Spring 5-12-2023

Application of epidemiologic methods to investigate the heterogenous impact of COVID-19

Sushma Dahal

Application of epidemiologic methods to investigate the heterogenous impact of COVID-19

by

Sushma Dahal

BPH, HOPE international College, Nepal

MPH, B.P. Koirala Institute of Health Sciences, Nepal

MPH, Georgia State University, Atlanta, USA

A Dissertation Submitted to the Graduate Faculty

of Georgia State University in Partial Fulfillment

of the

Requirements for the Degree

DOCTOR OF PHILOSOPHY IN PUBLIC HEALTH

ATLANTA, GEORGIA

30303

ABSTRACT

APPLICATION OF EPIDEMIOLOGIC METHODS TO INVESTIGATE THE HETEROGENOUS IMPACT OF COVID-19

By

SUSHMA DAHAL

Epidemiologic methods have been critical in shedding light on the dynamics and impact of the COVID-19 pandemic, including monitoring and quantifying morbidity and mortality over time to guide prevention and mitigation strategies. Here we apply different epidemiologic methods across different geospatial levels, population groups, and time scales to investigate the impact of COVID-19 using epidemiological data from Mexico.

In the first study, we assess the mortality impact of the COVID-19 pandemic by estimating absolute and relative excess mortality above an expected level of deaths and employ a generalized logistic growth model to generate short-term forecasts of excess mortality. We also evaluate the association between the excess mortality rate and the use of hashtag terms indicating death in tweets from Mexico. In the second study, we expand the estimation of the excess mortality rate per 10,000 population from the national level to the 'federal entity' level in Mexico and use multiple linear regression analysis and spatial lag models to assess the factors associated with excess mortality rate. In addition, we use functional data analysis to compare, cluster, and summarize the excess mortality growth rate curves. In the third study, we compare the COVID-19 mortality rates and investigate the transmission dynamics among indigenous and non-indigenous populations in Mexico by using different methods such as estimation of person-time mortality rates, Cox Proportional Hazards regression, and instantaneous reproduction number (R_t) over a weekly sliding window as well as for the early ascending phase of four different waves of COVID-19 among the two subpopulations.

The results from these studies indicate that Mexico was heavily affected by the COVID-19 pandemic, with central states exhibiting the highest excess mortality rates. The aging index, marginalization index, and average household size explained the variability in excess mortality rates across federal entities. The indigenous status was found to be a significant risk factor for COVID-19 mortality, with a 68% higher mortality among indigenous groups compared to non-

indigenous. Overall, the three studies presented here demonstrate the power of different epidemiologic methods to gain insights on the heterogenous impact of the COVID-19 pandemic.

APPROVAL PAGE

APPLICATION OF EPIDEMIOLOGIC METHODS TO INVESTIGATE THE HETEROGENOUS IMPACT OF COVID-19

By

SUSHMA DAHAL

Approved:

Gerardo Chowell

……..

Gerardo Chowell, PhD
Committee Chair

Ruiyan Luo

……

Ruiyan Luo, PhD
Committee Member

Svenn-Erik Mamelund

……

Svenn-Erik Mamelund, PhD
Committee Member

……

Lisa Sattenspiel, PhD
Committee Member

Date: 04/20/2023

Acknowledgments

Firstly, I want to express my sincere gratitude to my faculty advisor and the chair of my dissertation committee, Dr. Gerardo Chowell, for his valuable guidance and support throughout my graduate study journey. I am highly thankful to my committee member Dr. Ruiyan Luo for her helpful guidance in the statistical analyses performed in my studies. I would like to express my deepest appreciation to my committee members Dr. Svenn-Erik Mamelund and Dr. Lisa Sattenspiel for their insightful feedback and guidance.

I would like to acknowledge Georgia State University for awarding me with the Second Century Initiative (2CI) Fellowship for my PhD studies. I would also like to acknowledge the valuable contribution of my co-authors Dr. Kenji Mizumoto, Dr. Juan M Banda, Dr. Monica Swahn, Dr. Shannon Self-Brown, and Dr. Ana Bento who provided critical feedback and contributed in the writing of the manuscript. I highly appreciate Dr. Richard Rothenberg for his help and support in applying some epidemiological methods in my research works. I am thankful to all the collaborators from different organizations and from different countries with whom I got the opportunity to work during my graduate studies. I would also like to acknowledge the Center for Advanced Studies (CAS) in Oslo, Norway for partially supporting my third paper in this dissertation.

I am thankful to my Ph.D. colleagues at the School of Public Health at Georgia State University for their moral support. I would also like to acknowledge my lab mates Dr. Amna Tariq and Ms. Amanda Bleichrodt, it was a great experience working with you.

I would not have been here without my loving and supportive family; my parents, my parents-in-law, and my siblings. I am always grateful to have you all in my life.

My dissertation would not have been possible without my loving husband, Raj. I am grateful to you for your love, care, support, and motivation. Thank you for believing in me, and for handling everything during these arduous years of my graduate studies. And finally, tons of thanks to my daughter Diva and my son Dave. Your smiles motivate me to look forward. Thank you for being such sweet kids.

This dissertation is dedicated to my late father, Mr. Chetnath Dahal, who I know would be the proudest of my accomplishments.

Author's Statement Page

In presenting this dissertation as a partial fulfillment of the requirements for an advanced degree from Georgia State University, I agree that the Library of the University shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to quote from, to copy from, or to publish this dissertation may be granted by the author or, in his/her absence, by the professor under whose direction it was written, or in his/her absence, by the Associate Dean, School of Public Health. Such quoting, copying, or publishing must be solely for scholarly purposes and will not involve potential financial gain. It is understood that any copying from or publication of this dissertation which involves potential financial gain will not be allowed without written permission of the author.

Sushma Dahal

…….

Sushma Dahal

04/20/2023

Table of Contents

Chapter 1

1.1. Literature Review and Statement of Purpose

The novel coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in December 2019 in the seafood and poultry market in Wuhan, China. The first reported death due to this novel disease was on January 11, 2020 which was within a month of the report of the outbreak, and soon after on January 30, 2020, it was declared a 'public health emergency of international concern' by the World Health Organization (WHO) (1). Since then, the disease has spread to nearly every country in the world and as of March 29, 2023, there have been 761,402,282 total confirmed COVID-19 cases and 6,887,000 COVID-19 deaths globally (2). The highest number of COVID-19 confirmed cases have been reported from the European region (>274 millions), followed by the Western Pacific region (>201 millions), and the region of the Americas (>190 millions) (2). Likewise, the highest number of COVID-19 deaths have been reported from the region of Americas (>2.9 millions), followed by the European region (>2.2 millions), and Southeast Asia region (>800,000) (2). As of March 29, 2023, the top five countries with the highest number of reported COVID-19 deaths are United States of America (>1.1 million), Brazil (>699,000), India (>530,000), the Russian Federation (>397000), and Mexico (>333,000) (2). According to the data from Johns Hopkins University and Medicine (3), as of March 2023, Peru, Mexico, Ukraine, Iran, and Brazil were among the top countries most affected in terms of observed case fatality ratio (CFR) with the CFR of 4.9%, 4.5%, 2.1%, 1.9%, and 1.9% respectively. Likewise, Peru was the country with highest deaths per 100,000 population with the death rate of 665.85 followed by the US (341.11), Chile (336.22), Brazil (328.98), and Poland (314.45).

At the country level, several non-pharmaceutical interventions (NPIs) such as sealing country borders, school closure, wearing masks, social distancing, stay-at-home orders, etc. were implemented mainly during the initial waves of the pandemic to control the transmission of SARS-CoV-2. There were substantial between and within countries variations in both the levels of implementation as well as in the effectiveness of the implemented NPIs (4). In December 2020, a breakthrough in COVID-19 control occurred when two mRNA vaccines Pfizer-BioNTech and Moderna were granted Emergency Use Authorization (EUA) (5). However, there

is a wide country-level disparity and inequity in the COVID-19 vaccine rollout, suggesting large gaps mainly in low-income countries (6) that in turn affects the impact of the pandemic across different geographic locations and populations.

Since the start of the COVID-19 pandemic in 2019, researchers around the world have applied different epidemiologic methods to study its epidemiology, to monitor and quantify the mortality and morbidity burden of the pandemic, and to guide the actions to slow the spread and minimize the impact of the pandemic. Some of the common epidemiologic approaches used to assess the impact of past infectious disease pandemics such as the 1918 influenza pandemic and the 2009 H1N1 pandemic include assessment of the spatiotemporal distribution of cases and severe outcomes such as hospitalizations and deaths, assessment of age and gender patterns in cases and disease severity, estimation of transmission potential using the reproduction number, assessment of factors associated with the outcome, estimation of all-cause excess mortality rate above an expected level of death, and assessment of the effectiveness of public health intervention using mathematical models (7-12). Real-time forecasting the trajectory of an ongoing outbreak or pandemic using mathematical models is another important approach employed during an infectious disease outbreak that can provide a more complete picture of its transmission dynamics, help guide the resource allocation decision, and inform public health interventions during the outbreak (13-17). Here we apply different epidemiologic methods across different geospatial levels, population groups, and time scales to investigate the impact of COVID-19. In the three studies included in this dissertation, we utilize big epidemiologic data from Mexico which is one of the countries that was highly affected by the COVID-19 pandemic both in terms of the reported number of COVID-19 cases and deaths (2).

When an outbreak or a pandemic such as the COVID-19 is ongoing, different factors such as low testing rates, imperfect sensitivity of the tests, reporting delays, misclassification of the cause of death, increase in deaths from other causes not related to the outbreak, etc. pose challenges in estimating the true mortality burden of the pandemic (18). In such condition, compared to the observed number of deaths due to pandemic, estimating excess mortality above an expected level of death (detailed methods explained in paper 1) is considered as a more comprehensive measure of the total mortality impact of the pandemic because it includes both the direct (confirmed as well as not reported or incorrectly classified) and indirect deaths that are

attributable to the pandemic (18, 19). These indirect deaths include deaths due to denied or delayed care (20, 21), the disruption of the health care system due to pandemic (22), mental health conditions such as suicide (23), etc. In the first paper, we aim to estimate the excess mortality rate per 10,000 population at the national level and by sex, and for major geographic locations in Mexico. In the second paper, we aim to estimate the excess mortality rate at the subnational level for federal entities in Mexico and assess the factors associated with the excess mortality along with some additional analysis such as functional data analysis.

There has also been a substantial disparity in the effect of the COVID-19 pandemic on certain segments of the population such as racial and ethnic minority groups. When considering the past pandemics such as the 1918 influenza pandemic and the 2009 H1N1 pandemic, indigenous populations have been disproportionately affected in terms of infection, and disease severity including death. For example, during the 1918 influenza pandemic, the Māori population in New Zealand had a death rate 7.3 times that of the European populations (24). Likewise, American Indians and Alaska natives were four times more likely to die than the non-indigenous populations during the 2009 H1N1 pandemic (25). However, during the COVID-19 pandemic, initial studies have shown mixed results. For example, initial data from the USA, and Brazil suggest that indigenous populations are at a higher risk of COVID-19 infection and death compared to non-indigenous whereas the data from Canada, Ecuador, and Australia suggest the opposite (26). Since these studies included only the initial period of the COVID-19 pandemic, a better understanding of the situation can be obtained by assessing the differences in the mortality and morbidity outcome for the subpopulations for different time periods by using epidemiologic data of a longer period. Besides, there have also been limitations in the number of countries collecting and making public the COVID-19 data among indigenous populations (27, 28). Therefore, in the third study, I aim to assess the heterogenous impact of COVID-19 among indigenous and non-indigenous populations in Mexico. This is even more relevant because Mexico is also a country in the Americas with the largest number of indigenous people (28).

Over the three studies, major epidemiologic methods that we used are the estimation of excess mortality rate and excess mortality rate ratio using Serfling regression analysis, short-term forecasting of excess deaths using a generalized logistic growth model, correlation analysis of social media data and death data during the pandemic, multiple linear regression analysis to

assess the factors explaining subnational variability in excess death rate, cluster analysis to identify the clusters of states with similar shapes of the excess mortality growth rate curves, tests for spatial autocorrelation and a spatial lag regression model to assess spatial dependence of excess mortality rates at federal entities in Mexico, estimation of person-time mortality rate and rate ratio among indigenous and non-indigenous populations, survival analysis using Cox proportional hazards regression models, and the estimation of instantaneous reproduction number (R_t).

Study 1.

The first paper used weekly total mortality data from 2015 to 2020 for Mexico to characterize the all-cause excess mortality patterns during the COVID-19 pandemic in 2020 by estimating all-cause excess mortality rates per 10,000 population at the national level and by gender and for geographic areas categorized as Mexico City vs other federal entities. Short term forecasts of total excess deaths for the first four weeks of 2021 in Mexico were also estimated using a generalized logistic growth model. Excess mortality rates and rate ratio over baseline were estimated by fitting Serfling regression models. The study also assessed the trend of people's engagement with death chatter using hashtag terms such as death, dead, deceased etc. in social media Twitter from 2018 to 2020 in Mexico and then assessed the correlation of proportion tweets involving death chatter out of total tweets with excess mortality rate and covid-19 mortality rate.

Study 2.

The second paper estimated the excess mortality rate at the federal entity level in Mexico by using all-cause mortality data. Data on socio-demographic, climate, and population characteristics such as population density, aging index, average household size, marginalization index, climate type, rate of depression, and public spending on health was also utilized to assess whether these factors can explain the variability in excess death rate across the subnational level using multiple linear regression analysis. In addition, spatial autocorrelation and spatial lag model were also employed to assess the spatial dependence of the excess mortality rates. Functional data analysis was used to characterize the shape of the growth rate curve of the excess death rates of 32 federal entities including Mexico City and a total of four clusters of federal entities were classified based on the shapes of the growth rate curve. To our knowledge, this type

of clustering analysis has not been previously reported for excess mortality data during an ongoing epidemic.

Study 3.

The third paper used de-identified publicly available data on lab-confirmed RT-PCR-positive COVID-19 cases and deaths from February 2020 to March 2022, from the Ministry of Health of Mexico to estimate the mortality rate per 1000 person-weeks and mortality rate ratio among indigenous and non-indigenous populations separately at the national level as well as at federal entity level including Mexico City. These estimates were also calculated by year and for each of the four waves of the COVID-19 pandemic in Mexico separately for the indigenous and non-indigenous populations. We also estimated correlation coefficients for the proportion of indigenous populations and the estimated rate ratio for the federal entities. In the study, for the death cases, person time was calculated as the difference between the date of symptom onset and the date of death whereas for the censored cases the person time was defined as the difference between the date of symptom onset and the predefined cut-off date. In addition, multivariate Cox proportional hazards regression models were employed to assess the hazard ratio of COVID-19 deaths among indigenous compared to the non-indigenous for the total study duration as well as for each of the four waves of the pandemic. The study also estimated the instantaneous reproduction number (R_t) over a weekly sliding window from the start until the end of the study period as well as the average reproduction number during the early ascending phase of each of the four waves of the COVID-19 pandemic for indigenous and non-indigenous populations.

These three papers as a group contribute to literature in numerous ways. They primarily aim to explore the mortality impact of COVID-19 pandemic at the national level, federal entity level and for multiple subgroups of population including the indigenous groups and at different time periods as the pandemic progresses in the country. The results from the study can be valuable in not only quantifying the mortality impact of the pandemic but also in improving the current understanding about the mechanism that can explain the heterogeneity in COVID-19 mortality rate across spatial level and population subgroups. The findings from these studies can be important in guiding the preventive and control measures in an ongoing pandemic as well as for similar health emergencies in the future. Likewise, the three studies employ several epidemiological methods to address the study research questions ranging from estimation of

excess deaths to the estimation of hazard ratio of deaths. Therefore, these studies can also collectively be used as a reference to perform range of epidemiological analysis using different sets of data to explore the mortality impacts and to assess the transmission dynamics of infectious disease such as the COVID-19 pandemic.

1.2. Study context: Mexico, officially called the United Mexican States, is situated in the southern part of North America and is one of the most populous countries in the world (10^{th} rank as of 2020) (29) with 43.9 % and 8.5% population in 2020 living in poverty and extreme poverty respectively (30). The country is divided into 31 federal entities and the capital, Mexico City. In 2020, at the national level among the population aged 15 years and above 4.7% were illiterate and 29.6% had incomplete basic education (31). The informal sector accounts for around 55% of the employment in the country (32). In the Americas, Mexico has the largest number of indigenous populations with 68 different languages and 364 counted dialect variations. According to 2015 intercensal survey, 21.50% of the total population self-identified as indigenous, 65% of whom were concentrated in 8 of the 32 entities (33).

The first confirmed case of COVID-19 in Mexico was reported on February 27, 2020 (34). By the end of April 2020, the number of confirmed cases increased exponentially to 19224 of which around 10% were deaths (34). In March 2020, WHO declared Europe as a new epicenter of the COVID-19 pandemic, with Italy having the highest number of cases after China (35). Soon after in May 2020, Latin America was the new epicenter in which countries such as Brazil, and Mexico were seeing the record number of COVID-19 cases and death tolls (36).

To monitor the evolution of the COVID-19 pandemic, Mexico used a sample-based sentinel surveillance model which largely underestimated the true burden of COVID-19 cases and deaths in the country. The country followed a reactive rather than proactive approach to respond to the COVID-19 pandemic, leading to an unmanageable level of community spread of COVID-19 (37). For example, the government's COVID-19 control strategies were focused on increasing hospital bed capacity rather than on active case finding through proactive testing, case identification and contact tracing (37). The government of Mexico determined three phases of the contingency plan to fight COVID-19: viral import phase, community transmission phase, and the epidemic phase (38). The first phase, which started on February 28, 2020, and ended on March 23, 2020, placed no restrictions on greeting between people, and public events were

permitted in all settings. As the number of COVID-19 cases increased rapidly and local clusters of infection started to appear, the second phase was implemented on March 24 and lasted until April 20, 2020. During this phase, events requiring large public gatherings were banned or restricted, the general population, especially the elderly (60 years and above), those with immunosuppressed conditions, those with certain diagnosis such as diabetes, arterial hypertension, etc. including pregnant and postpartum women, were advised to remain at home, and nonessential activities in all financial sectors of the country were suspended (34). With the evidence of active outbreaks and propagation of COVID-19 in the country, the start of third phase was declared on April 21, 2020, during which all non-essential activities in the public, private and social sectors were suspended (34). Soon after, in early June, Mexico started to reopen economic activities under a four-tiered biweekly traffic light monitoring system with the aim of alerting the residents to the epidemiological risks of COVID-19 and provide guidance on restrictions on certain activities at a state level in the country (39).

Mexico with an under-resourced public health system, low testing rates, higher poverty levels, higher proportion of populations working in informal sector, higher number of indigenous populations, and lower COVID-19 vaccination rates is one of the highly affected countries throughout the pandemic which ranked second in terms of case fatality rate (CFR) (4.5%) preceded only by Peru (4.9%) as of March 2023 (3).

During the end of 2020, Mexico was one of the countries with lowest number of COVID-19 tests per capita with COVID-19 test rate of 27.31 per 1000 population compared to 769 per 1000 population in the US (40). There was a wide heterogeneity in timing and rigor of implementation of public health and social measures across federal entities and municipalities. For example, at the state level, by early March 2021, the reverse transcription-polymerase chain reaction (RT-PCR) and antigen test per 1000 population was as high as 189 in Mexico City, and as low as 4 in Chiapas. Of the 32 states, 13 had a testing rate less than 25, and 29 states had testing rates less than 50 per 1000 population (37). According to a study that analyzed the performance of states in public policies to respond to the COVID-19 pandemic, there was an absence of a uniform, coordinated, timely and rigorous national response and a wide variability in state level response (41). While states such as Jalisco, Nuevo Leon, Nayarit, and Colima performed better in implementing public policy index, states such as Campeche, Tabasco, and

San Luis Potos underperformed (41). By the end of 2021, 57% of the population were fully vaccinated against COVID-19 which increased to only 64% as of March 2023 (42). On this context, the three studies on this dissertation utilized data from Mexico to assess the impact of COVID-19 at national and subnational levels including population groups such as indigenous people and during different time periods.

1.3. References

1. Taylor DB. A Timeline of the Coronavirus Pandemic. The New York Times. March 17 2021.
2. WHO Coronavirus (COVID-19) Dashboard: Overview: WHO; 2023 [Available from: https://covid19.who.int/ [accessed on March 30, 2023]
3. Mortality in the most affected countries: Johns Hopkins University and Medicine; March 3, 2023 [Available from: https://coronavirus.jhu.edu/data/mortality
4. Banholzer N, Feuerriegel S, Vach W. Estimating and explaining cross-country variation in the effectiveness of non-pharmaceutical interventions during COVID-19. Scientific reports. 2022;12(1):7526.
5. Katella K. Our Pandemic Year—A COVID-19 Timeline. YaleMedicine. March 9, 2021.
6. Chen Z, Zheng W, Wu Q, Chen X, Peng C, Tian Y, et al. Global diversity of policy, coverage, and demand of COVID-19 vaccines: a descriptive study. BMC medicine. 2022;20(1):130.
7. Chowell G, Echevarría-Zuno S, Viboud C, Simonsen L, Tamerius J, Miller MA, et al. Characterizing the epidemiology of the 2009 influenza A/H1N1 pandemic in Mexico. PLoS medicine. 2011;8(5):e1000436.
8. Jhung MA, Swerdlow D, Olsen SJ, Jernigan D, Biggerstaff M, Kamimoto L, et al. Epidemiology of 2009 pandemic influenza A (H1N1) in the United States. Clinical Infectious Diseases. 2011;52(suppl_1):S13-S26.
9. Dahal S, Mizumoto K, Bolin B, Viboud C, Chowell G. Natality decline and spatial variation in excess death rates during the 1918–1920 influenza pandemic in Arizona, United States. American journal of epidemiology. 2018;187(12):2577-84.

10. Dahal S, Jenner M, Dinh L, Mizumoto K, Viboud C, Chowell G. Excess mortality patterns during 1918–1921 influenza pandemic in the state of Arizona, USA. Annals of epidemiology. 2018;28(5):273-80.
11. Ramiro D, Garcia S, Casado Y, Cilek L, Chowell G. Age-specific excess mortality patterns and transmissibility during the 1889–1890 influenza pandemic in Madrid, Spain. Annals of epidemiology. 2018;28(5):267-72.
12. Chowell G, Erkoreka A, Viboud C, Echeverri-Dávila B. Spatial-temporal excess mortality patterns of the 1918–1919 influenza pandemic in Spain. BMC infectious diseases. 2014;14:1-12.
13. Roosa K, Lee Y, Luo R, Kirpich A, Rothenberg R, Hyman JM, et al. Short-term forecasts of the COVID-19 epidemic in Guangdong and Zhejiang, China: February 13–23, 2020. Journal of clinical medicine. 2020;9(2):596.
14. Chowell G, Luo R, Sun K, Roosa K, Tariq A, Viboud C. Real-time forecasting of epidemic trajectories using computational dynamic ensembles. Epidemics. 2020;30:100379.
15. Chowell G, Hincapie-Palacio D, Ospina J, Pell B, Tariq A, Dahal S, et al. Using phenomenological models to characterize transmissibility and forecast patterns and final burden of Zika epidemics. PLoS currents. 2016;8.
16. Desai AN, Kraemer MU, Bhatia S, Cori A, Nouvellet P, Herringer M, et al. Real-time epidemic forecasting: challenges and opportunities. Health security. 2019;17(4):268-75.
17. Worden L, Wannier R, Hoff NA, Musene K, Selo B, Mossoko M, et al. Projections of epidemic transmission and estimation of vaccination impact during an ongoing Ebola virus disease outbreak in Northeastern Democratic Republic of Congo, as of Feb. 25, 2019. PLoS neglected tropical diseases. 2019;13(8):e0007512.
18. Weinberger DM, Chen J, Cohen T, Crawford FW, Mostashari F, Olson D, et al. Estimation of excess deaths associated with the COVID-19 pandemic in the United States, March to May 2020. JAMA internal medicine. 2020;180(10):1336-44.
19. Mathieu E, Ritchie H, Rodés-Guirao L, Appel C, Giattino C, Hasell J, et al. Coronavirus Pandemic (COVID-19). Our World in Data. 2020.
20. Schirmer CM, Ringer AJ, Arthur AS, Binning MJ, Fox WC, James RF, et al. Delayed presentation of acute ischemic strokes during the COVID-19 crisis. Journal of neurointerventional surgery. 2020;12(7):639-42.

21. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. The lancet oncology. 2020;21(8):1023-34.
22. Roberton T, Carter ED, Chou VB, Stegmuller AR, Jackson BD, Tam Y, et al. Early estimates of the indirect effects of the COVID-19 pandemic on maternal and child mortality in low-income and middle-income countries: a modelling study. The Lancet Global Health. 2020;8(7):e901-e8.
23. Kawohl W, Nordt C. COVID-19, unemployment, and suicide. The Lancet Psychiatry. 2020;7(5):389-90.
24. Wilson N, Barnard LT, Summers JA, Shanks GD, Baker MG. Differential mortality rates by ethnicity in 3 influenza pandemics over a century, New Zealand. Emerging infectious diseases. 2012;18(1):71.
25. Castrodale L. Deaths Related to 2009 Pandemic Influenza A (H1N1) Among American Indian/Alaska Natives---12 States, 2009. 2009.
26. Alves DE, Mamelund S-E, Dimka J, Simonsen L, Mølbak M, Ørskov S, et al. Indigenous peoples and pandemics. Scandinavian Journal of Public Health. 2022:14034948221087095.
27. Carroll SR, Akee R, Chung P, Cormack D, Kukutai T, Lovett R, et al. Indigenous peoples' data during COVID-19: from external to internal. Frontiers in Sociology. 2021:62.
28. IWGIA. Mexico; 2021. Available from: https://www.iwgia.org/en/mexico.html
29. worldometer. Countries in the world by population (2023) [Available from: https://www.worldometers.info/world-population/population-by-country/
30. coneval. Poverty in Mexico [Available from: https://www.coneval.org.mx/Medicion/Paginas/PobrezaInicio.aspx.
31. coneval. Poverty measurement, 2018-2020 [Available from: http://sistemas.coneval.org.mx/InfoPobreza/.
32. OECDiLibrary. OECD Economic Outlook-Mexico. [Available from https://www.oecd-ilibrary.org/sites/e608e40c-en/index.html?itemId=/content/component/e608e40c-en
33. National Institute of Indigenous Peoples. Socioeconomic Indicators of the Indigenous Peoples of Mexico, 2015: National estimates by federal entity. July 9, 2017. [Available from https://www.gob.mx/inpi/articulos/indicadores-socioeconomicos-de-los-pueblos-indigenas-de-mexico-2015-116128

34. Suárez V, Suarez Quezada M, Oros Ruiz S, Ronquillo De Jesús E. Epidemiología de COVID-19 en México: del 27 de febrero al 30 de abril de 2020. Rev Clin Esp. 2020;220:463–71.
35. Feuer W, Higgins-Dunn N, Jr BL. Europe is now the 'epicenter' of the coronavirus pandemic, WHO says. CNBC. March 13, 2020. [Available from https://www.cnbc.com/2020/03/13/europe-is-now-the-epicenter-of-the-coronavirus-pandemic-who-says.html
36. Rivers M. The world's new Covid-19 epicenter could be the worst yet. CNN. May 30, 2020. [Available from https://www.cnn.com/2020/05/30/americas/latin-america-covid-19-epicenter-intl/index.html
37. UCSF Institute for Global Health Sciences. Mexico's Response to COVID-19: A Case Study. April 21, 2021.
[Available from https://globalhealthsciences.ucsf.edu/sites/globalhealthsciences.ucsf.edu/files/mexico-covid-19-case-study-english.pdf
38. Mexico's COVID-19 contingency plan: three key phases to fight the coronavirus outbreak. EL UNIVERSAL March 14 2020. [Available from https://www.eluniversal.com.mx/english/mexicos-covid-19-contingency-plan-three-key-phases-fight-coronavirus-outbreak/
39. Mexico's COVID-19 Traffic Light Monitoring System: News for July 19–August 1, 2021: The National Law Review; July 23, 2021 [Available from: https://www.natlawreview.com/article/mexico-s-covid-19-traffic-light-monitoring-system-news-july-19-august-1-2021.
40. Our World in Data. Total COVID-19 tests per 1,000 people [Available from: https://ourworldindata.org/grapher/full-list-cumulative-total-tests-per-thousand?time=2020-02-21..latest&country=BRA~CHL~SLV~MEX~PER~AFG~IND~USA~ITA.
41. Knaul F, Arreola-Ornelas H, Porteny T, Touchton M, Sánchez-Talanquer M, Méndez Ó, et al. Not far enough: Public health policies to combat COVID-19 in Mexico's states. Plos one. 2021;16(6):e0251722.
42. statistica. Share of the population partially or fully vaccinated against COVID-19 in Mexico from December 24, 2020 to March 3, 2023 [Available from: https://www.statista.com/statistics/1104529/population-vaccinated-against-covid-19-mexico/.

Chapter 2

Characterizing all-cause excess mortality patterns during COVID-19 pandemic in Mexico

Citation: Dahal S, Banda JM, Bento AI, Chowell G. Characterizing all-cause excess mortality patterns during COVID-19 pandemic in Mexico. BMC Infectious Disease. 2021;21:432.

2.1. Introduction

SARS-CoV-2 continues to spread unabated in many parts of the world. In particular, Latin American countries are being heavily affected by the COVID-19 pandemic with a total of 22,467,574 cases including 709,062 deaths as of March 12, 2021 [1]. Mexico, one of the highly populated countries in the world with approximately 42% of the people living in poverty [2], documented the first imported COVID-19 case on 27th February, 2020 and currently ranks 3rd in the world in terms of numbers of COVID-19 reported deaths, with a total of 192,488 recorded deaths (7.33% of total deaths globally) as of March 12, 2021 [1]. Delays in the implementation of social distancing interventions, mixed reactions towards the stay-at-home order recommendations, and phased reopening of the country have facilitated sustained transmission of COVID-19 in Mexico [3].

Mexico has one of the lowest per-capita COVID-19 testing rates in the world with about 17 tests per 1000 people in total [4]. The low testing rates, compounded by reporting delays, hinders the estimation of the mortality burden associated with the COVID-19 pandemic based on surveillance data alone. Instead, a more reliable picture of the effect of COVID-19 pandemic on mortality can be derived by estimating excess deaths above a baseline or expected level of death [5, 6]. These estimates can provide information about the deaths that are directly or indirectly attributed to the pandemic [6]. Indeed, some deaths could be misclassified as COVID-19 deaths, or some could be occurring in the context of overburdened health care systems. Thus, tracking all-cause mortality in near real time can help assess whether excess deaths are occurring during a specific period of time and spatial area [6].

Here we report our estimates of the absolute and relative mortality impact of the COVID-19 pandemic in Mexico using cyclical Serfling regression models together with publicly available weekly all-cause mortality data from 2015 to 2020 by gender and for Mexico City and other areas of Mexico. Further, we collected and analyzed weekly twitter data from Mexico about 'deaths' during the COVID-19 pandemic in correlation with the excess all-cause death rate and COVID-19 death rate. We supplemented our analyses with social media data from Twitter, which has been found useful to interpret epidemiological trends [7]. In prior work, Google Trends, Wikipedia searches, and Twitter data have been used for predicting COVID-19 deaths [8]. Taking this data fusion approach even further, other researchers have used Twitter data, alongside smart thermometer data, up-to-date clinician search logs as well as Apple and Cuebiq mobility indices to build near-real time early warning systems for COVID-19 [9]. We also generated predictions of excess mortality for the first 4 weeks of January 2021 using generalized logistic growth model [10].

2.2. Methods

2.2.1 Data: We obtained weekly all-cause death counts based on epidemiological weeks for Mexico which were also stratified by gender and geographic region from January to December 2020 as well as for the preceding 5 years (2015-2019) in order to establish a baseline mortality level [11]. We accessed publicly available weekly mortality data available from National Institute of Statistics and Geography (INEGI) for the years from 2015 to 2018, and data available from National Population Registry (RENAPO) for the years 2019 and 2020 [11]. The last week of December 2020, also includes first 2 days of January 2021. To gauge the timing and relative intensity of the pandemic in Mexico, we examined surveillance data characterizing the weekly number of laboratory-confirmed COVID-19 cases and deaths, which were obtained from the official website of the Mexican Ministry of Health through the Directorate General of Epidemiology [12]. Population size estimates used to calculate mortality rates were obtained from National Population Council (CONAPO) of Mexico [13].

2.2.2 Statistical analysis: To investigate and quantify the mortality pattern associated with the COVID-19 pandemic in Mexico, we estimated excess all-cause mortality rates per 10,000 population at the national level and for Mexico City, and other areas of Mexico and by gender. The excess death rate corresponds to the overall mortality rate above a seasonal baseline of the

expected mortality rates in the absence of the COVID-19 pandemic using standard statistical methods [5, 14-17].

Definition of pandemic periods and excess mortality estimation: We estimated the baseline mortality level by fitting cyclical Serfling regression models to all-cause deaths in non-COVID-19 period, after excluding data from March to December 2020. We included a combination of linear terms with sine and cosine terms describing time trend and seasonal change respectively, which is described by the following equation [5, 15]:

$$\text{Weekly death rates}(t) = a + \alpha \times t + \beta * \sin(2 \times \pi/52.17 \times t) + \gamma * \cos(2 \times \pi/52.17 \times t), \quad (1)$$

Where, a is the intercept and t represents the epidemic week.

Once a weekly baseline and 95% CI were established, periods of COVID-19 pandemic were defined as the weeks in 2020 where the observed all-cause mortality rate exceeded the upper 95% confidence limit of the baseline mortality level. The same pandemic period was used for estimating the total excess mortality rate for entire Mexico, Mexico City, Mexico excluding Mexico City, and gender specific excess mortality rates using established methodology [5, 14-17]. Excess all-cause mortality rate was defined as the difference between the observed and model adjusted baseline mortality rates for each week constituting the pandemic period. Negative excess mortality estimates were replaced by zeros in our analyses. Overall pandemic excess mortality attributed to all cause for total population, each gender group, Mexico City, and Mexico excluding Mexico City was calculated by summing the excess death rates across the pandemic weeks in 2020 [14, 16]. We also calculated the rate ratio (RR), the ratio of observed all-cause mortality rate during pandemic period to the model predicted baseline mortality level in the absence of COVID-19 for the given group.

Twitter data analysis: We used a clean version of the publicly available dataset of tweets version 42 [18], the clean version of this dataset removes all re-tweets, keeping only directly initiated posts by users. We filtered all tweets, by removing all other languages via their ISO 639-1 language code, to only keep the tweets in Spanish (es) and those that originated from Mexico via its country code MX. Additionally, we removed tweets from news agencies and bot accounts. We used the following terms to subset the tweets per day: "muerto, muerta, fallecio, murio, deceso, fallecimiento, defunción, óbito, expiración, defuncion, obito, expiracion, perdio la vida,

sin vida". In English, these terms reflect the meanings “dead, deceased, died, death, expiration, lost life, lifeless”. We collected a total of 1,223,096 and 32,423,282 unique tweets reflecting death and total tweets respectively from March to December 2020. Next, we overlayed the curve of proportion of tweets on death out of total tweets in a given week over the mortality rate curve to inspect the relationship between the mortality rate and the proportion of tweets. We also calculated correlation coefficients between proportion of weekly tweets and the weekly excess death rate and the weekly COVID-19 death rate.

Short term forecast of excess deaths: We used generalized logistic growth model (GLM) to predict excess deaths during the first four weeks of 2021. GLM characterizes epidemic growth by estimating (i) the intrinsic growth rate, r (ii) a dimensionless “deceleration of growth” parameter, p and (iii) the final epidemic size, k_0. The deceleration parameter modulates the epidemic growth patterns including the sub-exponential growth ($0< p <1$), constant incidence ($p =0$) and exponential growth dynamics ($p =1$). The GLM model is given by the following differential equation:

$$\frac{dC(t)}{dt} = rC^p(t)(1 - \frac{C(t)}{k_0}) \qquad (2)$$

Where, $\frac{dC(t)}{dt}$ describes the incidence (of excess deaths) over time t and the cumulative number of excess deaths at time t is given by $C(t)$. To forecast the number of excess deaths during the first 4 weeks of 2021, we calibrated the model using weekly excess deaths during the last six weeks of 2020 (week starting from November 22 to the week starting from December 27, 2020). We utilized parametric bootstrapping approach with a Poisson error structure [10].

2.3. Results

Between March 1, 2020 and January 2, 2021, as of surveillance data updated on February 26, 2021, a total of 1,364,557 laboratory-confirmed COVID-19 cases, and 128,886 COVID-19-related deaths were captured by the epidemiological surveillance system in Mexico. The national daily series of new cases and deaths due to COVID-19 are shown in Fig. 1. The number of cases rapidly rises from April to July followed by a downward trend which again takes off from mid-

September. A similar temporal pattern can also be gleaned from the time series of COVID-19 related deaths.

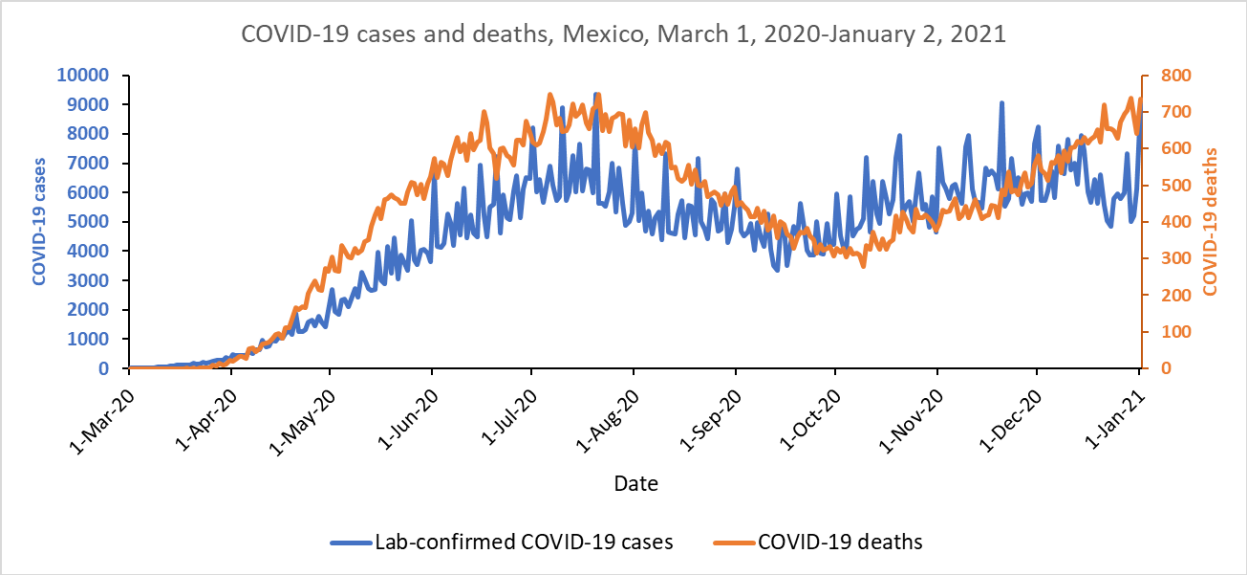


Fig. 1. Daily series of new laboratory-confirmed COVID-19 cases and deaths in Mexico, from March 1, 2020- January 2, 2021

Out of total 44 weeks from March 1, 2020 to January 2, 2021, 38 weeks starting from week 16 (April 12–18, 2020) had the excess death rate greater than 0. The excess death rate peaked on week 29 (July 12–18, 2020) with the excess death rate of 1.01 per 10,000 population, and on week 53 (December 27, 2020-January 2, 2021) with the excess death rate of 1.06 per 10,000 population. The weekly timeseries of all-cause mortality rate per 10,000 population in Mexico is shown in (Fig. 2). We found that peaks in all-cause death rates aligned with the peaks in COVID-19 laboratory-confirmed death rates captured by the surveillance system. The curve of weekly proportion of tweets from Mexico about death is overlaid with the mortality rate curve in Fig. 2.

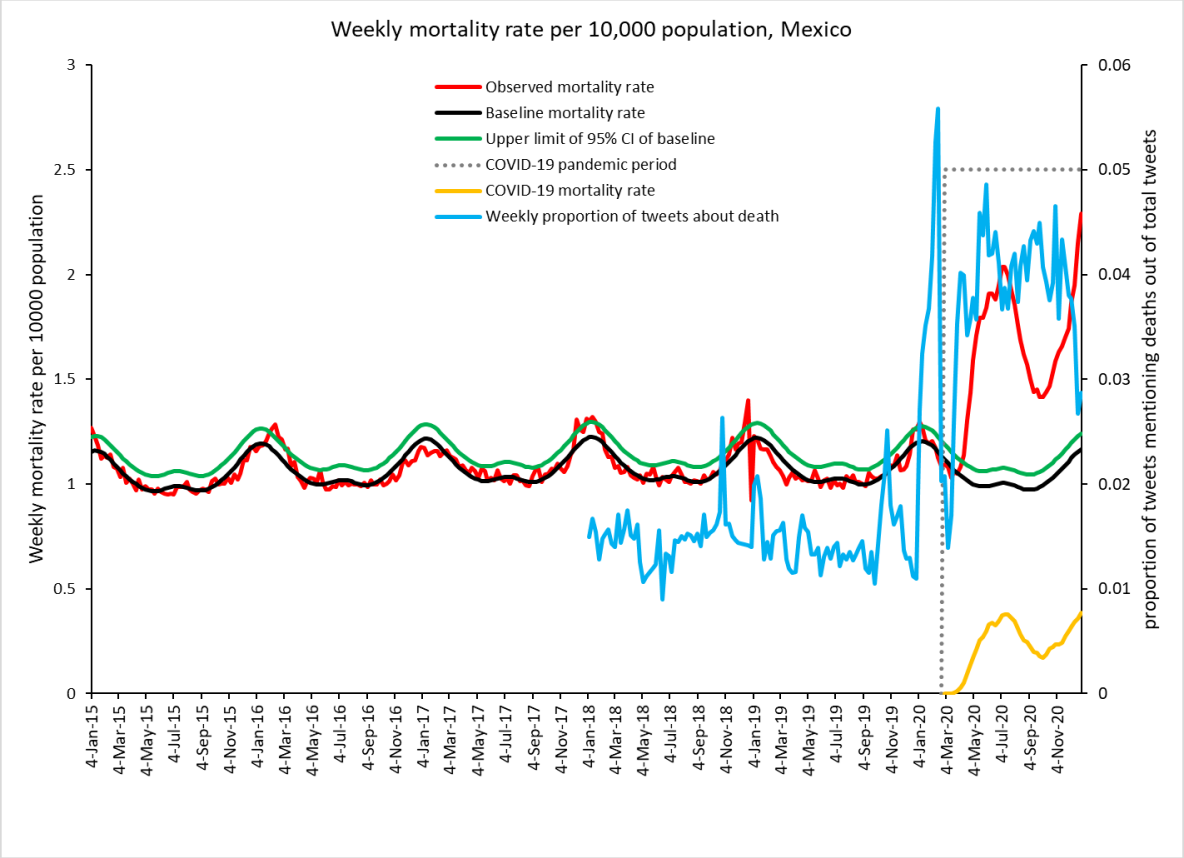


Fig. 2. Mortality rate per 10,000 population, Mexico, 2015–2020. The red line is the weekly all-cause death rate. COVID-19 death rate curve is shown in yellow. Dotted lines highlight 2020 COVID-19 pandemic period. The Serfling seasonal regression model baseline (*black curve*) and corresponding upper limit of the 95% confidence interval of the baseline (*green curve*) are also shown. The weekly frequency of tweets about death is shown by blue curve. Excess all-cause mortality rate is the difference between the observed and model adjusted baseline mortality rates for each week where observed total all-cause mortality rate exceeded the upper 95% confidence limit of the baseline.

Twitter trends show engagement of people in Mexico with the hashtag terms (Fig. 2). The trend of tweets with the hashtag term related to deaths (explained in the methods section) for the baseline years of 2018 and 2019 shows a sharp increase in the twitter chatter about deaths during the pandemic compared to the baseline years. There was a relatively weak but statistically significant correlation of the weekly proportion of tweets with the weekly excess mortality rate $\rho = 0.508$ [95% CI: 0.245, 0.701], p-value = 0.0004, and the weekly COVID-19 mortality

rate $\rho = 0.526$ [95% CI: 0.268, 0.714], p-value = 0.0002, in the study period. The weekly timeseries of all-cause mortality rate per 10,000 population in the country of Mexico by gender are displayed in Fig. 3.

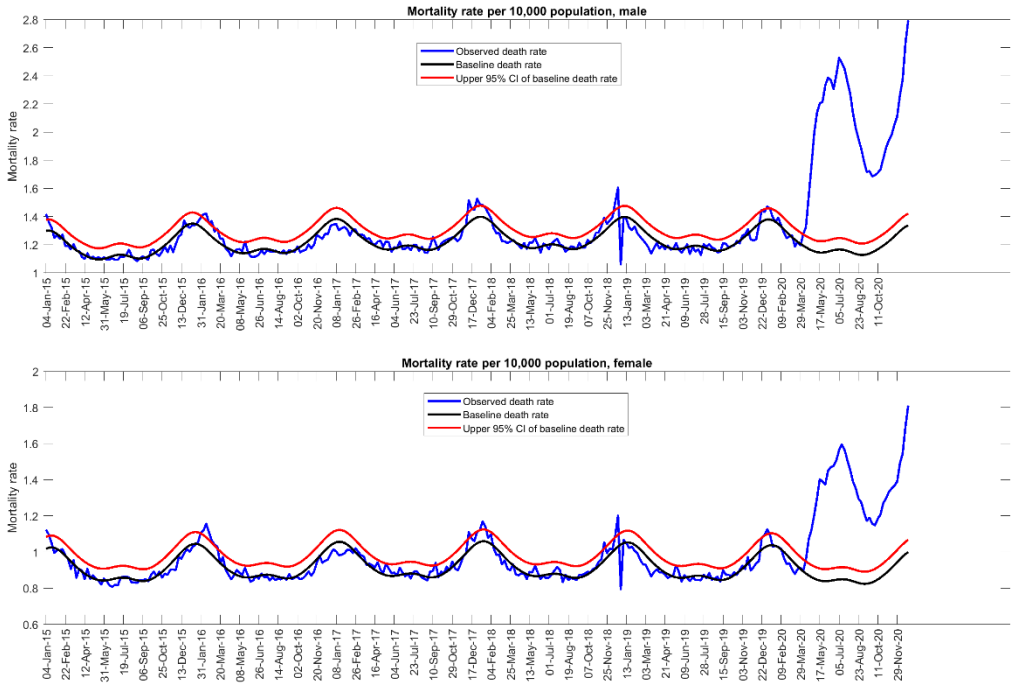


Fig. 3. Mortality rate per 10,000 by gender, Mexico. Excess all-cause mortality rate is the difference between the observed and model adjusted baseline mortality rates for each week where observed total all-cause mortality rate exceeded the upper 95% confidence limit of the baseline in the country.

Similarly, the weekly timeseries of all-cause mortality rate per 10,000 population for Mexico City and for the rest of Mexico are shown in Fig. 4.

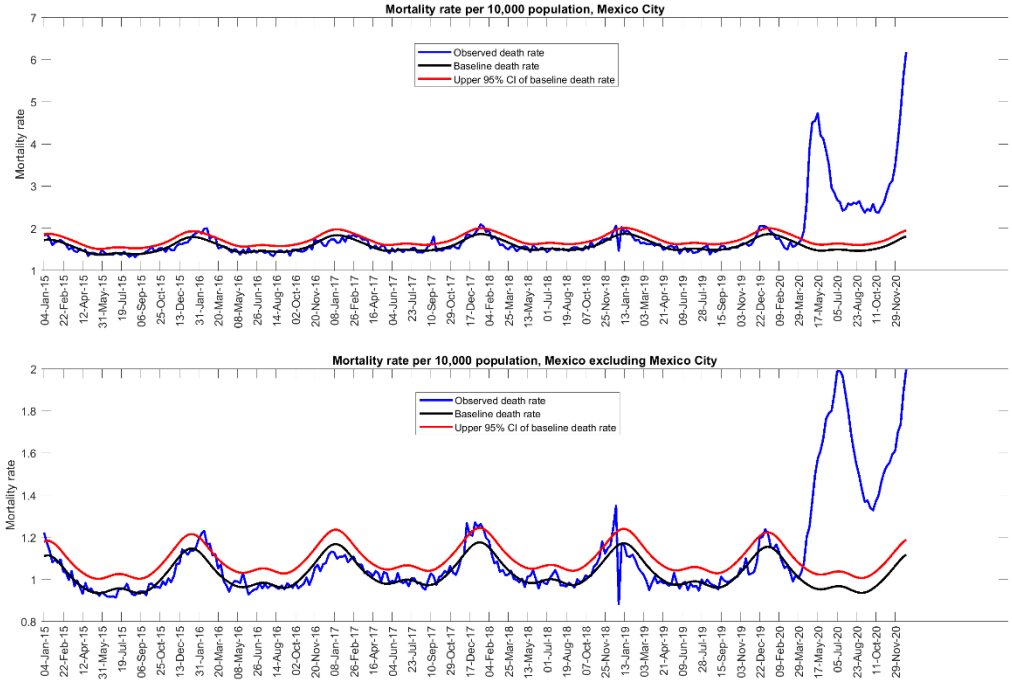


Fig. 4. Mortality rate for Mexico City and Mexico excluding Mexico City. Excess all-cause mortality rate is the difference between the observed and model adjusted baseline mortality rates for each week where observed total all-cause mortality rate exceeded the upper 95% confidence limit of the baseline in the country.

In Table 1, we present the estimates of all-cause excess mortality rate per 10,000 population and the rate ratio estimates for each studied group, including the estimates at the national level. We estimated an excess death rate at 26.10 per 10,000 population in Mexico from March 1 to January 2, 2021. This corresponds to 333,538 excess deaths during the pandemic period. In the same period, a total of 128,886 lab-confirmed COVID-19 deaths corresponds to 38.64% of the total estimated excess deaths.

Table 1. Estimates and their uncertainty for all-cause excess mortality rates per 10,000 population and RR during COVID-19 pandemic, Mexico, March 1, 2020- January 2, 2021.

	All-cause excess death rate per 10,000 population [95% CI]	**Rate ratio* [95% CI]**	**Total number of all-cause excess deaths [95% CI]**	**Deaths due to COVID-19 (% of total number of all-cause excess deaths)**
Mexico	26.10 [23.33-28.87]	1.67 [1.56-1.80]	333,538 [298,139-368,936]	128,886 (38.64%)
Mexico City	63.54 [58.15-68.92]	2.09 [1.91-2.30]	57,304 [52,443-62,157]	16,127 (28.14%)
Mexico excluding Mexico City	23.25 [20.58-25.93]	1.62 [1.51-1.75]	276,149 [244,436-307,980]	112,759 (40.83%)
Male, Mexico	33.99 [30.91-37.08]	1.76 [1.64-1.89]	212,667 [193,397-232,001]	81,489 (38.32%)
Female, Mexico	18.53 [15.97-21.08]	1.56 [1.45-1.69]	120,861 [104,164-137,494]	47,397 (39.22%)

** calculated as the ratio of total observed death rate to total baseline death rate during the pandemic period*

The excess mortality rate in Mexico City (63.54) was about 2.7-fold higher than the rest of the Mexico (23.25) (proportion test, p-value <0.0001). Interestingly, COVID-19 deaths in Mexico City accounted for only 28.14% % of the total estimated excess deaths in Mexico City, compared to 40.83% in the rest of Mexico. Excess mortality rate among males nearly doubled the rate among females (proportion test, p-value <0.0001, and the proportion of COVID-19

deaths out of total excess deaths was similar, 38.32% among males and 39.22% among females (proportion test, p-value <0.0001).

Our estimates of both the absolute and relative excess mortality rate as measured by the rate ratio of observed vs baseline mortality rate was highest for Mexico City (2.09) compared to other areas of Mexico (1.62) and for males (1.76). The rate ratio (RR) at the national level was estimated at 1.67. Finding from the average weekly forecast of excess deaths generated from the GLM model calibrated to weeks starting from November 22 to December 27, 2020 shows that Mexico had a total of ~61610 excess deaths in first four weeks of 2021 (Fig. 5).

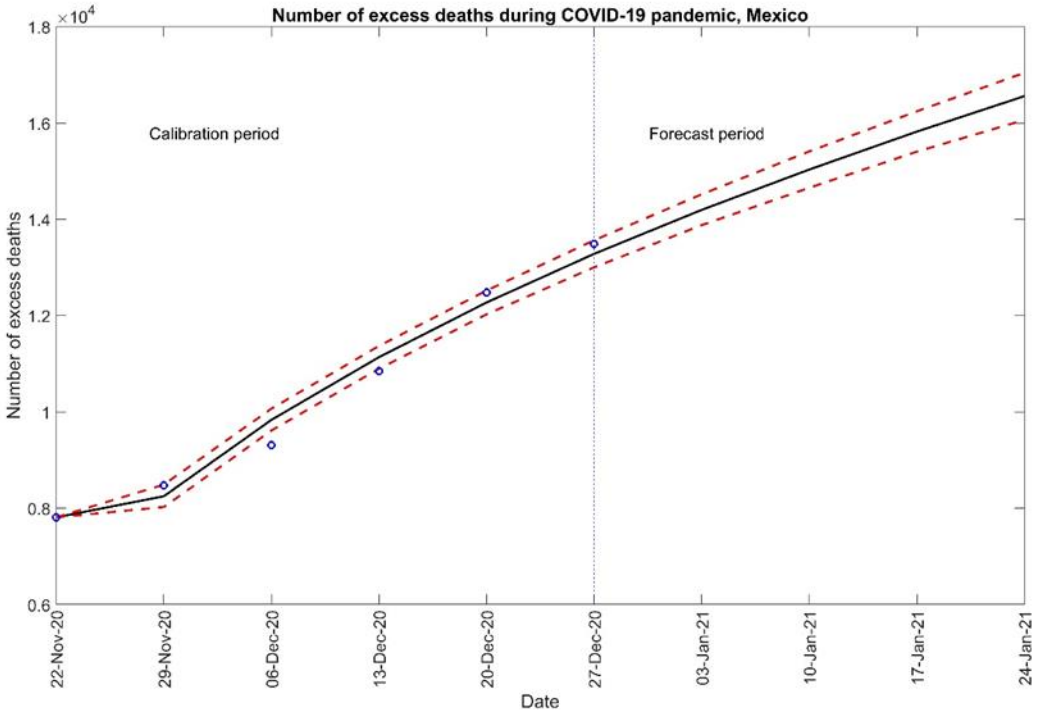


Fig. 5. Model-based forecast of excess number of deaths for first 4 weeks of 2021, Mexico. Blue circles are the estimates of excess mortality rate and model fit based on generalized logistic growth model are shown by the black line. The red dashed lines represent the upper and lower bound of 95% prediction interval. The vertical dashed black line denotes the end of calibration period and start of forecasting period.

2.4. Discussion

Monitoring the excess mortality rate during the course of a pandemic is one of the key approaches for evaluating pandemic mortality impact [19]. In this study we characterized the excess mortality impact during COVID-19 pandemic in Mexico from March 1, 2020 to January 2, 2021. The pandemic was associated with an excess mortality rate of 26.10 per 10,000 population (a total of 333,538 excess deaths). Further, COVID-19 laboratory-confirmed deaths comprised only 38.64% of total excess deaths during the studied period. Our findings indicate that the COVID-19 pandemic has exerted a particularly devastating mortality burden on the Mexican population. We found that the all-cause excess-death rate among males was twice as high as the excess death rate among women in Mexico. This finding is in line with the previous studies, indicating that more men die from COVID-19 than women [20-22]. Several factors such as differences in the prevalence of comorbidities [23] as well as risk behaviors such as smoking and drinking [24], frequency of hand washing [25-27] and delays in health care seeking [22] could be contributing to a higher risk of COVID-19 death among males.

We found that both the all-cause excess death rate and the rate ratio were the highest in Mexico City, compared to rest of the country. A previous study reported that Mexico City was the most affected area during 2009-10 A/H1N1 influenza pandemic in Mexico [28]. Mexico City is one of the most crowded cities in the world [29] and has been significantly affected by air pollution for decades [30]. Prior work has identified high population density [31, 32] and long-term exposure to ambient air pollution [33, 34] as significant predictors of COVID-19 death. Besides, the long term exposure to ambient air pollution, and living in overcrowded setting is not random and might interact with other social determinants of health [34] such as poverty, unemployment, and lack of healthcare access that increase the risk of death during natural disasters.

The fraction of COVID-19 attributed excess deaths was lower in Mexico (38.64%) compared to more than 65% in the USA [19, 35], and Germany [36]. From March to May 2020, the number of all cause excess deaths in the US was only 28% higher than the official record of COVID-19 deaths for that period [19]. Subsequently, from March 15, 2020 to January 30, 2021 an estimated 527,500 excess deaths occurred in the USA of which 83.3% were attributed to

COVID-19 [37]. In developed countries like Germany where the COVID-19 pandemic management has been considered a success story, the estimated excess number of deaths during the first wave of pandemic was lower than the reported number of COVID-19 deaths (+8071 estimated excess deaths vs. 8674 reported COVID-19 deaths) [36]. The low proportion of COVID-19 deaths out of total excess deaths could be driven by low COVID-19 testing rates in the country [4]**,** delays in reporting COVID-19 deaths [38], diagnostic delays for fatal conditions such as cancer [39], issues related to the sensitivity of reverse transcriptase-PCR (RTPCR) test [40], disruption of routine health care owing to the collapse of the health system, or intentional choices of not visiting health facilities due to fear of contracting the virus, exacerbating the effects on the health of vulnerable groups [41]. Moreover, the pandemic triggered a mental health crisis that has given rise to an increase in self-harm and suicide [42, 43]. Our forecast of excess deaths during the first four weeks of 2021 showed an increasing trend which was in line with the high morbidity trend of COVID-19 cases surrounding that time period [44].

Our Twitter signal indicate an increasing trend in the Twitter chatter about deaths from mid-January 2020 that peaked in mid-February 2020. This increase coincided with a series of events including the declaration of the novel coronavirus outbreak in Wuhan as a public health emergency of international concern (PHEC) (January 30, 2020), and the WHO-China joint mission of experts from different countries to inform planning on next steps in the response to COVID-19 outbreak (16-24 February, 2020) [45]. Following a short period of decline, the Twitter chatter showed a substantial increase, just as the trend in lab-confirmed COVID-19 deaths started to rise in Mexico. However, it substantially declined during the next few months probably due to pandemic fatigue. This normalization of the pandemic also reflects people's beliefs of the government signaling that the pandemic was subsiding during the second half of 2020 [46, 47].

Several factors could explain the large number of all-cause excess deaths in Mexico (333,538). First, Mexico has a high burden of non-communicable diseases. In 2019, the top 5 leading causes of deaths were ischemic heart disease, diabetes, chronic kidney disease, cirrhosis, and stroke [48]. These comorbidities have been found to be associated with severe outcomes including death due to COVID-19 [49, 50]. Therefore, COVID-19 pandemic in a country like Mexico with high prevalence of chronic diseases, as well as with a health system struggling with

absenteeism and health worker infections might have led to this alarming number of excess deaths [51, 52]. It is worth noting that, Mexico has the highest number of health worker deaths due to the COVID-19 pandemic (~1400 deaths) in the world [53-55].

The COVID-19 pandemic has a higher all cause excess mortality compared to 2009 A/H1N1 pandemic in Mexico [56] as shown in Table 2. Past work has reported estimates of respiratory excess mortality in Mexico City during the 1918-19 influenza pandemic [57]. Our all-cause excess mortality rate of 63.54 for Mexico City was less than the estimated respiratory excess mortality of 72.90 per 10,000 population for the three waves of 1918 influenza pandemic in Mexico City [57] (Table 2).

Table 2. Comparison of excess death rate and rate ratio across different pandemics in Mexico and Mexico City

Pandemic	Place	Mortality outcome	Time period	Excess death rate per 10000 population [95% CI]	Rate ratio
COVID-19 pandemic	Mexico	All cause	March 1, 2020 to January 2, 2021	26.10 [23.33, 28.87]	2.09
A/H1N1 pandemic [56]	Mexico	All cause	April 2009-April 2010	2.46 [1.95-2.96]	NA
COVID-19 pandemic	Mexico City	All cause	March 1, 2020 to January 2, 2021	63.54 [58.15, 68.92]	2.09 [1.91, 2.30]
1918 influenza pandemic in [57]	Mexico City	Respiratory	April 1918 to March 1920	72.90	NA
			April -May, 1918	6.60	1.2

			October to December, 1918	47.00	7.0
			February to March, 1920	19.30	2.6

Our study has several limitations. As excess death rates will be strongly different among subgroups (it is quite high among the elderly, and those with underlying diseases), overall estimate is affected by structure of the population. A detailed data on death certificate with age and underlying diseases information will provide more accurate estimates. Likewise, we cannot rule out the possibility of negative excess deaths following this elevated period of excess mortality due to new innovations on vaccination and treatment which might prevent serious complications and deaths, or due to the reduction of the vulnerable populations such as the elderly during the initial pandemic years. Similarly, the COVID-19 deaths data that we have used might be underestimated because of different factors such as very low testing rates in Mexico, and misclassification of COVID-19 deaths. Further studies are needed to shed light on the extent of deaths directly attributable to COVID-19 and those that are related to other causes.

2.5 Conclusion

Our estimate of all-cause excess mortality rate at 26.10 per 10,000 population during COVID-19 pandemic in Mexico provides a reliable estimate of the mortality impact of COVID-19 in a hard-hit Latin American country with a low testing rate. As more refined mortality data becomes available on different sub-groups of the population, further studies on excess mortality could elucidate the mortality impact of the COVID-19 pandemic in Mexico. Our findings indicate that Mexico has been disproportionately affected by the COVID-19 pandemic.

2.6. References

1. WHO Coronavirus (COVID-19) dashboard [https://covid19.who.int/].
2. Number of people living in poverty in Mexico between 2008 and 2018 (in millions) [https://www.statista.com/statistics/1039479/mexico-people-living-poverty/].

3. Tariq A, Banda JM, Skums P, Dahal S, Castillo-Garsow C, Espinoza B, et al. Transmission dynamics and forecasts of the COVID-19 pandemic in Mexico, March 20–November 11, 2020. medRxiv. 2021.
4. Ortega RP: Mexico's coronavirus czar faces criticism as COVID-19 surges In: *Science.* December 9 2020. [https://www.sciencemag.org/news/2020/12/mexico-s-coronavirus-czar-faces-criticism-covid-19-surges].
5. Serfling RE. Methods for current statistical analysis of excess pneumonia-influenza deaths. Public Health Rep. 1963;78(6):494. https://doi.org/10.2307/4591848.
6. CDC: Excess Deaths Associated with COVID-19 [https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm].
7. Mavragani A, Gkillas K. COVID-19 predictability in the United States using Google trends time series. Sci Rep. 2020;10(1):1–12.
8. O'Leary DE, Storey VC. A Google–Wikipedia–twitter model as a leading Indicator of the numbers of coronavirus deaths. Intell Syst Account Finance Manag. 2020;27(3):151–8. https://doi.org/10.1002/isaf.1482.
9. Kogan NE, Clemente L, Liautaud P, Kaashoek J, Link NB, Nguyen AT, et al. An early warning approach to monitor COVID-19 activity with multiple digital traces in near real time. Sci Adv. 2021;7(10):eabd6989.
10. Yan P, Chowell G. Quantitative methods for investigating infectious disease outbreaks, vol. 70. Switzerland: Springer; 2019.
11. Government of Mexico: Excess mortality in Mexico [https://coronavirus.gob.mx/exceso-de-mortalidad-en-mexico/].
12. Government of Mexico: Historical databases COVID-19: published on 26 February 2021 [https://www.gob.mx/salud/documentos/datos-abiertos-bases-historicas-direccion-general-de-epidemiologia?idiom=es].
13. CONAPO: Projections of the population of the municipalities of Mexico, 2015-2030.
14. Chowell G, Simonsen L, Flores J, Miller MA, Viboud C. Death patterns during the 1918 influenza pandemic in Chile. Emerg Infect Dis. 2014;20(11):1803–11. https://doi.org/10.3201/eid2011.130632.
15. Chowell G, Viboud C, Simonsen L, Miller MA, Acuna-Soto R, Díaz JMO, et al. The 1918–19 influenza pandemic in Boyaca, Colombia. Emerg Infect Dis. 2012;18(1):48–56. https://doi.org/10.3201/eid1801.101969.

16. Dahal S, Jenner M, Dinh L, Mizumoto K, Viboud C, Chowell G. Excess mortality patterns during 1918–1921 influenza pandemic in the state of Arizona, USA. Ann Epidemiol. 2018;28(5):273–80. https://doi.org/10.1016/j.annepidem.2017.12.005.
17. Viboud C, Eisenstein J, Reid AH, Janczewski TA, Morens DM, Taubenberger JK. Age- and sex-specific mortality associated with the 1918–1919 influenza pandemic in Kentucky. J Infect Dis. 2013;207(5):721–9. https://doi.org/10.1093/infdis/jis745.
18. Banda JM, Tekumalla R, Wang G, Yu J, Liu T, Ding Y, et al. A large-scale COVID-19 Twitter chatter dataset for open scientific research --an international collaboration. https://arxiv.org/abs/2004.03688.
19. Weinberger DM, Chen J, Cohen T, Crawford FW, Mostashari F, Olson D, et al. Estimation of excess deaths associated with the COVID-19 pandemic in the United States, march to may 2020. JAMA Intern Med. 2020;180(10):1336–44. https://doi.org/10.1001/jamainternmed.2020.3391.
20. Bhopal SS, Bhopal R. Sex differential in COVID-19 mortality varies markedly by age. Lancet. 2020;396(10250):532–3. https://doi.org/10.1016/S0140-6736(20)31748-7.
21. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ. 2020;11(1) 1–13:29. https://doi.org/10.1186/s13293-020-00304-9.
22. Griffith DM, Sharma G, Holliday CS, Enyia OK, Valliere M, Semlow AR, et al. Men and COVID-19: a biopsychosocial approach to understanding sex differences in mortality and recommendations for practice and policy interventions. Prev Chronic Dis. 2020;17:E63.
23. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2018;392(10159):1789–858. https://doi.org/10.1016/S0140-6736(18)32279-7.
24. Cai H. Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med. 2020;8(4):e20. https://doi.org/10.1016/S2213-2600(20)30117-X.
25. Suen LK, So ZY, Yeung SK, Lo KY, Lam SC. Epidemiological investigation on hand hygiene knowledge and behaviour: a cross-sectional study on gender disparity. BMC Public Health. 2019;19(1):401. https://doi.org/10.1186/s12889-019-6705-5.

26. Onion R. The long history of the hand-washing gender gap. In: Slate; 2020. [https://slate.com/technology/2020/02/women-hand-washing-more-than-men-why-coronavirus.html].

27. Krueger A. Where women are ahead of men: hand washing. In: The New York Times; 2020. [https://www.nytimes.com/2020/03/17/us/women-men-hand-washing-coronavirus.html].

28. Sarria-Guzmán Y, Bernal J, Biase MD, Muñoz-Arenas LC, González-Jiménez FE, Mosso C, et al. Using demographic data to understand the distribution of H1N1 and COVID-19 pandemics cases among federal entities and municipalities of Mexico. PeerJ. 2021;9:e11144. https://doi.org/10.7717/peerj.11144.

29. Diamond M. The 20 most crowded citites on earth. In: INSIDER; 2019. [https://www.insider.com/most-crowded-places-on-earth-2017-10].

30. Romo R. Mexico City's extreme air pollution, in photos. In: CNN; 2019. [https://www.cnn.com/2019/05/17/americas/mexico-city-pollution-in-photos-intl].

31. Roy S, Ghosh P. Factors affecting COVID-19 infected and death rates inform lockdown-related policymaking. PLoS One. 2020;15(10):e0241165. https://doi.org/10.1371/journal.pone.0241165.

32. Rosenthal BM: Density Is New York City's Big 'Enemy' in the Coronavirus Fight In: The New York Times. [https://www.nytimes.com/2020/03/23/nyregion/coronavirus-nyc-crowds-density.html].

33. Wu X, Nethery RC, Sabath M, Braun D, Dominici F. Air pollution and COVID-19 mortality in the United States: Strengths and limitations of an ecological regression analysis. Sci Adv. 2020;6(45):eabd4049.

34. Benmarhnia T. Linkages between air pollution and the health burden from COVID-19: methodological challenges and opportunities. Am J Epidemiol. 2020;189(11):1238–43. https://doi.org/10.1093/aje/kwaa148.

35. Rossen LM, Branum AM, Ahmad FB, Sutton P, Anderson RN. Excess deaths associated with COVID-19, by age and race and ethnicity—United States, January 26–October 3, 2020. Morb Mortal Wkly Rep. 2020;69(42):1522–7. https://doi.org/10.15585/mmwr.mm6942e2.

36. Stang A, Standl F, Kowall B, Brune B, Böttcher J, Brinkmann M, et al. Excess mortality due to COVID-19 in Germany. J Inf Secur. 2020;81(5):797–801. https://doi.org/10.1016/j.jinf.2020.09.012.
37. Katz J, Lu D, Sanger-Katz M. 527,000 More U.S. Deaths Than Normal Since Covid-19 Struck; 2021.
38. Gutierrez E, Rubli A, Tavares T: Delays in death reports and their implications for tracking the evolution of COVID-19. Available at SSRN 3645304 2020.
39. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol. 2020;21(8):1023–34. https://doi.org/10.1016/S1470-2045(20)30388-0.
40. Tahamtan A, Ardebili A. Real-time RT-PCR in COVID-19 detection: issues affecting the results. Expert Rev Mol Diagn. 2020;20(5):453–4. https://doi.org/10.1080/14737159.2020.1757437.
41. Roberton T, Carter ED, Chou VB, Stegmuller AR, Jackson BD, Tam Y, et al. Early estimates of the indirect effects of the COVID-19 pandemic on maternal and child mortality in low-income and middle-income countries: a modelling study. Lancet Glob Health. 2020;8(7):e901–8. https://doi.org/10.1016/S2214-109X(20)30229-1.
42. Sahoo S, Bharadwaj S, Parveen S, Singh AP, Tandup C, Mehra A, et al. Self-harm and COVID-19 pandemic: an emerging concern–a report of 2 cases from India. Asian J Psychiatr. 2020;51:102104. https://doi.org/10.1016/j.ajp.2020.102104.
43. Kawohl W, Nordt C. COVID-19, unemployment, and suicide. Lancet Psychiatry. 2020;7(5):389–90. https://doi.org/10.1016/S2215-0366(20)30141-3.
44. Mexico Coronavirus Map and Case Count. In: The New York Times 2021. [https://www.nytimes.com/interactive/2020/world/americas/mexico-coronavirus-cases.html].
45. WHO: Archived: WHO Timeline-COVID-19 [https://www.who.int/news/item/27-04-2020-who-timeline%2D%2D-covid-19].
46. Dominguez P. Coronavirus está controlado y a la baja en todo el país: secretario de Salud. In: La Mañanera; 2020. [https://www.milenio.com/politica/covid-19-pandemia-controlada-32-entidades-ssa].

47. Espino LA: Opinion: La verdad sobre la pandemia está en disputa en México. In: Wash Post, 2020. [https://www.washingtonpost.com/es/post-opinion/2020/07/08/la-verdad-sobre-la-pandemia-esta-en-disputa-en-mexico/].
48. IHME: Mexico [http://www.healthdata.org/mexico].
49. Jordan RE, Adab P, Cheng K. Covid-19: risk factors for severe disease and death. London: British Medical Journal Publishing Group; 2020.
50. Kim SJ, Bostwick W. Social vulnerability and racial inequality in COVID-19 deaths in Chicago. Health Educ Behav. 2020;47(4):509–13.
51. The Lancet: Latest global disease estimates reveal perfect storm of rising chronic diseases and public health failures fuelling COVID-19 pandemic [http://www.healthdata.org/news-release/lancet-latest-global-disease-estimates-reveal-perfect-storm-rising-chronic-diseases-and].
52. Dyer O. Covid-19: Mexico acknowledges 50 000 more deaths than official figures show. London: British Medical Journal Publishing Group; 2020.
53. Kahn C. Mexico records the highest number of health care worker deaths from COVID-19: NPR; 2020. [https://www.npr.org/2020/09/17/914103034/mexico-records-the-highest-number-of-health-care-worker-deaths-from-covid-19]
54. Mexico, Demographic data as of July 1, 2020, economic data for 2019 [https://www.census.gov/popclock/world/mx].
55. Covid: Mexico passes 100,000 coronavirus deaths. In: BBC News. 2020. [https://www.bbc.com/news/world-latin-america-55011840].
56. Charu V, Chowell G, Palacio Mejia LS, Echevarría-Zuno S, Borja-Aburto VH, Simonsen L, et al. Mortality burden of the a/H1N1 pandemic in Mexico: a comparison of deaths and years of life lost to seasonal influenza. Clin Infect Dis. 2011;53(10):985–93. https://doi.org/10.1093/cid/cir644.
57. Chowell G, Viboud C, Simonsen L, Miller MA, Acuna-Soto R. Mortality patterns associated with the 1918 influenza pandemic in Mexico: evidence for a spring herald wave and lack of preexisting immunity in older populations. J Infect Dis. 2010;202(4):567–75. https://doi.org/10.1086/654897.

Chapter 3

Geospatial Variability in Excess Death Rates during the COVID-19 Pandemic in Mexico: Examining Socio Demographic, Climate and Population Health Characteristics

Citation: Dahal S, Luo R, Swahn MH, Chowell G. Geospatial variability in excess death rates during the COVID-19 pandemic in Mexico: examining socio demographic, climate and population health characteristics. International Journal of Infectious Diseases. 2021;113:347-54.

3.1. Introduction

Monitoring all-cause excess mortality, above an expected level of total deaths, as a pandemic unfolds is one of the key ways to evaluate its mortality impact (Weinberger et al., 2020). All-cause excess mortality estimates include deaths that are directly or indirectly attributed to the pandemic (CDC, Serfling, 1963). Besides direct deaths due to COVID-19, deaths indirectly attributed to the COVID-19 pandemic include those related to denied or delayed care for acute emergencies (Maringe et al., 2020, Schirmer et al., 2020) or other chronic conditions (Douglas et al., 2020), the disruption of routine health care services in an overburdened health care system (Roberton et al., 2020), unaddressed mental health concerns including suicide and self-harm (Kawohl and Nordt, 2020, Sahoo et a;., 2020), and drug overdoses (Curie et al., 2021). Detailed analyses of excess mortality can inform prevention and mitigation strategies by determining where the mortality impact of the pandemic has been most significant.

Mexico is one of the countries in Latin America that is bearing the brunt of the COVID-19 pandemic with the fourth-highest number of COVID-19 deaths in the world, after the USA, Brazil, and India, as of late June 2021 (Statistica, 2021). In fact, Mexico has reported a total of 2 487 747 (1.38% of global cases) confirmed cases of COVID-19, including 231 847 deaths (5.96% of global deaths), as of June 25, 2021 (WHO, 2021). A previous study reported a high

all-cause excess death rate of 26.10 per 10 000 population in Mexico in 2020, with COVID-19 deaths accounting for only 38.64% of the estimated excess deaths (Dahal et al., 2021). Additionally, Mexico was identified as one of the countries with highest excess deaths in terms of absolute numbers, excess deaths per 100 000 population, and excess deaths as percent of annual deaths in recent research (Karlinsky and Kobak, 2021). While the relatively low proportion of COVID-19 deaths, out of all excess deaths, could be the result of low testing rates, misclassification of COVID-19 deaths, and delays in reporting COVID-19 deaths (Gutierrez et al., 2020), a substantial number of deaths during the pandemic could be due to the indirect causes (CDC, 2021) and need to be examined in more depth.

The distribution of indirect causes of deaths depends on several factors such as sociodemographic characteristics, population health and the selection, timing and intensity of any public health interventions, in addition to the efficiency and reach of the health and social care system (Kontis et al., 2020). In Mexico, pandemic control measures have varied widely (Knaul et al., 2021). Therefore, a more detailed understanding of the mortality burden of the pandemic can be obtained by quantifying spatial heterogeneity in excess deaths at a state level and by examining the influence of underlying sociodemographic, economic, and health system related factors, and also climate factors. In this study, we pose the question whether in a country such as Mexico, with very high COVID-19 mortality, potential spatial variability in the excess deaths can be explained by underlying sociodemographic, climate and population health indicators. To answer that research question, we first estimated the all-cause excess deaths during the COVID-19 pandemic in Mexico comprising 31 states and Mexico City. Next, we evaluated the potential associations between different sociodemographic factors, climate, and excess mortality patterns at the state level in Mexico. Furthermore, we also conducted a cluster analysis to characterize the shapes of the excess mortality curves into different groups that describe the potential geospatial variability in excess mortality. Analyses such as these are critically important for understanding excess mortality and for guiding intervention strategies.

3.2. Methods

3.2.1 Data

We obtained weekly all-cause death counts updated on May 25, 2021 for Mexico at the state level and for Mexico City, based on epidemiological weeks from January 2020 until April 10, 2021 and for the preceding 5 years (2015–2019) to establish a baseline mortality level (Government of Mexico). We accessed publicly available weekly mortality data from the National Institute of Statistics and Geography (INEGI) for the years from 2015 to 2018, and data from National Population Registry (RENAPO) for the years 2020 and 2021 (Government of Mexico). For the year 2019, we chose either INEGI or RENAPO as the data source, based on the value of weekly mortality of the last week of 2018 and the first week of 2019 for each state. We obtained the national and state-level population size estimates from the National Population Council (CONAPO) of Mexico (CONAPO, 2015-2030). Mortality data was not available for the state of Tlaxcala for the last six weeks of the study period. For this reason, this state was excluded from our regression and functional cluster analyses.

For each state, including Mexico City, we obtained data on seven variables: population density (2020), aging index (2020), average household size (2020), marginalization index (2020), rate of new cases of depression per 100 000 population (2019), public spending on health as percent of GDP (2019), and climate zone. Data on population density, aging index, average household size, and rate of new case of depression were obtained from INEGI (INEGI), data on public spending on health was obtained from the subsystem of health accounts at the federal and state level (SICUENTAS) (General Directorate of Health Information, 2021), and the data on the marginalization index was available from CONAPO (CONAPO, 2020). To model climate variation, we used the Köppen-Geiger classification system (Méndez-Arriaga, 2020) which divides Mexican states into three climatic groups: A, B, and C as follows:

Group A: Tropical/megathermal climates: warm humid climate; warm sub-humid climate; warm, semi-warm humid climate; and semi-warm sub-humid climate.

Group B: Dry (desert and semi-arid) climate: dry, warm and semi-dry climate; dry, temperate and semi-dry semi-cold climate; dry, warm dry climate; dry, temperate dry climate; dry, temperate dry winter rains; dry, warm very dry climate; dry, temperate and very dry semi-cold climate.

Group C: Temperate/mesothermal climates: temperate, semi-warm humid climate; temperate, semi-warm sub-humid climate; temperate, humid climate; temperate, sub-humid climate; temperate, semi-cold humid climate; temperate, semi-cold sub-humid climate. According to this grouping group A, B, and C include 11, 14, and 7 states respectively. States in Mexico based on this climate categorization are presented in Supplemental Figure 2.

Summary statistics of these variables from 31 states and Mexico City are provided in Table 1.

Table 1. Descriptive statistics for six continuous variables included in the multiple regression analysis of excess mortality in Mexico (*n*=32).

Variable	**Minimum**	**Mean (SD)**	**Median (IQR)**	**Maximum**
Population density (2020) (habitants per km^2)	10.80	309.68 (1078.69)	67.15 (127.20)	6163.30
Aging index (2020)	28.70	46.41 (10.44)	45.45 (7.40)	90.20
Average household size (2020)	3.6	3.91 (0.18)	3.90 (0.20)	4.4
Marginalization index (2020)	11.32	18.89 (2.73)	19.43 (3.23)	23.01
Rate of new case of depression per 100,000 population (2019)	22.06	114.88 (76.05)	92.14 (67.37)	348.17
Public spending on health as a percent of GDP (2019)	0.94	3.12 (1.02)	2.96 (1.32)	5.81

3.2.2 Pandemic period and excess deaths

For both the national data and the data for each state, we separately estimated the baseline mortality level by fitting cyclical Serfling regression models to all-cause deaths in the non-COVID-19 period, after excluding data from March 2020 to April 2021 by employing established methodology (Chowell et al., 2014, Chowell et al., 2012, Dahal et al., 2018a, Serfling, 1963, Viboud et al., 2013). Details on the model equation that was used can be

found in (Dahal et al., 2021). After establishing a weekly baseline and the corresponding 95% CI at the national level, we defined the periods of COVID-19 pandemic as the weeks in 2020 and 2021 where the observed all-cause mortality rate at the national level in Mexico exceeded the upper 95% confidence limit of the national baseline mortality rate. The excess mortality rate was estimated at the state level and for Mexico City for the same defined period of the COVID-19 pandemic. Excess all-cause mortality rate was estimated as the difference between the observed and model adjusted baseline mortality rates for each week constituting the pandemic period. The overall pandemic excess mortality in 2020 and 2021 was calculated by summing the excess death rates across the pandemic weeks in the given year (Chowell et al., 2014, Dahal et al., 2021, Dahal et al., 2018a). Negative excess mortality estimates were replaced by zeros in our analyses to account for underreporting due to reporting delays (Aron and Muellbauer, 2020, CDC, 2021).

3.2.3. Multiple regression analysis

After estimating the total excess mortality rate for each state, we explored the association between the total excess mortality rate and the predictor variables. Because the population density and rate of new case of depression distributions were skewed, we transformed these variables to log base 10. Since we identified Mexico City as a potential influential point, we performed sensitivity analysis by comparing the results of different models, including and excluding Mexico City. Since there was no significant change in the statistical inference of the parameters, we included Mexico City in the model, and parameters were estimated using ordinary least squares (OLS) method.

3.2.4. Cluster analysis

We followed the analytic methods described in (Srivastava and Chowell, 2020) to pre-process the weekly cumulative all-cause excess deaths for 30 states and Mexico City (excluding Tlaxcala, refer to study setting for details). Then, we analyzed the shapes of the excess all-cause death rate curves to compare, cluster, and summarize growth rates.

We employed the following steps to smooth and normalize the weekly all-cause excess death data:

a. Smoothing: Cumulative excess deaths curves were smoothed using smooth function in Matlab which uses a moving average filter over a 10-week span.

b. Time differencing: If $f_i(t)$ denotes the given cumulative number of excess deaths for state i on week t, then per week growth at time t is given by $g_i(t) = f_i(t) - f_i(t-1)$.

c. Re-scaling: We rescaled each curve by dividing each $g_i(t)$ by the total excess number of deaths for a given state i, which is equivalent to computing $h_i(t) = g_i(t)/r_i$, where $r_i = \sum_{k=1}^{K} g_i(t_k)$ and K is the number of weeks in the period.

d. Smoothing: We then smoothed the normalized curves over a 5-weeks span, using the smooth function in Matlab.

To identify the clusters by comparing the curves, we used a simple metric. For any two rate curves, h_i and h_j, we compute the norm $||h_i - h_j||$, where the double bars denote the L^2 norm of the difference function, i.e., $||h_i - h_j|| = \sqrt{\int \left(h_i(t) - h_j(t)\right)^2 dt}$ which is approximated by $\sqrt{\sum_k \left(h_i(t_k) - h_j(t_k)\right)^2 / K}$, where K is the number of weeks in the period.

To perform clustering of thirty-one curves into smaller groups, we applied the dendrogram function in Matlab using the "Ward's" linkage as explained in ref. (Srivastava and Chowell, 2020). The Ward's linkage minimizes the total within-cluster variance and tends to produce more compact clusters. It is also less sensitive to outliers than other linkages. The number of clusters was decided empirically by inspecting the overall clustering results. After clustering the states into different groups, we derived the average curve for each cluster using a time wrapping algorithm (Srivastava and Chowell, 2020, Srivastava and Klassen, 2016).

3.3. Results

From March 1, 2020 to April 10, 2021 (total of 58 weeks), the observed death rate was greater than the upper 95% confidence interval of the baseline starting from week of April 12-18, 2020 until the week of April 4-10, 2021 (total of 52 weeks) (Figure 1). For this period starting from

April 12, 2020, the first peak of weekly excess mortality rate occurred in the week of July 12-18, 2020, with the excess death rate of 1.04 per 10 000 population, then declined slightly for a few weeks and then increased again from the week of December 20-26, 2020, and reached a peak with an all-cause excess death rate of 1.99 per 10 000 population in the week of January 17-23, 2021. The excess death rate remained below 0.5 from the week of February 28, 2021 until the end of the study period.

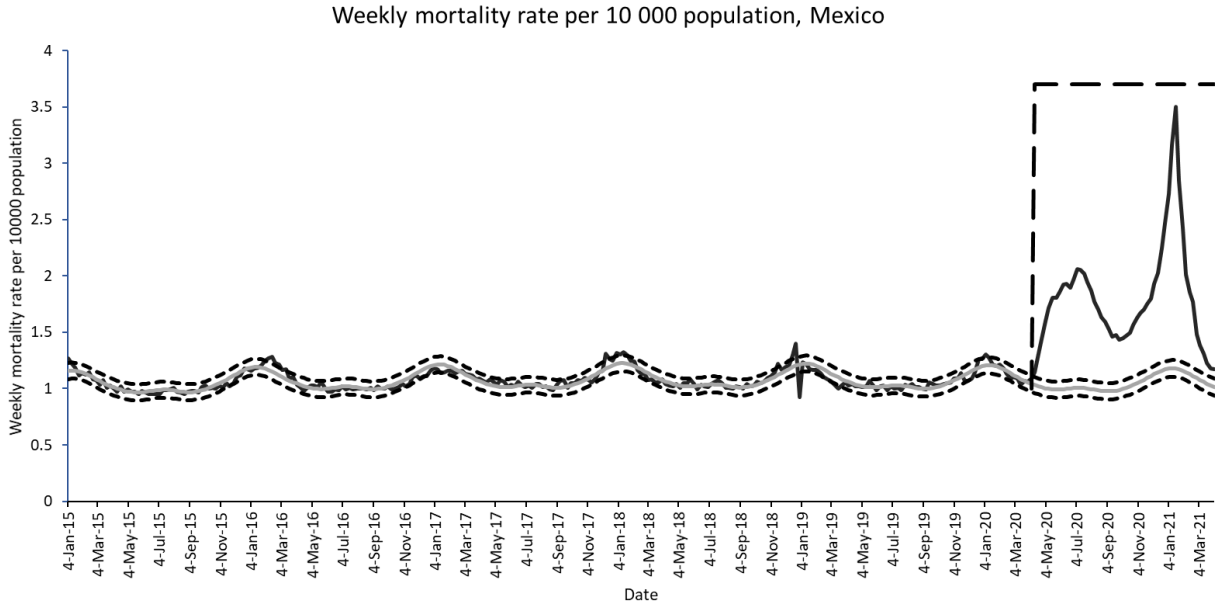


Figure 1. Mortality rate per 10 000 population, Mexico, January 2015–March 2021. The black curve is the observed weekly death rate. The grey curve is the predicted baseline death rate. Square dotted curves indicate the upper and lower 95% confidence intervals of the baseline death rate. The long-dashed line indicates the COVID-19 pandemic period.

All-cause excess death rates for the national level, Mexico City, and 31 states of Mexico are presented in Table 1. The map displaying state-level estimates is depicted in Figure 2.

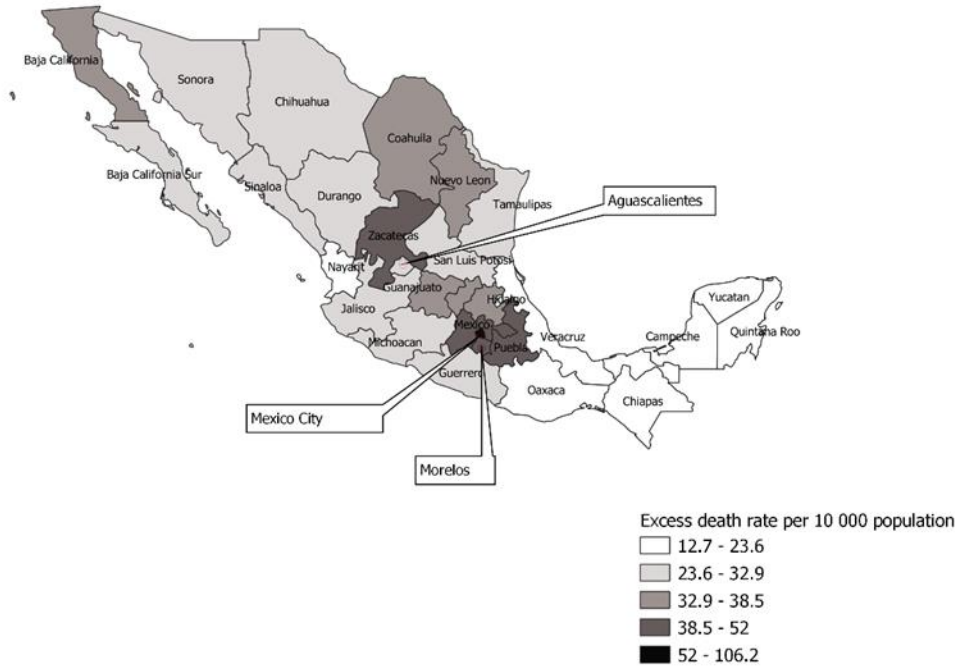


Figure 2. Map depicting excess death rate per 10 000 population by state in Mexico.

While the total excess death rate in Mexico was at 39.66 per 10 000 population, equivalent to a total of ~508 289 excess deaths, the excess mortality rate in Mexico City was the highest and estimated at 106.17 per 10 000 population (~95 690 total number of excess deaths). Among 31 states, Tlaxcala (51.99), Morelos (45.90), Puebla (45.12), and Mexico (44.43) were among the states with the highest excess mortality rates. The states with the lowest death rates included Chiapas (12.72), Oaxaca (13.42), Quintana Roo (19.41), and Yucatan (21.11) (Table 2). Only one state, Chiapas, had no excess deaths in 2021. COVID-19 accounted for only 42.16% of total excess deaths at the national level ranging from 20.97% in Chiapas to 76.05% in Quintana Roo.

Table 2. Estimates for all cause excess mortality rate by state per 10 000 population during COVID-19 pandemic in Mexico, March 1, 2020-April 10, 2021.

State/Region	All cause excess death rate per 10 000 population (March 1, 2020-April 10, 2021)	All cause excess death rate per 10 000 population in 2020 (Includes weeks starting from March 1, 2020, to December 27, 2020)	All cause excess death rate per 10 000 population in 2021 (Includes week starting on January 3, 2021, to April 4, 2021)	Total number of all cause excess deaths	COVID-19 deaths (Percentage of all cause excess deaths)
National	39.66	27.25	12.41	508 288.78	214 298 (42.16)
Aguascalientes	29.37	21.61	7.76	4228.25	2300 (54.39)
Baja California Sur	26.13	16.36	9.77	2118.75	1326 (62.58)
Baja California	38.55	31.78	6.77	14 051.54	8048 (57.27)
Campeche	22.25	21.02	1.22	2228.05	1183 (53.09)
Chihuahua	27.76	25.37	2.39	10 561.33	6467 (61.23)
Chiapas	12.72	12.72	0	7287.73	1528 (20.97)
Mexico City	106.17	62.93	43.24	95 689.73	32 166 (33.61)
Coahuila	38.33	30.88	7.45	12 369.31	6189 (50.03)
Colima	28.32	19.23	9.09	2234.78	1158 (51.82)
Durango	27.48	22.94	4.53	5142.23	2372 (46.13)
Guerrero	29.96	21.51	8.45	10 966.69	4231 (38.58)
Guanajuato	36.54	20.44	16.09	22 842.82	10 568 (46.26)
Hidalgo	36.39	22.86	13.52	11 277.96	5995 (53.16)

Jalisco	32.92	18.66	14.26	27 799.37	11 759 (42.30)
Mexico	44.43	28.67	15.76	77 705.35	33 571 (43.20)
Michoacan	31.12	16.69	14.43	15 063.24	5492 (36.46)
Morelos	45.90	24.16	21.75	9428.76	3052 (32.37)
Nayarit	23.64	15.08	8.55	3060.99	1766 (57.69)
Nuevo Leon	36.80	24.98	11.82	20 735.12	9305 (44.87)
Oaxaca	13.42	10.55	2.87	5565.51	3494 (62.78)
Puebla	45.12	36.50	8.62	29 849.45	11 142 (37.33)
Queretaro	35.86	18.79	17.06	8241.92	4063 (49.29)
Quintana Roo	19.41	16.95	2.46	3354.42	2551 (76.05)
San Luis Potosi	32.26	22.29	9.97	9266.51	5190 (56.01)
Sinaloa	31.53	24.97	6.56	9969.06	5927 (59.45)
Sonora	32.22	27.11	5.11	9924.27	6485 (65.34)
Tabasco	22.49	20.34	2.15	5791.32	3994 (68.96)
Tamaulipas	30.33	25.38	4.95	11 086.40	4800 (43.29)
Tlaxcala	51.99	34.93	17.06	7200.90	2367 (32.87)
Veracruz	22.35	17.46	4.89	19 111.79	9524 (49.83)
Yucatan	21.11	16.49	4.62	4781.42	3563 (74.52)
Zacatecas	43.22	29.81	13.41	7217.52	2721 (37.69)

Table 3 shows the results of fitting a taxonomy of multiple regression models of excess mortality rate at the state level in Mexico. To select a final model from among models 4, 6, 7, and 8, we performed a multiple partial F-test. In the multiple partial F-test, we failed to find a significant contribution of adding population density, depression rate, and public expenditure on health on predicting excess mortality rate after accounting for the contribution of aging index, marginalization index, and average household size ($F\text{-value}_{3,24}=0.39$, P-value=0.7631).

Table 3. Results of fitting a taxonomy of multiple regression models of excess mortality rate at the state level in Mexico (n=31)

	Parameter estimate (*se*)							
	Model 1	Model 2	Model 3	**Model 4**	Model 5	Model 6	Model 7	Model 8
intercept	- 19.21* (9.03)	-18.18 (18.09)	- 47.03** (13.61)	**-250.80*** (50.67)**	-200.36* (74.15)	-215.08** (63.11)	-230.65** (69.68)	-229.07** (72.97)
Aging index	1.12*** (0.19)		1.01*** (0.18)	**1.12*** (0.15)**	1.07*** (0.16)	0.99*** (0.20)	0.94*** (0.22)	0.94*** (0.22)
Marginalization index		2.72** (0.95)	1.76* (0.68)	**3.30*** (0.66)**	2.79** (0.87)	2.98*** (0.74)	2.94*** (0.76)	2.87** (1.02)
Average household size				**43.47*** (10.56)**	34.57* (14.31)	35.64* (13.39)	37.95* (14.18)	37.95* (14.47)
Tropical/megathermal					-5.60 (5.84)			
Dry					-3.56 (5.00)			
log10popdensity						3.79 (3.98)	4.38 (4.17)	4.49 (4.41)

log10depression_rate							4.20 (7.47)	4.24 (7.63)
Public expenditure on health as a percent of GDP								-0.22 (2.29)
Root MSE	10.97	14.41	10.04	**8.01**	8.18	8.02	8.13	8.30
R^2	0.55	0.22	0.63	**0.77**	0.78	0.78	0.78	0.79
Model *F*-test	35.18***	8.18***	24.31***	**31.09*** **	18.09***	23.46***	18.34***	14.68***
(df_1, df_2)	(1, 29)	(1,29)	(2, 28)	**(3, 27)**	(5, 25)	(4, 26)	(5, 25)	(6, 24)

*P<0.05, **P <0.01, ***P<0.001

We also tested for spatial autocorrelation using Moran I statistics. The result indicated the presence of spatial autocorrelation for the dependent variable (p-value =0.001). However, we failed to find statistically significant Moran I for the residuals for the Model with aging index, marginalization index, and average household size (p-value=0.4133). Hence, we fitted a spatial lag model with three predictors. The lag parameter (Rho) from the spatial lag model was not statistically significant (Rho=0.209, p-value=0.240). In addition, the value of AIC for the lag model (223.22) was slightly higher than that of the OLS model for Model 4 (222.71). Therefore, we chose Model 4 (Table 3) as our final model. Our final model was able to explain 77% of the observed variance in the excess mortality rate (Coefficient of determination (R^2)=0.77).

As shown in Table 4, we found a positive association of excess mortality rate with aging index, marginalization index, and average household size in the adjusted model at 0.05 level of significance.

Table 4. Results for the Final Regression Model 4 of excess mortality rate at the state level in Mexico (*n*=31).

	Parameter estimate	*Standard error*	P-value	*95% Confidence Limits*	*Standardized estimate*
intercept	-250.80	50.67	<.0001	-354.77, -146.83	0
Ageing index	1.12	0.15	<.0001	0.82, 1.42	0.74
Marginalization index	3.30	0.66	<.0001	1.95, 4.66	0.57
Average household size	43.47	10.56	0.0003	21.80, 65.13	0.48

The result of our clustering analyses is displayed in a dendrogram plot (Supplemental Figure 1). Specifically, we identified the following four prominent clusters based on the shapes of excess growth rate curves at state level:

Cluster 1: Baja California, Coahuila, Guanajuato, Hidalgo, Jalisco, Mexico, Mexico City, Michoacan, Morelos, Nayarit, Nuevo Leon, San Luis Potosi

Cluster 2: Aguascalientes, Chihuahua, Durango, Queretaro, Zacatecas

Cluster 3: Baja California Sur, Colima, Guerrero, Oaxaca, Puebla, Quintana Roo, Sinaloa, Sonora, Tabasco, Tamaulipas, Veracruz, Yucatan

Cluster 4: Campeche and Chiapas

Figure 3 shows the average growth rate curves and one standard deviation band around it. The growth patterns in each cluster are very distinct. For cluster 1, we see two different peaks in growth rate, first small peak in July 2020 and the second big peak in January 2021. For cluster 2, there is a rapid increase in growth rate since July 2021 that peaks on around December 2020. Unlike cluster 2, in cluster 3, the first big peak in July is followed by a small peak in January. Finally, in cluster 4, the growth rate rapidly increases from April to July followed by a rapid fall and a small rise in January 2021. Overall, the first peak in most of the states occurred in around July, 2020 and the second peak occurred in around January, 2021.

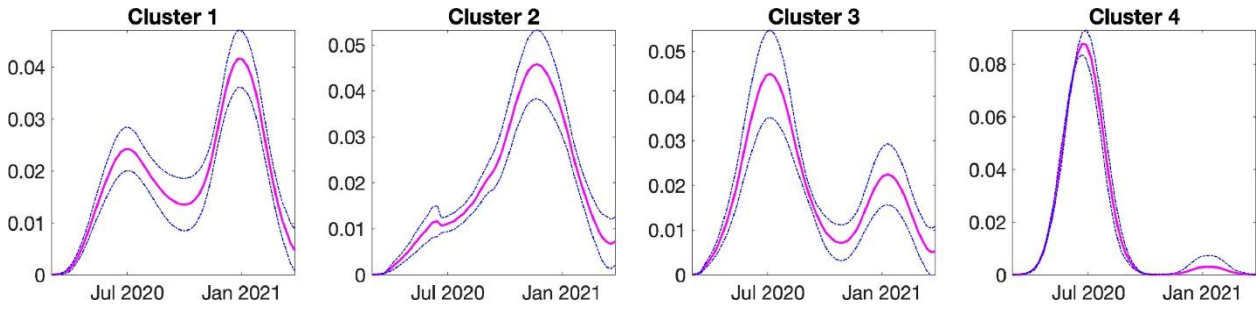


Figure 3. Average growth rate in each cluster, the dotted blue lines are the one standard deviation band around the average growth rate.

3.3. Discussion

In this study we investigated the excess mortality patterns during the COVID-19 pandemic at the national and subnational level in Mexico from March 1, 2020, to April 10, 2021. We estimated an excess all-cause mortality rate of 39.66 per 10 000 population at the national level (a total of ~508 289 excess deaths), indicating a devastating mortality impact of the COVID-19 pandemic in Mexico. Mexico City alone accounted for about 19% of total excess deaths in Mexico, with an excess mortality rate of 106.17 per 10 000 population. We found that the excess mortality rate has continuously declined after the second COVID-19 peak during the week of January 17-23, 2021.

Interestingly, we found that the states with the highest excess death rate (i.e., Mexico City, Tlaxcala, Morelos, Puebla, Mexico) were in the central states in Mexico, while the lowest excess death rates were observed in the southern states (i.e., Chiapas, Oaxaca, Quintana Roo, Yucatan, Campeche). In Mexico, the majority of the indigenous population are located in the southern states. According to intercensal Survey of 2015, 75% of the country's indigenous population lived in 8 states (highest in Oaxaca (14.42%), followed by Chiapas (14.19%), Veracruz (9.16%), Mexico (9.13), Puebla (9.10%), Yucatan (8.75%), Guerrero (5.67%), and Hidalgo (5.04%) (National Institute of Indigenous Peoples, July 9, 2017). Similarly, states with the highest proportion of native population as a proportion of state population in 2015 were Yucatan (50.2%), Oaxaca (43.7%), Chiapas (32.7%), Quintana Roo (32.5%), and Campeche (22.2%) (National Institute of Indigenous Peoples, July 9, 2017.) Compared to non-native groups, the indigenous populations across continents have suffered significant health disparities and a

greater burden of diseases, including higher infant mortality, and lower life expectancy (Curtice and Choo, 2020). During the pandemic, the indigenous populations have remained at higher risk of infection and death (CIDRAP, Power et al., 2020). A previous study demonstrated higher excess deaths in U.S. states with higher concentration of Native Americans during the 1918 influenza pandemic (Dahal et al., 2018b). Similarly, studies from New Zealand, Norway, and Alaska have also found that the indigenous populations in those regions were disproportionately affected by the 1918 influenza pandemic compared to the non-indigenous population (Mamelund, 2003, Mamelund et al., 2013, Rice, 2018). In contrast and very intriguingly, in this study we found a lower excess mortality rate during the pandemic in Mexican states with a higher proportion of the native indigenous population. This is an unexpected finding that warrants further inquiry and examination as it may provide great insight to factors that may potentially buffer against the impact of the pandemic and other adverse health events, including natural disasters, if the findings can be replicated in other studies.

In our analyses of data from Mexico, we found that COVID-19 specific deaths accounted for only 42.16% of total excess death at the national level, lowest in Chiapas (20.97%) and highest in Quintana Roo (76.05%). At the state level in Mexico, the timing and the rigor of implementation of public policies to contain the virus varied widely (Knaul et al., 2021). For example, some of the states, such as Veracruz, Yucatan, Nuevo Leon, and Tamaulipas, established policies to promote social distancing before the federal government enacted those policies (Knaul et al., 2021). While states such as Chiapas, Tabasco, San Luis Potosi, and Zacatecas underperformed in implementation of public policy measures (Knaul et al., 2021), some other states, with a relatively low excess mortality rate, such as Baja California Sur and Nayarit, implemented public information campaigns and international travel restrictions for longer periods, despite the potential adverse impact on tourism, which is a major economic activity (Knaul et al., 2021).

We found a positive association between the aging index and excess mortality in the adjusted model confirming previous studies linking older age and COVID-19. The aging index is defined as the number of older adults (60 years of age and older) for every 100 children and youth (0 to 14 years of age) (Instituto Nacional de Estadística y Geografía (INEGI)), and it increases as the population ages. Older age is a significant predictor of COVID-19 mortality as well as mortality

from other causes (Bello-Chavolla et al., 2020, Ho et al., 2020, CDC, 2021). Previous studies that analyzed excess mortality patterns during the first wave of COVID-19 in 21 industrialized countries have shown that those aged 65 years and above comprised 94% of all excess deaths, indicating a very high risk of death among older aged population specifically due to COVID-19 (Kontis et al., 2020).

Similarly, our finding of a positive association between the marginalization index and excess mortality supports previous research and reviews underscoring the close link between social disadvantage and COVID mortality (Saini et al., 2021) and the overall increased burden of the pandemic in marginalized populations. The marginalization index that we used is an indicator of the inequities in quality of housing, access to basic public services like electricity and drinking water, schooling, proportion of poorly paid population and other sociodemographic and population health characteristics (CONAPO 2020, World Bank. World Development Report 2009). There may be several explanations for our findings. For example, public health measures such as social distancing and sheltering in place to combat the COVID-19 pandemic resulted in a disproportionate burden to vulnerable and marginalized populations (Anderson et al., 2020, Benfer and Wiley, March 19 2020, Kantamneni, 2020). Marginalized groups are also more likely to be infected by the coronavirus due to the context of their living arrangements, which may limit the ability to self-isolate and socially distance. Similarly, it is well demonstrated that marginalized populations tend to have a higher prevalence of chronic conditions such as obesity, hypertension and diabetes, which are all strong risk factors associated with poor prognostic outcomes among those infected with COVID-19 (Anderson et al., 2020). To complicate matters further, marginalized populations are also often at greater risk of dying due to other indirect causes such as limited access to already-stressed health care systems, poor mental health outcomes, food insecurity, lower health literacy and lower consumption of health services, abuse, and violence, among other social ills (Anderson et al., 2020, Benfer and Wiley, March 19 2020, Evans et al., 2021).

Interestingly, Chiapas, a southern Mexico state with a high marginalization index (CONAPO, 2020), a higher concentration of indigenous population (32.7% indigenous population as of 2015) (National Institute of Indigenous Peoples, July 9, 2017), and lower average performance in implementation of public policies to combat COVID-19 (Knaul et al.,

2021), had the lowest excess mortality rate among the states examined in these analyses. While there is no clear explanation for these findings, the varying climate across the states examined may be a contributing factor. For example, the southern states in Mexico have a weak seasonality and a tropical climate throughout the year (Burton, 2013). According to previous studies conducted in Mexico (Méndez-Arriaga, 2020), tropical climate delayed the local transmission of SARS-CoV-2 at regional level. As such, the temperate climate regions like Tlaxcala and Jalisco may have been more vulnerable for local transmission than the tropical climate regions such as Chiapas and Veracruz (Méndez-Arriaga, 2020). However, it is interesting that in our analysis we did not find a significant difference in excess mortality rates across states that fall in three distinct climate groups in Mexico. These findings should be replicated in other settings that comprise multiple climate regions to determine the impact of seasonality in the transmission spread and impact of excess mortality patterns. Additionally, more research is needed to elucidate the factors associated with lower all-cause excess death rate in the relatively marginalized southern states as observed in this study. Such insight may provide mitigation strategies for other regions with higher impact.

We also found a positive association between average household size and excess death rate in the adjusted model. Although the links between average family size and excess death rate at the state level have not been reported elsewhere, the average family size could interact with other social determinants of health such as poverty, food insecurity, and lack of access to health care. However, since in our model we have controlled for marginalization index and aging index, household size could just be picking up a higher degree of exposure to COVID-19. Further studies are needed to understand the potential mechanism underlying this association and to more specifically consider family size as a potential population-level indicator of communities at risk for increased impact.

Our classification of excess deaths growth rate curves at the state level reflects four distinct categories of Mexican states. In all of the clusters the first peak of the excess deaths growth rate curve occurred in around July, 2020 which happened after the phased reopening of non-essential services in June, 2020 in Mexico. The reopening of the country coincided with an increase in both driving and walking trends, and the highest levels of COVID-19 deaths that remained at a high level during June and July 2020 (Tariq et al., 2021). The visual analysis of the growth rate

curve indicates that the coastal tropical southeastern states were most affected during the first few months of the pandemic compared to other states. However, these states exhibited the lower overall excess death rate, which could indicate the effect of temperature and other environmental factors. Moreover, information on the growth rate curves can be utilized at the state level to guide the implementation of medical and public health measures. Besides, learning from the public health measures implemented in states of one cluster (for example, cluster 4) can be helpful to the other states (for example, states in cluster 1).

We observed that most of the states in clusters 1 and 3 were adjacent to each other compared with the states in clusters 2 and 4. Clusters 1 and 3 are the clusters with double peaks and are similar compared to clusters 2 and 4. These similarities could be due to shorter distances or greater population connectivity. We note that a previous study on the 1918 influenza pandemic found that nearby areas have similar excess mortality patterns. For example, Northern counties in Arizona, USA, had higher excess deaths compared to the Southern counties (Dahal et al., 2018b). It is worth noting that the overall wave pattern of mortality in Mexico (Figure 1) is comparable with the wave pattern displayed by neighboring US states including Texas, Arizona, and California (CDC, 2021). This wave pattern is also consistent with cluster 1, which comprises 12 states, including Baja California, and which borders with California and Coahuila bordering Texas. Cluster 1 also includes the central states such as Morelos, Mexico, and Mexico City, which share high air traffic connectivity with the US. Therefore, the overall wave pattern in Mexico could have been dominated by those states that are highly connected to the United States. Likewise, the variations in the multiple wave patterns across other states could also reflect how Mexico is integrated into a more global epidemiologic system.

To our knowledge, this is the first study that assesses the growth rate curves of excess deaths at the state level in Mexico. In our study, the estimates of excess death rate, as well as the proportion of COVID-19 attributed deaths, could be underestimated due to factors such as low testing rates in Mexico, misclassification of COVID-19 deaths, and delay in reporting COVID-19 deaths. In our analyses, we replaced negative excess mortality by zeros to account for underreporting of deaths which may not adjust all potential periods of negative excess mortality. Since our analyses are based on state-level data, ecological fallacy should be considered when interpreting the results at the individual level in a particular state. Additionally, other potential

confounders that were not measured may explain the patterns of excess mortality across states. These limitations should be taken into account when interpreting our findings.

3.5. Conclusion

Our estimate of all-cause excess death rate in Mexico was 39.66 per 10 000, with central states exhibiting higher rates and southern states exhibiting lower rates. Our study highlights that several population measures including the aging index, marginalization index, and average household size were significantly associated with the all-cause excess mortality rates across Mexican states during the COVID-19 pandemic. Our excess mortality estimates can help tailor state specific medical and public health interventions to prevent excess mortality in vulnerable areas but targeting specific regions and socio-economic indicators. We also recommend further studies that investigate the lower excess death rate in southern states, and studies that explore the role of environmental factors, particularly the social determinants of health, in spatial variation in excess death rate in Mexico and other regions heavily impacted by COVID-19.

3.6. References

Anderson G, Frank JW, Naylor CD, Wodchis W, Feng P. Using socioeconomics to counter health disparities arising from the covid-19 pandemic. Bmj 2020;369.

Aron J, Muellbauer J. Transatlantic excess mortality comparisons in the pandemic. nine 2020.

Bello-Chavolla OY, Bahena-López JP, Antonio-Villa NE, Vargas-Vázquez A, González-Díaz A, Márquez-Salinas A, et al. Predicting mortality due to SARS-CoV-2: a mechanistic score relating obesity and diabetes to COVID-19 outcomes in Mexico. The Journal of Clinical Endocrinology & Metabolism 2020;105(8):2752-61.

Benfer EA, Wiley LF. Health Justice Strategies To Combat COVID-19: Protecting Vulnerable Communities During A Pandemic. Health Affairs 2020 March 19.

Burton T. Mexico's seven climate regions; 2013. Available from: https://geo-mexico.com/?p=9512 [Accessed 7/17/2021.

CDC. Excess Deaths Associated with COVID-19 2021; Available from: https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm [Accessed 6/27/2021.

CDC. Older Adults 2021; Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html.

Chowell G, Simonsen L, Flores J, Miller MA, Viboud C. Death patterns during the 1918 influenza pandemic in Chile. Emerging infectious diseases 2014;20(11):1803.

Chowell G, Viboud C, Simonsen L, Miller MA, Acuna-Soto R, Díaz JMO, et al. The 1918–19 influenza pandemic in Boyaca, Colombia. Emerging infectious diseases 2012;18(1):48.

CIDRAP. Reports detail high COVID-19 burden in Native Americans; Available from: https://www.cidrap.umn.edu/news-perspective/2021/04/reports-detail-high-covid-19-burden-native-americans [Accessed 6/29/2021.

CONAPO. Projections of the population of the municipalities of Mexico; 2015-2030.

CONAPO. Marginalization index by state 2020; 2020. Available from: https://datos.gob.mx/busca/dataset/indice-de-marginacion-carencias-poblacionales-por-localidad-municipio-y-entidad/resource/b0d4c947-ac1d-438b-8f96-1661ad021aeb. [Accessed 7/12/2021.

Currie JM, Schnell MK, Schwandt H, Zhang J. Trends in drug overdose mortality in Ohio during the first 7 months of the COVID-19 pandemic. JAMA network open 2021;4(4)-e.

Curtice K, Choo E. Indigenous populations: left behind in the COVID-19 response. The Lancet 2020;395(10239):1753.

Dahal S, Banda JM, Bento AI, Mizumoto K, Chowell G. Characterizing all-cause excess mortality patterns during COVID-19 pandemic in Mexico. BMC Infectious Diseases 2021;21(1):1-10.

Dahal S, Jenner M, Dinh L, Mizumoto K, Viboud C, Chowell G. Excess mortality patterns during 1918–1921 influenza pandemic in the state of Arizona, USA. Annals of epidemiology 2018a;28(5):273-80.

Dahal S, Mizumoto K, Bolin B, Viboud C, Chowell G. Natality decline and spatial variation in excess death rates during the 1918–1920 influenza pandemic in Arizona, United States. American journal of epidemiology 2018b;187(12):2577-84.

Douglas M, Katikireddi SV, Taulbut M, McKee M, McCartney G. Mitigating the wider health effects of covid-19 pandemic response. Bmj 2020;369.

Evans MC, Kapuscinska A, Greenholt M, Lin J, Liu X, Zhang T, et al. Designing a Self-Efficacy Game for Health Literacy in Marginalized Communities. Extended Abstracts of the 2021 CHI Conference on Human Factors in Computing Systems; 2021. p. 1-6.

General Directorate of Health Information. Subsystem of Health Accounts at the Federal and State Level (SICUENTAS); 2021. Available from: http://www.dgis.salud.gob.mx/contenidos/sinais/s_sicuentas.html [Accessed 7/12/2021.

Government of Mexico. Excess mortality in Mexico 2021. Available from: https://coronavirus.gob.mx/exceso-de-mortalidad-en-mexico/ [Accessed May 25, 2021.

Gutierrez E, Rubli A, Tavares T. Delays in death reports and their implications for tracking the evolution of COVID-19. Available at SSRN 3645304 2020.

Ho FK, Petermann-Rocha F, Gray SR, Jani BD, Katikireddi SV, Niedzwiedz CL, et al. Is older age associated with COVID-19 mortality in the absence of other risk factors? General population cohort study of 470,034 participants. PloS one 2020;15(11).

INEGI. Data 2021; Available from: https://www.inegi.org.mx/datos/.

Instituto Nacional de Estadística y Geografía (INEGI). Índice de envejecimiento por entidad federativa, serie de años censales de 1990 a 2020; 2021 Available from:

https://www.inegi.org.mx/app/tabulados/interactivos/?pxq=Poblacion_Poblacion_05_da611615-0bef-4433-933d-d6746c924ad4

Kantamneni N. The impact of the COVID-19 pandemic on marginalized populations in the United States: A research agenda. Journal of Vocational Behavior 2020;119.

Karlinsky A, Kobak D. Tracking excess mortality across countries during the COVID-19 pandemic with the World Mortality Dataset. Elife 2021;10:e69336.

Kawohl W, Nordt C. COVID-19, unemployment, and suicide. The Lancet Psychiatry 2020;7(5):389-90.

Knaul F, Arreola-Ornelas H, Porteny T, Touchton M, Sánchez-Talanquer M, Méndez Ó, et al. Not far enough: Public health policies to combat COVID-19 in Mexico's states. Plos one 2021;16(6).

Kontis V, Bennett JE, Rashid T, Parks RM, Pearson-Stuttard J, Guillot M, et al. Magnitude, demographics and dynamics of the effect of the first wave of the COVID-19 pandemic on all-cause mortality in 21 industrialized countries. Nature medicine 2020;26(12):1919-28.

Mamelund S-E. Spanish influenza mortality of ethnic minorities in Norway 1918–1919. European Journal of Population/Revue européenne de Démographie 2003;19(1):83-102.

Mamelund S-E, Sattenspiel L, Dimka J. Influenza-associated mortality during the 1918–1919 influenza pandemic in Alaska and Labrador: a comparison. Social Science History 2013;37(2):177-229.

Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. The lancet oncology 2020;21(8):1023-34.

Méndez-Arriaga F. The temperature and regional climate effects on communitarian COVID-19 contagion in Mexico throughout phase 1. Science of the Total Environment 2020;735.

National Institute of Indigenous Peoples. Socioeconomic Indicators of the Indigenous Peoples of Mexico, 2015: National estimates by federal entity Government of Mexico July 9, 2017.

Power T, Wilson D, Best O, Brockie T, Bourque Bearskin L, Millender E, et al. COVID-19 and Indigenous Peoples: An imperative for action. Journal of Clinical Nursing 2020.

Rice GW. Influenza in New Zealand before 1918: a preliminary report. American journal of epidemiology 2018;187(12):2524-9.

Roberton T, Carter ED, Chou VB, Stegmuller AR, Jackson BD, Tam Y, et al. Early estimates of the indirect effects of the COVID-19 pandemic on maternal and child mortality in low-income and middle-income countries: a modelling study. The Lancet Global Health 2020;8(7):e901-e8.

Sahoo S, Bharadwaj S, Parveen S, Singh AP, Tandup C, Mehra A, et al. Self-harm and COVID-19 Pandemic: An emerging concern–A report of 2 cases from India. Asian journal of psychiatry 2020.

Saini G, Swahn MH, Aneja R. Disentangling the coronavirus disease 2910 health disparities in African Americans: biological, environmental, and social factors. Open Forum Infectious Diseases. Oxford University Press US; 2021 p.ofab064.

Schirmer CM, Ringer AJ, Arthur AS, Binning MJ, Fox WC, James RF, et al. Delayed presentation of acute ischemic strokes during the COVID-19 crisis. Journal of neurointerventional surgery 2020;12(7):639-42.

Serfling RE. Methods for current statistical analysis of excess pneumonia-influenza deaths. Public health reports 1963;78(6):494.

Srivastava A, Chowell G. Understanding spatial heterogeneity of COVID-19 pandemic using shape analysis of growth rate curves. medRxiv 2020.

Srivastava A, Klassen EP. Functional and shape data analysis: Springer, 2016.

Statistica. Number of novel coronavirus (COVID-19) deaths worldwide as of June 24, 2021, by country; 2021. Available from: https://www.statista.com/statistics/1093256/novel-coronavirus-2019ncov-deaths-worldwide-by-country/ [Accessed 6/26/2021.

Tariq A, Banda JM, Skums P, Dahal S, Castillo-Garsow C, Espinoza B, et al. Transmission dynamics and forecasts of the COVID-19 pandemic in Mexico, March-December 2020. PloS one 2021;16(7).

Viboud C, Eisenstein J, Reid AH, Janczewski TA, Morens DM, Taubenberger JK. Age-and sex-specific mortality associated with the 1918–1919 influenza pandemic in Kentucky. The Journal of infectious diseases 2013;207(5):721-9.

Weinberger DM, Chen J, Cohen T, Crawford FW, Mostashari F, Olson D, et al. Estimation of excess deaths associated with the COVID-19 pandemic in the United States, March to May 2020. JAMA Internal Medicine 2020;180(10):1336-44.

WHO. Mexico situation; 2021. Available from: https://covid19.who.int/region/amro/country/mx [Accessed 6/26/2021.

World Bank. World Development Report 2009: Reshaping Economic Geography. Washington DC; 2009. p. 79.

Chapter 4

Investigating COVID-19 transmission and mortality differences between indigenous and non-indigenous populations in Mexico

Citation: Dahal S, Mamelund SE, Luo R, Sattenspiel L, Self-Brown S, Chowell G. Investigating COVID-19 transmission and mortality differences between indigenous and non-indigenous populations in Mexico. International Journal of Infectious Diseases. 2022;122:910-920.

4.1. Introduction

Globally, indigenous populations and ethnic minorities tend to suffer worse health outcomes than non-indigenous populations. For example, from 2010-2012 the life expectancy of indigenous Australians (Aboriginal and Torres Strait Islander) (69.1 years for males and 73.7 years for females) was around 10 years lower than that of non-indigenous Australians (79.7 years for males and 83.1 years for females) (Australian Institute of Health Welfare, 2014). A variety of factors such as transgenerational adverse effects of colonization, racism, lower socio-economic status, and lower levels of education, have contributed to existing health disparities among the indigenous population (Durey *et al.*, 2016; Hajizadeh *et al.*, 2018; Nazroo, 2003). Moreover, barriers within the healthcare setting, including lack of access to culturally appropriate healthcare services, poor health literacy, distance to medical centers, communication problems, and low health insurance coverage also increase negative health trajectories (Daws *et al.*, 2014; Walsh and Kangaharan, 2017).

Studies from many countries have reported disproportionately higher infection rates, hospitalizations, and deaths among indigenous and ethnic-minority groups from the beginning of the COVID-19 pandemic (Mallard *et al.*, 2021; Power *et al.*, 2020; Sharma and Bhaskar, 2021; Wiemers *et al.*, 2020; Yashadhana *et al.*, 2020). However, a few countries have reported the opposite early in the COVID-19 pandemic. For example, a review article from November 2020, covering COVID-19 studies reported that in six out of nine countries (including Mexico) that publicly reported mortality data among indigenous peoples, the rate of infection per 100,000 population was lower among indigenous groups (except Brazil, Peru, and USA), and

the case fatality ratio was lower in three countries (Mallard *et al.*, 2021). However, it was probably too early in the pandemic to assess this comparison since some indigenous communities tend to be more isolated (Tripp, 2022). Moreover, there are major gaps in reporting data on COVID-19 infection and outcomes for indigenous populations and many countries do not have publicly available data with socio-demographic profiles, leading to a dearth of studies that have empirically examined COVID-19 in indigenous populations vs. non-indigenous populations (Alves *et al.*, 2022). Therefore, there is a dire need to conduct studies that evaluate COVID-19 outcomes among indigenous and non-indigenous populations.

The COVID-19 pandemic widened existing health disparities among these groups as a result of the higher prevalence of underlying comorbid conditions and multimorbidity compounded by poor access to health care services, and unequal impact of lockdown measures (*e.g.*, higher unemployment, higher rates of mental health problems, more loss of schooling) (Katikireddi *et al.*, 2021; Kirby, 2020; Yashadhana *et al.*, 2020). Prior work indicates that indigenous status may influence pandemic outcomes through three key mechanisms: a) increased exposure (at work, at home, possibly through multigenerational living), b) increased medical susceptibility due to higher prevalence of non-communicable diseases, and c) limited access to care and or health literacy resulting in social disparities (Quinn and Kumar, 2014).

Mexico is a country in the Americas with the largest indigenous population (IWGIA, 2021). Mexico's indigenous population is highly vulnerable to the effects of the COVID-19 pandemic due to factors such as marginalization, discrimination, violence, land dispossession, and poor access to health services, social security, education and adequate housing (Díaz de León-Martínez *et al.*, 2020; IWGIA, 2021; Consejo Nacional de Evaluación de la Politica de Desrrollo Social, 2019). However, the COVID-19 prevention and mitigation strategies implemented in the country for indigenous populations are the same as those for the general population (Díaz de León-Martínez *et al.*, 2020). Preliminary analyses from Mexico have started to shed light on the severe health impacts of COVID-19 among indigenous populations compared to non-indigenous counterparts (Argoty-Pantoja *et al.*, 2021; Ibarra-Nava *et al.*, 2021; Mallard *et al.*, 2021). In this study, we aimed to assess the mortality impact of COVID-19 among indigenous populations by quantifying the mortality rate at sub-national level and by comparing the rates between indigenous and non-indigenous populations across the waves of the COVID-19 pandemic. In

addition, we compared the hazard ratios for death between indigenous and non-indigenous populations controlling for socio-demographic, comorbidity-related, and health service utilization-related factors. Furthermore, we estimate the reproduction number (R_t) among the two groups. These detailed analyses can help guide intervention strategies that effectively address the impact of infectious disease emergencies such as the COVID-19 pandemic among vulnerable populations.

4.2. Methods

4.2.1 Study setting

Mexico is inhabited by 128.97 million people (projected as of 2021) and is divided into 31 states and the federal district (Mexico City) collectively referred to as federal entities (CONAPO, 2019). According to the intercensal survey of 2015 in Mexico, 21.50% of the total population self-identified as indigenous, 65% of whom were concentrated in 8 of the 32 entities (National Institute of Indigenous Peoples, 2017) as shown in table 2.

4.2.2. Data source

The dataset for this study was retrieved from the website (Secretaría de Salud, 2022) of the General Directorate of Epidemiology of the Ministry of Health of Mexico which maintains an open-source repository of patients classified as ‘suspected cases of viral respiratory disease’ identified at medical facilities in Mexico through the Viral Respiratory Diseases Epidemiological Surveillance System (Secretaría de Salud, 2020). From this dataset, we obtained data on the selected variables: age (EDAD), sex (SEXO), state of patient's residence (ENTIDAD_RES), type of care the patient received (TIPO_PACIENTE), date of symptom onset (FECHA_SINTOMAS), date of admission to care (FECHA_INGRESO), date of death (FECHA_DEF), lab result (RESULTADO_LAB), patient's self-identification as indigenous (INDIGENA), and variables on the diagnosis of different conditions such as diabetes, hypertension, and obesity which have been specified in Table 1. We used the variable ‘lab result’ to select the confirmed cases of COVID-19 for our study. We categorized five groups based on age and created a composite variable ‘comorbidity category’ based on the presence or absence of nine different comorbid conditions (Table 1).

Table 1. Descriptive analysis of socio-demographic, comorbidity, and case management-related characteristics of COVID-19 positive cases among Indigenous and non-Indigenous populations.

	SARS-Cov 2 positive (n=2173036)		Mortality among SARS-Cov2 positive (n=238803)		Proportion of deaths among cases		
	Indigenous population (n=21896)	Non-Indigenous population (n=2151140)	Indigenous population (n=3831)	Non-Indigenous population (n=234972)	in Indigenous	in non-Indigenous	P-value[a]
Sex							
Female	10358 (47.31)	1079312 (50.17)	1473 (38.45)	89604 (38.13)	14.22	8.30	<0.0001
Male	11538 (52.69)	1071828 (49.83)	2358 (61.55)	145368 (61.87)	20.43	13.56	<0.0001
Age group							
Less than 18 years	861 (3.93)	90048 (4.19)	26 (0.68)	896 (0.38)	3.02	0.99	<0.0001
18-44 years	9113 (41.62)	1073787 (49.92)	335 (8.74)	24214 (10.31)	3.68	2.25	<0.0001
45-54 years	3914 (17.88)	407633 (18.95)	555 (14.49)	36798 (15.66)	14.18	9.03	<0.0001
55-64 years	3453 (15.77)	290059 (13.48)	945 (24.67)	58293 (24.81)	27.37	20.09	<0.0001
65 and above years	4555 (20.80)	289613 (13.46)	1970 (51.42)	114771 (48.84)	43.25	39.63	<0.0001
Type of care							
Outpatient	14179 (64.76)	1650958 (76.75)	254 (6.63)	15733 (6.70)	1.79	0.95	<0.0001
Hospitalized	7717 (35.24)	500182 (23.25)	3577 (93.37)	219239 (93.30)	46.35	43.83	<0.0001
Patient required admission to intensive care unit n (%)	732 (3.34)	41105 (1.91)	431 (11.25)	23809 (10.13)	58.88	57.92	0.603
Comorbidity							
Pneumonia, n (%)	6011 (27.45)	364845 (16.96)	3023 (78.91)	171513 (72.99)	50.29	47.01	<0.0001

Diabetes, n (%)	4156 (18.98)	300200 (13.96)	1425 (37.20)	86625 (36.87)	34.27	28.86	<0.0001
COPD, n (%)	625 (2.85)	26266 (1.22)	266 (6.94)	10240 (4.36)	42.56	38.99	0.070
Asthma, n (%)	521 (2.38)	48438 (2.25)	96 (2.51)	4231 (1.79)	18.43	8.73	<0.0001
Hypertension, n (%)	4521 (20.65)	387275 (18.00)	1520 (39.68)	104644 (44.53)	33.62	27.02	<0.0001
Other disease, n (%)	465 (2.12)	44684 (2.08)	146 (3.81)	11577 (4.93)	31.40	25.91	0.007
Cardiovascular disease, n (%)	438 (2.00)	36111 (1.68)	167 (4.36)	11859 (5.05)	38.13	32.84	0.019
Obesity, n (%)	3910 (17.86)	311392 (14.48)	907 (23.68)	51063 (21.73)	23.20	16.40	<0.0001
Chronic kidney failure, n (%)	417 (1.90)	37271 (1.73)	197 (5.14)	16097 (6.85)	47.24	43.19	0.097
Comorbidity category							
No comorbidity	9877 (45.11)	1239373 (57.61)	245 (6.40)	20485 (8.72)	2.48	1.65	<0.0001
1-2 comorbidities	9658 (44.11)	743630 (34.57)	2369 (61.84)	138669 (59.02)	24.53	18.65	<0.0001
Three or more comorbidities	2361 (10.78)	168137 (7.82)	1217 (31.77)	75818 (32.27)	51.55	45.09	<0.0001
Time related variables[c]					p-value [b]		
Time from symptom onset to seeking care[d] (n=2169701)	4.41 (3.20)	4.07 (3.17)	-	-	<0.0001		<0.0001
Time from symptom onset to death [e] (n=237401)	-	-	13.25 (8.22)	13.89 (8.53)	<0.0001		<0.0001
Time from seeking care to death [f]	-	-	7.63 (7.08)	8.45 (7.34)	<0.0001		<0.0001

(n=236134)							

[a] *Two-sample test for equality of proportions of mortality out of total cases among Indigenous and non-Indigenous groups for the given characteristic*

[b] *Non-parametric Wilcoxon two sample test for difference in mean time among Indigenous and non-Indigenous*

[c] *Mean (SD)*

[d] *Includes cases with time from 0-18 days*

[e] *Includes cases with time from 0-52 days*

[f] *Includes cases with time from 0-39 days*

4.2.3. Definition of confirmed case of COVID-19

Laboratory-confirmed cases were defined as a positive RT-PCR test (Ibarra-Nava et al., 2021).

4.2.4. Definition of indigenous populations

The use of self-identification as a proxy for ethnic classification has been used by the Mexican census since 2000 and this method is in line with the spirit of international legislation that considers the ability of the indigenous population to identify their ethnicity as a fundamental right (ILO, 1989). In this study, we used the variable 'INDIGENA' from the dataset to measure indigenous status based on patient self-identification. Records, where the indigenous status was missing, were omitted from further analysis.

Figure 1 displays the strategy used to determine inclusion of cases in our study. After excluding cases without information about indigenous status, a total of 2,173,036 COVID-19 positive cases, and 238,803 COVID-19 deaths remained.

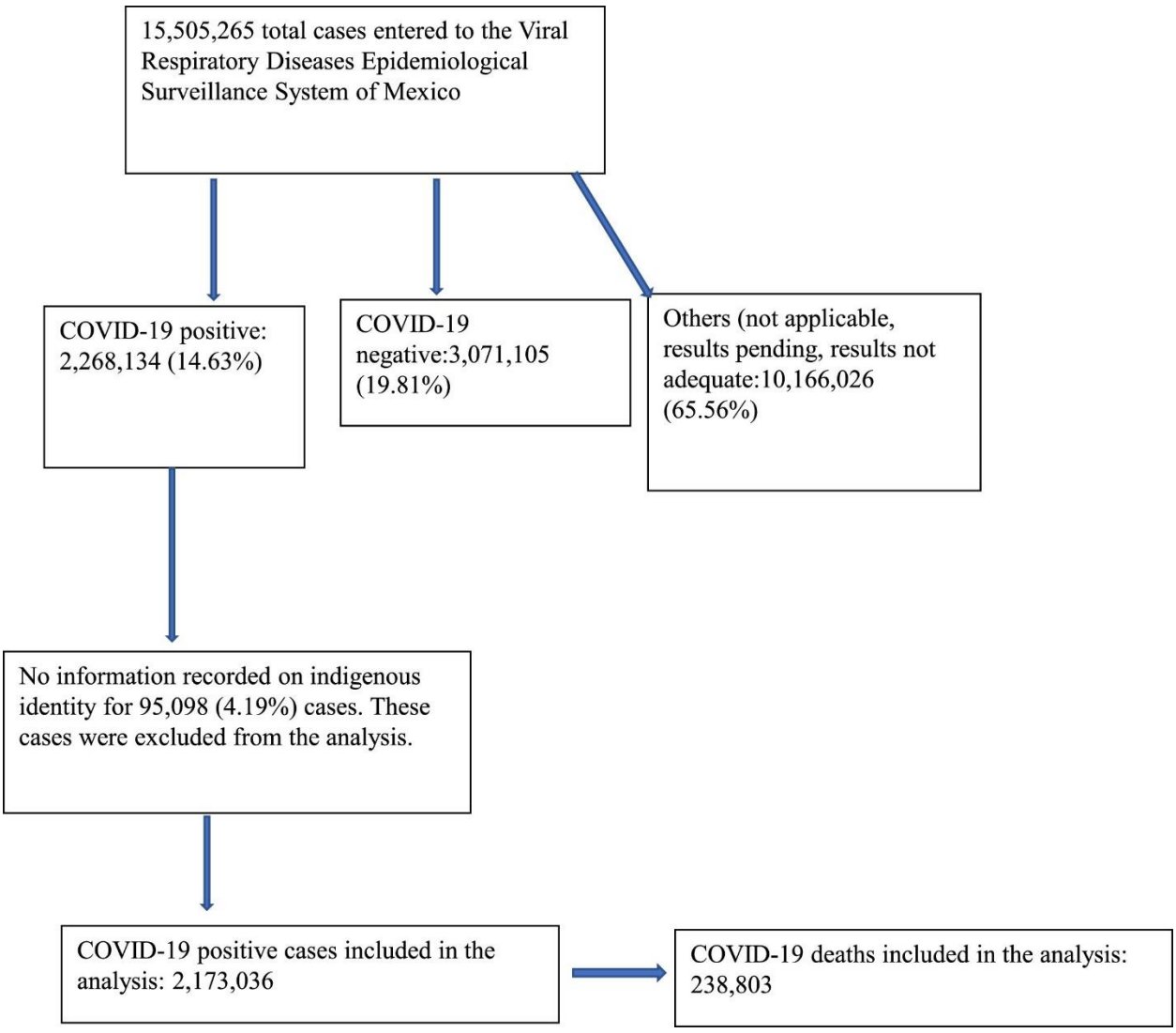


Figure 1. Flowchart showing the inclusion of cases and deaths in the study.

4.2.5 Data analysis

The earliest date of symptom onset for a COVID-19 positive case in our dataset was 19 February 2020. Therefore, we performed the statistical analysis using the surveillance data from 19 February 2020, to 25 March 2022.

a. Descriptive analysis of COVID-19 positive cases and deaths: To test the null hypothesis of no difference in the proportion of COVID-19 deaths among indigenous and non-indigenous positive cases for socio-demographic, comorbidity, and case management-related characteristics, we

performed two-sample tests for equality of binomial proportions at 0.05 level of significance. Similarly, to test the null hypothesis of no difference in the average days from 'symptom onset to seeking care', 'seeking care to death' and 'symptom onset to death' between indigenous and non-indigenous populations, we used the Wilcoxon two-sample test for difference in medians. For the analysis of these time-related variables, we excluded cases with negative days, and extreme outliers falling above three times the interquartile range.

b. Estimation of instantaneous reproduction number: R_t is the expected number of secondary infections occurring at time t, divided by the number of infected individuals, each scaled by their relative infectiousness at time t. We used EpiEstim R Package (Cori *et al.*, 2021) to estimate R_t from the curves of daily incidence of COVID-19 cases by date of symptom onset for indigenous and non-indigenous populations separately. We obtained the average R_t estimates over a weekly time interval for the entire study period by using the 7-day sliding window method. We also used the non-overlapping time window method to estimate the average R_t for the early ascending phase for each of the COVID-19 waves. For the R_t estimation, the distribution of serial interval was parametrically defined using a mean of 4.6 days and SD of 5.55 days (Ofori *et al.*, 2022; You *et al.*, 2020). We report the mean and 95% credible interval (CrL).

c. Estimation of person-time mortality rate: The person-time mortality rate was defined as the ratio of the number of deaths among COVID-19 cases and the person-time at risk of death during the study period. The mortality rate was estimated separately for indigenous and non-indigenous populations. The person-time at risk was expressed per 1000 person-weeks based on the date from symptom onset to date of death (Argoty-Pantoja *et al.*, 2021). For non-deaths, person-time at risk was the time between date of symptom onset until the last date of the study period. We also estimated the person-time mortality rate for each of the 32 federal entities. The 95% confidence intervals (CIs) and *P*-values were estimated using open-source statistics for public health (Sullivan *et al.*, 2013). The *P*-values were based on z-score tests and the 95% CIs were based on the Taylor series method. We also estimated the mortality rate for four different waves of COVID-19 as well as for the years 2020 and 2021 in Mexico. For the wave-wise comparison, person-time for non-deaths was estimated using the time elapsed between symptom onset date and the end date of the given wave. We also reported the ratio of COVID-19 mortality rate per

1000 person-week among indigenous populations vs. non-indigenous populations (rate ratio = RR).

We defined the epidemiological waves based on the descriptive analysis of time series of COVID-19 cases for Mexico according to the standard definition of epidemiological weeks used by the CDC (CMMCP, 2022) as follows:

First wave- 19 February 2020 to 3 October 2020; second wave- 4 October 2020 to 29 May 2021; third wave- 30 May 2021 to 18 December 2021; fourth wave- 19 December 2021 to 25 March 2022.

d. Estimation of hazard ratio (HR) for COVID-19 death and indigenous status: Multivariate Cox proportional hazards regression models were used for these analyses. The general equation of the model is

$$h(t) = h_0(t)exp(X\beta + \boldsymbol{Z}^T\boldsymbol{\gamma})$$

where $h(t)$ is the hazard function, $h_0(t)$ is the baseline hazard, X is a variable indicating Indigenous status, and $\boldsymbol{Z}$ is a vector of model covariates including age, sex, number of comorbidities, type of care received (outpatient vs. hospitalization), and days from symptom onset to seeking care. We used log-log survival curves to assess the constant proportionality assumption of the Cox hazard model. Because the curves showed parallel lines for Indigenous and non-Indigenous populations, the constant proportionality assumption was reasonable.

4.3. Results

Figure 2 shows the daily time-series of COVID-19 cases from 19 February 2021 to 25 March 2022 (panels A and D), and R_t among indigenous and non-indigenous populations in Mexico (panels B, C, E and F). The mean R_t was highest among both the groups during the early ascending phase of the fourth wave (indigenous: 1.426 (95% CrL: 1.405, 1.447), non-indigenous: 1.535 (95% CrL: 1.521, 1.549)) (Supplementary Figure 2).

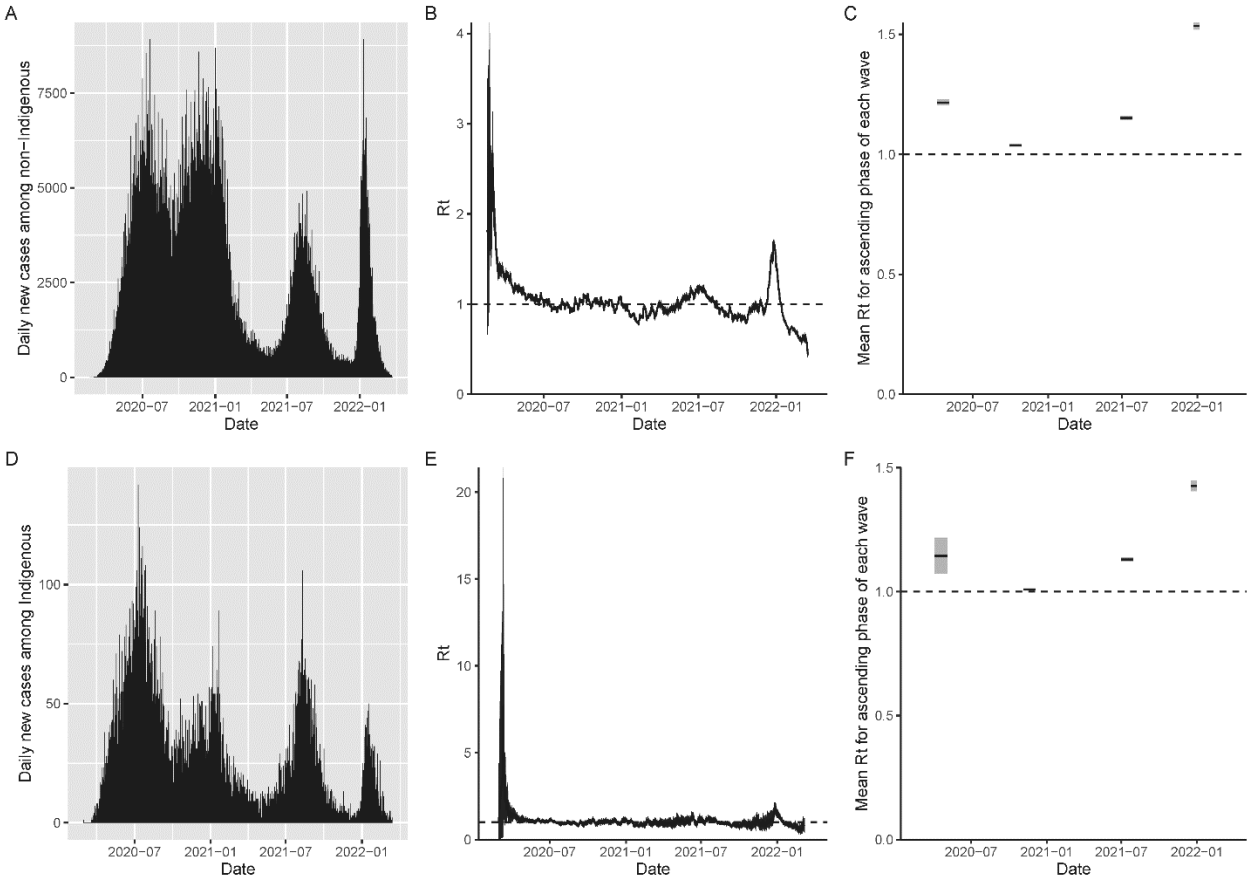


Figure 2. (A.) Daily incidence of COVID-19 cases among non-indigenous from 19 February 2020 - 25 March 2022 (B.) Time-varying R_t of COVID-19 cases among non-indigenous populations for the study period (C.) Mean R_t for the early ascending phase of four waves among non-indigenous (30 days from 5 April 2020 - 4 May 2020 for first wave, 30 days from 29 September 2020 – 28 October 2020 for second wave, 30 days from 27 June 2021 - 26 July 2021 for the third wave and 15 days from 23 December 2021 - 6 January 2022 for the fourth wave) (D.) Daily incidence of COVID-19 cases among Indigenous from 19 February 2020 -25 March 2022 (E.) Time-varying R_t of COVID-19 cases among indigenous populations for the study period (F.) Mean R_t for the early ascending phase of four waves among indigenous (30 days from 15 April 2020 - 14 May 2020 for first wave, 30 days from 15 November 2020 - 14 December 2020 for second wave, 30 days from 11 July 2021 - 9 August 2021 for the third wave and 15 days from 27 December 2021 - 10 January 2022 for the fourth wave). Dates indicate date of symptom onset. The shaded gray areas in B, C, E and F indicate 95% CrL.

CrL, credible interval; R_t, reproduction number

Table 1 summarizes socio-demographic, comorbidity, and case management-related characteristics among COVID-19 cases and deaths for the indigenous and non-indigenous populations. The proportion of deaths among the indigenous group was higher than that for non-indigenous for both males and females, across age groups, both hospitalized and outpatient cases, as well as the great majority of comorbidities (P <0.05). Compared to non-indigenous populations, the average time from symptom onset to seeking care was significantly higher for the indigenous populations (4.41 vs. 4.07 days; P<0.01) whereas both the average time from symptom onset to death (13.25 vs. 13.89 days; P<0.01) and the average time from seeking care to death (7.63 vs. 8.45 days; P<0.01) were significantly lower for the indigenous populations (Table 1). These findings indicate longer delays in care seeking for the indigenous population leading to lower average survival time compared to the non-indigenous populations.

Table 2 shows the federal entity-level COVID-19 mortality rate per 1000 person-weeks among indigenous and non-indigenous populations. At the national level, the mortality rates among indigenous and non-indigenous populations were significantly different (3.25 vs. 1.94 per 1000 person-weeks; P-value<0.05). Of the 32 federal entities, 23 exhibited higher COVID-19 mortality rate among indigenous compared to non-indigenous groups, with this difference being statistically significant in 13 entities. Figure 3, Figure 4 show the mortality rates by indigenous status and the RR across federal entities, respectively. We also assessed the association between the proportion of indigenous populations and the RR at the entities level (Pearson correlation coefficient = 0.37; P-value = 0.036; 95% CI: 0.02, 0.64).

Table 2. COVID-19 mortality rate per 1000 person-weeks among indigenous and non-indigenous population, Mexico, February 19, 2020 to March 25, 2022.

Region/entities	Proportion of self-identified Indigenous population	Total deaths		Mortality rate (95% CI)		
		Indigenous	non-Indigenous	Indigenous	non-Indigenous	P-value
National	21.49	3818	233,750	3.25 (3.15, 3.35)	1.94 (1.93, 1.94)	**<0.0001**

Aguacalientes	0.60	7	2544	3.19 (1.28, 6.56)	1.69 (1.63, 1.76)	0.089
Baja California	1.10	83	8862	3.96 (3.15, 4.90)	3.24 (3.17, 3.31)	0.069
Baja California Sur	0.40	10	1881	2.62 (1.25, 4.82)	0.97 (0.93, 1.02)	**0.001**
Campeche	1.56	79	1936	4.78 (3.78, 5.95)	2.51 (2.40, 2.63)	**<0.0001**
Coahuila	0.80	12	7143	1.68 (0.87, 2.93)	1.69 (1.66, 1.73)	0.976
Colima	0.57	6	1725	2.66 (0.97, 5.79)	2.53 (2.41, 2.65)	0.902
Chiapas	7.34	34	2008	2.00 (1.38, 2.79)	2.48 (2.37, 2.59)	0.206
Chihuahua	1.56	71	6595	3.12 (2.44, 3.93)	2.37 (2.31, 2.42)	**0.020**
Mexico City	3.05	127	26,972	1.44 (1.20, 1.72)	1.28 (1.27, 1.30)	0.183
Durango	0.54	12	2927	1.26 (0.65, 2.19)	1.29 (1.25, 1.34)	0.915
Guanajuato	2.08	11	12,344	1.01 (0.50, 1.81)	1.50 (1.47, 1.53)	0.188
Guerrero	4.66	144	4400	2.21 (1.86, 2.60)	1.95 (1.90, 2.01)	0.144
Hidalgo	4.03	315	6810	3.80 (3.40, 4.25)	3.27 (3.19, 3.35)	**0.008**
Jalisco	3.40	65	14,691	3.61 (2.78, 4.60)	2.94 (2.90, 2.99)	0.102
Mexico	10.71	224	31,415	3.36 (2.93, 3.82)	2.93 (2.90, 2.96)	**0.042**
Michoacan	4.94	190	6249	3.58 (3.08, 4.12)	2.17 (2.11, 2.22)	**<0.0001**
Morelos	2.08	30	3456	4.86 (3.27, 6.93)	3.83 (3.70, 3.96)	0.193
Nayarit	1.02	31	1899	2.91 (1.98, 4.13)	2.89 (2.76, 3.02)	0.966
Nuevo Leon	1.37	15	13,063	1.46 (0.82, 2.41)	1.71 (1.68, 1.74)	0.549
Oaxaca	10.15	436	3476	4.02 (3.65, 4.41)	1.27 (1.23, 1.31)	**<0.0001**
Puebla	8.47	313	11,266	7.51 (6.70, 8.39)	2.41 (2.37, 2.46)	**<0.0001**
Queretaro	1.52	13	4151	1.20 (0.64, 2.05)	1.19 (1.15, 1.23)	0.981
Quintana Roo	2.60	205	3452	5.44 (4.72, 6.24)	2.63 (2.54, 2.72)	**<0.0001**
San Luis Potosi	2.45	139	5188	1.34 (1.13, 1.58)	1.38 (1.34, 1.41)	0.768
Sinaloa	1.48	27	7078	3.47 (2.29, 5.06)	3.05 (2.97, 3.12)	0.494
Sonora	1.98	90	6795	4.81 (3.87, 5.91)	1.87 (1.83, 1.92)	**<0.0001**
Tabasco	2.40	76	5379	0.99 (0.78, 1.24)	0.92 (0.89, 0.94)	0.528
Tamaulipas	0.84	10	6125	1.35 (0.64, 2.48)	1.43 (1.39, 1.46)	0.854

Tlaxcala	1.25	18	2721	3.12 (1.85, 4.92)	2.33 (2.24, 2.42)	0.217
Veracruz	9.24	190	12,879	5.78 (4.99, 6.66)	3.19 (3.13, 3.24)	**<0.0001**
Yucatan	5.34	822	4935	4.04 (3.77, 4.33)	2.17 (2.11, 2.23)	**<0.0001**
Zacatecas	0.47	13	3385	2.06 (1.10, 3.52)	1.67 (1.62, 1.73)	0.451

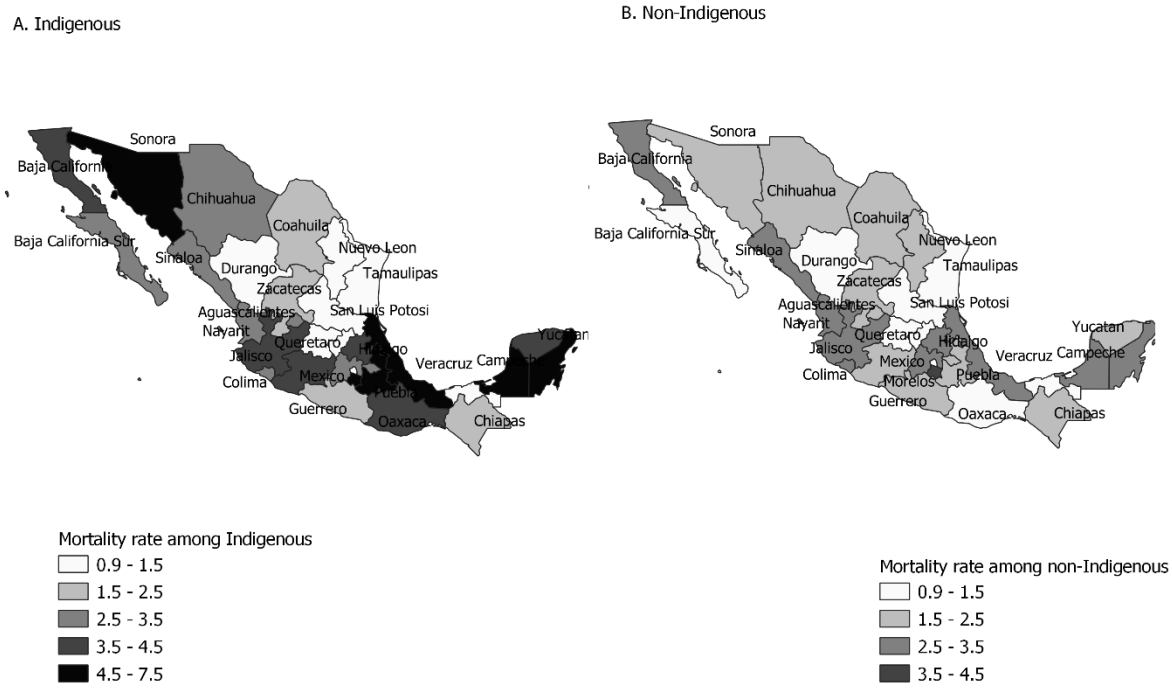


Figure 3. COVID-19 mortality rate per 1000 person-weeks in indigenous and non-indigenous populations in Mexico, February 2020 to March 2022.

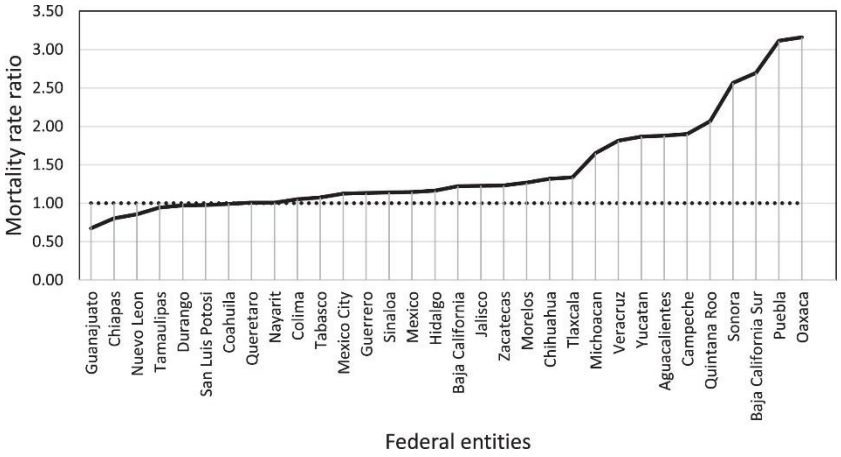


Figure 4. Rate ratio (RR) of COVID-19 mortality per 1000 person-weeks among indigenous and non-indigenous populations by federal entities in Mexico.

A stratified analysis of the mortality rate and the RR across four pandemic waves is given in Table 3. The RR was lowest in the first wave (1.55) and highest in the fourth wave (2.40). Similarly, the RR was higher in 2021 compared to 2020.

Table 3. Estimation of COVID-19 mortality rate per 1000 person-week among Indigenous and non-Indigenous groups across four pandemic waves and by year in Mexico.

Wave	Deaths indigenous	Deaths non-indigenous	Person-weeks indigenous	Person-weeks non-indigenous	Mortality rater per 1000 person-weeks indigenous (R1)	Mortality rater pwe 1000 person-weeks non-indigenous (R2)	Rate Ratio (R1/R2)
First wave 19 Feb 2020 – 3 Oct 2020	1679	83,002	99,912.42	7,693,327	16.71	10.79	1.55

Second wave 4 Oct 2020 – 29 May 2021	985	95,517	107,946.1	17,323,003	9.12	5.51	1.65
Third wave 30 May 2021 – 18 Dec 2021 (First case of Delta variant reported in 15 July 2021)	926	38,627	68,398.43	5,309,029	13.54	7.27	1.86
Fourth wave 19 Dec 2021 – 25 March 2022 (First case of Omicron variant reported on Dec, 3, 2021)	141	9666	10,932.43	1,800,412	12.90	5.37	2.40
2020 (19 Feb, 2020 – 31 Dec, 2021)	2055	127,131	902,822.9	93,530,292.14	2.28	1.36	1.67
2021 (1 Jan, 2021 – 31 Dec, 2021)	1533	85,195	262,511.9	25,549,998.29	5.84	3.33	1.75
Overall (19 Feb, 2020 – March 25, 2022)	3818	233,750	1,175,598	120,703,675.1	3.25	1.94	1.68

Note: The overall person-time was calculated as the difference between the date of symptom onset and death for events (death). For non-death cases (censored) the person-time was calculated as the difference between date of symptom onset and cutoff date of March-25, 2021. For wave-wise estimation, person-time was calculated for the interval period only. Person-week was calculated by dividing total person-days by 7.

Table 4 shows the results from fitting different survival regression models. Based on the goodness of fit of the models as deemed by their Akaike information criterion (AIC) values, we selected model 6 as our final model. In the unadjusted model, the hazard of death among indigenous populations was 67.1% (HR = 1.67; 95% CI: 1.62, 1.72) higher than that for non-indigenous populations. There was a statistically significant interaction between the type of care and the time from symptom onset to seeking care (care-seeking delay). After adjusting for sex, age, the number of comorbidities, and the interaction between type of care and care-seeking delay, the HR for indigenous groups compared to non-indigenous decreased to 1.08 and remained statistically significant. We used the variables in model 6 to fit survival regression models for each of the waves separately. Table 5 shows the results of these models. Tables with the estimated beta values for model 6 for the overall period, waves, and years are given in the supplementary file.

Table 4. Results of fitting a taxonomy of multiple survival regression models, February 2020 to March 2022.

	Hazard Ratio (HR) (95% CI)					
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
Indigenous (Comparison =Non-indigenous)	1.67 *** (1.62, 1.72)	1.24*** (1.20, 1.28)	1.61*** (1.56, 1.67)	1.12*** (1.09, 1.16)	1.08*** (1.05, 1.11)	**1.08*** (1.04, 1.11)**
Sex (comparison =Female)		1.55*** (1.54, 1.56)			1.27*** (1.26, 1.28)	**1.27*** (1.26, 1.28)**
Age		1.07*** (1.07, 1.07)			1.03*** (1.03, 1.03)	**1.03*** (1.03, 1.03)**

Time in days from symptom onset to seeking care			1.10*** (1.10, 1.10)	0.99*** (0.99, 0.99)	0.98*** (0.98, 0.98)	**-**
Type of care **(comparison=Outpatient)**				59.67*** (58.71, 60.65)	24.55*** (24.13, 24.99)	**-**
1-2 comorbidity **(comparison=No comorbidity)**					2.30*** (2.26, 2.34)	**2.28*** **(2.25, 2.32)**
3 or more comorbidity **(comparison=No comorbidity)**					2.96*** (2.91, 3.01)	**2.94*** **(2.90, 2.99)**
(Type of care) *(time in days from symptom onset to seeking care)						
Time in days from symptom onset to seeking care (for outpatients)						**1.07*** **(1.06, 1.07)**
Time in days from symptom onset to seeking care (for hospitalized)						**0.98*** **(0.97, 0.98)**
Type of care, when time from symptom onset to care=0 **(comparison=Outpatient)**						**36.29*** **(35.28, 37.33)**
Akaike information criterion	6,879,429.7	6,552,629.9	6,849,913.9	6,260,272.2	6,169,794.7	**6,168,502.6**

*P<0.05, **P<0.01, ***P<0.001, CI, Confidence Interval

Table 5. Results of multiple survival regression models across COVID-19 waves.

	Hazard Ratio (95% CI)			
	First wave	**Second wave**	**Third wave**	**Fourth wave**
Indigenous (Comparison =Non-indigenous)	1.09*** (1.03, 1.14)	1.04 (0.98, 1.11)	1.13** (1.06, 1.21)	1.03 (0.87, 1.22)
Sex (comparison =Female)	1.32*** (1.30, 1.34)	1.26*** (1.24, 1.28)	1.19*** (1.17, 1.22)	1.25*** (1.20, 1.30)
Age	1.03*** (1.03, 1.03)	1.03*** (1.03, 1.03)	1.02*** (1.02, 1.02)	1.03*** (1.03, 1.03)
1-2 comorbidity (comparison=No comorbidity)	2.69*** (2.62, 2.77)	2.06*** (2.01, 2.11)	1.93*** (1.87, 2.00)	1.88*** (1.76, 2.00)
3 or more comorbidity (comparison=No comorbidity)	3.69*** (3.58, 3.80)	2.58*** (2.51, 2.65)	2.41*** (2.32, 2.50)	2.25*** (2.09, 2.41)
Type of care*time in days from symptom onset to seeking care				
Time in days from symptom onset to seeking care (for outpatients)	1.04*** (1.03, 1.04)	1.07*** (1.07, 1.08)	1.03** (1.01, 1.05)	1.11*** (1.08, 1.15)
Time in days from symptom onset to seeking care (for hospitalized)	0.96*** (0.96, 0.96)	0.97*** (0.97, 0.97)	0.98*** (0.98, 0.98)	1.00 (0.99, 1.01)
Type of care, when time from symptom onset to care=0	21.57*** (20.70, 22.48)	43.62*** (41.64, 45.70)	67.95***	73.20*** (62.93, 85.15)

(comparison=Outpatient)			(61.32, 75.30)	
Akaike information criterion	2,038,299.00	2,312,173.70	881,563.05	198,461.41

For each of the waves, the adjusted HR for the indigenous population compared to the non-indigenous population was greater than 1 and was statistically significant for the first and third waves, indicating a higher hazard of COVID-19 mortality among indigenous populations compared to the non-indigenous counterparts (Table 5). We found that the unadjusted HR in 2020 was 1.69 (95% CI: 1.62, 1.77) compared to 1.62 (95% CI: 1.54, 1.70) in 2021. Similarly, in the adjusted model (model 6), the HR for 2020 decreased to 1.10 (95% CI: 1.05, 1.15) and the HR for 2021 decreased to 1.10 (95% CI: 1.04, 1.15).

The survival curves for indigenous and non-indigenous populations, stratified by hospitalized and outpatient status in Mexico are shown in Figure 5. The curves reflect a lower survival probability among hospitalized indigenous populations compared to the hospitalized non-indigenous population.

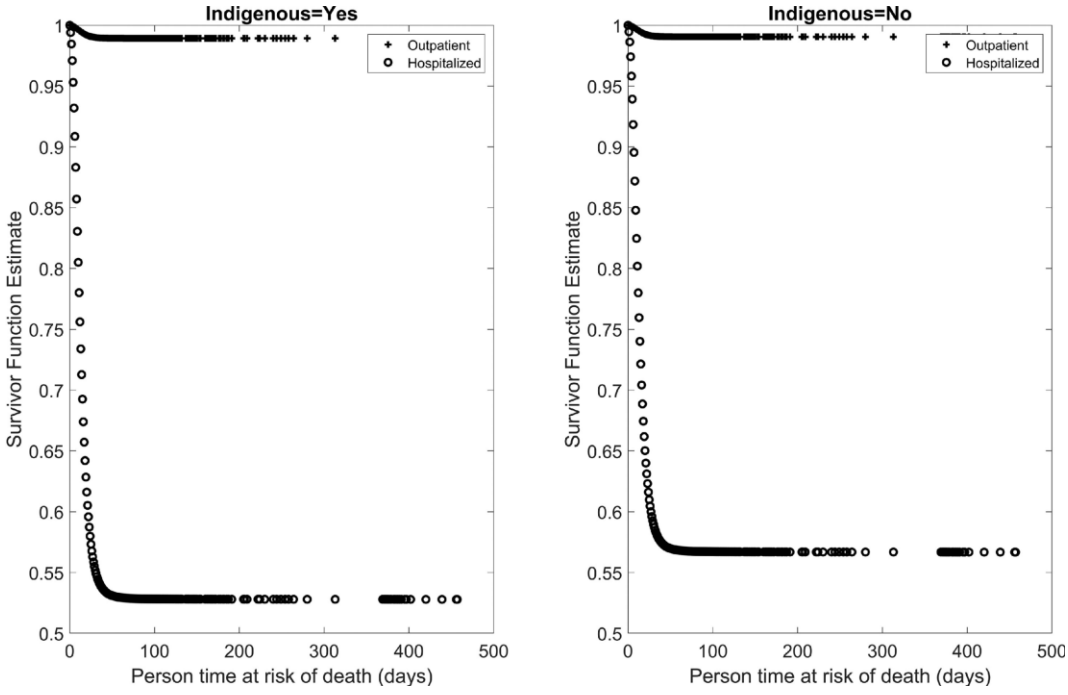


Figure 5. Survival curves for hospitalized and outpatient COVID-19 cases among indigenous and non-indigenous groups.

4.4 Discussion

The COVID-19 pandemic has exacerbated the existing health and socio-economic disparities among vulnerable indigenous populations globally because of the systemic structural disadvantages and higher burden of lockdown measures that put these groups at higher risk of infection and death (Carethers, 2021; Katikireddi *et al.*, 2021). This study assessed the mortality rate per 1000 person-weeks for indigenous and non-indigenous populations in Mexico from February 2020 to March 2022. At the national level, we estimated the COVID-19 mortality rate among indigenous groups to be substantially higher compared to non-indigenous populations (3.25 vs. 1.94 per 1000 person-weeks). Indigenous individuals experienced significant delays in care seeking for COVID-19 infection and a lower survival probability compared to non-indigenous counterparts.

We found that the COVID-19 mortality rate among indigenous populations was 68% higher than the non-indigenous populations (RR = 1.68). This estimate is similar to that reported in an earlier study from Mexico (RR = 1.65) covering the first 5 months of the pandemic (Argoty-Pantoja *et al.*, 2021). Another study from Mexico based on data as of November 2020 also reported a higher case fatality ratio of the indigenous group compared to the non-indigenous group (RR = 1.11) (Mallard *et al.*, 2021). Increased vulnerability and mortality among indigenous populations as compared to the general population during past pandemics is well established (CDC, 2009; Dahal *et al.*, 2018; Kelm, 1999; Wilson *et al.*, 2012). For example, during the 1918 influenza pandemic, the death rate among the Māori population was at least 7.3 times higher than that of the population of European descent in New Zealand (Wilson *et al.*, 2012). Also, during the 2009 H1N1 influenza pandemic, indigenous populations from Australia, Canada, and New Zealand had 3-8 times higher rates of hospitalization and death compared to non-indigenous populations (CDC, 2009).

We observed the highest COVID-19 mortality rate during the first wave followed by the third wave both for indigenous and non-indigenous groups. Indigenous populations were more heavily affected than the non-indigenous consistently across the waves. Social distancing guidelines were not strictly in place and vaccination was not yet available during the first wave whereas the third wave included the period during which the more contagious, severe, and deadly Delta

variant of the Coronavirus was circulating (CDC, 2021). RR increased from 1.55 in first wave to 1.65 in second wave to 1.86 in third wave and 2.40 in fourth wave, indicating that over subsequent pandemic waves, the indigenous groups were more likely to succumb to COVID-19. Similarly, the increase in RR from 1.67 in 2020 to 1.75 in 2021 could reflect the effect of social disparities in adopting non-pharmaceutical interventions (NPIs) such as handwashing, using facemasks, less frequent use of public transportation, and social distancing as well as vaccine uptake (Mamelund *et al.*, 2021). Among the indigenous Mexican populations, precarious socio-economic conditions and factors such as return of the indigenous population to their communities due to the pandemic, poor access to water, language barriers, and limited access to the Internet are important social factors that affect the adoption of preventive measures against COVID-19 (Díaz de León-Martínez *et al.*, 2020). However, no such data that compares the uptake of NPIs and vaccination among indigenous and non-indigenous groups is available for Mexico. The COVID-19 pandemic started as a rich man's disease within affluent communities and then spread to the poorer section, producing more severe outcomes (Bengali *et al.*, 2020; Khlat and Le Coeur, 2021; Plümper and Neumayer, 2020). This is consistent with indigenous groups exhibiting worsening mortality outcomes over subsequent pandemic waves. We also found that the R_t for both indigenous and non-indigenous groups was highest during the fourth wave (1.4 among indigenous vs. 1.5 among non-indigenous). Overall, the R_t for indigenous and non-indigenous groups was comparable, possibly reflecting the fact that indigenous groups in Mexico are well connected to the rest of the population through internal migration. For example, indigenous population in Mexico migrates to urban destinations where they occupy jobs that increase their vulnerability to COVID-19 infection and they in turn spread the disease to their home communities upon return (Díaz de León-Martínez *et al.*, 2020). However, the increased RR value could also indicate that the improvements in care and treatment of severe cases became more available to affluent patients than to the indigenous groups as the pandemic progressed.

COVID-19 vaccine uptake among indigenous populations may be influenced by several factors including the availability of accurate, accessible, and culturally relevant information, poor access to the vaccination sites, mistrust in government services, concerns over vaccine safety, past experiences of racism and abuse in healthcare settings, and the lack of involvement of

indigenous communities in the planning and implementation of vaccination programs (Castillo *et al.*, 2021). Many indigenous people live in geographically rural or remote areas, inhabit multigenerational housing, are poor, face food insecurity, have increased rates of chronic diseases, and have limited access to running water. Consequently, the one-size-fits-all response that was frequently implemented to address COVID-19 was often ineffective for these vulnerable groups (Power *et al.*, 2020; United Nations Department of Economic and Social Affairs, 2020). In Mexico specifically, indigenous populations have a higher prevalence of metabolic syndrome and its components such as low HDL-cholesterol levels, central obesity and elevated blood pressure (Mendoza-Caamal *et al.*, 2020) that increase the risk of severe COVID-19 (Steenblock *et al.*, 2021). In addition, indigenous communities in Mexico suffer from higher levels of social deprivation including lagging in education, access to health services and social security, housing quality and space, and basic housing services (Díaz de León-Martínez *et al.*, 2020; Consejo Nacional de Evaluación de la Politica de Desrrollo Social, 2019). As in many countries, the Mexican health administration recommended COVID-19 vaccination following sequential prioritization to health workers, people aged 60 years and above, and people aged 50-59 with comorbidities followed by the general population (de Vacunación Covid, 2021). However, social and ethnic vulnerability including indigenous status was not taken into account when designing these recommendations. Indeed, a 2017 review of pandemic preparedness plans across nations revealed that the risk groups for vaccination were based on medical conditions without regard to social risks (Mamelund, 2017; Mamelund and Dimka, 2021).

In Mexico, 23 federal entities out of 32 had a higher mortality rate among indigenous compared to non-indigenous, and this difference was statistically significant in 13 entities. For 9 states including Chiapas, Durango, and Nuevo Leon, the mortality rate was higher among non-indigenous groups, though not statistically significant. Further studies are needed to better understand the drivers leading to higher mortality among non-indigenous populations in these areas.

In summary, we found indigenous status to be an important risk factor for COVID-19 mortality in Mexico. While the crude hazard of death among the indigenous population was 67.1% higher than that of the non-indigenous, the hazard of death was only 8.0% greater among indigenous when controlling for sex, age, comorbidity category, and the interaction between type of care and

care-seeking delay. This indicates that 'indigenous status' alone is not a significant factor contributing to a higher risk of deaths due to COVID-19 among the indigenous population, but the associated socio-demographic, cultural and care-seeking practices in this group explain such differences. Moreover, epigenetic mechanisms could also mediate the effect of racialized experiences of colonization, oppression, and violence on COVID-19 outcomes among indigenous populations (Curtice and Choo, 2020; Encinosa, 2021). Similar to our Mexican study, in Brazil, which has high ethnic diversity, *Pardo* ethnicity was found to be the second most important risk factor for death due to COVID-19 after age. Compared to White Brazilians, *Pardo* and Black Brazilians who were admitted to the hospital suffered a significantly higher risk of mortality (HR for *Pardo*: 1.45; 95% CI: 1.33, 1.58) (Baqui *et al.*, 2020). Consistent with this study, we found declining survival curves for Mexican indigenous groups compared to non-indigenous for both the outpatient and hospitalized COVID-19 positive cases.

We found a significantly higher proportion of deaths among total cases in the indigenous population based on hospitalization and outpatient status. This was consistent with previous studies from Mexico (Argoty-Pantoja *et al.*, 2021; Ibarra-Nava *et al.*, 2021). We also found a statistically significant higher average care-seeking delay for the indigenous population compared to non-indigenous (4.41 days vs. 4.07 days) which could be due in part to longer travel distances between place of residence and health facility for the indigenous population compared to the non-indigenous populations besides other socio-economic disparities affecting health service utilization.

Our study has some notable limitations. First, the nature of available variables in the dataset did not allow us to fully understand the drivers behind the higher mortality rates in indigenous populations compared to the general population. For instance, variables related to COVID-19 vaccination status, self-reported adherence to NPIs such as mask wearing and shelter-in-place orders, and access to health care services could help us better understand COVID-19 mortality disparities. Results for waves other than the first wave may be confounded by the disparity in vaccine uptake and disparity in NPI use. It is also worth noting the possibility of underreporting of COVID-19 deaths among indigenous populations as reported for Brazil (Fellows *et al.*, 2021) where it was estimated a 103% underreporting of COVID-19 deaths among indigenous populations. Similarly, according to a previous study from Mexico (Dahal *et al.*, 2021),

confirmed COVID-19 deaths accounted for only ~38% of total excess deaths estimated for Mexico partly due to underreporting. Our results are therefore underestimating the toll of the disease burden on the indigenous peoples. Differences in underreporting between indigenous and non-indigenous populations need further investigation.

5.5 Conclusion

Our study found that the COVID-19 mortality rate among indigenous populations was 68% higher than that for the non-indigenous population (RR = 1.68) from February 2020 to March 2022, and both the R_t and RR were highest during the fourth wave of the COVID-19 pandemic, reflecting the possible impact of vaccine uptake and NPI use disparities between indigenous and non-indigenous population. Our findings indicate that indigenous status is an important risk factor for mortality in Mexico such that the hazard of death among indigenous populations was 67% higher among indigenous people compared to non-indigenous groups in the unadjusted model and 8% greater when controlling for sex, age, number of comorbidities and the interaction between type of care and care-seeking delay. Indigenous people showed higher delays in care seeking for COVID-19 infection and a lower survival probability compared to non-indigenous populations, pointing to a link between care seeking practices and indigenous status. Further studies are warranted to disentangle the mechanisms through which indigenous populations are disproportionately affected by COVID-19 compared to non-indigenous populations.

5.6 References

Alves DE, Mamelund SE, Dimka J, Simonsen L, Mølbak M, Ørskov S, et al. Indigenous peoples and pandemics. Scand. J. Public Health 2022 May 12.

Argoty-Pantoja AD, Robles-Rivera K, Rivera-Paredez B, Salmerón J. COVID-19 fatality in Mexico's Indigenous populations. Public Health 2021;193:69-75.

Australian Institute of Health Welfare. Mortality and life expectancy of Indigenous Australians: 2008 to 2012. Canberra: AIHW; 2014.

Baqui P, Bica I, Marra V, Ercole A, van der Schaar M. Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. Lancet Glob Health 2020;8:e1018-26.

Bengali S, Linthicum K, Kim V. How coronavirus—a 'rich man's disease'—infected the Poor. Los Angeles Times 2020;May 8. https://www.latimes.com/world-nation/story/2020-05-08/how-the-coronavirus-began-as-a-disease-of-the-rich (accessed 29 March 2022)

Carethers JM. Insights into disparities observed with COVID-19. J Intern Med 2021;289:463-73.

Castillo G, Montesanti S, Goveas D, Crawshaw J, Smith M, Trehan N, et al. Factors affecting COVID-19 vaccination among Indigenous peoples in Canada: a behavioural analysis. Ottawa: Ottawa Hospital Research Institute; 2021.

Centers for Disease Control and Prevention (CDC). Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/Alaska Natives-12 states, 2009. MMWR Morb Mortal Wkly Rep 2009;58(48):1341-4.

CDC. Delta variant: what we know about the science 2021. Available from: https://stacks.cdc.gov/view/cdc/108671 access date: 03/10/2022.

CMMCP. EPI Week Calendars 2008-2022., https://www.cmmcp.org/mosquito-surveillance-data/pages/epi-week-calendars-2008-2022 , 2022 (accessed 07/12/2022)

CONAPO. Projections of the population of the municipalities of Mexico, 2015-2030. Mexico: National Population Council; 2019.

Cori A, Cauchemez S, Ferguson NM, Fraser C, Dahlqwist E, Demarsh PA, et al. Package 'EpiEstim' Version 2.2-4. 2021.

Curtice K, Choo E. Indigenous populations: left behind in the COVID-19 response. Lancet 2020;395:1753.

Dahal S, Banda JM, Bento AI, Mizumoto K, Chowell G. Characterizing all-cause excess mortality patterns during COVID-19 pandemic in Mexico. BMC Infect Dis 2021;21:432.

Dahal S, Mizumoto K, Bolin B, Viboud C, Chowell G. Natality decline and spatial variation in excess death rates during the 1918–1920 influenza pandemic in Arizona, United States. Am J Epidemiol 2018;187:2577-84.

Daws K, Punch A, Winters M, Posenelli S, Willis J, MacIsaac A, et al. Implementing a working together model for Aboriginal patients with acute coronary syndrome: an Aboriginal Hospital Liaison Officer and a specialist cardiac nurse working together to improve hospital care. Aust Health Rev 2014;38:552-6.

de Vacunación Covid GTA. Sequential prioritization for vaccination against SARS-CoV-2 in the Mexican population. Preliminary recommendations. Salud Publ Mex 2021;63:286-307.

Díazd de León-Martínez L, de la, Sierra-de la Vega L, Palacios-Ramírez A, Rodriguez-Aguilar M, Flores-Ramírez R. Critical review of social, environmental and health risk factors in the Mexican indigenous population and their capacity to respond to the COVID-19. Sci. Total Environ 2020;733.

Durey A, McEvoy S, Swift-Otero V, Taylor K, Katzenellenbogen J, Bessarab D. Improving healthcare for Aboriginal Australians through effective engagement between community and health services. BMC Health Serv Res 2016;16:224.

Encinosa M. Embodied Injustices: COVID-19, Race, and Epigenetics. PANDION: the osprey Journal of Research and Ideas 2021;2:3.

Fellows M, Paye V, Alencar A, Nicácio M, Castro I, Coelho ME, et al. Under-reporting of COVID-19 cases among indigenous peoples in Brazil: a new expression of old inequalities. Front Psychiatry 2021:352.

Hajizadeh M, Hu M, Bombay A, Asada Y. Socioeconomic inequalities in health among Indigenous peoples living off-reserve in Canada: trends and determinants. Health Policy 2018;122:854-65.

Ibarra-Nava I, Flores-Rodriguez KG, Ruiz-Herrera V, Ochoa-Bayona HC, Salinas-Zertuche A, Padilla-Orozco M, et al. Ethnic disparities in COVID-19 mortality in Mexico: a cross-sectional study based on national data. PloS one 2021;16.

International Labour Organization (ILO). Indigenous and tribal peoples convention. Geneva: International labour organization; 1989.

IWGIA. Mexico. https://www.iwgia.org/en/mexico.html, 2021 (accessed February 13, 2022).

Katikireddi V, Hainey K, Beale S. The impact of COVID-19 on different population subgroups: ethnic, gender and age-related disadvantage. J R Coll Physicians Edinb 2021;51 :S40-6.

Kelm M-E. British Columbia First Nations and the influenza pandemic of 1918-19. BC Stud 1999;122:23-48.

Khlat M, Le Coeur S. COVID-19 Epidemic: Early Shift in the Socioeconomic Profile of the Affected Population. Int J Environ Res Public Health 2021; 18: 3185.

Kirby T. Evidence mounts on the disproportionate effect of COVID-19 on ethnic minorities. Lancet Respir Med 2020;8:547-8.

Mallard A, Pesantes MA, Zavaleta-Cortijo C, Ward J. An urgent call to collect data related to COVID-19 and Indigenous populations globally. BMJ Glob Health 2021;6.

Mamelund S-E. Social inequality–a forgotten factor in pandemic influenza preparedness. Tidsskr Nor Laegeforen 2017; 137:911-13.

Mamelund S-E, Dimka J. Not the great equalizers: Covid-19, 1918–20 influenza, and the need for a paradigm shift in pandemic preparedness. Popul Stud (Camb) 2021;75:179-99.

Mamelund S-E, Dimka J, Bakkeli NZ. Social Disparities in Adopting Non-pharmaceutical Interventions During COVID-19 in Norway. J Dev Soc 2021;37:302-28.

Mendoza-Caamal EC, Barajas-Olmos F, García-Ortiz H, Cicerón-Arellano I, Martínez-Hernández A, Córdova EJ, et al. Metabolic syndrome in indigenous communities in Mexico: a descriptive and cross-sectional study. BMC Public Health 2020;20;339.

National Institute of Indigenous Peoples. Socioeconomic Indicators of the Indigenous Peoples of Mexico, 2015: National estimates by federal entity. INPI; July 9, 2017. URL: https://www.gob.mx/inpi/articulos/indicadores-socioeconomicos-de-los-pueblos-indigenas-de-mexico-2015-116128. (accessed 11/18/2021)

Nazroo JY. The structuring of ethnic inequalities in health: economic position, racial discrimination, and racism. Am J Public Health 2003;93:277-84.

Ofori SK, Ogwara CA, Kwon S, Hua X, Martin KM, Mallhi AK, et al. SARS-CoV-2 transmission potential and rural-urban disease burden disparities across Alabama, Louisiana, and Mississippi, March 2020—May 2021. Ann Epidemiol 2022;71:1-8

Plümper T, Neumayer E. Wealthier districts were hit by Covid-19 first in Germany, but their lockdowns were more effective. VoxEU Org 2020;11.

Power T, Wilson D, Best O, Brockie T, Bearskin LB, Millender E, et al. COVID-19 and Indigenous Peoples: An imperative for action. J Clin Nurs 2020;29:2737-41.

Quinn SC, Kumar S. Health inequalities and infectious disease epidemics: a challenge for global health security. Biosecur Bioterror 2014;12:263-73.

Secretaría de Salud. Lineamiento estandarizado para la vigilancia epidemiológica y por laboratorio de la enfermedad respiratoria viral (Standardized guidelines for epidemiological and laboratory surveillance of the respiratory viral disease). Secretaría de salud, Mexico: Gobierno de Mexico; 2020.

Secretaría de Salud. Datos abiertos dirección general de epidemiología, https://www.gob.mx/salud/documentos/datos-abiertos-152127, 2022 (accessed 25 March 2022).

Sharma K, Bhaskar A. How indigenous communities faced off against COVID-19 globally. DownToEarth; 2021. URL https://www.downtoearth.org.in/blog/health/how-indigenous-communities-faced-off-against-covid-19-globally-75046. (accessed 03/19/2021)

Consejo Nacional de Evaluación de la Politica de Desrrollo Social. La pobreza en la población indígena de México 2008-2018. Comisión Nacional para el Desarrollo de los Pueblos Indígenas; 2019.

Steenblock C, Schwarz PE, Ludwig B, Linkermann A, Zimmet P, Kulebyakin K, et al. COVID-19 and metabolic disease: mechanisms and clinical management. Lancet Diabetes Endocrinol 2021;9:786-98.

Sullivan KM, Dean AG, MM S. OpenEpi: open source epidemiologic statistics for public health, Version 3.01. https://www.openepi.com/PersonTime2/PersonTime2.htm, 2013 (accessed 9 March 2022).

Tripp L. Overlooking the Canadian Indigenous demographic data: a response to Mallard et al's call for data on COVID-19 and Indigenous populations. BMJ Glob Health 2022;7.

United Nations Department of Economic and Social Affairs. COVID-19 and Indigenous peoples, https://www.un.org/development/desa/indigenouspeoples/covid-19.html, 2020. (accessed 19 March 2022)

Walsh WF, Kangaharan N. Cardiac care for Indigenous Australians: practical considerations from a clinical perspective. Med J Aust 2017;207:40-5.

Wiemers EE, Abrahams S, AlFakhri M, Hotz VJ, Schoeni RF, Seltzer JA. Disparities in vulnerability to severe complications from COVID-19 in the United States. National Bureau of Economic Research 2020 Working Paper No. 27294.

Wilson N, Barnard LT, Summers JA, Shanks GD, Baker MG. Differential mortality rates by ethnicity in 3 influenza pandemics over a century, New Zealand. Emerg Infect Dis 2012;18:71-7.

Yashadhana A, Pollard-Wharton N, Zwi AB, Biles B. Indigenous Australians at increased risk of COVID-19 due to existing health and socioeconomic inequities. Lancet Reg Health West Pac 2020;1.

You C, Deng Y, Hu W, Sun J, Lin Q, Zhou F, et al. Estimation of the time-varying reproduction number of COVID-19 outbreak in China. Int J Hyg Environ Health 2020;228.

Chapter 5

5.1 Dissertation Summary

Use of epidemiologic methods is crucial in exploring the epidemiology of a novel disease such as the COVID-19 and in guiding the prevention and mitigation strategies. In the three studies included in this dissertation, we apply different epidemiologic methods across different geospatial levels such as national and federal entities, population groups such as indigenous and non-indigenous groups, and across time span such as by waves of the pandemic to investigate the impact of COVID-19 pandemic using epidemiologic data from the country of Mexico.

In the first study, we utilize Serfling regression analysis to estimate weekly excess mortality rates per 10,000 population in Mexico during the first year of COVID-19 pandemic. The study showed that Mexico was heavily affected by the pandemic with an estimated all-cause excess mortality rate of 26.10 per 10,000 population. While males had around two times higher excess mortality rate compared to females, the excess mortality rate in Mexico City was about three times higher than the rate in the rest of Mexico. The lab-confirmed COVID-19 deaths accounted for only about 39% of the total estimated excess deaths indicating either the effect of low testing or reporting delay or a substantial increase in deaths due to other causes during the first year of the pandemic in Mexico. This also reflects the importance of using excess mortality rate to assess the mortality burden of an ongoing pandemic.

We also demonstrate the application of a phenomenological dynamic growth model based on ordinary differential equations, such as the generalized logistic growth model with three parameters, in generating short term forecasts during an ongoing pandemic. We specifically apply it in generating the four weeks ahead forecasts of excess deaths. Our model forecasted that a total of ~61610 excess deaths would be accumulated during the first four weeks of 2021. To compare our forecast estimates with the actual estimated excess deaths, we performed excess mortality calculation for the first four weeks of 2021 and estimated total excess deaths of ~95664. In January 2021, Mexico marked new daily records for COVID-19 deaths. For example, 1803 COVID-19 deaths were recorded on January 21, exceeding the previous record of 1500 in the same week (1). Not only in Mexico but the record number coronavirus death rates were

reported across the globe in the month of January (2). For example, January 2021 was recorded as the deadliest month in the US since the start of pandemic to that date (3). This surge in mortality was considered to be led by interstate travel and holiday celebrations (3). In the second paper, we also use big data from the mainstream social media platform, Twitter, to both analyze the trend of deaths chatter from 2018 to 2020 and to assess the correlation of people's engagement with the death chatter in Twitter with COVID-19 mortality rate and excess mortality rate. This type of social media data can be utilized in other analyses such as in assessing the socio-economic disparity in COVID-19 cases and deaths or the impact of interventions such as vaccination.

In the second study, we expand the analysis of excess mortality rate from the national level to the federal entity level to estimate all-cause excess mortality rate for 32 federal entities in Mexico including Mexico City for 2020, 2021 and the total, along with the proportion of COVID-19 attributed deaths out of total excess deaths for each location. In addition, we also apply other epidemiologic methods such as multiple linear regression analysis, analysis using Moran's I statistics and spatial lag model, in assessing the factors associated with excess mortality rate at the subnational level in Mexico. We apply clustering analysis and identify four clusters of states with similar excess mortality growth rate curves in Mexico. We present the average growth rate curves and one standard deviation band around the curve. To our knowledge, the assessment of excess mortality growth rate curves in generating clusters of states with similar curve has been done for the first time though similar studies utilizing cases or deaths data have been reported. We show that this type of clustering analysis is important in multiple ways: first, the information on growth rate curve can be utilized by the corresponding states in implementing public health and medical interventions. For example, the states such as Baja California that fall into the first cluster with an inclining second peak in the excess deaths growth rate can formulate timely prevention and control measures to slow down the growth rate. Second, knowledge of public health measures that were in place in the states that fall into one cluster can be useful for the states that fall into another cluster. In our study for example, the states in cluster 3 and 4 saw a major peak during July 2020 followed by smaller peak in January 2021. In this context, learning about public health measures that were implemented in states of in cluster 3 and 4 leading to a smaller growth of excess deaths can be useful for applying preventive measures in

other states such as those in cluster 1 in which a sharp increase in growth rate curve of excess death was observed during the same period. Moreover, it can also provide information regarding which groups of states are dominant in determining the overall pattern of pandemic wave in the country.

Our method of excess mortality estimation presented in chapter 2 and 3 is not exempt from limitations. First, in estimation of excess mortality we have replaced any negative excess deaths by zero to account for the effect of reporting delays when a pandemic is ongoing. This approach of replacing negative values by zero has also been applied by the CDC in estimating excess deaths associated with COVID-19 (4). In our analysis, however by replacing negative excess deaths by zero, we might have missed some actual negative excess deaths if any. During the COVID-19 pandemic there have been reports of mortality improvements from countries such as New Zealand (5). Some of the factors that can lead to a decline in mortality are less severe influenza season in 2020 and 2021 compared to previous years, health system geared up to respond, compliance with public health and social measures such as mask use, social distancing etc. leading to reduced transmission of other infectious diseases as well, populations being more sensitive to health issues and seeking health care, etc. (6). Likewise, in our second paper we did not take into account the hierarchical nature of the data. Similarly, given the availability of COVID-19 death data, estimating excess death rate separately by both including and excluding COVID-19 deaths for the pandemic period would provide a clearer picture of indirect deaths attributed to the pandemic. In our study, we only used the total deaths and not the deaths excluding COVID-19 counts. We provide a detailed description of our methods, results and a thorough discussion that can serve as a guide to applying these epidemiologic methods in assessing mortality impact of diseases such as COVID-19 at the national and the subnational level.

In the third study, we utilize epidemiologic methods to compare the mortality impact of COVID-19 pandemic among indigenous and non-indigenous populations in Mexico using data of more than 2 million COVID-19 cases and more than 238,000 COVID-19 deaths. This study is important because the available preliminary research indicates mixed results on the impact of COVID-19 pandemic on indigenous populations even though the data from past pandemics such as the 1918 influenza pandemic, and the 2009 H1N1 pandemic show a higher burden of cases

and severe impacts including deaths among indigenous compared to the general populations. Moreover, given a dearth of countries that record and make available the COVID-19 data among indigenous populations, it is important to utilize the available big epidemiologic dataset from the country with the largest number of indigenous populations in the Americas to generate comparative evidence on the mortality impact of the COVID-19 pandemic among the two population groups. In line with the spirit of the international legislation that considers the ability to self-identify one's ethnicity as indigenous as a fundamental human right, we defined the ethnic populations as those who self-identify themselves as indigenous. Specifically, we estimate COVID-19 mortality rate per 1000 person-weeks from February 2020 to March 2022 at the national level and for 32 federal entities including Mexico City separately for indigenous and non-indigenous populations. We report the mortality rate and mortality rate ratio by year and for each of the four waves of the pandemic in the country for both groups of populations. The results indicate a higher value for the wave-wise analysis compared to the overall. This is because the follow-up period for wave wise rate is just the 'wave duration' leading to shorter person-time values while overall rates are based on the longer follow-up period especially for those cases from the initial waves. In the study, we also use survival regression models to estimate the unadjusted and adjusted hazard of death among indigenous compared to the non-indigenous groups. We also estimate the instantaneous reproduction number over the weekly sliding window for the entire pandemic period for indigenous and non-indigenous populations separately as well as report the average reproduction number during the early ascending phase of each of the four pandemic waves for both groups.

We report a substantially higher mortality rate among indigenous groups compared to non-indigenous with a mortality rate ratio of 1.68. Similarly, the hazard of death among indigenous populations was 67% and 8% higher in the unadjusted and adjusted models respectively. We found an increasing mortality rate ratio from the first to second to third to the fourth wave which could reflect the disparities between the two groups in the uptake of non-pharmaceutical and vaccination interventions. Therefore, we highlight that indigenous status is an important risk factor for COVID-19 mortality in Mexico. In contrast to these findings, in our second study we observed lowest excess death rate in southern states such as Chiapas, Oaxaca, Quintana Roo, Yucatan, and Campeche. In Mexico higher proportion of indigenous population

live in the southern region. It should be noted however that the second study was based on the aggregate death data at state level and no information on the deaths for subpopulations such as indigenous and non-indigenous was used whereas in the third study we used individual case data. Therefore, based on second study we cannot infer that indigenous populations had lower excess death rate because of possibility of bias due to ecological fallacy. We recommend further studies to explore the mechanism through which indigenous populations remain at an increased risk of adverse outcomes during an infectious disease pandemic.

In summary, the three studies presented in chapters 2-4 in this dissertation report, demonstrate the power of different epidemiologic methods to gain insights on the heterogenous impact of the COVID-19 pandemic. Overall, we employ different epidemiologic methods such as estimation of excess mortality rate estimation, short-term forecasting of excess deaths, correlation analysis of social media and deaths data, estimation of instantaneous reproduction number, multiple linear regression analysis, test for spatial autocorrelation and spatial lag regression model, cluster analysis, estimation of person-time mortality rate, and survival analysis. These epidemiological approaches have their own implications in answering different epidemiological questions. For example, estimates of excess mortality quantify the deaths that were in excess during a pandemic period whereas instantaneous reproduction number is a measure of diseases transmission. Moreover, the metrics such as hazard ratio from survival analysis compare rates of events such as deaths between study groups over time. Regression analyses are useful to assess potential risk and protective factors and clustering using shape analysis of growth rate curves are helpful in identifying broad categories of spatial areas with distinct trajectories. We applied these methods across places, people, and time to measure the heterogenous impact of COVID-19 in Mexico. We provide a detailed description of the methodology and present the results, interpretation, and policy implication of our findings in the respective chapters. Overall, the methods used in the three studies can be useful in guiding need-based and equitable planning in a limited resource setting especially during the public health emergencies such as COVID-19.

5.2. References

1. Mexico marks new daily record in deaths from pandemic. REUTERS. January 21, 2021. [Available from https://www.reuters.com/business/healthcare-pharmaceuticals/mexico-fatalities-covid-19-rise-single-day-record-1803-2021-01-22/

2. Tatyana K. January sees record coronavirus death rates across the globe: kazinform; 12 January 2021 [Available from: https://www.inform.kz/en/january-sees-record-coronavirus-death-rates-across-the-globe_a3740304.

3. Feuer W, Rattner N. U.S. reports record number of Covid deaths in January as new strains threaten progress. CNBC. January 27, 2021. [Available from https://www.cnbc.com/2021/01/27/us-reports-record-number-of-covid-deaths-in-january.html

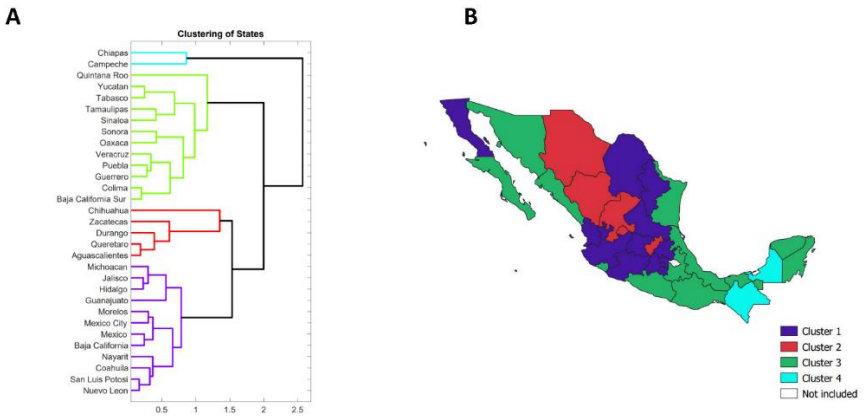
4. CDC. Excess Deaths Associated with COVID-19 [Available from: https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm.

5. Kung S, Doppen M, Black M, Hills T, Kearns N. Reduced mortality in New Zealand during the COVID-19 pandemic. The Lancet. 2021;397(10268):25.

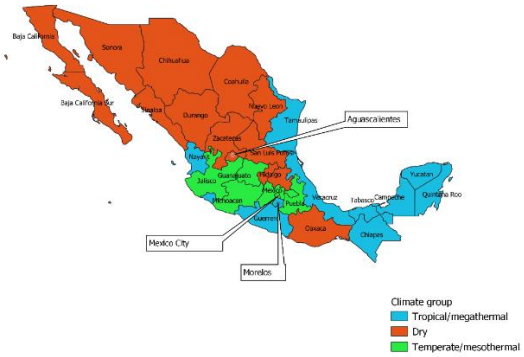
6. Msemburi W, Karlinsky A, Knutson V, Aleshin-Guendel S, Chatterji S, Wakefield J. The WHO estimates of excess mortality associated with the COVID-19 pandemic. Nature. 2023;613(7942):130-7.

Appendices

Appendix 1. Supplemental figures for Chapter 3. Geospatial variability in excess death rates during the COVID-19 pandemic in Mexico: Examining sociodemographic, climate, and population health characteristics



Supplemental Figure 1. A: Dendrogram plot, B: map of Mexico showing the states in four different clusters



Supplemental Figure 2. States in Mexico by climate groups based on Köppen-Geiger classification

Appendix 2. Supplementary tables for Chapter 4. Investigating COVID-19 transmission and mortality differences between indigenous and non-indigenous populations in Mexico

Table 1. Results of survival regression model fitting for the overall period of February 2020-March 2022

Variables	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
Indigenous (Comparison =Non-Indigenous)	0.07595	0.01633	21.6287	<.0001
Sex (comparison =Female)	0.23675	0.00425	3097.0809	<.0001
Age	0.02969	0.0001366	47231.2656	<.0001
1-2 comorbidity (comparison=No comorbidity)	0.82586	0.00792	10869.6863	<.0001
3 or more comorbidity (comparison=No comorbidity)	1.07978	0.00849	16163.1624	<.0001
Type of care (comparison=Outpatient)	3.59156	0.01446	61700.6881	<.0001
Time in days from symptom onset to seeking care	0.06715	0.00236	806.3952	<.0001
Time in days from symptom onset to seeking care * Type of care (for hospitalized)	-0.09134	0.00243	1410.1076	<.0001

Table 2. Results of survival regression model fitting for wave 1

Variables	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
Indigenous (Comparison =Non-Indigenous)	0.08312	0.02469	11.335	0.0008
Sex (comparison =Female)	0.27533	0.00721	1457.5052	<.0001
Age	0.03328	0.0002398	19251.5747	<.0001
1-2 comorbidity (comparison=No comorbidity)	0.99098	0.01417	4890.912	<.0001
3 or more comorbidity (comparison=No comorbidity)	1.3061	0.01507	7511.4447	<.0001
Type of care	3.07156	0.02107	21247.1226	<.0001

(comparison=Outpatient)				
Time in days from symptom onset to seeking care	0.03637	0.00334	118.3415	<.0001
Time in days from symptom onset to seeking care * Type of care (for hospitalized)	-0.07797	0.0035	496.9234	<.0001

Table 3. Results of survival regression model fitting for wave 2

Variables	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
Indigenous (Comparison =Non-Indigenous)	0.04366	0.03206	1.854	0.1733
Sex (comparison =Female)	0.2309	0.00666	1202.412	<.0001
Age	0.03064	0.0002251	18523.6798	<.0001
1-2 comorbidity (comparison=No comorbidity)	0.72317	0.01245	3374.9327	<.0001
3 or more comorbidity (comparison=No comorbidity)	0.94848	0.01335	5048.2123	<.0001
Type of care (comparison=Outpatient)	3.77555	0.02372	25338.2613	<.0001
Time in days from symptom onset to seeking care	0.07258	0.00385	355.8948	<.0001
Time in days from symptom onset to seeking care * Type of care (for hospitalized)	-0.09927	0.00395	632.8939	<.0001

Table 4. Results of survival regression model fitting for wave 3

Variables	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
Indigenous (Comparison =Non-Indigenous)	0.12505	0.03327	14.1267	0.0002
Sex (comparison =Female)	0.1771	0.0103	295.5501	<.0001
Age	0.02421	0.0002995	6532.2749	<.0001
1-2 comorbidity (comparison=No comorbidity)	0.65908	0.01765	1394.2923	<.0001
3 or more comorbidity (comparison=No comorbidity)	0.87962	0.01932	2073.6605	<.0001

Type of care (comparison=Outpatient)	4.2188	0.05242	6476.5947	<.0001
Time in days from symptom onset to seeking care	0.03273	0.01048	9.7626	0.0018
Time in days from symptom onset to seeking care * Type of care (for hospitalized)	-0.04879	0.01056	21.3404	<.0001

Table 5. Results of survival regression model fitting for wave 4

Variables	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
Indigenous (Comparison =Non-Indigenous)	0.02886	0.08487	0.1157	0.7338
Sex (comparison =Female)	0.22551	0.02083	117.1928	<.0001
Age	0.02902	0.0006009	2333.1974	<.0001
1-2 comorbidity (comparison=No comorbidity)	0.63029	0.03341	355.9483	<.0001
3 or more comorbidity (comparison=No comorbidity)	0.81006	0.03586	510.3142	<.0001
Type of care (comparison=Outpatient)	4.29321	0.07714	3097.5692	<.0001
Time in days from symptom onset to seeking care	0.10829	0.01649	43.1133	<.0001
Time in days from symptom onset to seeking care * Type of care (for hospitalized)	-0.10789	0.01674	41.5223	<.0001

Table 6. Results of fitting multiple survival regression model, for the year 2020

Variables	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
Indigenous (Comparison =Non-Indigenous)	0.09467	0.02224	18.1178	<.0001
Sex (comparison =Female)	0.26999	0.00581	2162.1285	<.0001
Age	0.03332	0.0001947	29291.4326	<.0001
1-2 comorbidity (comparison=No comorbidity)	0.90697	0.01117	6590.5248	<.0001
3 or more comorbidity	1.21744	0.0119	10474.848	<.0001

(comparison=No comorbidity)				
Type of care (comparison=Outpatient)	3.31377	0.01647	40502.6929	<.0001
Time in days from symptom onset to seeking care	0.0406	0.0025	263.0257	<.0001
Time in days from symptom onset to seeking care * Type of care (for hospitalized)	-0.08204	0.00263	974.7448	<.0001

Table 7. Results of fitting multiple survival regression model, for the year 2021

Variables	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
Indigenous (Comparison =Non-Indigenous)	0.09164	0.02577	12.6413	0.0004
Sex (comparison =Female)	0.19839	0.00696	812.3824	<.0001
Age	0.02639	0.0002153	15034.7984	<.0001
1-2 comorbidity (comparison=No comorbidity)	0.7195	0.01266	3228.4775	<.0001
3 or more comorbidity (comparison=No comorbidity)	0.92014	0.01372	4500.4212	<.0001
Type of care (comparison=Outpatient)	3.78607	0.01995	36017.7363	<.0001
Time in days from symptom onset to seeking care	0.0225	0.00138	266.5836	<.0001
Time in days from symptom onset to seeking care * Type of care (for hospitalized)	-0.04063	0.00163	622.5196	<.0001

Table 8. Instantaneous reproduction number (R_t) for early ascending phases of four different waves

Non-Indigenous		Indigenous	
Early ascending phase	Mean R_t (95% Credible Interval)	Early ascending phase	Mean R_t (95% Credible Interval)
For 1st wave: April 5 – May 4, 2020	1.216 (1.203, 1.228)	For 1st wave: April 15 – May 14, 2020	1.144 (1.073, 1.217),

For 2nd wave: Sep 29– Oct 28, 2020	1.037 (1.032, 1.042)	For 2nd wave: Nov 15 – Dec 14, 2020	1.009 (1.004, 1.013)
For 3rd wave: June 27 – July 26, 2021	1.151 (1.143, 1.159)	For 3rd wave: July 11 – Aug 9, 2021	1.129 (1.121, 1.137)
For 4th wave: Dec 23, 2021 – Jan 6, 2022	1.535 (1.521, 1.549)	For 4th wave: Dec 27, 2021 – Jan 10, 2022	1.426 (1.405, 1.447)