Infectious Disease Modelling 9 (2024) 557–568

Contents lists available at ScienceDirect

Infectious Disease Modelling

journal homepage: www.keaipublishing.com/idm

Modelling the unexpected dynamics of COVID-19 in Manaus, Brazil

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ARTICLE INFO

Article history:
Received 25 July 2023
Received in revised form 13 February 2024
Accepted 26 February 2024
Available online 6 March 2024
Handling Editor: Dr. Raluca Eftimie

Keywords:
Modelling
COVID-19
Reproduction number
Herd immunity
Reinfection

ABSTRACT

In late March 2020, SARS-CoV-2 arrived in Manaus, Brazil, and rapidly developed into a large-scale epidemic that collapsed the local health system and resulted in extreme death rates. Several key studies reported that ~76% of residents of Manaus were infected (attack rate AR ≃ 76%) by October 2020, suggesting protective herd immunity had been reached. Despite this, an unexpected second wave of COVID-19 struck again in November and proved to be larger than the first, creating a catastrophe for the unprepared population. It has been suggested that this could be possible if the second wave was driven by re-infections. However, it is widely reported that reinfections were at a low rate (before the emergence of Omicron), and reinfections tend to be mild. Here, we use novel methods to model the epidemic from mortality data without considering reinfection-caused deaths and evaluate the impact of interventions to explain why the second wave appeared. The method fits a "flexible" reproductive number $R_0(t)$ that changes over the epidemic, and it is demonstrated that the method can successfully reconstruct $R_0(t)$ from simulated data. For Manaus, the method finds AR ≃ 34% by October 2020 for the first wave, which is far less than required for herd immunity yet in-line with seroprevalence estimates. The work is complemented by a two-strain model. Using genomic data, the model estimates transmissibility of the new P.1 virus lineage as 1.9 times higher than that of the non-P.1. Moreover, an age class model variant that considers the high mortality rates of older adults show very similar results. These models thus provide a reasonable explanation for the two-wave dynamics in Manaus without the need to rely on large reinfection rates, which until now have only been found in negligible to moderate numbers in recent surveillance efforts.

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Peer review under responsibility of KeAi Communications Co., Ltd.

https://doi.org/10.1016/j.idm.2024.02.012

1. Introduction

The arrival of SARS-CoV-2 in Manaus, Brazil, in late March 2020, led to an explosively growing epidemic, resulting in death rates so extreme that they captured worldwide media attention and concern. The situation was characterized by the failure and breakdown of the local health system and the appearance of mass grave sites as the number of COVID-19 deaths became unmanageable (Brazil Ministério da Saúde Opendatasus, 2020). Moreover, local Amazonian indigenous communities often went completely without medical services, to the point where international warnings of genocide were issued. The epidemic proceeded to rapidly decline and was then followed by a lull in July (see Fig. 1). A key study (Buss et al., 2020) estimated that by October 2020, approximately 76% of the city's population had already become infected by the first wave. An "Attack Rate" of this magnitude (AR_1~76%) indicated that herd immunity had been achieved (we refer to the Attack Rate of the first wave as AR_1). As such, the population should have been protected and safe from further major COVID-19 outbreaks, at least for a reasonably lengthy period into the future. However, in reality, allusions to herd immunity, which were being discussed at the time, just provided a false sense of security. Instead, in December 2020, a vicious, unexpected second wave of COVID-19 erupted, resulting in more than 170 deaths in the population per day and rapidly triggering yet another collapse in the city's rundown healthcare system (Phillips, 2021). Alarmingly, the second COVID-19 wave in Manaus proved to be even larger than the first in terms of the number of COVID-19-related deaths and number of people clinically infected (Brazil Ministério da Saúde Opendatasus, 2020; Sabino et al., 2021), as visualised in the mortality data in Fig. 1. Moreover, the same two-wave epidemic dynamics were duplicated over the whole state of Amazonas, of which Manaus is the capital and largest city, and were similar in many other cities of Brazil as well, as shown in Figs. 1 and 2. It thus seems highly unlikely that Manaus achieved an AR_1~76% over the first wave (Murchu et al., 2022). Indeed, some researchers have suggested that the ~76% Attack Rate estimate (AR_1) of the first wave, obtained by seroprevalence testing, may have been inflated as a result of biases (Amigo, 2020; Backhaus, 2020) in the blood donor data (Buss et al., 2020).

The events that occurred in Manaus warrant further serious epidemiological investigation. Here we explore alternative and complementary epidemiological modelling analyses of publicly available mortality datasets to help understand why the first wave of the COVID-19 outbreak "crashed,", why a second wave suddenly appeared in Manaus in December 2020 contrary to expectations, and what led the second wave to be larger than the first. The approach is specially designed to take human behavioural responses and non-pharmaceutical interventions (NPIs) into account when modelling the spread of COVID-19. Such mitigation activities act to depress the size of epidemics by reducing the reproductive number $R_0(t)$ over time (Brauer, 2019; Britton et al., 2020; Chowell et al., 2016; Stone et al., 2020; Zhao et al., 2018). Despite the infamously disorganized and often ineffective interventions in Brazil, there were still significant time periods when mitigation practices had an impact. The key to this modelling is finding a way to estimate $R_0(t)$, which is a measure of the transmission rate as it changed over the epidemic.

In more formal terms, the reproductive number $R_0(t)$ is defined as the average number of secondary infections a typical infectee can generate over the period of the disease, at time t, in a fully susceptible population. Brauer (2019) modelled behavioural interference by assuming that $R_0(t)$ reduces exponentially over time, while other studies of cholera and influenza use similar parametric approaches (Chowell et al., 2016; King et al., 2008). Here we generalise this principle by fitting a "flexible" $R_0(t)$ to the data without pre-imposing any specific functional form (He et al., 2010; Stone et al., 2020; Zhao et al., 2018). Our method makes it possible to reconstruct how $R_0(t)$ changes in time and factor this in when calculating AR and levels of immunity in the population.

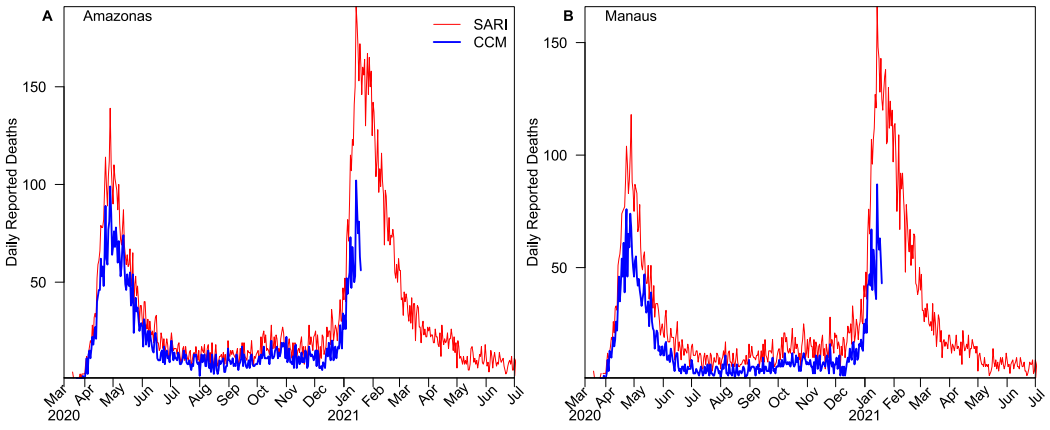

Fig. 1. Comparison of Confirmed COVID-19 Mortality (CCM) and SARI mortality datasets. Daily deaths in (A) the state of Amazonas and (B) Manaus, the capital city of Amazonas, from March 2020. Manaus had ~4600 such deaths up to October 2020, followed by ~8120 deaths until May 2021. Thus, the second wave was characterized by 1.76 times more COVID-19-related deaths than the first.

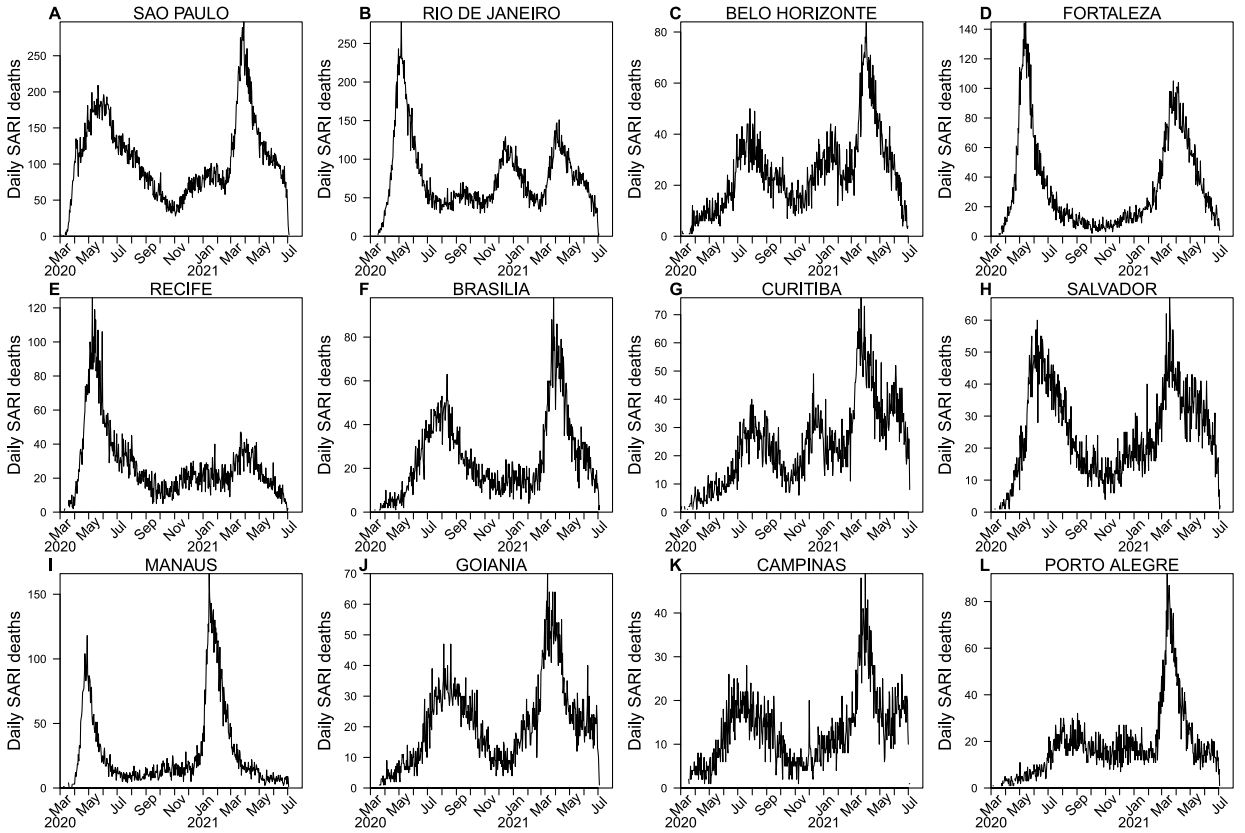

Fig. 2. Daily SARI daily deaths in cities across Brazil were plotted over 2020–2021. Data from Ref. Phillips (2021). The two waves in Manaus appeared in many other cities in Brazil, with some showing a more complex multi-wave character. The control of SARS-CoV-2 and thus the daily deaths is function of the cities mitigation activities, the build up over extended time of immunity, and the appearance of the highly transmissible variant of concern P.1 which spread through most of Brazil in December 2020 after spreading from Manaus.

Although He et al. (Elizabeth Pereira et al., 2021) recently presented an analysis of the outbreaks in Manaus by making a comparison with related occurrences in the nearby city of Iquitos, Peru (both cities are located in the Amazon), here we extend this analysis in several important ways. First, we provide a full justification of the methodology and demonstrate that it is possible to accurately reconstruct $R_0(t)$ as it changes in time by applying the method to hypothetical outbreak simulations. After the method is applied to the Manaus dataset, we extend the analysis by considering a two-age-class model and a multiple-strain model. In all cases, the method accurately reproduces the two-wave COVID-19 dynamics in Manaus without considering large reinfection rates, as in other studies (Buss et al., 2020; Faria et al., 2021a). The modelling analysis also gives important information on the attack rate (AR), the impact of mitigation practices, the questionable attainment of herd immunity, and provides estimates on the transmission of the SARS-CoV-2 virus and the new P.1 lineage.

2. Data

The analysis makes use of two types of daily mortality datasets that are publicly available. Mortality data should reflect trends in disease dynamics with reasonable reliability and provide a useful reference frame, particularly when the quality of other surveillance datasets might be in question, as is often the case.

The first dataset, provided by Brazil's Ministry of Health (Brazil Ministério da Saúde Opendatasus, 2020), consisted of Severe Acute Respiratory Illness (SARI) daily deaths taken from hospitalized cases (including COVID-19 confirmed) across Brazil. The same SARI deaths have been used in a number of recent key studies where they were considered a proxy for true COVID-19 mortality (Buss et al., 2020; de Souza et al., 2020). It is our understanding there were no other respiratory disease over the pandemic that had significant impact on the death rates. During the pandemic, COVID-19 replaced influenza as the major respiratory mortality disease (Centers for Disease Control Prevention, 2022). Because of this, the SARI data should be seen as a reasonable index of mortality and justifies its use by other similar modelling studies as well (e.g., Buss et al., 2020). The data is available for cities and all 27 Confederate units in Brazil. For Manaus and Amazonas, we also analysed the COVID-19 Confirmed Mortality (CCM) datasets (Amazonas and Manaus daily COVID, 2021), which were continually updated with retrospective corrections. The data was collected and compiled by the local government in collaboration with the FVS

(Fundação de Vigilância em Saúde do Amazonas) and Brazil's Ministry of Health (Amazonas and Manaus daily COVID, 2021). The two datasets are compared in Fig. 1 for the two waves of the epidemic in Manaus and Amazonas, beginning in March 2020. The CCM dataset of daily deaths appears to suffer from relatively minor under-reporting, but only to a limited extent, and it is quite likely that the CCM dataset is a proper subset of the SARI deaths. When estimating attack rates, we only used the SARI dataset so as to minimise the effects of any under-estimation. In general, we repeated all analyses on the two datasets, and there was generally little difference.

3. Results

The SEIRD-type epidemiological model was utilized to analyze mortality datasets in Brazil, providing valuable insights into the dynamics of the COVID-19 epidemic and its impact on different subpopulations. Turning specifically to Manaus, we explored several different scenarios, which are discussed in turn.

3.1. Largely unmitigated epidemic

We began by asking the question: "Was the first wave a largely unmitigated epidemic?", as was suggested in Ref. Brazil Ministério da Saúde Opendatasus (2020). A largely unmitigated epidemic would correspond to a model with a fixed transmission rate i.e., $R_0(t) = constant$. Which is, in fact, the usual configuration of SEIRD-type models when simulating single epidemics. We fitted a constant transmission model to the data, but it was found that any such fit yielded outcomes that did not appear to be meaningful. For example, Fig. 3a shows the best fit to the Manaus daily death data with a constant transmission rate. The modelling predicted a large fixed $R_0 = 3.1$ over the whole period through January 2021 (blue dashed line) and provided a very poor fit to the data. Specifically, the observed epidemic curve (of the daily deaths – red) sits far from the median, while the 95% range based on 1000 simulations (grey shaded region) is extremely broad. Hence, we reject the possibility of Manaus having experienced a largely unmitigated epidemic in the first wave, especially given the model's inability to capture a second wave.

3.2. Modelling with flexible $R_0(t)$

We, then proceeded to model the mortality data with a flexible fitting of $R_0(t)$ that allowed for changes in the reproductive number as the epidemic evolved in time. This would allow determination of when and to what degree $R_0(t)$ changed, presumably due to mitigation activities. Fig. 3b and c show that for this scenario, an excellent fit of the Manaus mortality data is readily obtained. Fig. 3b gives fits for CCM mortality data (from Ref. Amazonas and Manaus daily COVID (2021)) while Fig. 3c fits SARI mortality data. Note how the observed epidemic mortality dynamics (red line) sit within the 95% range based on 1000 simulations (grey shaded region) and close to the median of the model simulations (black). Moreover, a characteristic feature of the fit is that $R_0(t)$ (blue dashes) decreased rapidly in April. The city's partial-lockdown and mitigation activities were presumably responsible for this decrease, and it was typical of regions in most of Brazil, as seen in Fig. 4 and SI Fig. S2.

This feature may have allowed a low stationary endemic state to be maintained from July to November, as was actually the case. (Note that $R_0(t)$ should not be confused with the effective reproductive number $R_e(t) = R_0(t)S(t)$ mentioned in our Supplementary Material, which is not plotted here.) In the first phase of the epidemic, our estimated reproduction number for Manaus is $R_0 = 2.250$ 95% CI(1.79, 2.79) (see SM1) with data from Amazonas and Manaus daily COVID (2021), which is similar

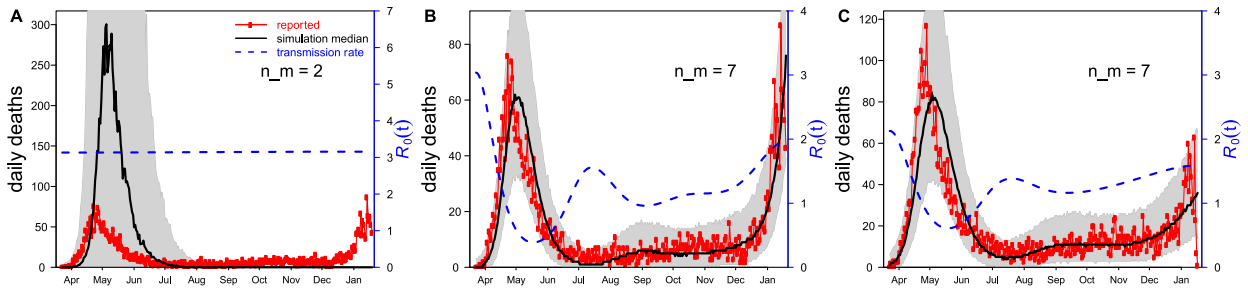

Fig. 3. The SEIRD model was used to fit the reported daily COVID-19 confirmed deaths (CCM) in Manaus (red). The flexible transmission rate $R_0(t)$ plotted as a blue dashed line and scaled according to RH axis. The black line is the median of model simulations of the mortality data, and the grey shading indicates the 95% range based on 1000 simulations. (A) A constant transmission rate (constant R_0) fails to fit the major wave well (panel a; number of nodes in transmission rate spline $n_m = 2$). CCM data from Ref. Amazonas and Manaus daily COVID (2021). (B) When the spline's number of nodes was increased to 7, this gave a flexible $R_0(t)$, and the fitting performance was improved. Based on the 2nd-order Akaike Information Criterion (AICc), the best performance was found for $n_m = 7$. CCM data from Ref. Amazonas and Manaus daily COVID (2021). (C) Same as panel b but based on SARI mortality data in Manaus from Brazil Ministério da Saúde Opendatasus (2020) (red).

to other studies (de Souza et al., 2020; Mellan et al., 2020; Naveca et al., 2021). A full test of the "flexible $R_0(t)$" methodology is given in the Supplementary Notes (SI10).

Through fitting and simulation, the model estimated that by October 2020 in Manaus, the attack rate of the first wave was approximately $AR_1 \simeq 34\%$ (~30–38% see Fig. S5b). Our model estimate is far less than $AR_1 \simeq 76\%$, as estimated in Refs. Buss et al. (2020), Faria et al. (2021a), and far less than the herd immunity threshold estimated as 60–66% (Buss et al., 2020). It would nevertheless appear reasonable given the large ongoing second wave that re-emerged in December only a few months later. We will discuss this further shortly.

Buss et al. (2020) argued that a high estimate of $AR \simeq 76\%$ for Manaus in the first wave implies that the infection fatality rate (IFR) must be meagre to maintain consistency. It was claimed on average IFR $\simeq$ 0.018–0.26%, which is similar to some earlier reports of the IFR in Manaus (Levin et al., 2020) (see Discussion). However, we were unable to fit mortality dynamics sensibly when assuming such low values of IFR (Fig. S3). The model estimates from fitting the mortality data indicated that the IFR in Manaus is approximately $IFR \simeq 0$. years-0.83% (see Discussion and Fig. S5b). Buss et al. suggested that the IFR of Manaus was almost 40% lower than that of São Paulo. But this appears to contradict what is observed in the ASFR (Age SARI Fatality Rate, which should be a proxy for the IFR) data, as shown in SI Fig. S4. In fact, the ASFR of Manaus is larger than most other cities in Brazil. This conflicting information makes the comparison between Manaus and São Paulo complex and insights regarding the differences in AR are inconclusive, despite its use in other studies.

3.3. Attack rate of first wave considering population two-age class demographics

In order to estimate attack rates, we also included the population's demographic characteristics to take into account, e.g., the fact that older members of the population are more susceptible to COVID-19. Manaus has a very young population with relatively low mean age (Buss et al., 2020). We thus, chose the age group threshold at 50 years, rather than the usual 65 years, such that the elderly age group has a reasonable population size. In other words, Manaus can be qualitatively approximated as a two age-class system. Some 20% of the population are older than 50 years of age with high infection fatality rate (IFR) and contribute significantly to COVID-19 related deaths, while the remaining 80% of the population are under 50 years of age and have such low IFR that they contribute little (<7%) to the COVID-19 deaths, according to Levin et al. (2020), in an analysis of the first wave. Thus, when estimating attack rates, we also made use of a two age-class model, which was constructed as a natural extension of the basic model (see Methods). Qualitative arguments (given in SI5), however, led us to believe that adding the age-class dynamics might not change the results in a major way, as proved to be the case.

The model estimates found that by October 2020 in Manaus, $AR_1 \simeq 34\%$ [~32–38%] with a two age-class model, as based on SARI mortality data.

3.4. Modelling the full two-waves with a two-strain model

Following the rapid explosion of the second wave of COVID-19 in December 2020, a new highly transmissible P.1 lineage of SARS-CoV2 were identified. Initially, it was thought to appear close to January 11, 2021, but the same lineage was later identified in samples that date back to early December 2020 and most likely was already present in November 2020 (Faria et al., 2021a, 2021b; Naveca et al., 2021). We, therefore, attempted to also model the full two waves of the Manaus epidemic using an explicit two-strain model (Fig. 5a) that included both the P.1 and non-P.1 variants. Given the significantly low cases of reinfection found to date, it was assumed that the strains share full cross immunity, such that recovery from infection by one of the strains precludes becoming infected by the second strain. Structurally, the second strain was integrated into our original model by adding compartments that explicitly represent the different epidemiological states associated with the P.1 strain (i.e., Exposed, Infectious, Hospitalized, Recovered and Dead). This was also an opportunity to estimate the unknown transmission rate of the P.1 variant. As such, the parameter η was introduced to denote the relative transmission of P.1 variant compared to non-P.1 strain.

To facilitate the partitioning of the model fit between two strains, we used data from Naveca et al. (2021) that gave the relative proportion of P.1 cases among all cases as a function of time based on genomic analyses as plotted in Fig. 5b (see also SI Fig. S7). The goal was to check whether both simulated daily mortality data would match the observed data and simulated strain proportion would match the observed strain proportion (open circles in Fig. 5b) as a function of time. The value of the parameter η, which gave the best fit to the data was deduced numerically (i.e., in terms of the smallest sum of squared error (SSE)).

Fig. 5a shows the results of the two-strain model fit to the SARI data until March 1, 2021. In this fit, 34% of the population was infected by October 2020 (i.e., $AR_1 = 34\%$), while 67% was infected by the end of February 2021. A good fit to the population data was only possible if the P.1 transmission rate was 1.9-fold that of the non-P.1 strain (Coutinho et al., 2021; Faria et al., 2021b) as seen in Fig. 5b–d. This is similar to estimates in Coutinho et al. (2021), Faria et al. (2021b), which suggested the transmission rate of the P.1 was 2.2 times greater, although based on smaller sample size for their genomic data (SI Fig. S7). Naveca et al. (2021) give several hundred sequence samples per month compared to Faria et al. (2021a), who used a sample size of several dozen per month.) The fit of the genomic data in Fig. 4b is at least as good as and mostly better than other attempts (Coutinho et al., 2021; Faria et al., 2021b). Finally, it should be noted that similar to all other related studies we are aware of, the model did not take into account that during the second wave of the Manaus epidemic, the proportion of those

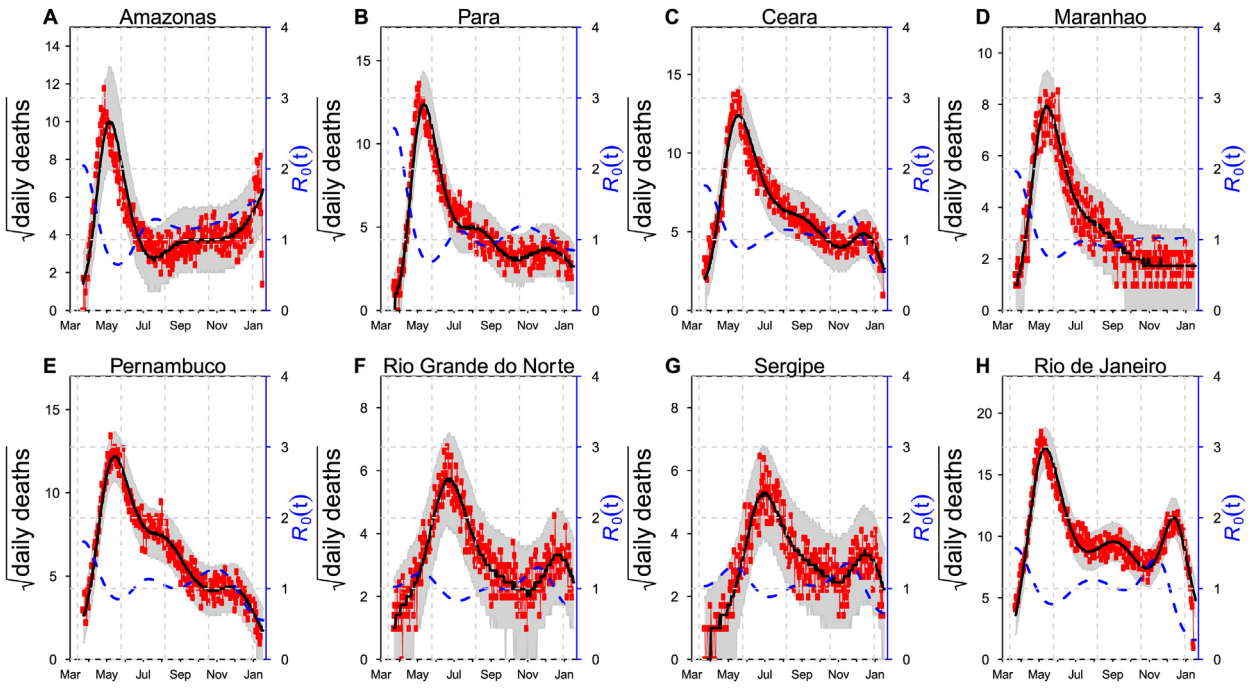

Fig. 4. An SEIRD model is fitted to reported daily SARI deaths in eight Brazilian states (Brazil Ministério da Saúde Opendatasus, 2020) (red). The number of nodes in transmission rate spline was set at $n_m = 7$. Red points represent real data in terms of deaths per day, the black line is the median of model simulations of the mortality data, and the grey shading indicates the 95% range based on 1000 simulations. The reproductive number $R_0(t)$ appears as a blue dashed line as scaled according to RH axis. Supplementary Fig. S2 gives plots for all other federative units.

infected in the population of younger age (also having a lower IFR) significantly increased. This would tend to increase the Attack Rate making our total estimate of AR≃67% by February 2021 conservative.

3.5. Checking the method

Finally, as a test of the methodology, which is based on iterated filtering (Ionides et al., 2006), we generated three fictitious time-series from March 2020 to January 2021 with $R_0(t)$ arbitrarily varying in time $0.5 < R_0(t) < 2.2$ (Fig. 6a–c, blue dashed curve). These time-series were used to drive the model parameterised for Manaus in order to generate dummy datasets of daily mortality numbers (red trajectory with circles). We could then use our method to reconstruct $R_0(t)$ (plotted in green). The results show that the reconstructed $R_0(t)$ is a very close estimate of the original value (dashed blue) in each case. Similar to Figs. 3–5, the black curve and grey regions were based on simulations of the SEIRD model using the same reconstructed $R_0(t)$. This confirms the capability of the method to reconstruct $R_0(t)$ and that our analysis of the Manaus data is reliable. Variations of the methodology has been tested in other contexts in our own work and by several independent teams (Camacho et al., 2011; He et al., 2011; King et al., 2008).

4. Discussion

It is not uncommon for potentially large-scale epidemic outbreaks to die out before predictions of conventional epidemiological models, and well before herd-immunity has developed (Brauer, 2019). Brauer (2019) explored this when studying the Ebola outbreak in Sierra Leone and Guinea in 2014 (Althaus, 2014), which began with an initially susceptible population of 5,360,000 residents. While a conventional SEIRD-type model predicted ~5,000,000 Ebola cases (Brauer, 2019), the epidemic resulted in “only” 14,120 infected individuals. We documented a similarly perplexing account of a catastrophic epidemic outbreak in WW2 (Stone et al., 2020). Using a similar modelling approach to that proposed here, it was shown that a dangerous outbreak of pandemic typhus crashed well before herd immunity was reached, and just before winter when the number of infected cases should accelerate. As emphasised in Brauer's work, human behavioural responses act to depress the size of epidemics by reducing the reproductive number $R_0(t)$ over time (Brauer, 2019; Britton et al., 2020; Chowell et al., 2016; Stone et al., 2020; Zhao et al., 2018), providing a “protection” effect based on behaviour rather than immunity. Here, we attempt to take the latter into account by fitting a “flexible” $R_0(t)$ to the data (He et al., 2010; Stone et al., 2020; Zhao et al., 2018).

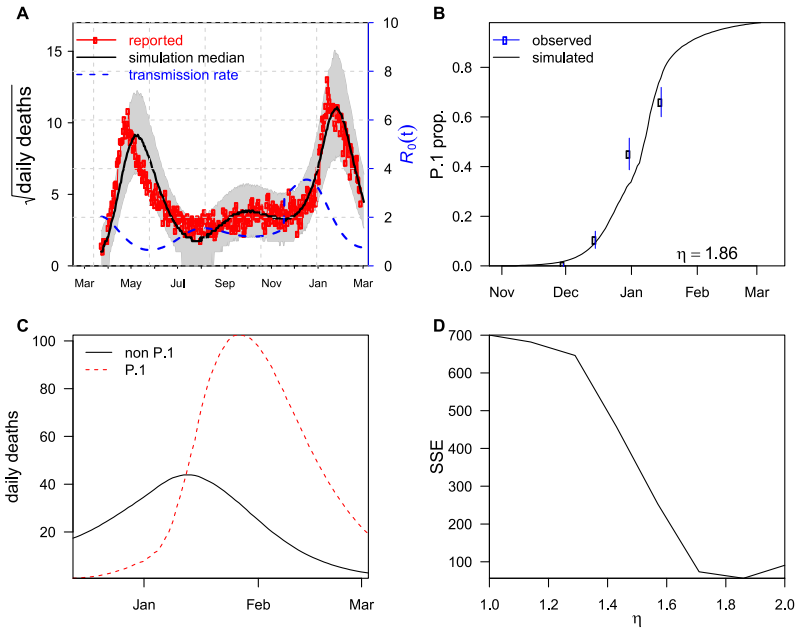

Fig. 5. Fitting a two-strain model to SARI mortality data and sequencing proportion of P.1 strain simultaneously. η denotes the relative transmission of P.1 variant compared to non-P.1 strain. $\eta = 1.9$ yields the best fit for both SARI deaths (a) and sequence proportion (b), the latter taken from Ref. Faria et al. (2021b). Panel (c) shows the simulated daily deaths due to P.1 and non-P.1 strains. Panel d shows the sum of squared error (SSE) based on sequence proportion data (b) as function of η. Smaller or larger η leads to mismatching between simulated and observed sequence proportion.

The dynamics in time of $R_0(t)$ in Manaus and Amazonas was similar to what was found right across Brazil as can be seen in Fig. 4 which plots the daily number of SARI daily and our estimates of $R_0(t)$ in eight arbitrarily selected Brazilian states (data from Ref. (Brazil Ministério da Saúde Opendatasus, 2020); Supplementary Fig. S2 gives plots for all other federative units). The reproductive number $Ro(t)$, which is the focus here should not be confused with the effective reproductive number $R_e(t) = R_0(t)S(t)$ used in other contexts, which we deliberately avoid in this paper (see SI). This is because we are trying to evaluate the impact of mitigation such as lockdowns which directly impact $R_0(t)$ (through the contact rate $\beta(t)$; *see Methods*). The graphs indicate that the epidemic curve of the first wave was roughly synchronized over all of Brazil in the period May–July. All 27 federative units peaked in this 2-month period, some earlier than others, and then declined within several months. The differences in timing between states presumably relate to spatial spread and differences in local NPI policies in terms of initiation and intensity, as well as differences in local physical circumstances. The outbreaks in the first wave appear to have turned around due to the impact of mitigation procedures in Brazil (NPIs including social-distancing, facemasks, hand-

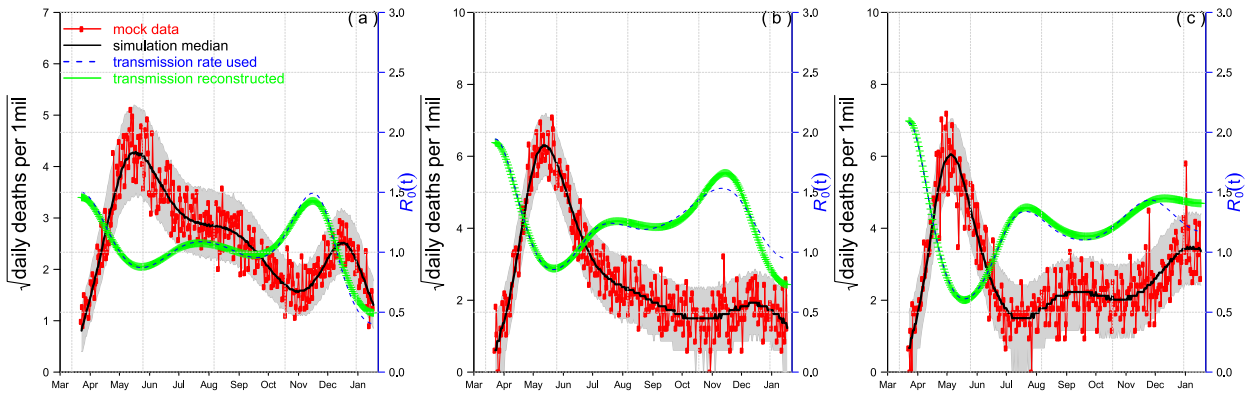

Fig. 6. Fitting $R_0(t)$ from mock data. We generated three simulated time series of $R_0(t)$ changing over time in an arbitrary way between March 2020 and February 2021 (blue dashed lines). Each time series of $R_0(t)$ was used to generate a simulation of mortality data from the SEIRD model (mock data, red trajectory with circles), and basically three different patterns of death data resulted as seen in (a), (b), (c). Then we used our fitting method to reconstruct $R_0(t)$ (green trajectories) from the mock data. The solid black lines and grey regions, similar to Figs.1 and 2, were based on simulations using the reconstructed $R_0(t)$. The reconstructed $R_0(t)$ proves to be a good estimate of the initial $R_0(t)$.

sanitizing, work stoppages, lockdowns, travel bans, restrictions on gatherings, etc.) as seen by the fall in $R_0(t)$, and not the attainment of herd immunity. This is correspondingly seen in the major reduction in the reproductive number $R_0(t)$ in Fig. 4 early in the first wave of the epidemic in most regions. The epidemics were curtailed even though the mitigation activities were often flawed, mishandled, and often not taken seriously by many sectors of society, including powerful figures in government (see SI8). Better handling of the public health catastrophe could have prevented the extreme death rates in Manaus and all over Brazil. In Manaus regulatory measures at the end of March 2020 were introduced to limited mobility and travelling, to shut-down all non-essential services, to practice social distancing and isolation, and in early May, usage of face masks was compulsory. The effects are well reflected in the drop in local mobility index (Lalwani, Araujo-Castillo, et al., 2021).

The model estimates an attack rate in Manaus of $AR_1 \simeq 34\%$ up until October 2020, and thus far below herd immunity. This is very close to results found in a recent independent seroprevalence study based on 3046 residents of Manaus (Lalwani, Salgado, et al., 2021). For the same period, Lalwani, Salgado, et al. (2021) estimated a crude AR_1 of 29% (but possibly up to an adjusted AR_1 of 40% when using an atypically high seroreversion rate). Our estimates of AR_1 are also in-line with the work of Mellan et al. (2020) and Hallal et al. (2020), who reported similarly low attack rates. The seroprevalence survey of Hallal et al. (2020) reported an AR = 14.6% with a 95% confidence interval CI: (8.9%, 22.1%) by June 7, 2020, while our model estimates AR = 20% by this time. Some researchers have also suggested that the ~76% Attack Rate estimate (AR_1) of the first wave, obtained by seroprevalence testing, may have been inflated as a result of biases (Amigo, 2020; Backhaus, 2020) in the blood donor data (Buss et al., 2020).

4.1. Reinfections

Although the results reported here quantitatively confirm that the AR in Manaus was likely to be far less than $AR_1 = 76\%$ by October 2020 (as estimated in Ref. Buss et al., 2020), they point to another danger that was overlooked at the time – the possible development of a second wave. With the appearance of the second wave in December 2020, it has become clear that either the estimated (Buss et al., 2020) AR_1 of 76% was incorrect or there were widespread reinfections generating the second wave. But to date, only 3 confirmed reinfections have been recognized by the health officials in Amazonas (da Saúde, 2021), so this latter argument appears implausible. Another large-scale study of N = 154,000 infected individuals in Israel found a reinfection rate of 0.1% (two PCR-positive at least 100 days apart) (Perez et al., 2021) again highlighting our point. Another large-scale study in Denmark found a rate of 0·65% two PCR-positive at least 3 months apart) (Hansen, Michlmayr, Gubbels, Mølbak, & Ethelberg, 2021). As far as is currently known pre-Omicron reinfections are minimal in other countries. In a systematic review of 11 large-scale cohort studies in different countries, reinfection of SARS-COV-2 was found to be rare (0%–1.1%), and immunity did not wane for at least 10 months post-infection (O Murchu et al.). Similarly, a comprehensive large-scale UK study on the "analysis of reinfections" (released in October 2021) found 133 reinfection out of 17,434 participants (those had a positive test >90 days ago or four negative tests since a positive results). That is a low raw reinfection rate of 133/17,434 = 0.76% (Elizabeth Pereira et al., 2021). They included all data from across the UK collected since the survey commenced on 26 April 2020 up to 5 June 2021, making it the largest such study in the UK. In this work, we did not model reinfection, thus reinfection-led deaths were ignored. In our other work (He et al. PNAS 2023 (He et al., 2023)), we considered immune waning and immune escaping and our key conclusion holds. Finally, a very recent study of Gamma reinfections in different regions of Brazil makes clear "a low overall risk of severe Gamma reinfections, supporting that the abrupt increase in hospital admissions and deaths observed in Amazonas and other Brazilian states during the Gamma wave was mostly driven by primary infections" (Naveca et al., 2023).

4.2. Infection fatality rate

The attack rate estimates of Faria et al. (2021a) are based on accepting an IFR that is close to IFR = 0.32%, which was used as an informed prior in their Bayesian model. Older studies that might suggested a low IFR (Levin et al., 2020) may need updating based on newly available data. The key problem is that an IFR = 0.32% would automatically set AR_1>66% in the first wave, given that the records show 4600 SARI deaths in Manaus in that period (since $AR_1 = 4,600/0.32/2.18$ million. 100%). For the case of almost full cross immunity (few reinfections), the model of Faria et al. (2021a, 2021b) is unable to fit the data unless the P.1 strain has an IFR three times that of the non-P.1 strain, which we believe to be extreme, and largely an outcome result of trying to maintain a large AR>66% in the first wave with minimal mitigation allowed for.

The discrepancy between our model and that of Faria et al. (2021a, 2021b) and Buss et al., 2020 has been outlined in detail elsewhere but relates to their unusually high estimates of seroreversion decay rates, low estimates for IFR and a Bayesian model based on questionable informed priors that do not comprehensively take into account the potential effects of mitigations. The more likely explanation for the second wave is that the AR of the first wave was far less than AR = 76%, so a large pool of susceptibles remained after the first. Thus relaxed mitigation efforts in late 2020 combined with the appearance of the highly transmissible P.1 variant led to the triggering of the second wave and the large numbers of deaths that rapidly followed. (The model estimates that the P.1 variant is 1.9 times more transmissible than the original strain.) Through modelling, we estimate that ~70% of the Manaus population became infected by March 2021 and that IFR ≃ 0.8 over the two waves according to Fig. S5 (assuming that the P.1 and non-P.1 have similar characteristics for a first approximation).

Our work highlights the difficulties policy makers face when attempting to predict herd immunity, as well as the importance of developing and using complementary mechanistic epidemiological modelling tools when assessing outbreaks

with one or more virus strains. The methods used here based on a "flexible number $R_0(t)$," are instrumental in cases where NPIs and human behaviour impact the temporal development of epidemiological dynamics, for which other traditional methods can fail. The experiences in Manaus with regard to COVID-19 make clear the need for future research characterizing the nature of reinfection and protective immunity, for which we currently have limited understanding and the epidemiological dynamics they induce at the level of the host population. Incorrect assumptions or viewpoints about underlying processes can lead to major misconceptions on how to most responsibly address upcoming challenges of COVID-19. This will be all the more problematical with respect to characterizing the emergence of de-novo strains and their potential trajectories of adaptation, such as immune escape, evolution of vaccine resistance and virulence. Thus, in this paper we deliberately discuss the importance of modelling the COVID-19 waves and Attack Rates correctly allowing for the possibility of multiple waves. Errors can lead to a mistaken prediction of herd immunity, and a false impression of protection. The deadly events that occurred in Manaus, and the appearance of a second wave against epidemiological predictions of the time, highlights the importance of the principles discussed here when dealing with any future pandemics.

Finally, while our study offers significant contributions to the understanding of COVID-19 transmission dynamics in Manaus, Brazil, it is critical to recognize and deal with the inherent limitations in the model and the data. First, the comprehensiveness and reliability of reported data, especially in the Severe Acute Respiratory Illness (SARI) daily deaths taken from hospitalized cases (including COVID-confirmed) datasets, which might result in a potential underestimation or misrepresentation of disease burden and transmission patterns. However, we have checked our results by repeating the analyses on CCM data and there is little difference. Moreover, by using the exact same SARI datasets as Buss et al. and Faria et al., it became possible to compare results.

Secondly, the assumptions embedded within the SEIR model we used pose inherent limitations. For instance, our model assumes exponentially distributed transition rates between susceptible (S) and exposed (E) individuals, E and infectious (I) individuals, and so forth. While exponential distributions offer mathematical tractability and simplicity, they do not fully capture the complex dynamics of COVID-19 progression and transmission (such as in asymptomatic cases), particularly in heterogeneous populations or under varying environmental conditions. Hence some bias and uncertainty could be introduced into the disease predictions and parameter estimation due to limitations in the model and data. We have made attempts to check for sensitivity and found results to be reasonably robust. However, identifying and acknowledging such limitations underscores the need for improved data collection, and refined modelling approaches, to enhance understanding of COVID-19 dynamics in order to inform effective public health responses.

5. Methods

In order to explore the dynamics in more depth, we fitted an SEIRD-type epidemiological model to the mortality datasets. This requires compartmentalizing the population into mutually exclusive classes based on epidemiological states (i.e., Susceptible, Exposed, Infected, Hospitalized, Recovered and Dead) and modelling the disease transmission between the compartments. The model was later extended, when needed, to a two age-class model and multiple-strain model. A full description of the model is given below (and SM5).

5.1. The SEIHRD epidemic model

We used an susceptible-exposed-infectious-recovered (SEIRD) type model with a flexible time-varying transmission rate $\beta(t)$ to the reported mortality data:

$$\dot{S} = -\frac{\beta SI}{N},$$

$$\dot{E} = \frac{\beta SI}{N} - \sigma E,$$

$$\dot{I} = \sigma E - \gamma I,$$

$$\dot{H} = \theta\gamma I - \kappa H,$$

$$\dot{D} = \pi\kappa H,$$

$$\dot{R} = (1-\theta)\gamma I + (1-\pi)\kappa H,$$

Here the compartments S, E, I, and R denote the conventional susceptible, exposed, infectious, and recovered individuals, respectively. The constant N is the total population size of the city or state, H denotes the hospitalized cases (or severe cases), and D denotes the total of SARI-deaths. Parameters $\beta(t), \sigma, \gamma, \kappa$ denote the transmission rate, the infectiousness emergence rate, the infectiousness disappearance rate, and the removal rate (due to death or recovery) of hospitalized cases, respectively. Parameters θ and π denote the ratio of hospitalized cases out of all infected cases and the proportion of deaths out of hospitalized cases, respectively. Thus, the overall case fatality rate (or infection fatality rate) equals $\theta\pi$. All parameters are

constant except $\beta(t)$ being time-varying. The above model was used for studying the Amazonas SARI mortality data (Brazil Ministério da Saúde Opendatasus, 2020), and a very similar model was used to study Manaus COVID confirmed mortality data (Amazonas and Manaus daily COVID, 2021).

We follow closely our previous work for fitting a "flexible" time varying transmission rate $\beta(t)$ (He et al., 2020; Stone et al., 2020; Zhao et al., 2018) based on fitting the mortality data. The former requires defining $\beta(t) = \exp(cubic\_spline)$ as an exponential cubic spline with n_m nodes evenly distributed over the study period. After this was fitted, we estimated $R_0(t) = \frac{\beta(t)}{\gamma}$. For the model, we set time step size as one day and integrated $\dot{D}$ for one day to obtain the simulated daily deaths D_t. We defined the reported deaths as C_t, where:

$$C_t \sim \text{NegativeBinomial}(\text{mean} = D_t, \text{variance} = D_t(1 + \tau D_t)).$$

Here, τ denotes the overdispersion, and accounts for the measurement noise due to surveillance and heterogeneity among individuals.

The parameter values of σ, γ, κ were taken as 365/2, 365/3.5, and 365/12 per year, respectively. Thus, the mean latent period and mean infectious period (the reciprocals of σ and γ) were set as 2 and 3.5 days, respectively. The generation time GI, Svensson (2007) the sum of mean latent period and mean infectious period, equals 5.5 days, which is in line with three key studies which provided estimated GI (Griffin et al., 2020; Prete et al., 2021; Zhao et al., 2020). According to Hawryluk et al. (2020) the delay between the first symptom onset and the death is ~14 days, which justifies the choice of 12 days (the reciprocal of κ) from loss of infectiousness to death. Namely the onset of infectiousness was taken to be 2 days ahead of first symptom onset. In addition, we assume 5% proportion of the population has pre-existing immunity (Lin et al., 2020; Ng et al., 2020), which only changes the initially large available susceptible pool by a small amount.

The Euler-multinomial simulation approach was used to simulate our model with a time-step size 1 day. The popular iterated filtering method (He et al., 2010; King et al., 2008; Zhao et al., 2018) (note that at least 25 applications use this method, see a list at https://en.wikipedia.org/wiki/Iterated_filtering) was implemented to fit our model to the observed data and to obtain the maximum likelihood estimates of unknown parameters, including values of nodes in $\beta(t)$ and π while holding $\theta = 0.1$. Namely, we assumed 10% of cases were hospitalized (or severe cases), as widely reported. The fitting is insensitive to the choice of θ, but sensitive to the product of π and of θ, which is equivalent to the infection fatality rate (IFR). We assumed uniform priors for all parameters. We hypothesized that the IFR lay in the interval (0.002, 0.008), and fit the daily SARI mortality data with a flexible transmission rate. The method finds the best fitting parameters including IFR. We used the 2nd-order Akaike Information Criterion (AICc) (He et al., 2020; Stone et al., 2020; Zhao et al., 2018) to find the best number of nodes in the transmission spline n_m. The same method was used to fit the two-age-class model.

A test of the Method on reconstructing epidemic dynamics from mortality timeseries is given in SI10.

5.2. Age-class model

In the two-age-class model, the population in each city was divided into two age groups: <50 and 50+ years of age. The population of each group was then divided into six S-E-I-H-R-D sub-groups. It was assumed that the cross-group transmission is the same as the in-group transmission. We obtained population size and age structure (the population ratio between <50 and + 50) from online sources, e.g., Brinkhoff (2021a, 2021b).

The daily Severe Acute Respiratory Illness (SARI) deaths were aggregated into two age groups: <50 and 50+ years of age, and time series were constructed for each group. The daily deaths from our model to the two time-series were fitted simultaneously. The total log likelihood of the model was taken to be the sum of the two log likelihoods for each time series.

The infection fatality ratio (IFR) was taken to be different for the two groups, with the IFR for <50 group being much smaller than that of the 50+ group. Both IFRs were estimated by our procedure. It was only assumed that the IFR for the 50+ group was between 1% and 4.5%. We assumed a flexible transmission rate (exp-cubic-spline with 7 nodes). Parameters were estimated including IFRs for both age groups, number of nodes in the transmission rates, and initial conditions. For Manaus, Fig. S5 shows the fitting performance in terms of log likelihood of the two-age-class model given the data, as a function of the IFR for the 50+ group, and that for the single-age-model.

Declarations

Ethical approval and consent to participate are not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data used are publicly available.

Code availability

The codes are available upon request to the corresponding author.

CRediT authorship contribution statement

Daihai He: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Yael Artzy-Randrup:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **Salihu S. Musa:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **Tiago Gräf:** Data curation, Investigation, Methodology, Resources, Writing – review & editing. **Felipe Naveca:** Investigation, Methodology, Resources, Validation, Writing – review & editing. **Lewi Stone:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Daihai He is an associate editor of the journal, but he was not involved in the review procedure. This paper is handled by another Editor Board Member. All other authors declared no conflict of interest.

Acknowledgment

DH was supported by Hong Kong Research Grants Council Collaborative Research Fund (C5079-21G). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All authors are thankful to the Handling Editor and anonymous reviewers for the insightful comments.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idm.2024.02.012.

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