ARTÍCULO ORIGINAL

TIP Revista Especializada en Ciencias Químico-Biológicas, 25: 1-15, 2022.
https://doi.org/10.22201/fesz.23958723e.2022.474

SARS-CoV-2 variants and associated cases during four epidemic waves in Sinaloa, Mexico

Jorge Luis Batista-Roche[1], Marian Mirabent-Casals[1], Bruno Gómez-Gil[2], César Berlanga-Robles[3] and Alejandra García-Gasca[1]*

[1]Lab. Molecular and Cellular Biology, [2]Lab. Microbial Genomics, [3]Lab. Environmental Management, Centro de Investigación en Alimentación y Desarrollo, Mazatlán, Sinaloa 82112, Mexico. E-mail: *alegar@ciad.mx

Abstract

The COVID-19 pandemic is a global public health problem that has revealed deficiencies and challenges in health systems worldwide. To date, four waves (each one driven by different viral variants and showing different behaviors) have affected Mexico. Here we describe the COVID-19 pandemic behavior in the population of Sinaloa, Mexico after four epidemic waves. Epidemiological data were obtained from public federal databases from March 2020 to February 2022, and genomes of SARS-CoV-2 variants of interest (VOI) and concern (VOC) in Sinaloa were downloaded from the GISAID database from January 2021 to May 2022. The relative risk (RR) of SARS-CoV-2 infection was calculated from public data. Sinaloa presented four epidemic waves from March 2020 to February 2022, and each wave was driven by different variants with different degrees of transmissibility and severity. Interestingly, the delta variant (which dominated the third wave) was probably the most severe, producing a large number of cases per day and high mortality rates, while the omicron variant (which dominated the fourth wave) produced the largest number of cases per day but decreased mortality rates. Most of the COVID-19 cases in Sinaloa occurred among people between 30 and 45 years old, and the average age of the deceased was above 60 years old in all waves. Older people showed higher risk of infection than infants and younger people; however, the relative risk (RR) for people older than 60 years old decreased in the third and fourth waves. Men older than 60 years old showed higher RR than women of the same age group. The COVID-19 pandemic has shown changing behaviors in time, mostly derived from different emerging viral variants and the immunization of the population. Overall, these results show that SARS-CoV-2 infections appear in timely waves, each one driven by different variants (and subvariants or sublineages), with different degrees of transmissibility and severity. The population should continue with preventive measures to avoid infection.
Key words: SARS-CoV-2 variants, relative risk, COVID-19; Sinaloa, vaccine.

Variantes de SARS-CoV-2 y los casos asociados a cuatro olas epidemiológicas en Sinaloa, México

Resumen

La pandemia de COVID-19 es un problema de salud pública que ha revelado las deficiencias y los retos presentes en el funcionamiento de los sistemas hospitalarios del mundo. En México, hasta el momento de finalizar esta recopilación, se han manifestado cuatro "olas epidemiológicas", cada una dominada por variantes virales con comportamientos diferentes. En este reporte se describe el progreso de la pandemia COVID-19 en la población de Sinaloa, México, durante las cuatro olas epidemiológicas. La información se obtuvo de las bases de datos públicas federales durante el período de marzo del 2020 a febrero del 2022 y los genomas de las variantes de SARS-CoV-2 de interés y preocupación en Sinaloa se tomaron de la base de datos GISAID de enero del 2021 a mayo del 2022. El riesgo relativo (RR) de contraer SARS-CoV-2 fue calculado a partir de documentos públicos. Sinaloa presentó cuatro olas epidemiológicas, entre marzo del 2020 y febrero del 2022, cada una estuvo dominada por variantes diferentes, también en grado de transmisión y severidad. Es un hecho de interés que la variante delta (presente en la tercera ola) fue la más severa, por el alto número de enfermos por día y las altas tasas de mortalidad, a diferencia de la variante omicron (en la cuarta ola) que produjo el mayor número de pacientes por día, pero menores tasas de mortalidad. La mayoría de los contagios por COVID-19 en Sinaloa se presentaron en la población de entre 30 y 45 años de edad, con una edad promedio de los fallecidos superior a los 60 años en todas las olas; estos últimos por ser adultos mayores, fueron más vulnerables que los infantes y las personas más jóvenes, sin embargo, el riesgo relativo (RR) para personas mayores disminuyó en la tercera y cuarta olas. Los hombres mayores de 60 años presentaron un RR más alto que las mujeres de la misma edad. En el transcurso de la pandemia, los cambios de comportamiento del virus se deben a la emergencia de las nuevas variantes y a la respuesta de la población inmunizada. En general, los resultados indican que las variantes (subvariantes o sublinajes) del SARS-CoV-2 cada vez que surgen en lo que se denomina como "una ola", el grado de severidad y su transmisión es distinta, lo que conlleva a la población a una permanente prevención.
Palabras clave: variantes de SARS-CoV-2, riesgo relativo, COVID-19, Sinaloa, vacuna.

Artículo recibido el 03 de junio del 2022.
Artículo aceptado el 01 de septiembre del 2022.

Introduction

SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2) is the causative agent of Coronavirus Disease-19 (COVID-19) in humans. The entry of the virus into the cells is favored by the affinity of the Spike protein to the angiotensin-converting enzyme 2 (ACE2) in the host cell membrane (Gadanec *et al*., 2002), and most SARS-CoV-2 mutations detected worldwide are found within the Spike protein (Becerra-Flores & Cardozo, 2020). These mutations have produced different variants and lineages. According to the Center for Disease Control and Prevention (CDC), a lineage is a "group of closely related viruses with a common ancestor", whereas a variant refers to the "viral genome that may contain one or more mutations that differentiate it from other variants"; thus variants with similar mutations have been designated as Variants of Concern (VOC) or Variants of Interest (VOI) depending on their severity, transmissibility, immune response, or treatment efficacy (https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html).

SARS-CoV-2 variants have been named after the country they were identified for the first time, the Pango lineage, and letters from the Greek alphabet convened by the World Health Organization (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/). For instance, VOCs include alpha (B.1.1.7) found for the first time in the United Kingdom, gamma (P.1) first found in Japan and Brazil, delta (original lineage B.1.617.2) found in India, beta (B.1.351) and omicron (original lineage B.1.1.529) found in South Africa. Different variants show different degrees of transmissibility and severity (Davies *et al*., 2021). In Mexico, in addition to VOCs, the epsilon variants (B.1.427 and B.1.429) found for the first time in California (USA) and the B.1.1.519 lineage found in Mexico have also been reported.

The extension of the country (1.9 million km^2 of continental surface), the environmental, socioeconomic, and cultural heterogeneity, as well as a decentralized health system, caused different dynamics in the pandemic among regions and/or states (suppl. Figure S1); Sinaloa is a state located in the northwestern coast of Mexico, it sustains important economic activities such as agriculture, aquaculture, and tourism; the latter is the main source of income in the port of Mazatlán (located at the southern side of the state), which holds crowded touristic activities, creating a suitable environment for viral transmission. Thus, the aim of this work was to describe the COVID-19 pandemic behavior in Sinaloa after four epidemic waves.

Methodology

The genomes of SARS-CoV-2 variants reported for Sinaloa were obtained from the GISAID database https://www.gisaid.org (last accessed June 14th, 2022, suppl. file S2). The lineages were determined with Pangolin v4.0. COVID-19 cases and deaths reported in Sinaloa, from March 2020 to February 2022, were obtained from the General Directorate of Epidemiology (DGE in Spanish) database https://www.gob.mx/salud/documentos/datos-abiertos-bases-historicas-direccion-general-de-epidemiologia?idiom=es (last accessed March 13, 2022). Number of waves in Sinaloa was identified from the epidemiological curve (number of cases per day of onset of symptoms), and Mood's median test and the *post hoc* pairwise median test were performed to detect differences in age between the waves, with total sample sizes of 75 for cases and 150 for deaths, estimated from previous analyzes with a total sample of 10 by wave, a significance level of $\alpha = 0.05$ and power of $\gamma = 0.9$. The Relative Risk (RR) of infection with SARS-CoV-2, defined as the ratio of sick individuals in a given age group to the general population belonging to the same age group, was calculated according to Sun, Chen & Viboud (2020):

$$R_i = \frac{\frac{C_i}{\sum_i C_i}}{\frac{N_i}{\sum_i N_i}}$$

where C_i is the number of cases in age group i and N_i is the population size of age group i.

The population size of the age group (N_i) for Sinaloa was obtained from the official Mexican census of 2020 https://datamexico.org/es/profile/geo/sinaloa-si (last accessed February 28, 2022). Multifactorial ANOVA and Sidak HSD tests were used to assess the influence of sex, age, and epidemic waves in the Relative Risk (model: RR ~ sex + age + wave). All analyses were performed in R v4.0.

Results

Variants of SARS-CoV-2 detected in Sinaloa, Mexico

A total of 2,090 genomes were recovered from GISAID, of these, two were not considered as they lack a complete sampling date. Genomes were obtained from different locations in Sinaloa: Ahome (26), Culiacán (469), El Fuerte (1), Guasave (16), Los Mochis (119), Mazatlán (414), Navolato 1, and not specified (1,044); 10 samples were taken in 2020, 1,768 in 2021, and 312 in 2022. 719 were obtained from females, 801 from males, and 570 from unknown sex; 2,085 samples were human, and 5 were environmental.

According with GISAID records, predominant SARS-CoV-2 variants in Sinaloa, from February 2021 to May 2022, were alpha (B.1.1.7), gamma (P.1), delta (original lineage: B.1.617.2) and its lineages AY, lambda (C.37), Mu (B.1.621), and omicron (original lineage: B.1.1.529) and its lineages B.1 and B2, and sublineages (Figure 1).

The COVID-19 pandemic in Sinaloa from March 2020 to February 2022 showed four epidemic waves; the first wave

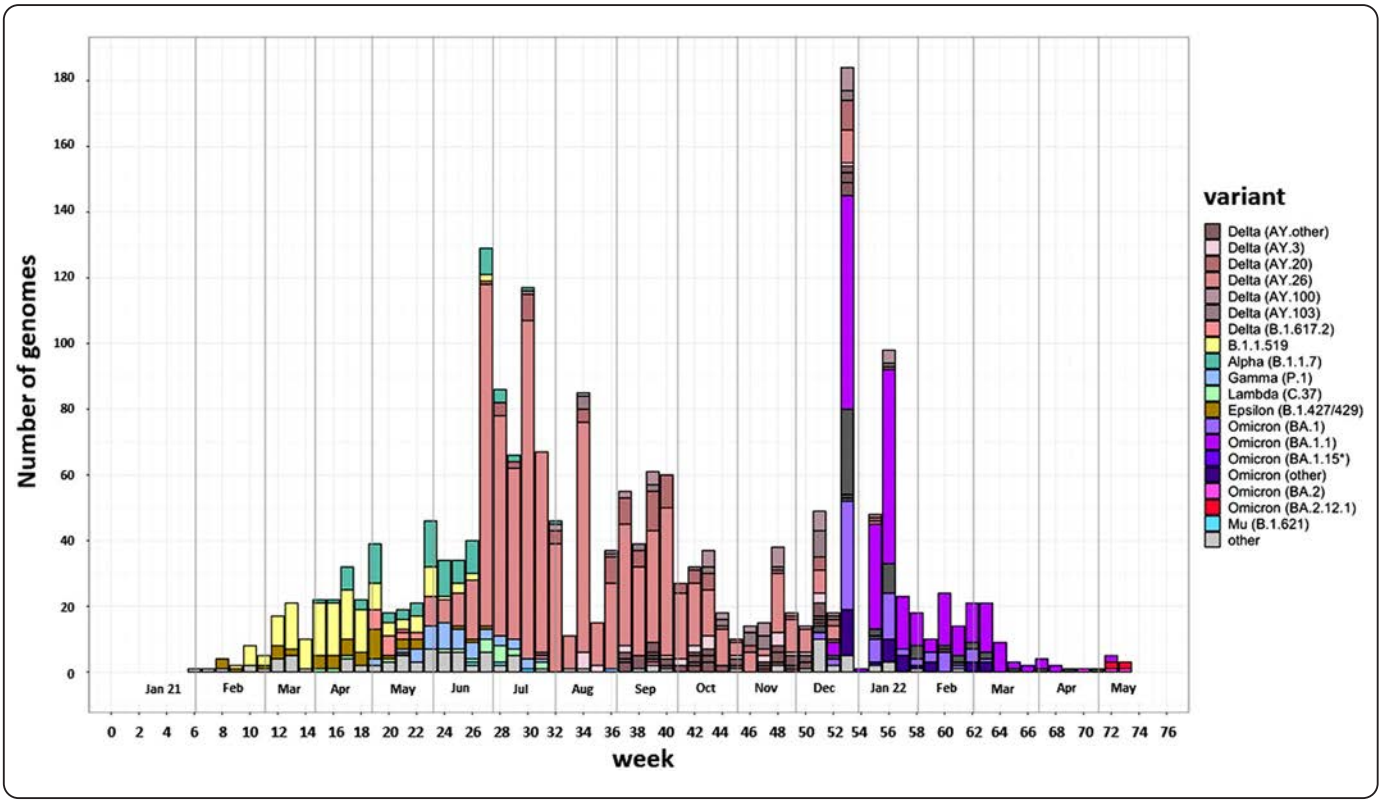


Figure 1. SARS-CoV-2 genomes (2088) sequenced from samples collected in Sinaloa, Mexico, from January 2021 to May 2022. * Lineages and sublineages.

presenting a peak between May and June 2020; the second between February and March 2021; the third between June and August 2021; and the fourth between January and February 2022. The first wave presented a plateau descent of around four months, and the highest numbers of cases per day were recorded during the third and fourth waves. Likewise, the highest numbers of deaths per day were observed during the first and third waves (Figure 2). Epsilon variants (B.1.427 and B.1.429) and the B.1.1.519 lineage dominated the second wave. During the third wave, the delta variant and its AY lineages displaced the previous ones, although alpha and gamma variants were also detected. In the fourth wave, the omicron variant and its lineages (BA.1, BA.1.1) dominated and almost displaced the delta variant. No genomic information was available in the GISAID database for Sinaloa for the first wave.

The median age of positive cases was 44 years old in the first wave, 41 years old in the second wave, 36 years old in the third wave, and 37 years old in the fourth wave (Figure 3A). Significant differences among medians of the "age" factor were also detected between the first and third waves, the second and third waves, and the third and fourth waves (Mood's median test: $p = 0.0000713$, wave1-wave3: $p = 0.01017$, wave2-wave3: $p = 0.00000272$, wave3-wave4: $p = 0.045$). The age distribution of SARS-CoV-2-associated deaths (Figure 3B) was skewed towards older age groups with a median of 67 years old for the first wave, 69 years old for the second wave, 61 years old for the third wave, and 74 years old for the fourth wave. A significant decrease in median age was detected in the third wave with respect to the first, second, and fourth waves, and between the first and second with respect to the fourth wave (Mood's median test: $p = 0.000000158$, wave1-wave3: $p = 0.000807$, wave1-wave4: $p = 0.000445$, wave2-wave3: $p = 0.000164$, wave2-wave4: $p = 0.00679$, wave3-wave4: $p = 0.00000000598$).

More COVID-19 cases were observed in the third and fourth waves compared with the first and second waves, and total mortality was lower in the fourth wave (Figure 4). Few infections among children were confirmed by the adjustment of age demographics of Sinaloa, with an RR below 0.5. The RRs were above 1 in people over 60 years old in the first and second waves; however, during the third and fourth waves the risk decreased for this age group (which was one of the first to be vaccinated). Also, men older than 60 years old showed higher RR than women of the same age group. The RRs were also above 1 in people from 30 to 59 years old mostly during the third and fourth waves, indicating that this age group was exposed during this period, presenting a high probability of infection. Also, the age group of 15-29 in the third wave

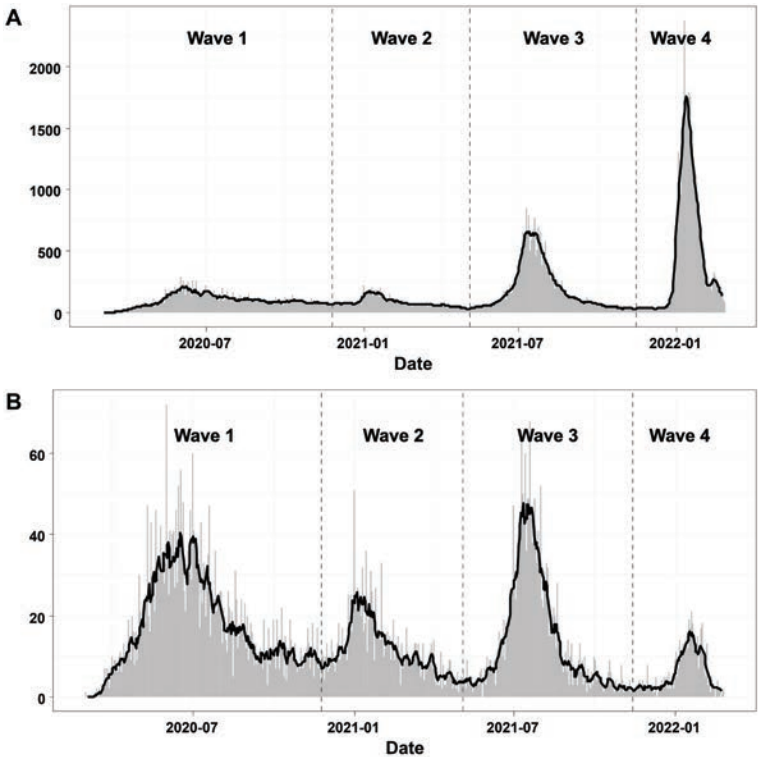


Figure 2. SARS-CoV-2 epidemic waves in Sinaloa, Mexico from March 2020 to February 2022. (A) Cases per day and (B) deaths per day.

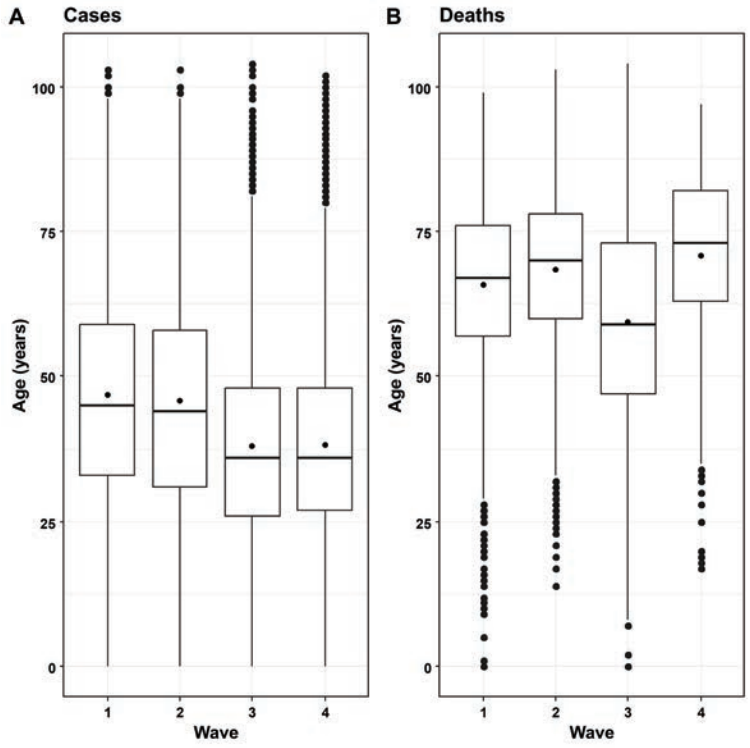


Figure 3. Age distribution of SARS-CoV-2-associated (A) cases, and (B) deaths, according to epidemic waves. Black dots indicate mean values.

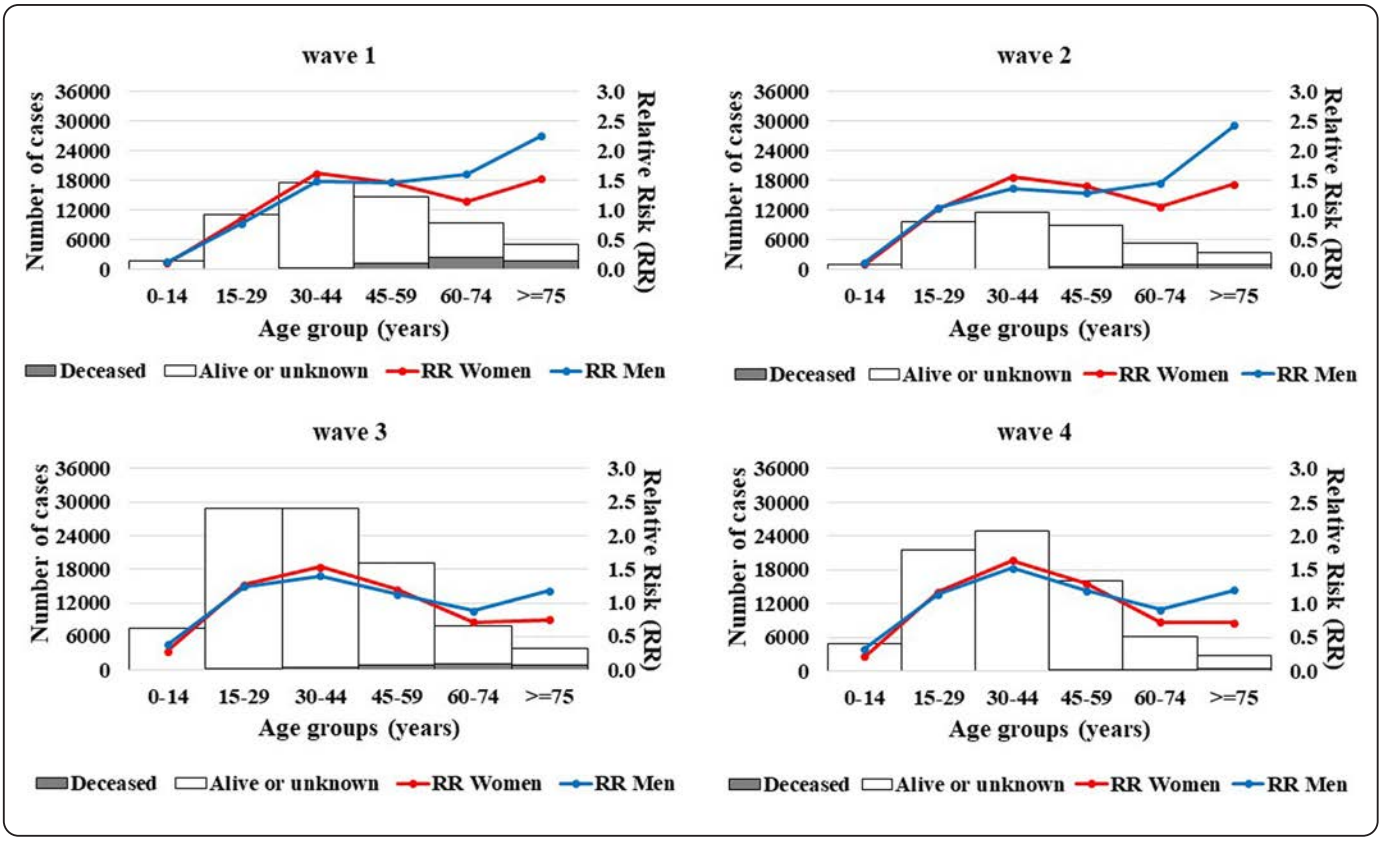


Figure 4. Distribution of SARS-CoV-2-associated cases and deaths, and the Relative Risk (RR) of infection by sex and age groups, according to epidemic waves in Sinaloa, Mexico.

showed an RR above 1, indicating that this age group was also exposed (Figure 4). ANOVA showed that the factor "age", but not the factor "wave" or "sex" influenced the RR significantly ($p = 6.33e\text{-}10$ for age; 0.154 for wave, and 0.137 for sex). In the *post-hoc* analysis, significant differences were detected for $\alpha = 0.05$ between the 0-14 age group and the other age groups ($p < 0.0001$), and for $\alpha = 0.1$ between the 30-44 age group and both 15-19 and 60-74 age groups ($p = 0.061$) (suppl. Figure S3).

Discussion

Viral variants have arisen due to different mutations, with implications for transmissibility since they can modify the affinity of the Spike protein with ACE2 receptors in humans, affecting both viral entry and replication (Zhou & Wang, 2021), plus they may also evade the immune system (García-Beltrán *et al*., 2021). Current vaccines for SARS-CoV-2 have been selected based on their ability to generate neutralizing antibodies (Kyriakidis, López-Cortés, González, Grimaldos & Prado, 2021; Krammer, 2020). Vaccination in Sinaloa started at the beginning of the second wave, on January 12, 2021 for health professionals, and on May 16 for teachers, school workers, and people over 50 years old. During the third wave, a large percent of the adult population had received at least the first dose of the vaccine. From January 13th, 2021 to date, five vaccines have been applied in the population of Sinaloa, under the federal vaccination program: AZD1222, CoronaVac, BNT162b2, Ad5-nCOV, and mRNA-1273 from the companies AstraZeneca, Sinovac, Pfizer-BioNTech, CanSinoBio, and Moderna respectively (https://saludsinaloa.gob.mx/). Vaccines developed by AstraZeneca and CanSinoBio are based on non-replicative viral vectors (Folegatti *et al*., 2020; Wu, 2020) such as simian or human adenovirus, which produce the Spike glycoprotein to improve humoral and cellular responses in mammalian cells. CoronaVac vaccine from Sinovac contains inactivated SARS-CoV-2 (Zhang, Zeng & Pan, 2021). Pfizer-BioNTech and Moderna successfully developed a vaccine consisting of the full-length Spike mRNA (Martínez-Flores *et al*., 2021).

All these vaccines were initially designed to fight the original variant of SARS-CoV-2 (Wuhan strain NC_045512); however, mutation and recombination rates mostly in the receptor-binding domain (RBD) of the Spike protein have posed a challenge for acquired immunity (Duarte *et al.*, 2022). A new generation of vaccines should achieve better recognition of viral variants and boost immunity to cope with subsequent epidemic waves.

New SARS-CoV-2 variants present mutations that allow a more efficient internalization into the host cell and/or immune response evasion (McCallum *et al.*, 2022). For example, N501Y and E484K mutations are present in the RBD of B.1.1.7, B.1.351 and P.1 lineages. N501Y increases the affinity to ACE2, whereas E484K and L452R (found in the RBD of B.1.617 and B.1.427/429 linages) enable the escape from several monoclonal antibodies as well as antibodies in plasma from convalescent patients (Harvey *et al.*, 2021; Iijima *et al.*, 2022); thus, new variants with the proper combination of mutations could potentially generate a new COVID-19 wave.

Delta and omicron variants were more contagious than previous variants (Daria, Asaduzzaman, Shahriar & Islam, 2021), and dominated the third and fourth waves, respectively, in Sinaloa. The median age of the deceased was above 60 years old in all waves, and most of the cases occurred in people between 30 and 45 years old; importantly, this age group makes up a significant portion of the labor force in the state. A previous study showed that susceptibility to SARS-CoV-2 infection in individuals under 20 years old is approximately half of adults aged over 20 years old (Davies *et al*., 2020). Older age is an especially strong and independent risk factor for hospitalization, mechanical ventilation, and death (Clarfield & Dwolatzky, 2021). Younger people are more likely to have stronger immune systems compared to older people (Turke, 2020). In addition, older adults have more incidences of pre-existing chronic diseases affecting the immune system and therefore the response against the virus (Balboa-Castillo *et al*., 2021).

As mentioned before, there were more SARS-CoV-2-associated cases in the third and fourth waves compared with the first and second waves; however, the number of deaths per day was higher in the first and third waves. In addition, total mortality was higher in the first, second, and third waves, decreasing in the fourth wave. This behavior could be due to the combination of several factors; the presence of SARS-CoV-2 variants, with high prevalence of the contagious delta and omicron lineages during the third and fourth waves; the lack of vaccines and treatments, as well as insufficient medical facilities for patient care and hospitalization mostly in the first wave; the severity of delta linages during the third wave; the vaccination program starting in January 2021 (at the beginning of the second wave) immunizing the most exposed or vulnerable population first, achieving complete vaccination schemes (including boosting doses) during the fourth wave; and a better understanding of SARS-CoV-2 pathology as the pandemic evolved.

Recently, Torres-Ibarra *et al*. (2022) estimated infection fatality rates (IFRs) after the first epidemic wave in Mexico and found that IFRs were higher for men than for women and increased with age. They also observed that urban and metropolitan areas experienced higher IFRs than rural areas, and suggested that the large heterogeneity of IFRs across regions could be due to structural factors, such as population density, hospital saturation, or quality of care. In addition, they explained some limitations of the estimation of IFRs such as the misclassification due to lack of testing at the beginning of the pandemic, the variability in IFRs that can be introduced depending on selected dates, and the underestimation of seroprevalence because some subgroups at high risk of SARS-CoV-2 infection were not considered in ENSANUT 2020 Covid-19 database. Here, we did not estimate the IFRs for Sinaloa, but we calculated the RRs in the four epidemic waves, which considered the positive cases over the total population. We found that a higher relative risk was detected in men than in women older than 60 years old in the first and second waves, which agrees with previous reports suggesting differences in interferon responses between both sexes (Ciarambino, Para & Giordano, 2021).

This study has some limitations that should be considered because DGE bases are biased due to underreporting, and sampling of isolates for genomic sequencing may also be biased because successful sequencing depends on relatively high viral loads, and may not necessarily represent all circulating variants in Sinaloa.

Conclusions

The COVID-19 pandemic in the state of Sinaloa showed four epidemiological waves in the period from January 2020 to February 2022. Different SARS-CoV-2 variants drove each wave. The decrease in the number of deaths during the fourth wave could be related to the vaccination program, more efficient and affordable testing alternatives, and the use of preventive measures (such as masks and virtual work) during the pandemic. COVID-19 waves in Sinaloa seem to occur during summer and winter, not necessarily coinciding with massive events, and precise triggering factors are still not clear. Preventive measures might be partially relaxed only during "interwave" periods, but reinforced as the wave arrives. It is important for the population to understand the behavior of the COVID-19 pandemic, and, continue with preventive and containment measures.

Acknowledgements

The authors would like to thank the Mexican Consortium of Genomic Surveillance, Carlos F. Arias and Blanca Taboada from the CoViGen project, Julissa Enciso-Ibarra for SARS-CoV-2 sequencing, and Daniel Fregoso-Rueda for logistic and administrative support. We are grateful to the authors and laboratories responsible for obtaining the specimens, and the laboratories where genetic sequencing data were generated and shared via the GISAID initiative, on which this research is based (suppl. file S2). We are also thankful to the National Council for Science and Technology (CONACYT, Mexico) for scholarships granted to Jorge Luis Batista-Roche and Marian Mirabent-Casals for doctoral studies.

Authors' contributions

Conceptualization, Jorge Luis Batista-Roche, Marian Mirabent-Casals; methodology, Jorge Luis Batista-Roche, Marian Mirabent-Casals, César Berlanga-Robles; validation, César Berlanga-Robles, Bruno Gómez-Gil, Alejandra García-Gasca; formal analysis, Luis Batista-Roche, Marian Mirabent-Casals, César Berlanga-Robles; writing—original draft preparation, Jorge Luis Batista-Roche, Marian Mirabent-Casals, Alejandra García-Gasca; writing—review and editing, Jorge Luis Batista-Roche, Marian Mirabent-Casals, Alejandra García-Gasca, César Berlanga-Robles, Bruno Gómez-Gil; supervision, Alejandra García-Gasca. All authors read and approved the manuscript.

Availability of data and material

The authors confirm that the data supporting the findings of this study are available within the article (public databases).

Declaration of Competing Interest

All authors declare no conflict of interest.

Funding

No funding was received to assist with the preparation of this manuscript.

References

Balboa-Castillo, T., Andrade-Mayorga, O., Marzuca-Nassr, G. N., Morales Illanes, G., Ortiz, M., Schiferlli, I., Aguilar-Farías, N., Soto, Á. & Sapunar, J. (2021). Pre-existing conditions in Latin America and factors associated with adverse outcomes of COVID-19: A review. Condiciones pre-existentes en Latino América y factores asociados con resultados adversos en COVID-19: Una revisión. *Medwave*, **21(4)**, e8181. https://doi.org/10.5867/medwave.2021.04.8180

Becerra-Flores, M. & Cardozo, T. (2020). SARS-CoV-2 viral spike G614 mutation exhibits higher case fatality rate. *International Journal of Clinical Practice*, **74(8)**, e13525. https://doi.org/10.1111/ijcp.13525

Ciarambino, T., Para, O. & Giordano, M. (2021). Immune system and COVID-19 by sex differences and age. *Women's Health*, **17**, 1-6. https://doi.org/10.1177/17455065211022262

Clarfield, A. M. & Dwolatzky, T. (2021). Age and ageing during the COVID-19 pandemic; challenges to Public health and to the health of the public. *Frontiers in Public Health*, **9**, 655831. https://doi.org/10.3389/fpubh.2021.655831

Daria, S., Asaduzzaman, M., Shahriar, M. & Islam, M. R. (2021). The massive attack of COVID-19 in India is a big concern for Bangladesh: The key focus should be given on the interconnection between the countries. *The International Journal of Health Planning Management*, **36(5)**, 1947–1949. https://doi.org/10.1002/hpm.3245

Davies, N. G., Abbott, S., Barnard, R. C., Jarvis, C. I., Kucharski, A. J., Munday, J. D., Pearson, C., Russell, T. W., Tully, D. C., Washburne, A. D., Wenseleers, T., Gimma, A., Waites, W., Wong, K., van Zandvoort K. & Silverman, J. D., CMMID COVID-19 Working Group, COVID-19 Genomics UK (COG-UK) Consortium, Diaz-Ordaz, K., Keogh, R., Eggo, R. M., Funk, S., Jit, M., Atkins, K. E. & Edmunds, W. J. (2021). Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science*, **372(6538)**, eabg3055. https://doi.org/10.1126/science.abg3055

Davies, N. G., Klepac, P., Liu, Y., Prem, K. & Jit, M. (2020). Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nature Medicine*, **26(8)**, 1205-1211. https://doi.org/10.1038/s41591-020-0962-9

Duarte, C. M., Ketcheson, D. I., Eguíluz, V. M., Agustí, S., Fernández-Gracia, J., Jamil, T., Laiolo, E., Gojobori, T. & Alam, I. (2022). Rapid evolution of SARS-CoV-2 challenges human defenses. *Scientific Reports*, **12**, 6457. https://doi.org/10.1038/s41598-022-10097-z

Folegatti, P. M., Ewer, K. J., Aley, P. K., Angus, B., Becker, S., Belij-Rammerstorfer, S., Bellamy, D., Bibi, S., Bittaye, M., Clutterbuck, E. A., Dold, C., Faust, S. N., Finn, A., Flaxman, A. L., Hallis, B., Heath, P., Jenkin, D., Lazarus, R., Makinson, R., Minassian, A. M., Green, C., Douglas, A. D., Hill, A. V. S., Lambe, T., Gilbert, S. C., Pollard, A. J. & Oxford COVID Vaccine Trial Group. (2020). Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *The Lancet*, **396(10249)**, 467–478. https://doi.org/10.1016/S0140-6736(20)31604-4

Gadanec, L. K., McSweeney, K. R., Qaradakhi, T., Ali, B., Zulli, A. & Apostolopoulos, V. (2021). Can SARS-CoV-2 Virus Use Multiple Receptors to Enter Host Cells? *International Journal of Molecular Science*, **22**, 992. https://doi.org/10.3390/ijms22030992

García-Beltrán, W. F., Lam, E.C., St Denis, K., Nitido, A. D., Garcia, Z. H., Hauser, B. M., Feldman, J., Pavlovic, M. N., Gregory, D. J., Poznansky, M. C., Sigal, A., Schmidt, A. G., Iafrate, A. J., Naranbhai, V. & Balazs, A. B. (2021). Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. *Cell*, **184(9)**, 2372–2383.e9. https://doi.org/10.1016/j.cell.2021.03.013

Harvey, W. T., Carabelli, A. M., Jackson, B. Gupta, R. K., Thomson, E. C., Harrison, E. M., Ludden, C., Reeve, R., Rambaut, A., COVID-19 Genomics UK (COG-UK) Consortium, Peacock, S. J. & Robertson, D. L. (2021). SARS-CoV-2 variants, spike mutations and immune escape. *National Reviews. Microbiology*, **19(7)**, 409–424. https://doi.org/10.1038/s41579-021-00573-0

Iijima, T., Ando, S., Kanamori, D., Kuroda, K., Nomura, T., Tisi, L., Kilgore, P. E., Percy, N., Kohase, H., Hayakawa, S., Seki, M. & Hoshino, T. (2022). Detection of SARSCoV-2 and the L452R spike mutation using reverse transcription loop-mediated isothermal amplification plus bioluminescent assay in realtime (RT-LAMP-BART). *PLoS ONE*, **17(3)**, e0265748. https://doi.org/10.1371/journal.

Krammer, F. (2020). SARS-CoV-2 vaccines in development. *Nature*, **586**, 516–527. https://doi.org/10.1038/s41586-020-2798-3

Kyriakidis, N. C., López-Cortés, A., González, E. V., Grimaldos, A. B. & Prado, E. O. (2021). SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. *NPJ Vaccines*, **6(1)**, 28. https://doi.org/10.1038/s41541-021-00292-w

Martínez-Flores, D., Zepeda-Cervantes, J., Cruz-Reséndiz, A., Aguirre-Sampieri, S., Sampieri, A. & Vaca, L. (2021). SARS-CoV-2 Vaccines Based on the Spike Glycoprotein and Implications of New Viral Variants. *Frontiers in Immunology*, **12**, 701501. https://doi.org/10.3389/fimmu.2021.701501

McCallum, M., Czudnochowski, N., Rosen, L. E., Zepeda, S. K., Bowen, J. E., Walls, A. C., Hauser, K., Joshi, A., Stewart, C., Dillen, J. R, Powell, A. E., Croll, T. I., Nix, J., Virgin, H. W., Corti, D., Snell, G. &Veesler, D. (2022). Structural basis of SARS-CoV-2 Omicron immune evasion and receptor engagement. *Science*, **375(6583)**, 864–868. https://doi.org/10.1126/science.abn8652

Sun, K., Chen, J. & Viboud, C. (2020). Early epidemiological analysis of the coronavirus disease 2019 outbreak based on crowdsourced data: a population-level observational study. *The Lancet Digital Health*, **2(4)**, e201–e208. https://doi.org/10.1016/S2589-7500(20)30026-1

Torres-Ibarra, L., Abreu, A. B., Carnalla, M., Torres-Álvarez, R., Sánchez, F. R., Hernández-Ávila, J. E., Palacio-Mejía, L. S., Alpuche-Aranda, C., Shamah-Levy, T., Rivera, J. A. & Barrientos-Gutiérrez, T. (2022). SARS-CoV-2 infection fatality rate after the first epidemic wave in Mexico. *International Journal of* Epidemiol*ogy*, **51(2)**, 429–439. https://doi.org/10.1093/ije/dyac015

Turke, P. W. (2020). Five reasons COVID-19 is less severe in younger age groups. *Evolucion, Medicine & Public Health*, **9(1)**, 113-117. https://doi.org/10.1093/emph/eoaa050

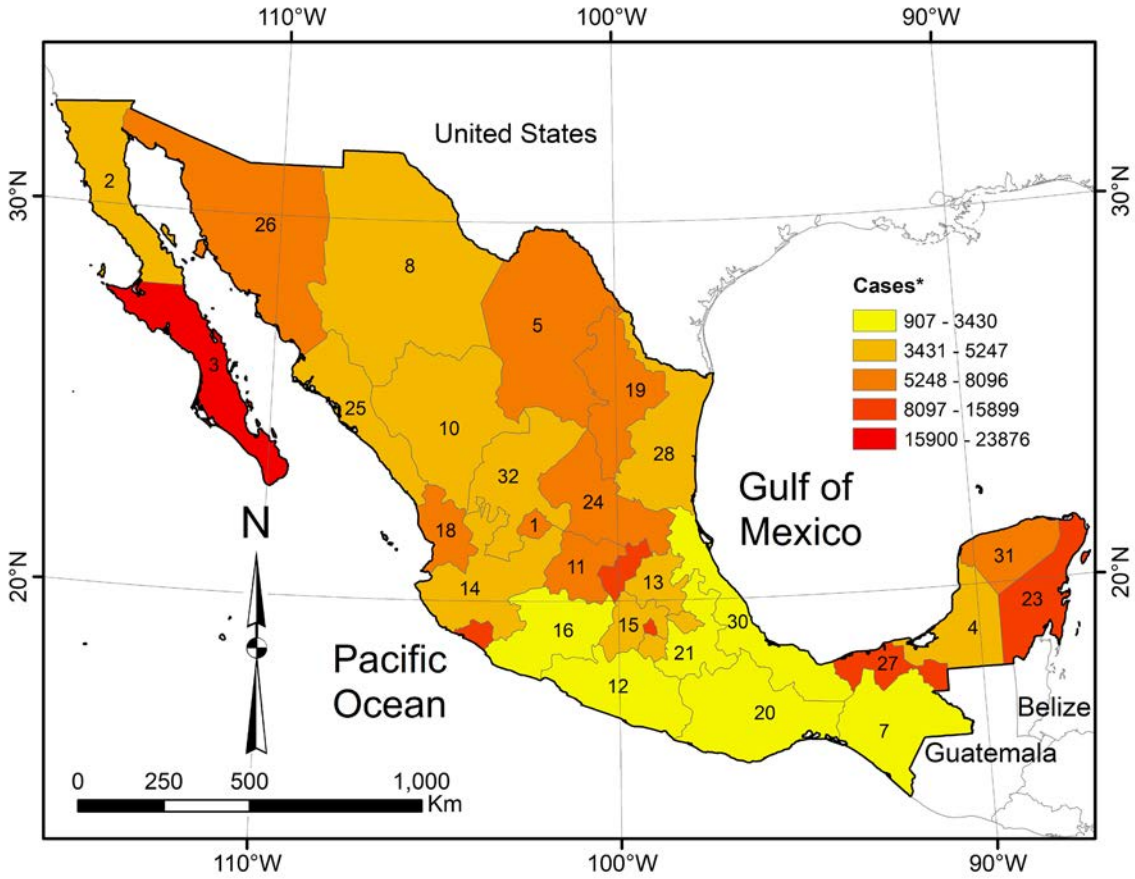
Wu, S., Zhong, G., Zhang, J., Shuai, L., Zhang, Z., Wen, Z., Wang, B., Zhao, Z., Song, X., Chen, Y., Liu, R., Fu, L., Zhang, J., Guo, Q., Wang, C., Yang, Y., Fang, T., Lv, P., Wang, J., Xu, J., Li, J., Yu, C., Hou, L., Bu, Z. & Chen, W. (2020). A single dose of an adenovirus-vectored vaccine provides protection against SARS-CoV-2 challenge. *Nature Communications*, **11(4081)**, 1-7. https://doi.org/10.1038/s41467-020-17972-1

Zhang, Y., Zeng, G. & Pan, H. (2021). Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. The *Lancet Infectious Diseases*, **21**, 181–192. https://doi.org/10.1016/S1473-3099(20)30843-4

Zhou, W. & Wang, W. (2021). Fast-spreading SARS-CoV-2 variants: challenges to and new design strategies of COVID-19 vaccines. *Signal Transduction and Targeted Therapy*, **6(1)**, 226. https://doi.org/10.1038/s41392-021-00644-x

https://doi.org/10.22201/fesz.23958723e.2022.474

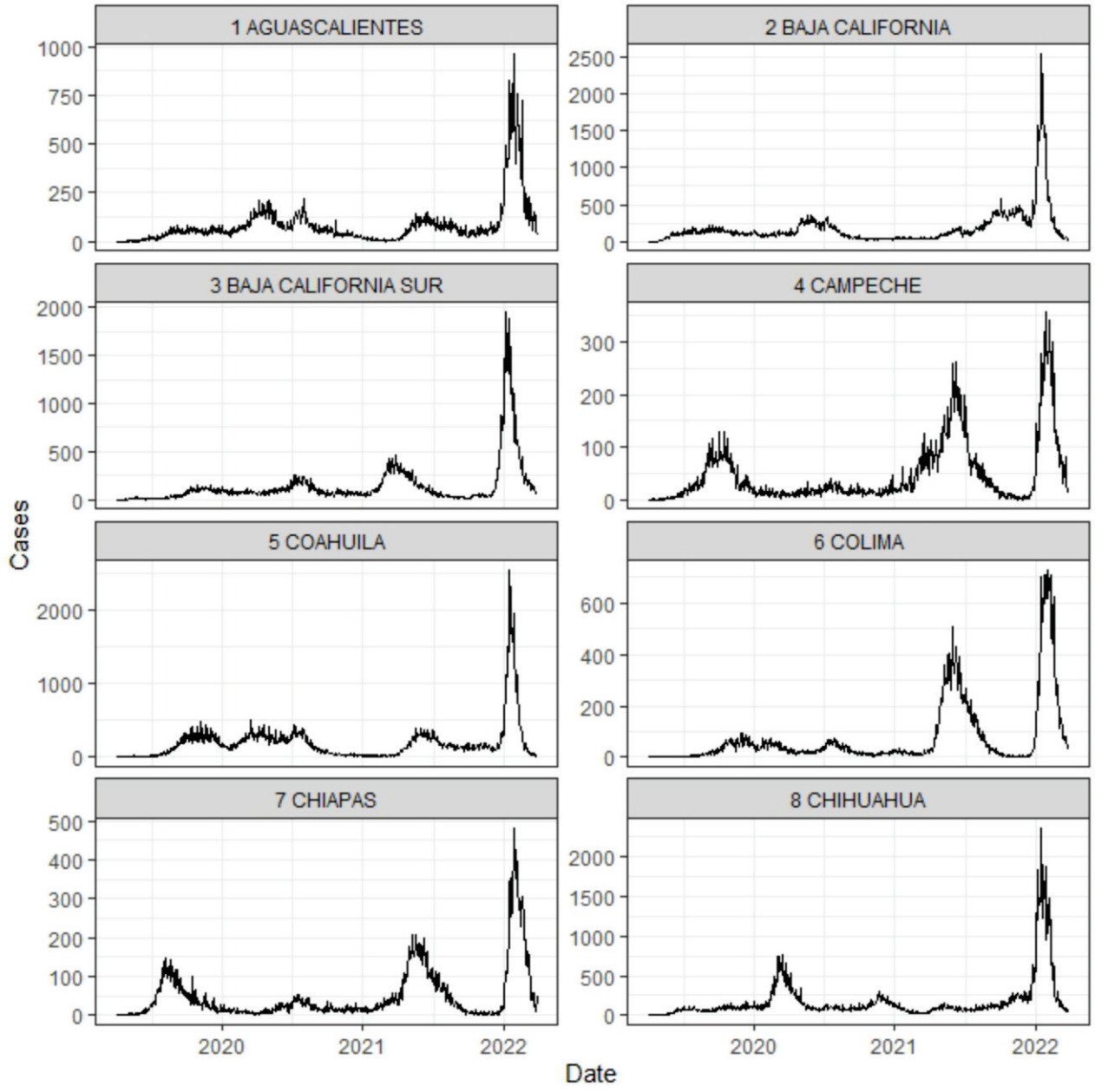
Supplementary Figure S1
COVID-19 pandemic dynamics in Mexico
(Cases by symptom onset by Federal entity)



Federal entity of Mexico. Cases*: accumulated cases from 2020-03-01 to 2022-02-26 per 100,000 people. Sources: Geostatistical Framework, June 20161; Admin or Countries 4.72. General Directorate of Epidemiology database.

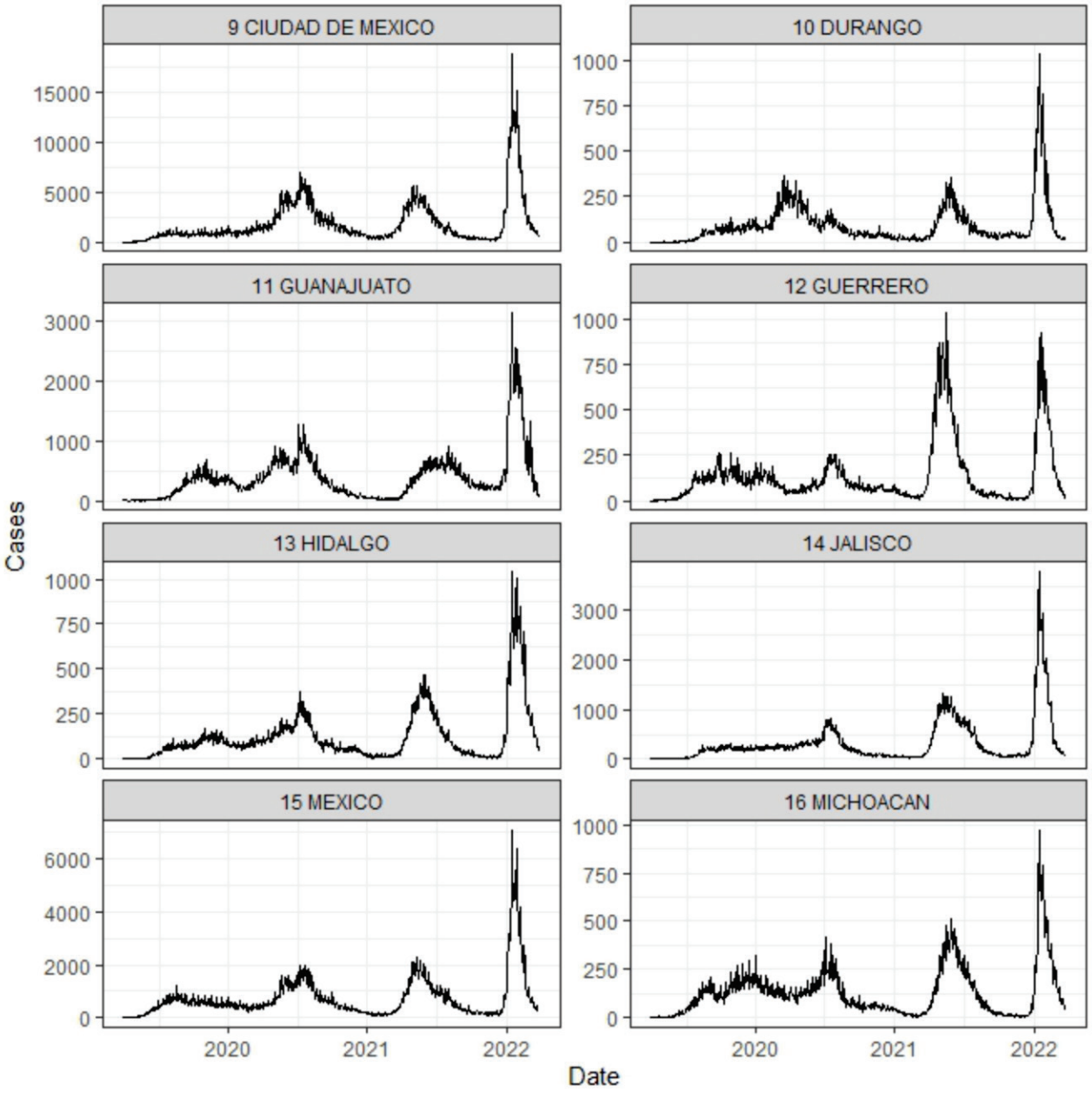
[1]INEGI, https://www.inegi.org.mx/app/biblioteca/ficha.html?upc=702825217341

[2]Natural Earth, http://www.naturalearthdata.com/downloads/10m-culturalvectors/



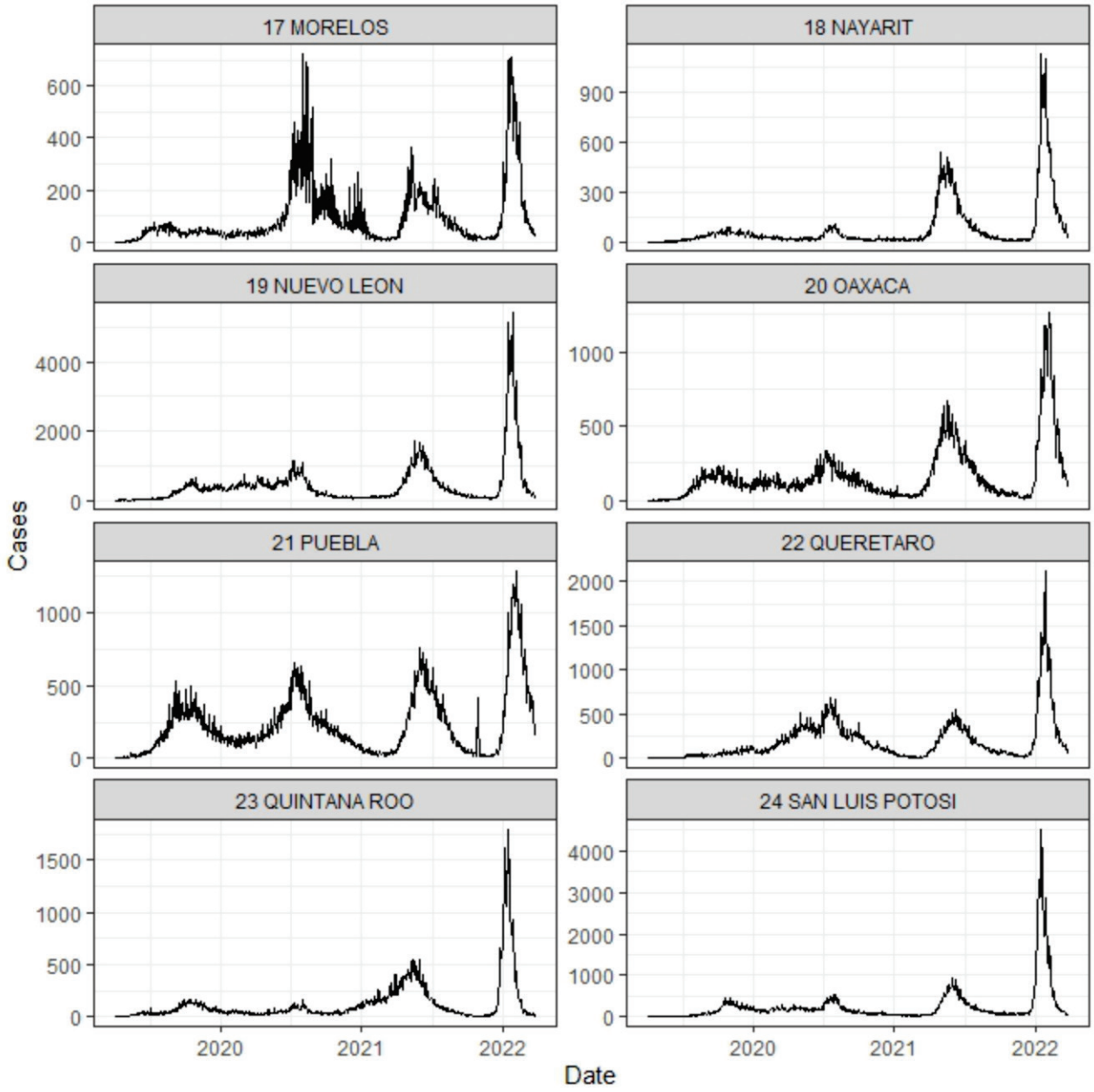
Source: General Direction of Epidemiology database:

https://www.gob.mx/salud/documentos/datos-abiertos-bases-historicasdireccion-general-de-epidemiologia?idiom=es



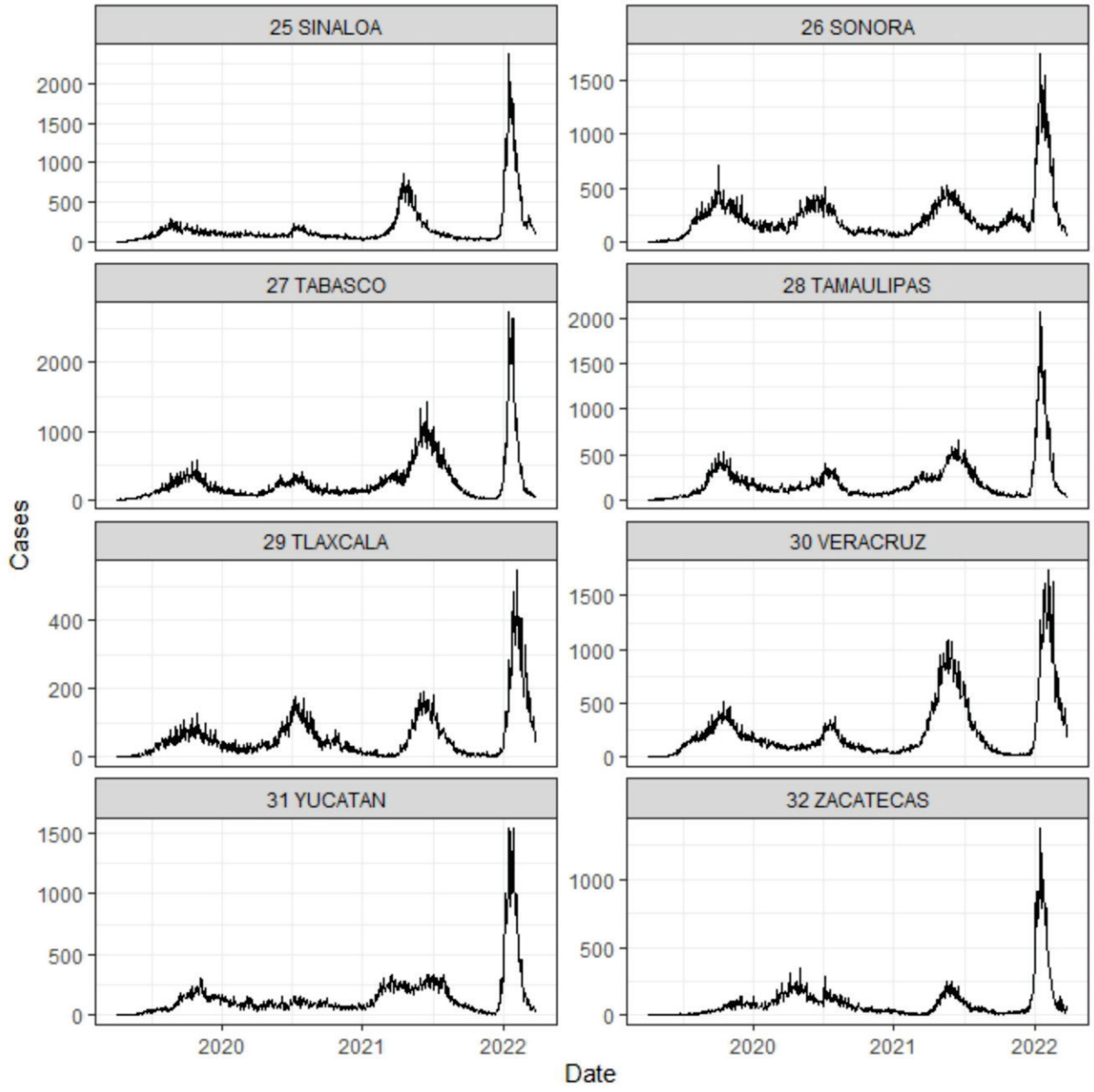
Source: General Direction of Epidemiology database:

https://www.gob.mx/salud/documentos/datos-abiertos-bases-historicasdireccion-general-de-epidemiologia?idiom=es



Source: General Direction of Epidemiology database:

https://www.gob.mx/salud/documentos/datos-abiertos-bases-historicasdireccion-general-de-epidemiologia?idiom=es



Source: General Direction of Epidemiology database:

https://www.gob.mx/salud/documentos/datos-abiertos-bases-historicasdireccion-general-de-epidemiologia?idiom=es

Supplemental table

Data Availability
GISAID Identifier: EPI_SET_20220614xp
DOI: https://doi.org/10.55876/gis8.220614xp
All genome sequences and associated metadata in this dataset are published in GISAID's EpiCoV database. To view the contributors of each individual sequence with details such as accession number, Virus name, Collection date, Originating Lab and Submitting Lab and the list of Authors, visit https://doi.org/10.55876/gis8.220614xp
Data Snapshot
• EPI_SET_20220614xp is composed of 2,090 individual genome sequences. • The collection dates range from 2020-04-02 to 2022-05-23; • Data were collected in 1 countries and territories; • All sequences in this dataset are compared relative to hCoV-19/Wuhan/WIV04/2019 (WIV04), the official reference sequence employed by GISAID (EPI_ISL_402124). Learn more at https://gisaid.org/WIV04.

Supplementary Figure S2
ANOVA for the relative risk (RR) of infection with SARS-CoV-2 for sex, age, and wave factors, in COVID-19 patients in Sinaloa, Mexico.

ANOVA table for the model RR = sex + age + wave.

Source	Sum Sq	Df	F value	p
sex	0.2022	1	2.3083	0.137
age	9.0572	5	20.6803	6.327e-10
wave	0.4869	3	1.8531	0.154
Residuals	3.3285	38		

Post-hoc comparison with Sidak method for the estimated marginal means (Least-square means) of the RR response to the age factor.

contrast	estimate	SE	df	t.ratio	p.value
0-14 - 15-19	-0.8605	0.1480	38	-5.8147	0.000015
0-14 - 30-44	-1.3115	0.1480	38	-8.8629	0.000000
0-14 - 45-59	-1.0993	0.1480	38	-7.4289	0.000000
0-14 - 60-74	-0.8558	0.1480	38	-5.7833	0.000017
0-14 - >=75	-1.2314	0.1480	38	-8.3215	0.000000
15-19 - 30-44	-0.4511	0.1480	38	-3.0481	0.060852
15-19 - 45-59	-0.2389	0.1480	38	-1.6142	0.839359
15-19 - 60-74	0.0047	0.1480	38	0.0314	1.000000
15-19 - >=75	-0.3710	0.1480	38	-2.5068	0.221815
30-44 - 45-59	0.2122	0.1480	38	1.4340	0.926535
30-44 - 60-74	0.4557	0.1480	38	3.0796	0.056082
30-44 - >=75	0.0801	0.1480	38	0.5414	0.999999
45-59 - 60-74	0.2435	0.1480	38	1.6456	0.820215
45-59 - >=75	-0.1321	0.1480	38	-0.8926	0.999187
60-74 - >=75	-0.3756	0.1480	38	-2.5382	0.207243

Results are averaged over the levels of: sex, wave. P value adjustment: Sidak method for 15 tests.

Confident interval at 95% (α = 0.05) and 99% (α = 0.1) levels for estimated marginal means (Least-square means) of the RR response to the age factor.

				α = 0.05			α = 0.1		
age	mean	SE	df	lower.CL	upper.CL	group	lower.CL	upper.CL	group
0-14	0.208	0.105	38	-0.082	0.498	a	-0.052	0.468	a
60-74	1.064	0.105	38	0.774	1.354	b	0.804	1.324	b
15-19	1.069	0.105	38	0.778	1.359	b	0.808	1.329	b
45-59	1.307	0.105	38	1.017	1.598	b	1.047	1.568	bc
>=75	1.439	0.105	38	1.149	1.730	b	1.179	1.700	bc
30-44	1.52	0.105	38	1.229	1.810	b	1.259	1.780	c

Results are averaged over the levels of: sex, wave. Confidence level used: 0.95 and 0.9. Conf-level adjustment: Sidak method for 6 estimates. P value adjustment: Sidak method for 15 tests significance level used: alpha = 0.05 and 0.01.

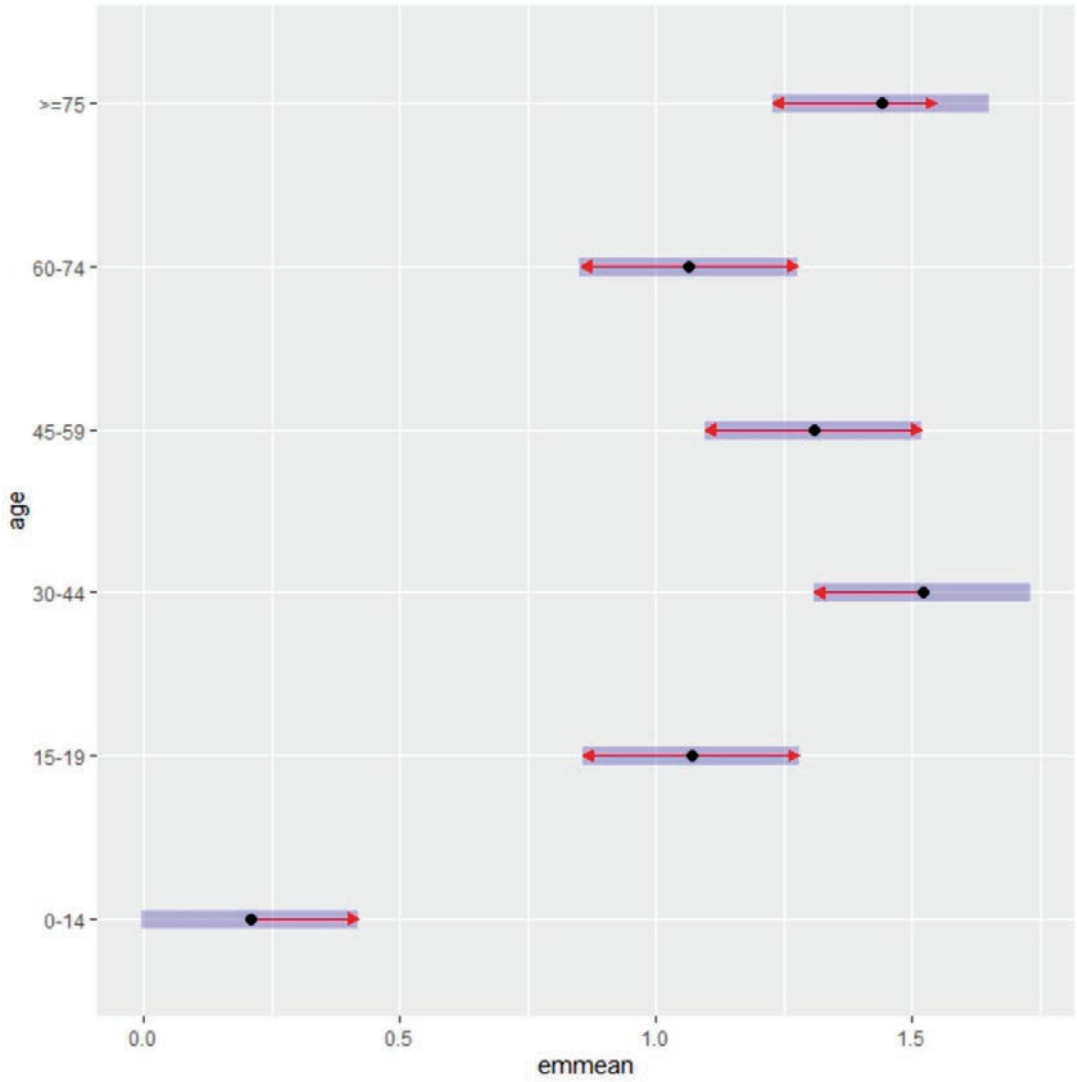


Figure S2. Estimated marginal means (Least-square means) of the RR response to the age factor in COVID-19 patients in Sinaloa, Mexico. The purple stripes indicate the 95% confidence interval, and the red arrows the contrast between age groups for alpha = 0.05.