously proposed rate 2.6 times higher than that of the original variant (Coutinho et al., 2021) because the higher rate was based on an overestimated SARS-CoV-2 attack rate during the second wave of COVID-19 in Manaus and an underestimated rate for the loss of population immunity (Ferrante et al., 2021b).

Our model estimates that the gamma variant became predominant in infections observed in Manaus only in early January 2021 (Fig. 2c). The initiation of the second wave cannot be attributed to the gamma variant, since this wave was already underway, with the beginning of the peak of cases, deaths, and hospitalizations being in progress at the time that the gamma lineage is estimated to have appeared (Naveca et al., 2021). The appearance of the gamma lineage coincides with the beginning of the period of reduced social isolation in Manaus, with return of in-person classes that preceded the Christmas and New Year's celebrations (Fig. 3a, b).

Genomic data indicate that the gamma variant appeared in Manaus and then spread to other locations (Naveca et al., 2021). According to our results, on November 15, 2020 there already were 2000 active cases of gamma-variant infection in Manaus, so it is ruled out that the gamma variant emerged due to the agglomerations during the November 2020 elections or the end-of-year festivities (Fig. 3a). In addition, viral transmission rates increased by more than 40% in Manaus due to the return of in-person classes at the end of September and beginning of October: exactly 21 days (the mean viral cycle length) after the resumption of classes the number of hospitalizations increased, leading to the doubling that inaugurated the second wave (Fig. 3a, b). This increase in viral transmission in Manaus due to the return of face-to-face classes is indicated by the SEIRS model as the event that caused the emergence of the gamma variant and its proliferation (Fig. 2a, b). This conclusion is supported by phylogenetic analyses that trace the origin of the gamma variant (Naveca et al., 2021). Thus, our results show that the second wave was not initiated by the gamma variant, but rather this wave was the cause of the appearance of the gamma variant. The same was observed for the alpha variant (or B.1.1.7) that appeared in late summer 2020 in the United Kingdom, where early easing of social distancing was the cause of the explosion of cases that consequently gave rise to the alpha variant (Volz et al., 2021). Our results also indicate that the scenario in Manaus (Fig. 2c) was aggravated by the early easing of restrictions that occurred at the end of December 2020 (such as greater flexibility in shopping malls), which increased community transmission of SARS-CoV-2, boosting the transmission of the gamma variant in the population.

The return of in-person classes was a strategy of the governor of the state of Amazonas (Wilson Lima) and the president of Brazil (Jair Messias Bolsonaro) to make Manaus reach herd immunity, as was declared by the vice-governor of the state (Ferrante et al., 2021c). Wilson Lima went so far as to declare that the state of Amazonas no longer had any reported deaths and that official government data contained gross errors that as had been pointed out by researchers from the director's office of the Foundation for Health Vigilance (FVS) at a meeting organized by the Public Ministry of the State of Amazonas (Felizardo, 2020). Other official government communiqués declared that there was no risk of a second wave and that COVID-19 in Manaus had ended, with the return of in-person classes being safe (Felizardo, 2020).

Thus, both the beginning of the second wave of COVID-19 in Manaus and the emergence of the gamma variant can be attributed to the disastrous management by the governor, the president and the former minister of health (General Eduardo Pazuello), which included promoting the early opening of economic activities and the return of in-person classes that stimulated community transmission of SARS-CoV-2 (Ferrante et al., 2021c). Our results further indicate that the gamma variant caused two-thirds of the COVID-19 deaths in Manaus up to August 2021. This proportion of deaths caused by the gamma variant can be extrapolated to the total deaths in Brazil, which on August 5, 2021 were officially over 559,000 but could potentially reach double this number (Ferrante et al., 2021c).

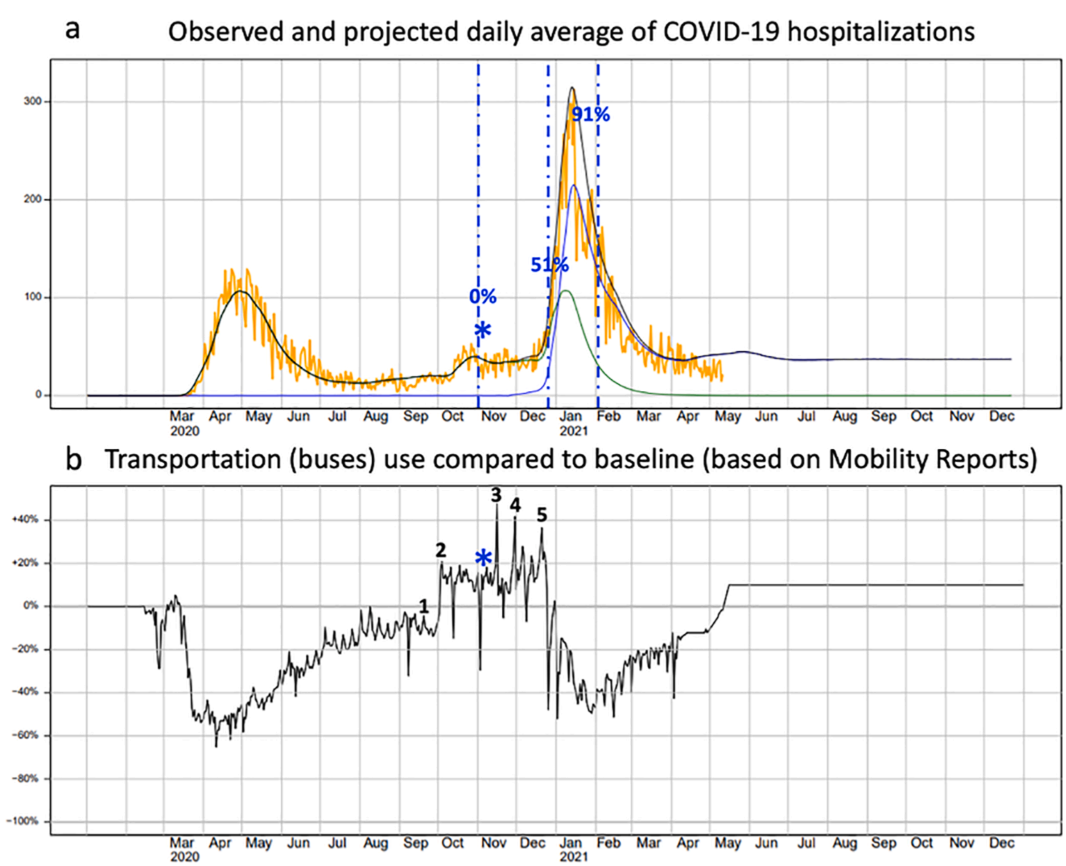

Fig. 3. **a** Observed and projected daily average COVID-19 hospitalizations. Yellow line: Observed hospitalization; Green line = Original lineage of SARS-CoV-2; Blue asterisk = appearance of the gamma variant; Blue line = gamma variant; blue dotted lines = percentages of the gamma variant for different dates. **b** Manaus urban mobility index compared to the baseline. Blue asterisk = appearance of the gamma variant; 1- call to return to face-to-face classes in elementary schools; 2 – Actual observed return of students in schools; 3- First round of elections for mayor and governor (according to the SEIRS model, an estimated 2000 individuals had been infected by the gamma variant by this date); 4- Second round of elections for mayor and governor; 5- Christmas. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Based on the mortality rates observed for the city, only 51.6% of the population had had contact with SARS-CoV-2 as of December 15, 2020. In addition, the models that best fit the observed course of the pandemic in Manaus, both for the number of infected individuals and for the number of deaths, demonstrate that the numbers of cases and deaths would only be possible with levels of reinfection in the population of 1.3% for the SARS-CoV-2 strain and 0% for the gamma variant on December 14th; 3.9% for the original strain and 1.4% for the gamma variant on December 31st and 14.7% for the original strain and 17.4% for the gamma variant on January 31st (Fig. 2c). Thus, the conclusion that Manaus had achieved herd immunity, as suggested by Buss et al., (2021), is completely ruled out by our SEIRS model and by long-term case studies that have shown a natural decline of IgG levels in patients who had natural contact with the virus, in addition to the absence of an immune response to the gamma variant in cases of reinfection (Ferrante et al., 2021a).

Although politicians and media reports blame the second wave in Manaus on the new variant (Ferrante et al., 2021c), this politically

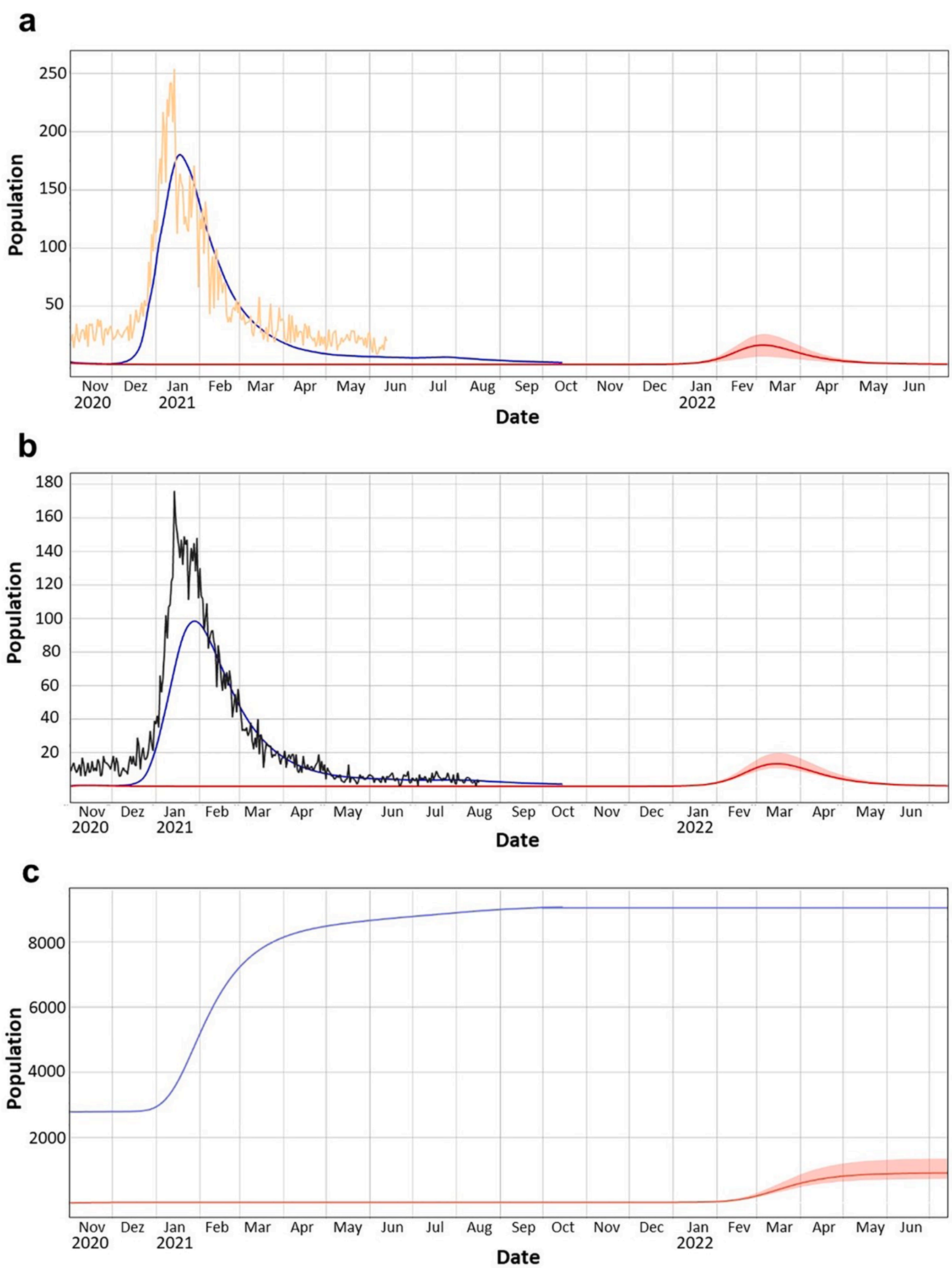

Fig. 4. **a** Projected hospitalizations from the delta variant: Yellow line: Observed hospitalization; Blue line = Projection of gamma variant; Red line = Projection of delta variant. **b** Projection of deaths from the delta variant: Black line: Observed deaths; Blue line = Projection of the gamma variant; Red line = Projection of the delta variant. c Projection of cumulative deaths caused by the gamma and delta variants until the pool of susceptible individuals is exhausted: Blue line = Projection of the gamma variant; Red line = Projection of the delta variant. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

convenient conclusion is not supported by our study. Modeled results with parameters for the "old" variant fit the observed cases and deaths in the second wave and are explained by the negligence of government authorities over the course of the pandemic [See Ferrante et al., 2020; 2021c]. The continued circulation of the virus in the population of Manaus may foment the emergence of still more new strains due to mutations (such as the K4174N mutation in the spike protein, which originated in the state of Amazonas) (Ferrante et al., 2021c). Because of this, we recommend that certain activities, such as face-to-face classes with schoolchildren, return only when teachers and students are completely vaccinated. Warnings to contain the COVID-19 pandemic in the Amazon have been given in peer-reviewed journals since April 2020 (Ferrante and Fearnside, 2020a), including warning of the possibility of a second wave in Manaus (Ferrante et al., 2020). It was also warned that the strategies of Bolsonaro, Pazuello and Lima implied an early resumption of classes in Manaus as a way to achieve herd immunity (Ferrante et al., 2021c).

3.2. The third wave and the delta variant

Our results indicate that, with just over 63.3% of the total population of Manaus immunized (second doses + single doses) by December 20, 2021 (FVS, 2021b), a third wave of COVID-19 caused by the delta variant would be expected, given that the proportion of susceptible individuals is still high (Fig. 4a, b). The model also indicates herd immunity via vaccination control of community transmission to delta variant only after 85 to 90% of the population of Manaus has been vaccinated with the second dose or single dose. Almost 13 daily deaths would be expected in Manaus at the peak of the third wave according to the most conservative scenario, with an estimated number of more than 911 new deaths occurring from the delta variant alone before the population reaches herd immunity via vaccination and exhaustion of the pool of susceptible individuals (Fig. 4c). In a new drastic scenario, with a new health system collapse and lack of oxygen, 26 daily deaths would be expected in Manaus at the peak of the third wave, with an estimated total number of more than 1355 deaths only by the delta variant (Fig. 4c). In either scenario there would be a greater impact on outpatient care in comparation with the number of hospitalizations.

It is unlikely that Manaus will shut down businesses and schools again; however, this must be considered because high community transmission has the potential to give rise to new variants (Ferrante et al., 2021b; 2021c). According to the SEIRS model, the delta variant was estimated to account for 1% of active cases in Manaus in August 2021, which is supported by genomic sequencing of patients who tested positive for SARS-CoV-2 (N = 400 with 4 patients infected with the delta variant) (Amazonas Atual, 2021). For the months before the third wave, the SEIRS model presents an average for hospitalizations caused by the gamma variant that fits the observed data perfectly; however, the average indicated by the model for deaths from June to August 2021 is slightly higher than the official data, which suggests underreporting, probably due to classification of deaths from COVID-19 as being from other causes.

Although these rates were still low in November 2021, the model indicates explosive behavior of the third wave, meaning that a new collapse of the health system could occur, with a consequent increase in fatalities as was observed during the first two waves. Thus, the state of Amazonas and the city of Manaus must prepare for the same hospital admission rates as those observed during the second wave, considering both regular beds and intensive-care unit (ICU) beds. Although vaccination tended to reduce the mortality rate during the third wave in the model, the absence of beds and oxygen would increase lethality, requiring the state to prepare to avoid another catastrophe in Manaus.

The day after the Brazilian Health Regulatory Agency (ANVISA) approved the vaccination of children aged 5 to 11 years on December 15, 2020, President Bolsonaro intimidated the technical staff who participated in this approval by requesting their personal data from ANVISA and announcing this to his (often violent) followers in a "live" on social media (G1, 2021). Three days later a flood of threats lead ANVISA to request police protection for its staff (Garcia, 2021). President Bolsonaro had already promoted the dismantling of ANVISA over the course of his first two years in office, and he has repeatedly tried to influence the body's actions on an ideological basis (Ferrante and Fearnside, 2019). Following a pre-dawn telephone call from the president, Health Minister Marcelo Queiroga announced that the vaccination of children aged 5 to 11 years would only be undertaken after a public consultation (Camarotto, 2021; G1, 2021). The president has formally requested the health minister to require a medical prescription for the vaccination of each child, in addition to written permission from the parents (Garcia, 2021). Current vaccination levels in Manaus are not sufficient to curb the third wave of COVID-19 that our SEIRS model projects (Fig. 4). The SEIRS model points to wide community circulation of SARS-CoV-2 in the absence of vaccination of this portion of the population, and the pandemic would continue due to the large portion of young people in the population of Manaus.

By December 15, 2021, Brazil had already recorded three cases of the omicron variant, and the spread of this variant has the potential to converge with the third wave of COVID-19 that is predicted by our model. Thus, a scenario might occur similar to the one observed in Manaus in January 2021, when the then-new gamma variant boosted the second wave, causing the health and cemetery systems to collapse in Manaus.

All of the intensive-care units in the state of Amazonas are located in Manaus, a fact that would add to mortality in the interior of the state with proliferation of the delta variant. The state of Amazonas, including the capital (Manaus), is home to a substantial part of Brazil's indigenous population (Ferrante et al., 2021a), which is a COVID-19 risk group (Ferrante and Fearnside, 2020a) and which has higher mortality than other ethnic groups (Ferrante et al., 2021c). The fact that elderly people are more vulnerable to COVID-19 represents a particularly serious risk to maintaining indigenous ethnic groups in the Amazon because traditional knowledge is transmitted orally by the elders (Ferrante et al., 2020). The federal government has failed to protect indigenous peoples from COVID-19, with provision of even basic resources such as drinking water being vetoed by the president himself (Ferrante et al., 2021c). Chloroquine and other medicines that are ineffective against COVID-19 have been distributed to indigenous peoples by the government (Ferrante and Fearnside, 2020b; Ferrante et al., 2021c). Given the increase in invasions of indigenous lands (Ferrante and Fearnside, 2020c; 2021), including those around Manaus (Ferrante and Fearnside, 2020b; 2021; Ferrante et al., 2021c), we recommend that measures be taken to ensure the basic rights of these peoples and that programs be created to protect them during and after the third wave that is projected in the region as a result of the delta and omicron variants. Decision makers in Brazil, especially in the Amazon region, should cease their denial of science and consequent insistence on early flexibilization of social-distancing measures, rejection of masking and opposition to a vaccine passport; these positions contribute to continuation of the COVID-19 pandemic (Diele-Viegas et al., 2021; Ferrante et al., 2021c; Ribeiro et al., 2021).

4. Conclusions

Our results indicate that, even if the new variant that originated in Amazonas (gamma or P.1) had appeared earlier than indicated, and even if its transmission rate were five times higher than the original strain, it would be implausible that this new lineage was responsible for initiating the second wave of COVID-19 in Manaus. The most plausible scenario, which best fits the second wave of COVID-19 in Manaus, corroborates a mixed hypothesis and indicates that the levels of infection by SARS-CoV-2 were overestimated by those foreseeing herd immunity. We estimate that 51.6% of the population had had contact with SARS-CoV-2 in mid-December 2020 and 60.0% by the end of January 2021. In addition, our model estimates that 32.1% of the cases were due to reinfection at the end of January 2021, with loss of immunity occurring after about 240 days and contact with one strain not conferring immunity to other strains. These results make it implausible that natural immunity is possible. Our results also indicate that the gamma variant originated after the beginning of the second wave and has a transmissibility rate twice that of the original SARS-CoV-2 strain, becoming predominant in the population in early January 2021. Under a conservative scenario in the absence of appropriate action to contain the delta variant, infections would culminate in a third wave with the potential to lead to an additional 911 deaths in Manaus before ample vaccination coverage is achieved. The model also indicates herd immunity via vaccination control of community transmission to delta variant only after 85 to 90% of the population of Manaus has been vaccinated with the second dose or single dose. The likely concurrent spread of the omicron variant during a third wave of COVID-19 in Manaus caused by the delta variant will only add further pressure on the health system, potentially leading to a new collapse of the system if appropriate action is not taken.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

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

Availability of data and materials

All data are available in the main text or the references.

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