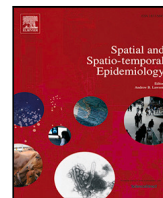




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Original Research

Mathematical modeling to study the impact of immigration on the dynamics of the COVID-19 pandemic: A case study for Venezuela

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ARTICLE INFO

Keywords:

SARS-CoV-2 virus
Basic reproduction number
Immigration
Epidemiology
Venezuela
Mathematical modeling

ABSTRACT

We propose two different mathematical models to study the effect of immigration on the COVID-19 pandemic. The first model does not consider immigration, whereas the second one does. Both mathematical models consider five different subpopulations: susceptible, exposed, infected, asymptomatic carriers, and recovered. We find the basic reproduction number \mathcal{R}_0 using the next-generation matrix method for the mathematical model without immigration. This threshold parameter is paramount because it allows us to characterize the evolution of the disease and identify what parameters substantially affect the COVID-19 pandemic outcome. We focus on the Venezuelan scenario, where immigration and emigration have been important over recent years, particularly during the pandemic. We show that the estimation of the transmission rates of the SARS-CoV-2 are affected when the immigration of infected people is considered. This has an important consequence from a public health perspective because if the basic reproduction number is less than unity, we can expect that the SARS-CoV-2 would disappear. Thus, if the basic reproduction number is slightly above one, we can predict that some mild non-pharmaceutical interventions would be enough to decrease the number of infected people. The results show that the dynamics of the spread of SARS-CoV-2 through the population must consider immigration to obtain better insight into the outcomes and create awareness in the population regarding the population flow.

1. Introduction

The world is suffering one of the worst pandemics in history due to the SARS-CoV-2 virus (Gandhi and Rutherford, 2020; Syal, 2020; Li et al., 2020a). The SARS-CoV-2 virus causes a disease called COVID-19 that can result in severe pneumonia and death (Lovato et al., 2020; Pinky and Dobrovolny, 2020). Several factors affect the spread of SARS-CoV-2 in the human population, such as social behavior, age, altitude, weather variables, mutation of the virus, and immune system (Arias-Reyes et al., 2021; Mandal et al., 2020; Reis et al., 2020; Wang et al., 2020; Pinky and Dobrovolny, 2020; Dobrovolny, 2020; Zhang et al., 2020; Ran et al., 2020; Yang and Duan, 2020). This COVID-19 pandemic has caused more than 594 million confirmed cases and more than 6.34 million deaths (Johns Hopkins University and Medicine, 2020; Dong et al., 2020). In Venezuela, more than 527,000 cases and 5735 deaths have been reported (Johns Hopkins University and Medicine, 2020). Neighboring countries such as Brazil and Colombia have reported more than 32.5 and 6.18 million cases of people infected

by the SARS-CoV-2, respectively. Moreover, these countries suffered more than 672,000 and 140,000 deaths, respectively (July 2022).

During the last decade, numerous Venezuelans have migrated to other countries due to the economic crisis. Approximately, more than four million have left the country between 2014 and 2020 (Berry et al., 2020; Burki, 2020; Chami et al., 2020; Daniels, 2020; Doocy et al., 2019a; Fernández-Niño and Bojorquez-Chapela, 2018; John, 2019; Mazzoli et al., 2020; Rodríguez, 2019; Tuite et al., 2018; Freier and Luzes, 2020). Many of the Venezuelans migrated to neighbors South American countries (Fernández-Niño et al., 2020; Mazzoli et al., 2020; Palotti et al., 2020). Several countries in South America have extremely high rates of labor informality. In particular, 61% in the case of Ecuador, 47% in Colombia, and 73% in Peru. During the COVID-19 pandemic, non-pharmaceutical interventions such as curfews, lockdowns, and quarantines reduced the number of informal workers and left them without income and in difficult economic situations. Migrants comprise a large part of the informal labor in part because of the

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<https://doi.org/10.1016/j.sste.2022.100532>

Received 29 July 2021; Received in revised form 8 July 2022; Accepted 15 August 2022

Available online 28 August 2022

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lack of work permits. By May of 2020, 90% of Venezuelans surveyed in Colombia declared never having signed an employment contract in their host country; 83.4% of Venezuelan respondents in Ecuador declared the same (Freier and Luzes, 2020). Moreover, in Peru, the case is even worse, with 93% of Venezuelan migrants in February 2020 (Freier and Luzes, 2020) responded being in the same situation. In addition, the migrant population often lacks legal status and therefore cannot access public social services, including health care (Blouin and Freier, 2019; Freier and Luzes, 2020).

During the first weeks of the lockdowns, employment in the migrant and refugee populations decreased dramatically since governments across South America shut down their economies in hopes of stopping the spread of COVID-19. In Ecuador, a study conducted in May 2020 found that 35.4% of the Venezuelan migrant population surveyed lost their jobs during the quarantine period (Freier and Luzes, 2020). In Colombia, a report published in May showed that, after the lockdown, only 20% of households reported having paid work, and 48% did not have any source of income (Freier and Luzes, 2020). Before the pandemic, most Venezuelan migrants worked in services (especially restaurants) despite being highly educated compared to the local population (Freier and Luzes, 2020; Palotti et al., 2020). Due to the aforementioned economic factors, over 100,000 Venezuelans returned to their country, where at least they could have a roof over their heads (Fernández-Niño et al., 2020; Liendo, 2020; NBC News, 2020; Analytica, 2020; van Roekel and Koopman, 2020). Moreover, by October 30, 2020, more than 136,000 Venezuelan migrants and refugees had returned to Venezuela from other countries in the region (United Nations Office for the Coordination of Humanitarian Affairs, 2020). At its peak, 600 Venezuelans returned from Colombia daily, and an average of 88 Venezuelans returned from Brazil daily via the border at Pacaraima (IOM's Global Migration Data Analysis Centre (GMDAC), 2020). We are interested in studying the effect of immigration on the COVID-19 pandemic. We choose Venezuela due to the particular migration factors mentioned above. Moreover, the health authorities in Venezuela were one of the first in Latin America to implement non-pharmaceutical interventions (Zavarce Castillo and Zavarce Castillo, 2020). The Executive authorities of Venezuela issued an alert decree that called on citizens to "stay at home" through a mandatory social quarantine that was implemented for 100 days, from March 15, 2020, to avoid propagating SARS-CoV-2 in the population (Zavarce Castillo and Zavarce Castillo, 2020). This lockdown was started even before some European countries, such as the United Kingdom. Thus, the unique situation of Venezuela during the COVID-19 pandemic is an important case study from an epidemiological perspective since it includes a large number of Venezuelans that returned from abroad despite the closure of the national borders and lockdown. Another important unique case that has been studied is the well-known case of the propagation of the SARS-CoV-2 in the Diamond Princess cruise, which has been mentioned as a benchmark epidemiological situation (Mizumoto et al., 2020). The Diamond Princess cruise ship presents a unique environmental case study, with a known number of passengers, crew members, and COVID-19 cases over time, discovered through high rates of testing, and a relatively high degree of knowledge of several important human and environment factors (Azimi et al., 2021).

Introduction of SARS-CoV-2 through migration has been documented in other countries and has been studied as a natural disease diffusion process (Adegboye et al., 2021; Chu et al., 2021; Escalera-Antezana et al., 2020; Liu et al., 2020a; Menkir et al., 2021; Russell et al., 2021). There are few studies regarding the effect of immigration on the COVID-19 pandemic and the basic reproduction number (Adegboye et al., 2021; Adhikari et al., 2021; Chu et al., 2021; Kassa et al., 2021; Tilahun and Alemneh, 2021). In Adhikari et al. (2021), the authors found that during the controlled phase most of the recorded cases were imported from outside the country with a small number generated from local transmission. Few studies have

focused on the particular situation of Venezuela regarding the COVID-19 pandemic and do not consider the effect of imported cases in general (Zavarce Castillo and Zavarce Castillo, 2020; Isea, 2020). In Zavarce Castillo and Zavarce Castillo (2020), the authors suggested that the dynamics were stochastic, and they used the Hurst exponent to support their results. In Isea (2020), the authors proposed an epidemiological SIR-Type model based on a non-autonomous system of ordinary differential equations. The authors made some predictions 60 days ahead based on the proposed mathematical model. However, forecasting of the COVID-19 pandemic has been challenging. Researchers have found that many forecasts related to the COVID-19 pandemic disagree with each other due to various uncertainties in key characteristics related to the spread of the SARS-CoV-2 virus in the human population (Alberti and Faranda, 2020; Arvisais-Anhalt et al., 2020; Roda et al., 2020; Holmdahl and Buckee, 2020; Fain and Dobrovlny, 2020; Jewell et al., 2020; Sperrin et al., 2020; Thomas et al., 2020; Kucharski et al., 2020; Stutt et al., 2020; Ferguson et al., 2020; Kuniya, 2020; Zhong et al., 2020; Buitrago-Garcia et al., 2020). However, mathematical modeling in combination with computational and statistical techniques are useful to study the impact of some specific factors and measure to some extent their role in the spread of the SARS-CoV-2 virus (Brauer et al., 2001; Hethcote, 2005; Diekmann et al., 2009; Murray, 2002). Mathematical models, and computational and statistical techniques have been used to study the spread of the SARS-CoV-2 virus under various scenarios, including interventions, vaccination and mutations (Anggriani et al., 2021; Bastos et al., 2021; Kucharski et al., 2020; Gupta et al., 2021; Lemos-Paião et al., 2020; Stutt et al., 2020; Ferguson et al., 2020; Dobrovlny, 2020; Kuniya, 2020; Zhong et al., 2020; Martinez-Rodriguez et al., 2021; Gonzalez-Parra et al., 2021; Riyapan et al., 2021; Savi et al., 2020). Several of these models are SIR-type or SEIR-type (Postnikov, 2020; Barmparis and Tsironis, 2020; Rahman et al., 2020a; Chaves et al., 2020; Grauer et al., 2020; Hou et al., 2020; Matrajt et al., 2020). Other mathematical models used curve fitting of growth models to the data. Artificial intelligence techniques have been considered to fit models to real data related to the COVID-19 (Roques et al., 2020; Liu et al., 2020b).

This study analyzes the impact of immigration on the spread of SARS-CoV-2 in a country. In addition to the migration factors mentioned above, we consider the case of Venezuela for two additional reasons. The first is related to the fact that the number of international flights per million inhabitants before the beginning of the COVID-19 pandemic was very small (Analytica, 2016; Garcia Zea, 2020). Thus, the potential number of infected individuals arriving to the country by air was small. The second reason is that the Venezuelan government was one of the first to close its borders and implement intervention strategies to avoid the transmission of the SARS-CoV-2 virus (Zavarce Castillo and Zavarce Castillo, 2020). It is important to point out that despite the closure of its borders, there were still people crossing during the COVID-19 pandemic (Liendo, 2020; Analytica, 2020; van Roekel and Koopman, 2020; NBC News, 2020). Moreover, government health authorities were able to report the number of infected cases of individuals that crossed the border. These cases were reported as imported cases (Isea, 2020). This phenomenon might be a crucial factor in explaining the difference in observed patterns between some countries (Mahajan and Kaushal, 2020; Pachetti et al., 2020; Reis et al., 2020; Gupta et al., 2020; Li et al., 2021). Therefore, the results of the present study are important to the population's health because of the increased understanding of the impact of immigration on the spread of the SARS-CoV-2 virus. Furthermore, this study can provide insights into the dynamics of the COVID-19 pandemic and future pandemics.

Infected cases in Venezuela shows just one wave until mid-August of 2020 (Johns Hopkins University and Medicine, 2020). This differs from the situation in other countries but is similar to neighboring countries such as Colombia and Brazil (Johns Hopkins University and Medicine, 2020). This pattern and the fact that the Executive authorities of Venezuela implemented fast and tight non-pharmaceutical

interventions suggest that the transmission rate did not vary greatly over the time period of this study. The appearance of waves of infection have been documented in various regions of the world for influenza during a relatively short period of time in between seasons (Aleta et al., 2020; Chowell et al., 2006; Andreasen et al., 2008; Marmarelis, 2020; Rios-Doria and Chowell, 2009; González-Parra et al., 2011). However, it is not totally clear yet which are the mechanisms responsible for the generation of multiple pandemic influenza waves. Some studies have proposed different mechanisms for the generation of multiple waves during the 1918 influenza pandemic, including the impact of social distancing (Caley et al., 2009; Rios-Doria and Chowell, 2009) and behavior changes (Epstein et al., 2008). Multiple wave patterns could also result from the delayed introduction of the virus in different communities within the same region or even due to re-entry of the virus into the same community (Rios-Doria and Chowell, 2009; González-Parra et al., 2011).

Our aim is to construct and use two different mathematical models to study the effect of immigration on the transmission rates of SARS-CoV-2. The first model does not consider immigration, whereas the second one does. Both mathematical models consider five different subpopulations: susceptible, exposed, infected, asymptomatic carriers, and recovered. We find the basic reproduction number \mathcal{R}_0 using the next-generation matrix method. As we are interested in studying the dynamics of the COVID-19 pandemic for a short period (from mid-March to the end of July, 2020), the stability analysis is not studied further. However, the basic reproduction number \mathcal{R}_0 is strongly related to the effective importance of the reproduction number \mathcal{R}_t which is time-varying. These numbers or thresholds are of interest because they indicate the dynamics of the COVID-19 pandemic. In addition, we provide estimates of the basic reproduction number \mathcal{R}_0 of COVID-19 for the particular case of Venezuela without considering immigration since we do not define when immigration is included in the model (Lai et al., 2020; Marimuthu et al., 2020; Buckman et al., 2020; Das, 2020). However, we estimate the transmission rates for the mathematical model that considers immigration in order to compare the two models.

This paper is organized as follows. In Section 2, we present the mathematical model of SARS-CoV-2 transmission and disease progression. Section 3 is devoted to the computation of the basic reproduction number \mathcal{R}_0 and the analysis of the model. In addition, we present the numerical results and the estimation of parameters using the Markov Chain Monte Carlo (MCMC) method and the mathematical model of SARS-CoV-2 transmission. Finally, discussions and conclusions are presented.

2. Materials and methods

Mathematical models, statistical analysis, and computational techniques are crucial tools for studying different processes, including testing hypotheses and understanding how and which factors affect the processes. The outcomes of infectious disease processes under various conditions are generally challenging to predict without using mathematical models and computational techniques. However, even with these techniques, there are caveats and uncertainties. Thus, the results resulting from this type of study should be taken cautiously with the awareness of the hypotheses of the mathematical models and/or unreliable data (Roda et al., 2020; Holmdahl and Buckee, 2020; Jewell et al., 2020; Sperrin et al., 2020). Regarding uncertainty, there are statistical procedures for dealing with uncertainty in the parameters, but not with regard to the fundamental hypothesis of the models. Note that the results of the simulations can sometimes be counter-intuitive but at the same time provide insight into the process being modeled. The outcomes of this study are important to better understand the impact of migration during the COVID-19 pandemic, and thus indicate suitable interventions to reduce the spread of the SARS-CoV-2 virus (Kucharski et al., 2020; Stutt et al., 2020; Ferguson et al., 2020;

Haushofer and Metcalf, 2020; Zhang et al., 2020; Ran et al., 2020; Yang and Duan, 2020; Chowell et al., 2006).

Using mathematical models to forecast the COVID-19 pandemic is a very challenging task due to the high degree of uncertainty presented in the non-pharmaceutical interventions and the change in the social behavior of people during the pandemic. Thus, many forecasts disagree, and the results regarding the characteristics of the COVID-19 pandemic are varied (Buitrago-Garcia et al., 2020; Roda et al., 2020; Holmdahl and Buckee, 2020; Jewell et al., 2020; Sperrin et al., 2020; Kucharski et al., 2020; Stutt et al., 2020; Ferguson et al., 2020; Kuniya, 2020; Zhong et al., 2020). In this study, we use some accepted hypotheses that allow us to study the effect of immigration on the basic reproduction number \mathcal{R}_0 and therefore of the transmission rate of SARS-CoV-2. In this study, our aim is not to forecast the dynamics of SARS-CoV-2. The current situation requires the formulation of mathematical models that include mutation, vaccination, and time varying-social behavior (Adegbeye et al., 2021; Hong and Li, 2020; Gonzalez-Parra et al., 2021; Martinez-Rodriguez et al., 2021; Peng et al., 2021).

The mathematical models that we propose in this study have some degree of uncertainty, but not to a great extent. Moreover, as we use the data from the past, we already know in some way what happened. This allows us to estimate the basic reproduction number \mathcal{R}_0 under some weak assumptions and account for parameter uncertainty to obtain qualitative conclusions. Thus, using real data, it is possible to characterize and understand better the dynamics of the SARS-CoV-2 virus spread in Venezuela. It is important to mention that fitting mathematical models to past epidemiological data is less challenging than the complex problem of forecasting the future. In the proposed mathematical model, we do not consider mutations because, for the period of study, we assumed there were no important changes related to different variants.

The compartmental mathematical models we use in this study include asymptomatic people and the latent stage, where individuals have SARS-CoV-2 but are still unable to transmit the virus to other persons. It has been argued that asymptomatic individuals are important contributors in the transmission of the SARS-CoV-2 (Dobrovlny, 2020; Bai et al., 2020; Huang et al., 2020; Mizumoto et al., 2020; Park et al., 2020; Shao et al., 2020; Gandhi et al., 2020; Kinoshita et al., 2020; Han et al., 2020; Teixeira, 2020). Quantitative SARS-CoV-2 viral loads were found to be similarly high for infected individuals with symptoms, pre-symptomatic, or asymptomatic (Havers et al., 2020).

We collected data from different sources, and some particular sources of data related to COVID-19 can be found in Johns Hopkins University and Medicine (2020), Dong et al. (2020) and Wu et al. (2020). Using specific data from Venezuela that include confirmed cases, imported cases, and deaths from mid-March to the end of July of 2020, we estimate the basic reproduction number \mathcal{R}_0 and the death rate parameter. Note that the \mathcal{R}_0 is in general different for different regions, countries, cities, and communities. We perform identifiability analysis to provide reliable qualitative results regarding \mathcal{R}_0 and death rate. Performing identifiability analysis is essential for the credibility of the mathematical model and testing the reliability of predictions (Zhang et al., 2021; Raue et al., 2009; Davison and Hinkley, 1997). We calibrate the mathematical models using the real data related to reported infected cases and deaths, minimizing the summed square of the residuals. We rely on the MCMC method to study the identifiability of the parameters (Goodman and Weare, 2010). This method gives insight into whether the parameters are identifiable with the available data. Moreover, MCMC methods have been used in many studies related to epidemiological data (De Oliveira et al., 2020; González-Parra and Dobrovlny, 2019; González-Parra et al., 2019a).

We use a mathematical model called a SEIARD-type epidemiological model. The constructed mathematical model based on deterministic differential equations is given as follows:

$$\dot{S}(t) = \pi_S - (\beta_I I(t) + \beta_A A(t)) \frac{S(t)}{N(t)},$$

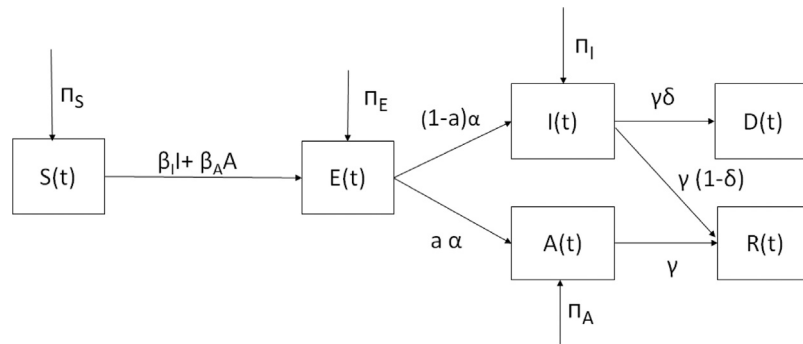


Fig. 1. Diagram for the COVID-19 mathematical model (1). The boxes represent the subpopulation, and the arrows the transition between the subpopulations. Arrows are labeled by their corresponding model parameters.

$$\begin{aligned}
 \dot{E}(t) &= \pi_E + (\beta_I I(t) + \beta_A A(t)) \frac{S(t)}{N(t)} - \alpha E(t), \\
 \dot{I}(t) &= \pi_I + (1 - a) \alpha E(t) - \gamma I(t), \\
 \dot{A}(t) &= \pi_A + a \alpha E(t) - \gamma A(t), \\
 \dot{R}(t) &= \gamma (1 - \delta) I(t) + \gamma A(t), \\
 \dot{D}(t) &= \gamma \delta I(t),
 \end{aligned} \tag{1}$$

where $S(t)$ denotes the number of susceptible individuals. When a susceptible and an infectious individual come into infectious contact, the susceptible individual contracts the disease and transitions to the latent compartment $E(t)$. Individuals in compartment $E(t)$ are infected (carry the virus) but cannot spread the virus. Compartment $I(t)$ represents individuals who have been infected and show symptoms. These individuals are capable of infecting susceptible individuals after being in the $E(t)$ subpopulation. The subpopulation $A(t)$ represents the individuals who have been infected but are asymptomatic. These individuals can infect susceptible individuals after being in the $E(t)$ subpopulation. The compartment $D(t)$ represents the number of deaths due to the SARS-CoV-2 virus from the beginning of the simulation period. The model assumes that people in states $E(t)$ and $R(t)$ do not transmit the infection. In this model, we consider that COVID-19 confers immunity after recovery. The total population $N(t)$ satisfies the following equation $N(t) = S(t) + E(t) + A(t) + I(t) + R(t)$.

The parameters of the mathematical model (1) are described as follows. The incubation period is represented by α^{-1} , the infectious period is given by γ^{-1} , the disease-induced death rate is represented by $\gamma \delta$, and the proportion of asymptomatic is given by the parameter a . The transmission rate between classes S and I is given by β_I . The transmission rate between classes S and A is given by β_A . There are two mathematical models embedded in the ODE system (1). First, if all the parameters π_S, π_E, π_I and π_A are zero then the model does not consider immigration. Conversely, if at least one of the parameters π_S, π_E, π_I and π_A are non-zero, then the model includes immigration (Almarashi and McCluskey, 2019). The parameters π_S, π_E, π_I and π_A are the rate of immigrants that are susceptible, latent, infected, and asymptomatic, respectively (see Fig. 1).

2.1. Parameter values

Venezuela is a country on the northern coast of South America, as shown in Fig. 2. It is divided into 23 states, a capital district corresponding to the city of Caracas, and the Federal Dependencies (a special territory). Venezuela is further subdivided into 335 municipalities; these are subdivided into over one thousand parishes. Venezuela is a developing country and ranks 113th on the Human Development Index. It has the world's largest known oil reserves and has been one of the world's leading exporters of oil (Wikipedia, 2021). In this study, we are interested in understanding how the immigration of infective people affects the estimation of \mathcal{R}_0 and the rate of transmission in Venezuela

during the beginning of the first epidemic wave. Nevertheless, the proposed general methodology and mathematical model could be applied to other countries. We obtain parameter values from the scientific literature, even though small differences in our models would not change the qualitative conclusions. We assume that the rates of virus transmission in asymptomatic and symptomatic individuals are constant from the beginning of the simulation. This assumption implies that people would maintain approximately the same behavior (on average) regarding SARS-CoV-2 spread protection. This assumption is reasonable for the beginning of the first wave; as mentioned in the introduction, the Venezuelan government was one of the first to close its borders and implement non-pharmaceutical interventions (Zavarce Castillo and Zavarce Castillo, 2020). This approach of constant transmission for particular time periods is common in this type of epidemiological study. Moreover, the approach was used in several studies related to SARS-CoV-2, influenza and other diseases (Benlloch et al., 2020; Paltiel et al., 2020; Ehrhardt et al., 2019; Iboi et al., 2020; Eikenberry et al., 2020; González-Parra et al., 2015; Kim et al., 2020a; Nistal et al., 2021). If the behavior of people changes, it would be more realistic to include time-varying transmissibility, which has been used to study other infectious diseases (IHME COVID-19 Forecasting Team, 2020; Law et al., 2020; Kucharski et al., 2020; Kim et al., 2020a; Eikenberry et al., 2020). The estimation of parameters is more complex when parameters are time-varying, and identifiability issues might arise. Nevertheless, even with constant parameters, the number of effective contacts between the susceptible and infected vary over time due to the variation of these subpopulations (for more details, see Brauer et al. (2001), Hethcote (2005), van den Driessche and Watmough (2002) and Van den Driessche and Watmough (2008)).

We assume that the parameters related to the infectious stage are similar for asymptomatic and symptomatic individuals. The literature shows great uncertainty in this aspect, but we use a plausible conservative approach (Centers for Disease Control and Prevention, 2021). Studies have indicated that the antibody titers may decline over time in patients who have recovered from COVID-19 (Xia et al., 2020). In this regard, we assume that recovered people maintain enough antibodies for the period of study to avoid reinfection with SARS-CoV-2. Regarding hospitalizations, we do not have data; thus, the mathematical model does not include hospitalized subpopulations as in other studies (Ferguson et al., 2020; Kim et al., 2020b; Hoseinpour Dehkordi et al., 2020; Yehia et al., 2020). Notice that, in general, the hospitalized subpopulation is not a relevant factor in the estimation of \mathcal{R}_0 .

For the proportion of asymptomatic cases per infection, we also relied on data from several sources (Centers for Disease Control and Prevention, 2020; Chen et al., 2020; McEvoy et al., 2021; Ferguson et al., 2020; Kinoshita et al., 2020; Mizumoto et al., 2020; Orenes-Piñero et al., 2021; Oran and Topol, 2020; Zhao et al., 2020). The literature shows great uncertainty in the proportion of asymptomatic cases, but we use a plausibly conservative approach that the proportion of asymptomatic cases per infection is 40% (Centers for Disease



Fig. 2. Map of South America. Venezuela has Colombia and Brazil as neighbors countries (South America, 2021).

Control and Prevention, 2021; Zhang et al., 2021). For the transmissibility of the SARS-CoV-2 of asymptomatic individuals with respect to symptomatic, we reviewed the literature, and again there are caveats. We assume that an asymptomatic individual is 75% as infectious as one symptomatic (Centers for Disease Control and Prevention, 2020). Thus, we consider that $\beta_I > \beta_A$, and we take $\beta_A = \epsilon \beta_I$ where $\epsilon = 0.75$. Surprisingly, one article found that asymptomatic carriers have a higher viral load, implying that asymptomatic carriers might have larger infectiousness than symptomatic people (Hasanoglu et al., 2020). Moreover, it seems likely that asymptomatic people are less likely to follow social isolation. The values of the β_I and β_A transmission parameters vary depending on the social behavior and therefore on the non-pharmaceutical interventions of each region or country (Paltiel et al., 2020; Iboi et al., 2020; Le Page, 2021; Li et al., 2020b; Tang et al., 2020; Eikenberry et al., 2020).

The proposed mathematical models do not consider vital dynamics such as birth and death rates because, for a short period of study, it has a very small impact on the dynamics. The time scale of the demography rates is much shorter than the disease rates (Hethcote, 2005). The values of the parameters of the mathematical model (1) are given in Table 1.

2.2. Raw epidemiological data

For the mathematical model including immigration, we use the imported infected cases, i.e., individuals that crossed the border. These reported cases were infected people who went to health institutions for assistance and self-reported that they had been abroad (Ministerio del Poder Popular para la Comunicación e Información, 2020). Most of the first corona-virus tests were performed using rapid test kits donated by the Chinese government (Reuters, 2020). Only positive tests certified by that public facility — the National Institute of Hygiene, were included in the government's official coronavirus case count (Reuters, 2020). The death data were collected from a government's website (Ministerio del Poder Popular para la Comunicación e Información, 2020). The immigration data can be related to the parameters of the model that are presented in Table 2. Immigration data was collected from various sources including newspapers (NBC News, 2020; van Roekel and Koopman, 2020; United Nations Office for the Coordination of Humanitarian Affairs, 2020). However, the most relevant data is the imported infected

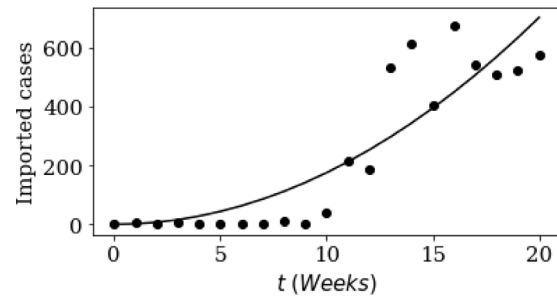


Fig. 3. Smoothing (by linear regression) the imported cases using a quadratic polynomial under the restriction that imported cases must be greater or equal to zero during the period of study.

cases that we described before. As in many other countries, the data has some degree of uncertainty. We will discuss this aspect in the conclusions section. It is important to point out that, as in many countries, the data cannot be 100% accurate. Moreover, crossing the borders of Venezuela was illegal during the period of study (mid-March to the end of July). Thus, it was more difficult to track exactly the total number of imported cases despite the high alertness and surveillance of COVID cases. In addition, it is well-known that reported cases suffer from underreporting, non-uniformity and delay (Alves et al., 2020; Arvisais-Anhalt et al., 2020; Azmon et al., 2014; Do Prado et al., 2020; Lau et al., 2020; Rasjid et al., 2021; Reis et al., 2020; Saberi et al., 2020). Thus, the data of imported cases by week is smoothed using a quadratic polynomial under the restriction that imported cases must be greater or equal to zero during the period of study (Rasjid et al., 2021). We used other functions to fit the imported cases data and used them in the numerical fitting process using Monte Carlo Markov Chain (MCMC), and the qualitative results were similar. We decided to maintain the quadratic fit for simplicity. In Fig. 3, we present the smoothing (by linear regression) of the imported cases using a quadratic polynomial under the restriction that imported cases must be greater or equal to zero during the period of study. Notice that the quadratic polynomial is used to approximate $\Pi_I(t)$ in the model. Then $\Pi_A(t)$ is estimated using the assumption that the proportion of asymptomatic cases per infection is 40% (Centers for Disease Control and Prevention, 2020; Zhang et al., 2021).

2.3. Initial conditions for the scenarios

For the initial conditions, we use the reported estimation of the population of Venezuela and use the reported data of infected cases and deaths at the beginning of the pandemic (Mid-March of 2020). As we have mentioned above, it is expected that the reported infected cases have uncertainties due to several factors such as sensitivity and specificity of COVID-19 tests (Bisoffi et al., 2020; Surkova et al., 2020). However, because the executive authorities of Venezuela issued an early alert decree calling on citizens to stay at home through a mandatory social quarantine starting on March 25, 2020, the number of infected cases, exposed individuals, and asymptomatic carriers are taken to zero at the beginning of the period of study. Taking into account these and using Venezuela as a particular case study, we set the initial conditions presented in Table 2.

2.4. Methodology of fitting the mathematical models to the epidemiological data

We implemented a Bayesian approach using the MCMC technique to estimate parameters and study the identifiability of the estimated parameters. We minimized the sum of squared residuals (SSRs) first as the initial estimates for implementing the Bayesian approach (Goodman and Weare, 2010; Talwar and Aundhakar, 2016). The minimization

Table 1
Mean values of parameters used to perform numerical simulations of the different scenarios.

Parameter	Symbol	Value or range
Latent period	α^{-1}	5.2 days (Li et al., 2020a; Lauer et al., 2020; IHME COVID-19 Forecasting Team, 2020)
Infectious period	γ^{-1}	7 days (Li et al., 2020a)
Proportion of asymptomatic per infection	a	0.4 (Centers for Disease Control and Prevention, 2020; Oran and Topol, 2020)
Transmission rate between classes S and I	β_I	Fitting by data
Transmission rate between classes S and A	β_A	$\epsilon \beta_I$
Infectiousness of asymptomatic with respect to symptomatic	ϵ	0.75 (Centers for Disease Control and Prevention, 2020; Zhang et al., 2021)
Disease induce death rate	$\gamma \delta$	Fitting by data
Immigration rate of susceptible individuals	π_S	1500 (NBC News, 2020; van Roekel and Koopman, 2020)
Immigration rate of latent individuals	π_E	$5.2 \pi_I / 7$
Immigration rate of infected individuals	π_I	Provided data (La Iguana TV, 2020; Ministerio del Poder Popular para la Comunicación e Información, 2020)
Immigration rate of asymptomatic individuals	π_A	$0.4 \pi_I / 0.6$

Table 2
Initial conditions assumed for the different subpopulations using the case study of Venezuela (13th of March of 2021).

Subpopulation	Symbol	Value
Total population	$N(0)$	33,428,135 (Wikipedia, 2020)
Infected	$I(0)$	2 (Johns Hopkins University and Medicine, 2020; La Iguana TV, 2020; Ministerio del Poder Popular para la Comunicación e Información, 2020)
Latent	$E(0)$	0
Asymptomatic	$A(0)$	0
Recovered	$R(0)$	0
Susceptible	$S(0)$	$N(0) - I(0)$

is performed using the Python optimize.minimize routine, but other algorithms could be used (Snyman and Wilke, 2018). MCMC is designed to sample from the posterior PDF efficiently (Foreman-Mackey et al., 2013; MacKay and Mac Kay, 2003). In our algorithm, we draw samples from a multivariate Gaussian density which is a common approach. Setting up the specific values of the hyperparameters in two dimensions (β_I and δ) are required. We also need to decide how many walkers, which are in some sense independent paths, to reach the maximum of the likelihood function (Goodman and Weare, 2010). One of the best techniques to initialize each of the walkers is to start in a small ball around an a priori preferred position (Foreman-Mackey et al., 2013). In the MCMC process, the walkers will spread out and explore the whole space for the two parameters. The aim is to find the maximum of the likelihood function, which is a Gaussian. Finally, we can use MCMC to obtain estimates and confidence intervals for each of the parameters. As an extra benefit of MCMC, we can explore correlations among the parameters.

Particularly, we have used MCMC to find the posterior distributions of the transmission rate β_I (β_A depends on it) and the death rate δ . We have considered informative prior as uniform and normal for β_I and the death rate δ . Because we have reported data on infected cases and deaths, the sum of squared residuals is composed of two terms. For the infected reported cases, we fit the state variable $I(t)$ of the mathematical model (1), and for the accumulated reported deaths, we fit the state variable $D(t)$. Notice that $D(t)$ is the cumulative death and $I(t)$ is the number of active infected cases at time t . Fitting active infective cases is more challenging than fitting cumulative ones. Moreover, the reported infective cases are different from the infective cases. However, much research that involves fitting uses the difference between them to represent the error of the model. Note that even though those quantities are different when the mean infectious period is one week and the reported cases are given by the week (as in this work), then $I(t)$ represents approximately the number of infected active cases. Therefore, we can do the fitting by minimizing the difference between both quantities. Thus, to fit the model to the real data, we use the SSR that comprises two terms related to the difference between the model and the reported data sets (infected and cumulative deaths).

We use uniform prior distributions for all the non-fixed parameters in order to have more robustness in the results and because it is commonly used in this type of study (Nielsen and Wakeley, 2001; Knappe and De Valpine, 2012; Gilks et al., 1995; Gamerman and Lopes, 2006; González-Parra et al., 2019a; González-Parra and Dobrovoly, 2019; Wu et al., 2018).

We use the emcee in python, which is an implementation of the Goodman and Weare affine invariant ensemble MCMC sampler to perform MCMC estimation (Goodman and Weare, 2010; Foreman-Mackey et al., 2013). It is required that we initialize the ensemble of walkers in a Gaussian neighborhood around the initial guess. We used a Gaussian-type likelihood function, which is a common choice in similar studies and has suitable asymptotic properties. Minimizing the constructed likelihood function minimizes the difference between the reported data corresponding to infected cases and deaths and the values of the state variables $I(t)$ and $D(t)$ generated by the mathematical model (1), respectively. Note that under some conditions, minimizing a Gaussian likelihood is equivalent to the least squares method. For numerically solving the ODE system, we used the Python integrator scipy.integrate.odeint that uses lsoda from the FORTRAN library odepack. This routine automatically switches between nonstiff and stiff solvers depending on the behavior of the ODE system (Wood, 2015).

3. Results

Here we present the numerical results of the estimation of \mathcal{R}_0 . First, we use the mathematical model without considering immigration. We find the steady-state solutions, and then we compute \mathcal{R}_0 , which is defined as the average number of new cases of infection due to one infected individual, in a population comprising only susceptible individuals (Hethcote, 2005; van den Driessche and Watmough, 2002).

In particular, we use the next generation matrix to compute \mathcal{R}_0 of the mathematical model (1). It is important to remark that the effective reproduction number \mathcal{R}_t is time-varying and depends on the basic reproduction number \mathcal{R}_0 . Thus, under certain conditions $\mathcal{R}_t = \mathcal{R}_0 S(t)/N$, which relates the value of the virus transmissibilities β_I and β_A to the effective reproduction number (Hethcote, 2005; Yan and Chowell, 2019).

3.1. Computing the basic reproduction number \mathcal{R}_0

In the epidemiological models represented by differential equations, the local and global behavior of the solutions depend on the population flow parameters inherent in the model. A special parameter is the basic reproduction number \mathcal{R}_0 , which is defined as the number of secondary cases produced by an infectious individual entering the susceptible population, and which measures the magnitude of the disease (van den

Driessche and Watmough, 2002; Van den Driessche and Watmough, 2008; Ma and Earn, 2006; Miller, 2012). This threshold parameter is influenced by the health control policies that need to be taken so that the infected population solutions tend to a steady-state associated with the absence of COVID-19 (Morato et al., 2020).

3.2. Analysis of the mathematical model without immigration

For $\pi_S = \pi_A = \pi_E = \pi_I = 0$, the mathematical model (1) without considering immigration has a continuous point of disease-free equilibrium (DFE), which is obtained by setting the right-hand sides of the equations for the rate of change of each of the state variables in (1) to zero and is given by

$$DFE = (S^0, E^0, I^0, A^0, R^0) = (N(0) - R^0, 0, 0, 0, R^0). \tag{2}$$

where $N(0)$ is the initial total population size and $S^0 + E^0 + I^0 + A^0 + R^0 \leq N(0)$. The next generation matrix methodology can be used to deduce the asymptotic linear stability of the DFE point, van den Driessche and Watmough (2002) and Van den Driessche and Watmough (2008). Thus, we can obtain an algebraic expression of the parameter \mathcal{R}_0 , as the spectral radius of the matrix $\mathcal{F}\mathcal{V}^{-1}$, where \mathcal{F} is the matrix of the new infection cases and the matrix \mathcal{V} is that of the transition terms associated with the model (1). For this case, we write the system (1) as

$$\begin{pmatrix} \dot{E}(t) \\ \dot{I}(t) \\ \dot{A} \\ \dot{R}(t) \\ \dot{S}(t) \end{pmatrix} = \begin{pmatrix} (\beta_I I(t) + \beta_A A(t)) \frac{S(t)}{N(t)} \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} - \begin{pmatrix} \alpha E(t) \\ -(1-a)\alpha E(t) + \gamma I(t) \\ -\alpha E(t) + \gamma A(t) \\ -\gamma((1-\delta)I(t) + A(t)) \\ (\beta_I I(t) + \beta_A A(t)) \frac{S(t)}{N(t)} \end{pmatrix}. \tag{3}$$

Thus,

$$\mathcal{F} = \begin{pmatrix} 0 & \beta_I \frac{S^0}{N^0} & \beta_A \frac{S^0}{N^0} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \text{ and } \mathcal{V} = \begin{pmatrix} \alpha & 0 & 0 \\ (a-1)\alpha & \gamma & 0 \\ -\alpha & 0 & \gamma \end{pmatrix}.$$

By direct calculation,

$$\mathcal{V}^{-1} = \begin{pmatrix} \frac{1}{\alpha} & 0 & 0 \\ \frac{1-a}{\gamma} & \frac{1}{\gamma} & 0 \\ \frac{a}{\gamma} & 0 & \frac{1}{\gamma} \end{pmatrix},$$

and the next generation matrix is given by

$$\mathcal{F}\mathcal{V}^{-1} = \begin{pmatrix} \mathcal{R}_0 & \frac{\beta_I}{\gamma} \frac{S^0}{N^0} & \frac{\beta_A}{\gamma} \frac{S^0}{N^0} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

where

$$\mathcal{R}_0 = \frac{\beta_I(1-a)}{\gamma} \frac{S^0}{N^0} + \frac{\beta_A}{\gamma} \frac{S^0}{N^0}, \tag{4}$$

is the spectral radius of the matrix $\mathcal{F}\mathcal{V}^{-1}$. Thus, we arrive to the following theorem:

Theorem 3.1. *The disease-free equilibrium point given in (2) of the model (1) is locally asymptotically stable if $\mathcal{R}_0 < 1$. If $\mathcal{R}_0 > 1$, the component $I(t)$ of the solution reaches a peak and then ends up dropping to zero.*

Proof. Applying Theorem 2 given in van den Driessche and Watmough (2002), the result is confirmed. \square

Therefore, if there is no immigration, the system has only one disease-free equilibrium DFE. Now, if $\mathcal{R}_0 > 1$, then the epidemic rises to a peak and then eventually declines to zero (Gumel et al., 2021).

3.3. Analysis of the mathematical model with immigration

The mathematical model (1) with immigration considers that at least one of the parameters π_S, π_E, π_I and π_A is different from zero. For this case, there is no disease-free equilibrium point or endemic equilibrium point. The lack of disease-free equilibrium means there is no basic reproduction number (Sigdel and McCluskey, 2014). Thus, in some sense, it is mathematically incorrect to report on the basic reproduction number for this case. However, it is possible to estimate the transmission rates β_I and β_A of SARS-CoV-2 between individuals. Moreover, we can use these transmission rates in (4) to estimate \mathcal{R}_0 that would be obtained without immigration for comparison purposes regarding the risk of the COVID-19 pandemic.

Note that this study focuses on a short time period at the beginning of the introduction of the SARS-CoV-2 in Venezuela or in a particular region. Therefore, long-term behavior is not crucial here. More importantly, with the introduction of vaccination programs, the situation changes drastically (Paltiel et al., 2020; Martinez-Rodriguez et al., 2021). Furthermore, the appearance of new SARS-CoV-2 variants implies the need for a different, more complex, mathematical model in order to obtain insight regarding the effect of immigration (Davies et al., 2021; Gonzalez-Parra et al., 2021). In this study, we do not perform any forecasting or prediction, which are more complex tasks, which has been proven by this COVID-19 pandemic (Roda et al., 2020; Holmdahl and Buckee, 2020; Jewell et al., 2020; Sperrin et al., 2020; Taylor, 2021).

3.4. Markov chain Monte Carlo for estimation of parameters

As explained in the previous section, we use MCMC techniques to estimate parameters and study the identifiability of the estimated parameters. For the reported infected cases, we fit the state variable $I(t)$ of the mathematical model (1), and for the reported deaths, we fit the state variable $D(t)$. The joint posterior distribution of parameters was explored by MCMC techniques. For the Markov chain Monte Carlo simulations, the posterior distributions were determined using four walkers, 5000 samples, and drawn with 200 burn-in samples in every chain. We used different initial values for the number of walkers, samples, burn-in samples, and parameters β_I and δ . The results were robust to changes in these MCMC simulations and initial values. Posterior distributions were determined using a different number of walkers, samples, and burn-in samples. The results are robust, varying all these numbers, which makes the results more reliable.

Fig. 4 shows that the mathematical model without immigration fits well with the reported data of infected cases and deaths. We obtain that the best fit parameter values are $\beta_I \approx 2.12$ (week scale) and $\delta \approx 0.018$. With these values, we obtain $\mathcal{R}_0 \approx 1.9$. In addition, in Fig. 5 all the one- and two-dimensional projections of the posterior probability distributions of the parameters can be seen. This allows us to observe all of the covariances between parameters. The histograms show the marginalized distribution for a parameter or a set of parameters using the results of MCMC. Fig. 5 shows the marginalized distribution for each parameter independently in the histograms along the diagonal and the marginalized two-dimensional distributions in the other panels (Foreman-Mackey et al., 2013). The maximum likelihood function profile is also presented. We can say that to have two uncorrelated parameters, the level curves plot should be similar to circles, with no particular relationship between the parameters. For the death rate parameter δ , the plot shows no correlation with the transmissibility parameter β_I . Thus, the MCMC results strongly suggest that these two parameters are, therefore, the epidemic threshold parameter \mathcal{R}_0 are identifiable. This result agrees with previous results regarding identifiability for COVID-19 pandemic models when similar data is available (Zhang et al., 2021). This is not surprising since for estimating the parameters β_I and δ , we have time series for the infected cases and deaths. Further identifiability analysis about the parameters can be

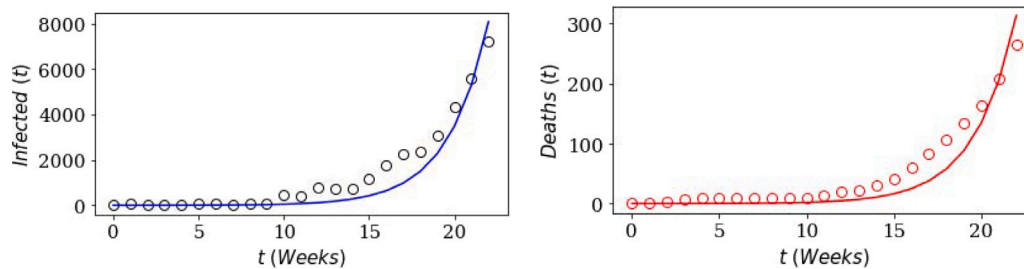


Fig. 4. Fit results of the mathematical model without migration (1). On the left hand side it can be seen the reported infected cases (circles) and on the right hand side the reported number of deaths (circles). The period of study was from the March 13 to July 31, 2020.

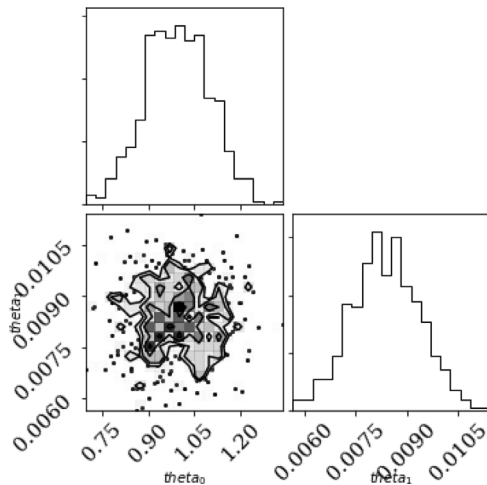


Fig. 5. Identifiability assessment of the mathematical model without migration (1) fit to the reported data of infected cases and deaths in the population of Venezuela in the time period of study from March 13 to July 31, 2020. Correlation plots generated with MCMC for two parameters δ and β_I .

performed using bootstrap technique, structural and practical identifiability (Raue et al., 2009; González-Parra et al., 2019a,b; González-Parra and Dobrovolny, 2019).

For the fitting process of the mathematical model with immigration, we used a slightly shorter time period since we do not have the reported number of infected cases, and therefore we cannot determine Π_I and Π_A for the same time period that we used for the model without immigration. However, the difference is less than three weeks and does not greatly affect the main results. Fig. 6 shows the fitting of the mathematical model with immigration. The quality of the fitting is similar to that obtained without immigration. However, in this case we obtain that $\beta_I \approx 1.0$ (week scale) and $\delta \approx 0.01$. With these values, we obtain a basic reproduction number of $\mathcal{R}_0 \approx 0.90$. As we have mentioned previously in the theoretical results for the case of immigration, there is no disease-free equilibrium point. Therefore, there is no theoretical basic reproduction number (Sigdel and McCluskey, 2014). However, it is possible to estimate the transmission rates β_I and β_A and estimate some quantity $\bar{\mathcal{R}}_0$ just for comparison purposes. In addition, in Fig. 7 all the one- and two-dimensional projections of the posterior probability distributions of the parameters can be seen. This allows us to observe all of the covariances between parameters. The histograms show the marginalized distribution for a parameter or a set of parameters using the results of MCMC. Fig. 7 shows the marginalized distribution for each parameter independently in the histograms along the diagonal, and the marginalized two-dimensional distributions in the other panels (Foreman-Mackey et al., 2013). For the death rate parameter δ , the plot shows no correlation with the transmissibility parameter β_I . Thus, the MCMC results strongly suggest that these two parameters and, therefore, the epidemic threshold parameter \mathcal{R}_0 are identifiable.

This result agrees with previous results regarding identifiability for COVID-19 pandemic models when similar data is available (Zhang et al., 2021). Finally, we would like to point out that from Figs. 5 and 7 we can see that the posterior distributions for the two unknown parameters resemble a nice Gaussian distribution. Moreover, we can obtain credible intervals for both parameters under the two different nested models. It is clear that the estimations of the parameters are different for each of the nested models.

4. Discussion and conclusions

The COVID-19 pandemic is a worldwide public health challenge and has caused more than 594 million confirmed cases and more than 6.34 million deaths (Johns Hopkins University and Medicine, 2020; Dong et al., 2020). In Venezuela, more than 527,000 cases and 5735 deaths have been reported (Johns Hopkins University and Medicine, 2020). Neighboring countries such as Brazil and Colombia have reported more than 32.5 and 6.18 million cases of people infected by the SARS-CoV-2, respectively. Moreover, these countries have suffered more than 672,000 and 140,000 deaths, respectively (July 2022). The differences in the outcomes between these countries and Venezuela are substantially different. There could be many factors involved in these huge differences. It has been argued that obesity is an important factor in the severity and progression of the covid disease (Edwards et al., 2021; Stefan et al., 2021; Yang et al., 2021). Several Latin American countries, including Brazil, have suffered from the high prevalence of obesity (Goodman et al., 2020). In contrast, Venezuela is a particularly salient case as it is currently undergoing an economic and socio-political crisis that has led to widespread food shortages and malnutrition (Goodman et al., 2020; Doocy et al., 2019b; Page et al., 2019; Rodríguez, 2019; Weisbrot and Sachs, 2019). However, there are other important factors, such as gasoline shortage, which drastically reduces the transportation within the country (Pietrosemoli and Rodríguez-Monroy, 2019). In addition, due to the crisis, the number of active companies has gone down dramatically in the last decade, which is also a factor in the mobility of people (Caraballo-Arias et al., 2018; Page et al., 2019). In addition to all the before mentioned factors, there are the more usual factors related to surveillance of an epidemic such as underreporting of data and delay in the reported cases (Alves et al., 2020; Arvisais-Anhalt et al., 2020; Azmon et al., 2014; Bernard et al., 2014; Burki, 2020; Do Prado et al., 2020; Lau et al., 2020; Rasjid et al., 2021; Reis et al., 2020; Saberi et al., 2020). In particular, for the COVID-19 pandemic in Brazil, an average underreporting of 40.68% (range 25.9–62.7%) for COVID-19-related deaths has been estimated (e Silva et al., 2020). Thus, the reported data from Venezuela probably also suffers from underreporting as in other countries. We do not know to what extent the data from Venezuela varies with respect data from Colombia or Brazil. However, based on the reported number, it is unlikely that the great difference would be only due to underreporting. We mentioned several factors that could be important to explain the low number of infected cases and deaths. However, the unique situation from a different perspective makes the

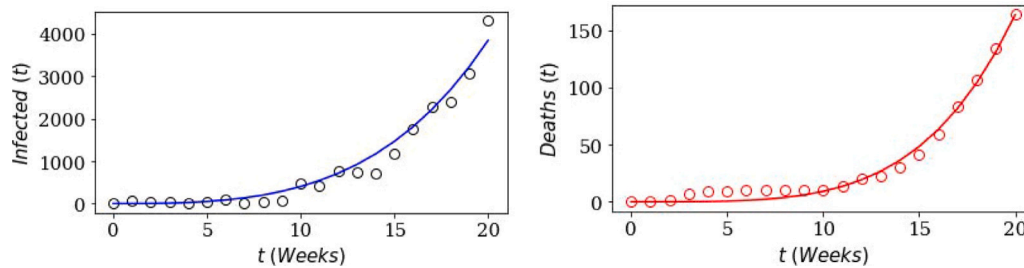


Fig. 6. Fit results of the mathematical model with immigration (1). On the left hand side it can be seen the reported infected cases (circles) and on the right hand side the reported number of deaths (circles). The period of study was from of March 13 to July 31, 2020.

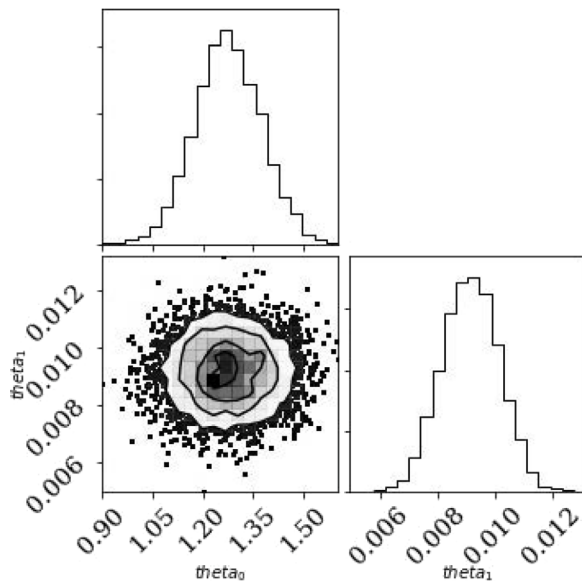


Fig. 7. Identifiability assessment of the mathematical model with immigration (1) fit to the reported data of infected cases and deaths in the population of Venezuela in the period of study from March 13 to July 31, 2020. Correlation plots generated with MCMC for two parameters δ and β_1 .

case of Venezuela worthy of study. As has been mentioned in several studies, the number of migrants from Venezuela has been one of the greatest per capita during recent years (Berry et al., 2020; Burki, 2020; Chami et al., 2020; Daniels, 2020; Doocy et al., 2019a; Fernández-Nino and Bojorquez-Chapela, 2018; John, 2019; Mazzoli et al., 2020; Rodríguez, 2019; Tuite et al., 2018; Freier and Luzes, 2020). The COVID-19 pandemic changed the labor conditions in South-American countries and especially the informal labor sector, which caused a sudden return of Venezuelans to Venezuela (van Roekel and Koopman, 2020; NBC News, 2020). Moreover, the Venezuelan health authorities could perform surveillance and recognize imported cases. In this study, we assumed that in addition to the symptomatic imported cases, there were also asymptomatic imported cases, as should be expected. Thus, we studied the effect of migration on the COVID-19 pandemic in a country, particularly a case study for Venezuela.

Mathematical epidemiological models can provide the dynamic evolution of a pandemic. However, they are based on multiple assumptions, including parameters that have to be adjusted over the duration of the pandemic (Brauer et al., 2001; Hethcote, 2005; Yan and Chowell, 2019; Zhang et al., 2021). Usually, if the mathematical model includes many details or increases the heterogeneity, the available data would not be sufficient to identify in a unique way the values of the model's parameters. Forecasting the future of the dynamics of the COVID-19 pandemic using available data from the past and using mathematical models have been proven a very complex task with poor

results (Arvisais-Anhalt et al., 2020; Roda et al., 2020; Holmdahl and Buckee, 2020; Fain and Dobrovolny, 2020; Jewell et al., 2020; Sperrin et al., 2020; Thomas et al., 2020; Kucharski et al., 2020; Stutt et al., 2020; Ferguson et al., 2020; Kuniya, 2020; Zhong et al., 2020; Buitrago-Garcia et al., 2020). The complexity of the forecasting process is due to different factors. First, during the COVID-19 pandemic, the non-pharmaceutical interventions make the transmission rate and the basic reproduction number R_0 of the SARS-CoV-2 vary over time. Models cannot predict how and when official health authorities would change these interventions. Moreover, some individuals decide to change their social behavior regardless of official interventions. Second, the mathematical models have parameters with uncertainty, and these, in many cases, cannot be identifiable in a unique way (Raue et al., 2009; González-Parra et al., 2019a,b; Zhang et al., 2021). Thus, even if the fit to the reported data is good, there could be another combination of parameter values that produce the same quality of fit. Therefore, once the parameter values have been estimated, the model might forecast wrong dynamics just based on the fact that the values were not correct or unidentifiable. Despite all these difficulties mathematical modeling in combination with computational and statistical techniques are useful for studying the impact of specific interventions on the spread of the SARS-CoV-2 virus (Brauer et al., 2001; Hethcote, 2005; Diekmann et al., 2009; Murray, 2002). Note that the changes in social behavior for influenza every year do not change drastically because it is something that has become part of the normal life.

We studied the impact of immigration on the evolution and characterization of the COVID-19 pandemic. In particular, we chose Venezuela due to its unique situation regarding migration over the last few years and in particular during the COVID-19 pandemic. The situation of Venezuela during the COVID-19 pandemic is an important case study from an epidemiological perspective. The situation of Venezuela regarding infected cases shows just one wave until mid-August of 2020 (Johns Hopkins University and Medicine, 2020). This differs from the situation in other countries, but is similar to neighboring countries such as Colombia and Brazil (Johns Hopkins University and Medicine, 2020). This pattern and the fact that the executive authorities of Venezuela implemented rapid and strict non-pharmaceutical interventions suggest that the transmission rate was not varying greatly over the period of this study.

We constructed two nested mathematical models to study the effect of immigration on the estimation of the transmissibility of the SARS-CoV-2 and R_0 in Venezuela. The first model does not consider immigration, while the second does. Both mathematical models considered the subpopulation of asymptomatic carriers. We found the theoretical R_0 using the next-generation matrix method. Using reported data of infected cases, imported cases, and deaths, we estimated the transmissibility of the SARS-CoV-2 and R_0 in Venezuela. We compared these numerical estimations of the mathematical models with and without immigration. Moreover, we observed that the transmissibility of SARS-CoV-2 is lower when the mathematical model considers immigration and imported cases. As a consequence, R_0 is also lower in this case. This result has important implications as it measures how

effective the non-pharmaceutical interventions are during the period of study. In addition, this result shows the importance of taking into account immigration to control the epidemic. Notice that even if we obtain a \mathcal{R}_0 lower than one in the model with immigration that does not necessarily translate in the controllability of the epidemic since infected cases are being imported at a constant rate. We found that for the mathematical model with immigration, the estimated \mathcal{R}_0 was slightly lower than one. This suggests that the transmission within Venezuela would be under control if there were no imported infected cases coming from neighboring countries with higher prevalence.

We performed further estimations using shorter periods, and the estimated basic reproduction numbers \mathcal{R}_0 were higher when immigration was not considered. Nevertheless, one crucial result is that when the immigration was considered, \mathcal{R}_0 was smaller than one. Further, the estimated \mathcal{R}_0 closer to one indicated that additional, light, non-pharmaceutical interventions could reduce the severity of the COVID-19 pandemic (with no imported infected cases). Moreover, this is of paramount importance since values close to unity for the basic reproduction number \mathcal{R}_0 in the imported cases can change the dynamics of the local epidemic drastically, as mentioned in Russell et al. (2021). As well, for the same period, neighboring countries, such as Brazil and Colombia, showed larger basic reproduction numbers and, therefore, more community transmission, which translates into more risk for imported cases in Venezuela (Rahman et al., 2020b; Severein et al., 2020; Yue et al., 2021). In Colombia, the first case was reported on March 6. In Yue et al. (2021) the authors estimated that \mathcal{R}_0 reached its peak of 21.2 on March 17.

We also provide estimates of the disease-induced death rate for infected cases using a mathematical model with and without immigration. The variation of this death rate was small and in accordance with rates from other countries, which makes sense since this is more an intrinsic feature of the disease. We estimated the death rate by fitting the real data related to reported infected cases and deaths to the corresponding state variables generated by the mathematical models. We used MCMC methods to study the identifiability of the parameters (Goodman and Weare, 2010). The results show that the transmission and death rate parameters are identifiable with the available epidemiological data. These results agree with other important studies related to identifiability regarding the COVID-19 pandemic (Zhang et al., 2021).

The proposed general framework and mathematical models presented here are useful and applicable to other regions where migration could be a large factor during a pandemic. We provided guidelines concerning how to tackle the immigration of infected cases into a region and the identifiability of model parameters. Note that for regions where there are vaccination programs, a different mathematical model, either discrete or continuous, would be necessary (Paltiel et al., 2020; Martínez-Rodríguez et al., 2021). In this study, we do not perform any forecasting or prediction, which is a more difficult task, and this COVID-19 pandemic has proven its difficulties. In the case of Venezuela and other countries, initial lock-downs changed after the initial phase. Therefore, assuming constant values for the transmission rates would be an oversimplification of the real situation with important consequences. Moreover, after some long period of lock-downs and non-pharmaceutical interventions, people suffer from fatigue and change their social behavior, which would also affect transmission rates (Morgul et al., 2020).

Finally, we would like to point out the importance of characterizing the COVID-19 pandemic in Venezuela by considering immigration. The results presented here show the importance of imported cases in the estimation of transmissibility and \mathcal{R}_0 . These results are highly correlated to the efficacy of non-pharmaceutical interventions to reduce the burden of the COVID-19 pandemic. The situation of Venezuela and its current crisis provides a unique situation that is worthy of study. As in any typical study of this type, there are limitations in the mathematical models, such as the assumed values for the duration

of the exposed and infectious stages. Nevertheless, we used parameter values that have been used in previous studies and by the Center for Disease Control and Prevention (Centers for Disease Control and Prevention, 2020). In addition, it is important to point out that evidently, the data has some degree of uncertainty. However, the mathematical models proposed here would not be affected by this uncertainty, but the numerical results might be. Nevertheless, if imported infected cases were underreported, the qualitative results would not change since the real basic reproduction numbers related to both mathematical models would be larger, but still these numbers would be different. Thus, we still can see the importance of taking into account the immigration of infected people.

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.

Data availability

Data will be made available on request.

Acknowledgments

The authors are grateful to the reviewers for their careful reading of this manuscript and their useful comments to improve the content of this paper. This research is supported by an Institutional Development Award (IDEA) from the National Institute of General Medical Sciences (P20GM103451) of the National Institutes of Health under grant number P20GM103451.

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