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COVID-19

SARS-CoV-2 infection fatality rate after the first epidemic wave in Mexico

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Abstract

Background: Estimates of SARS-CoV-2 infection fatality rates (IFRs) in developing countries remain poorly characterized. Mexico has one of the highest reported COVID-19 case-fatality rates worldwide, although available estimates do not consider serologic assessment of prior exposure nor all SARS-CoV-2-related deaths. We aimed to estimate sex- and age-specific IFRs for SARS-CoV-2 in Mexico.

Methods: The total number of people in Mexico with evidence of prior SARS-CoV-2 infection was derived from National Survey of Health and Nutrition-COVID-19 (ENSANUT 2020 Covid-19)—a nationally representative serosurvey conducted from August to November 2020. COVID-19 mortality data matched to ENSANUT's dates were retrieved from the death-certificate registry, which captures the majority of COVID-19 deaths in Mexico, and from the national surveillance system, which covers the subset of COVID-19 deaths that were identified by the health system and were confirmed through a positive polymerase chain reaction test. We analysed differences in IFRs by urbanization and region.

Results: The national SARS-CoV-2 IFR was 0.47% (95% CI 0.44, 0.50) using death certificates and 0.30% (95% CI 0.28, 0.33) using surveillance-based deaths. The IFR increased with age, being close to zero at age $<$30 years, but increasing to 1% at ages 50–59 years in men and 60–69 years in women, and being the highest at $\geq$80 years for men (5.88%) and women (6.23%). Across Mexico's nine regions, Mexico City (0.99%) had the highest and the Peninsula (0.26%) the lowest certificate-based IFRs. Metropolitan areas had higher certificate-based IFR (0.63%) than rural areas (0.17%).

Conclusion: After the first wave of the COVID-19 pandemic, the overall IFR in Mexico was comparable with those of European countries. The IFR in Mexico increased with age and was higher in men than in women. The variations in IFRs across regions and places of residence within the country suggest that structural factors related to population characteristics, pandemic containment and healthcare capabilities could have influenced lethality at the local level.

Key words: SARS-CoV-2, COVID-19, fatality, infection fatality rate, pandemic, seroepidemiologic study, Mexico

Key Messages

- The COVID-19 case-fatality rate was estimated at 9.1% early in Mexico's epidemic. This estimate was based on sentinel surveillance data and largely limited to symptomatic COVID-19 cases that were tested, thus biasing the fatality estimate upwards.
- During the study period, 145 975 people died because of COVID-19 according to death certificates; of those, 94 217 were registered in the surveillance system, which covers cases that were captured by the health system and had a positive polymerase chain reaction test.
- The infection fatality rate in Mexico was 0.47% using certificate-based deaths up to November 2020 and 0.30% using surveillance-based deaths, comparable to infection fatality rates (IFRs) observed in other countries.
- Within the country, we observed large heterogeneity of IFRs, being as high as 0.99% in Mexico City or as low as 0.26% in the Peninsula.
- The heterogeneity of infection fatality rates across regions and places of residence within the country suggests that SARS-CoV-2 lethality could have been influenced by structural factors, such as population density, hospital saturation or quality of care.

Introduction

Throughout the pandemic, the estimation of deaths attributable to SARS-CoV-2 infection has remained controversial. Studies that analysed lethality during the first pandemic wave (up to August 2020) reported a case-fatality rate (CFR) ranging from 2% to 3% across different countries.[1,2] These estimates were under-ascertained both in the numerator (due to delays or failures in the registry of deaths) and in the denominator, which only considered cases of COVID-19 as registered by surveillance systems. Problems with the denominator were evidenced as soon as seroprevalence estimates became available.[3,4] These estimates evidenced the large differences between CFRs and infection fatality rates (IFRs), driven by asymptomatic cases and the intensity of testing, that lead to case underreporting.

In March 2021, Mexico ranked second in COVID-19 CFR in the world, with 9.1 deaths per 100 COVID-19 cases, compared to 2.2% worldwide.[5] However, this reported CFR overestimates the IFR because Mexico has one of the lowest testing rates globally, undercounting the number of cases exposed to SARS-CoV-2. The surveillance system in Mexico tests 100% of severe cases and a varying proportion of cases with mild to moderate symptoms, with no coverage of asymptomatic cases or cases that did not seek or receive medical attention. The surveillance system also underestimates COVID-19 deaths, as it covers only 62% of deaths as registered in death certificates[6]; however, considering that the extent of undercounting of cases (denominator) is greater compared with the undercounting of deaths (numerator), the CFR overestimates the IFR.

In this study, we aimed to estimate sex- and age-specific IFR for SARS-CoV-2 in Mexico. Based on serologic data from the 2020 National Survey of Health and Nutrition-COVID-19 (ENSANUT 2020 Covid-19), we estimated the cumulative number of people who were exposed to the SARS-CoV-2 virus in Mexico and who survived, being surveyed in the ENSANUT data collection period (August to

November 2020). Then, we used two sources of data to incorporate all COVID-19 deaths accumulated up to one month after the mid-point of ENSANUT's data collection by region: (i) the number of COVID-19 deaths as reported by the national surveillance system, and (ii) COVID-19 deaths as captured by death certificates in the Epidemiological and Statistical Death Registry. Finally, we analysed the IFR by urbanization level and region of the country.

Methods

SARS-CoV-2 cases in Mexico

To estimate the total number of people infected with SARS-CoV-2 in Mexico between the onset of the pandemic and late 2020, we obtained seroprevalence data from ENSANUT 2020 Covid-19—a survey that is representative at the national and regional levels (nine regions), and is also representative for both urban and rural areas.[7,8] Briefly, fieldwork teams visited households and randomly selected one person from each of six potential age groups (1–4, 5–9, 10–19, 20–34, 35–49 and ≥50 years) to provide a blood sample. A total of 9640 serum samples (51% participation rate) for SARS-CoV-2 antibody determination were obtained between August and November 2020 (Supplementary Table S1, available as Supplementary data at *IJE* online, presents all regions surveyed and collection dates). The ENSANUT 2020 Covid-19 survey did not include virologic testing for prevalent SARS-CoV-2 infection.

Seroprevalence (N-protein) was corrected by an internal validation study, which established that Roche's Elecsys assay had a 92.02% sensitivity (95% CI 88.57, 94.5) and a 99.52% specificity (95% CI 97.35, 99.92).[8] Estimates of seroprevalence were calculated using sampling weights, whereas the absolute number of people with evidence of recent or prior infection was estimated by multiplying the age- and sex-specific adjusted seroprevalence by the total size of the corresponding population group, according to the 2020 census.[9] The same procedure was used to calculate the number of seropositive people by region and urbanization strata.

Considering the challenges to generalizability conferred by the 51% participation rate, in a previous study, we conducted a sensitivity analysis of the magnitude of possible selection bias in ENSANUT 2020 Covid-19.[8] After adjustment, the national seroprevalence changed from 24.9% (95% CI 22.2, 26.7) to 23.8% (95% CI 21.3, 25.4). More information on this adjustment can be found elsewhere.[8] Because the 95% CIs overlapped,[8] we used the original estimate in this paper, without adjusting.

COVID-19 deaths

We used two overlapping sources of information for COVID-19 deaths: deaths registered by death certificates, which cover most COVID-19 deaths in Mexico; and deaths captured by the surveillance system, which includes the subset of COVID-19 deaths that were captured by the health system and had a positive reverse transcription polymerase chain reaction (RT-PCR) test.

Deaths in the surveillance system

The Surveillance System for Viral Respiratory Disease (SISVER, by its acronym in Spanish) is the national epidemiological surveillance system for monitoring viral respiratory infections, including SARS-CoV-2, and it is managed by the Mexican Ministry of Health. It includes individuals who sought medical attention and were tested for SARS-CoV-2 in the public sector. SISVER captures 100% of hospitalized patients, but a varying proportion of outpatients (minimum 10%), depending on the resources of each monitoring healthcare facility. We included all deaths confirmed by a RT- PCR test. We used a dataset updated on 6 January 2021, to account for delays in reporting.

Deaths reported by death certificates

We used the Epidemiological and Statistical Deaths Registry (SEED, by its acronym in Spanish) for the year 2020, updated on 22 February 2021, as issued by the General Direction for Health Information of the Health Ministry. SEED is an information subsystem based on death certificates that contains information of all certified deaths by cause, place of residence, date and other sociodemographic characteristics. We selected all death records with a basic cause of death coded as U07.1 (COVID-19, virus identified) or U07.2 (COVID-19, virus not identified: clinically epidemiologically diagnosed COVID-19, probable and suspected COVID-19), according to the 10th revision of the International Classification of Disease, updated in 2020.[10] COVID-19 deaths reported by death certificates are a subset of all-cause excess mortality which includes COVID and non-COVID related deaths. Until February 2021, COVID-19-specific mortality, as reported by death certificates, represented 70% of all excess deaths in Mexico.[6] By law, every death in Mexico needs to be certified before burial or cremation[11], thus, >90% of deaths are certified.[12]

Estimation of IFRs

We estimated IFRs by dividing the number of surveillance or death-certificate COVID-19 deaths by the estimated total number of seropositive people in Mexico during the

same time period. To match survey dates by region, we used the cumulative number of deaths that were reported 1 month after the midpoint date of the survey period at each region (Supplementary Tables S2 and S3, available as Supplementary data at *IJE* online), as suggested by Levin *et al.*[4]

IFRs were then stratified by sex, age, geographical region and urbanization. Sex and age in years were self-reported for living persons in the individual questionnaire of the ENSANUT 2020 Covid-19 or (for deceased persons) retrieved from the death-certificate database or the SISVER data set. To estimate the level of urbanization, we linked the individual data of place of residence of the deceased with the database of census results by locality. Information on the population size of each locality was obtained from the Unique Catalog of Keys for Localities and Geostatistical, State, and Municipal Areas updated to 2021 and published by the National Institute of Statistics and Geography.[13] Urbanization was classified according to the number of inhabitants in each locality: rural <2500, urban 2500–100 000 and metropolitan >100 000 inhabitants. We estimated region-specific sex- and age-standardized IFRs using Mexico City as the reference. Besides, with the intent of comparing IFRs by level of urbanization, we estimated sex- and age-standardized IFRs in the three categories of urbanization with the metropolitan area as the reference. We computed 95% CIs using simulation with 100 000 random replications from a normal distribution for adjusted seroprevalence and observed deaths for each sex and age stratum. Confidence intervals were obtained from the 2.5 and 97.5% percentiles of the simulated distribution as described in Supplementary Methods S1 (available as Supplementary data at *IJE* online).

Sensitivity analysis

It is challenging to define the time lags between the onset of infection, death and death reporting. For that reason, we conducted a sensitivity analysis using the cumulative deaths registered 1 month after the end of the fieldwork in each region for both sources of deaths. We obtained IFR estimates using this 1-month lag in each sex- and age-specific stratum.

Results

From 27 February 2020—when the epidemic began in Mexico—to the collection date of the survey in each region, 94 217 cumulative surveillance-based deaths and 145 975 certificate-based deaths were registered. Across sex and age groups, the ratio of certificate-based to surveillance-based deaths ranged from 1.1 in men <10 years of age to 1.8 in men aged 20–29 years, whereas for women it varied from 1.3 for those <10 years old to 1.7 in women >80 years old. We also found heterogeneity in the ratio of deaths across the nine geographic areas, ranging from 1.3 in Central Pacific, North Pacific and Center-North to 2.0 in Mexico City.

Table 1 presents the IFR calculated using the surveillance- and certificate-based deaths. Overall, we found 94 217 deaths with the surveillance system and 145 975 with the death-certificate system in the analysed period. All of the deaths recorded by the surveillance system were also reported in the death-certificate system, since surveillance-based deaths are a subset of certificate-based deaths. IFR was 0.30% (95% CI 0.28, 0.33) with surveillance-based deaths and 0.47% for certificate-based deaths (95% CI 0.44, 0.50). Surveillance-based IFRs were 0.39% and 0.22% for men and women, respectively, compared with 0.61% in men and 0.33% in women for certificate-based IFR. We observed that IFR increased with age. Surveillance-based IFR for people <20 years of age was <0.01%, increasing to 1.03% in men and 0.46% in women aged 50–59 years, compared with 1.61% in men and 0.68% in women of the same age for certificate-based IFR. The highest IFR was observed among people aged ≥80 years, in whom the surveillance-based IFR was 3.71% for men (95% CI 2.34, 8.76) and 3.73% for women (95% CI 2.18, 11.56) and 5.88% for men (95% CI 3.72, 13.88) and 6.23% for women (95% CI 3.63, 19.27) with the certificate-based IFR.

Table 2 shows the estimated IFRs by region. Regions with the highest age- and sex-standardized certificate-based IFR were Mexico City (IFR 0.99%; 95% CI 0.68, 1.19), followed by the Border (IFR 0.71%; 95% CI 0.49, 1.51) and the State of Mexico (IFR 0.57%; 95% CI 0.41, 1.07). In contrast, the Peninsula had the lowest age- and sex-standardized IFR with 0.26% (95% CI 0.19, 0.41), followed by the Pacific South with 0.36% (95% CI 0.25, 0.87). Surveillance-based IFRs varied from 0.53% (95% CI 0.38, 0.64) in Mexico City to 0.18% (95% CI 0.13, 0.27) in the Peninsula.

After stratification by urbanization, metropolitan areas had the highest IFR due to COVID-19 (Table 3). The estimate was 0.40% (95% CI 0.37, 0.44) for surveillance-based IFR and 0.63% (95% CI 0.58, 0.69) for certificate-based IFR. In contrast, rural areas had the lowest IFR due to COVID-19, with a surveillance-based IFR of 0.15% (95% CI 0.14, 0.18) and a certificate-based IFR of 0.17%

Table 1 Infection fatality rate by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by sex and age in Mexico (August–November 2020)

Sex, age group (years)	Population size (*N*)	Seroprevalence (ENSANUT 2020 Covid-19)	Population with SARS-CoV-2 antibodies	Deaths in surveillance system[a]	COVID-19 deaths by death certificates[b]	Ratio death certificates/ surveillance system	Infection fatality rate surveillance system	Infection fatality rate COVID-19 deaths by death certificates
	N	% (95% CI)	*N*	*N*	*N*		% (95% CI)	% (95% CI)
National	124 950 278	24.9 (22.2, 26.7)	31 104 751	94 217	145 975	1.5	0.30 (0.28, 0.33)	0.47 (0.44, 0.50)
Men (overall)	60 923 788	25.3 (22.3, 27.4)	15 400 530	59 963	93 725	1.6	0.39 (0.36, 0.43)	0.61 (0.56, 0.67)
1–9	9 779 292	18.0 (12.6, 23.3)	1 748 672	73	77	1.1	0.00 (0.00, 0.01)	0.00 (0.00, 0.01)
10–19	11 127 081	26.5 (21.3, 31.8)	2 939 712	81	146	1.8	0.00 (0.00, 0.00)	0.00 (0.00, 0.01)
20–29	11 634 554	29.2 (24.8, 33.6)	3 391 185	690	1244	1.8	0.02 (0.02, 0.02)	0.04 (0.03, 0.04)
30–39	7 153 413	26.3 (21.1, 31.5)	1 868 550	2683	4396	1.6	0.14 (0.12, 0.18)	0.24 (0.19, 0.30)
40–49	8 542 912	30.9 (25.7, 36.0)	2 648 950	7445	11 796	1.6	0.28 (0.24, 0.34)	0.45 (0.38, 0.54)
50–59	5 115 386	26.0 (20.2, 31.7)	1 325 576	13 592	21 402	1.6	1.03 (0.85, 1.30)	1.61 (1.33, 2.05)
60–69	3 802 326	21.9 (16.5, 27.3)	834 357	16 267	25 103	1.5	1.95 (1.56, 2.59)	3.01 (2.41, 4.00)
70–79	2 834 384	16.5 (10.3, 22.7)	468 058	12 625	19 251	1.5	2.70 (1.97, 4.29)	4.11 (3.00, 6.55)
≥80	934 441	18.8 (7.6, 30.1)	175 471	6507	10 310	1.6	3.71 (2.34, 8.76)	5.88 (3.72, 13.88)
Women (overall)	64 026 490	24.5 (22.0, 26.9)	15 704 221	34 254	52 250	1.5	0.22 (0.20, 0.24)	0.33 (0.31, 0.36)
1–9	9 500 215	23.0 (16.0, 30.0)	2 180 160	55	69	1.3	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
10–19	10 809 485	22.2 (17.6, 26.7)	2 410 149	82	141	1.7	0.00 (0.00, 0.00)	0.01 (0.00, 0.01)
20–29	11 024 401	26.5 (22.4, 30.6)	2 917 249	405	624	1.5	0.01 (0.01, 0.02)	0.02 (0.02, 0.03)
30–39	8 848 943	29.5 (24.6, 34.3)	2 598 867	1219	1752	1.4	0.05 (0.04, 0.06)	0.07 (0.06, 0.08)
40–49	9 162 476	28.1 (23.8, 32.5)	2 570 133	3406	5088	1.5	0.13 (0.12, 0.16)	0.20 (0.17, 0.23)
50–59	6 258 098	24.5 (20.3, 28.7)	1 530 997	7048	10 482	1.5	0.46 (0.39, 0.55)	0.68 (0.58, 0.82)
60–69	4 824 502	21.2 (16.6, 25.9)	1 031 111	9880	14 738	1.5	0.96 (0.79, 1.21)	1.43 (1.18, 1.80)
70–79	2 653 824	13.1 (8.0, 18.2)	350 392	7864	12 183	1.5	2.24 (1.64, 3.56)	3.48 (2.54, 5.52)
≥80	944 547	12.0 (3.2, 20.7)	115 163	4295	7173	1.7	3.73 (2.18, 11.56)	6.23 (3.63, 19.27)

[a]Deaths due to COVID-19 (positive laboratory test result) registered in the national surveillance system named SISVER up to the epidemiological week of each region.

[b]COVID-19-specific mortality from all death records for which basic cause of death was coded as U07.1 and U07.2 according to the International Classification of Disease 10th revision (updated in 2020) up to the epidemiological week of each region.

Table 2 Infection fatality rate by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by nine regions in Mexico 2020 using deaths for national surveillance system and excess of deaths attributed to COVID-19

Region	Population size	Epidemiological week	Seroprevalence ENSANUT 2020Covid-19	Population with SARS-CoV-2 antibodies	Deaths in surveillance system[a]	COVID-19 deaths by death certificates [b]	Ratio death certificates/ surveillance system	Infection fatality rate surveillance system	Sex-age-adjusted infection fatality rate[c] surveillance system	IFR COVID-19 deaths by death certificates	Sex-age-adjusted IFR[c] deaths by death certificates
	N		% (95% CI)	*N*	*N*	*N*		% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Pacific North	11 702 669	46	31.0 (25.0, 36.6)	3 627 373	12 708	17 505	1.4	0.35 (0.31, 0.40)	0.33 (0.23, 0.49)	0.48 (0.42, 0.56)	0.44 (0.31, 0.68)
Border	16 067 477	48	21.0 (15.6, 25.5)	3 379 348	14 115	23 474	1.7	0.42 (0.36, 0.50)	0.42 (0.29, 0.90)	0.69 (0.59, 0.83)	0.71 (0.49, 1.51)
Pacific Center	13 711 124	46	19.4 (12.7, 25.2)	2 663 860	7396	9920	1.3	0.28 (0.23, 0.34)	0.28 (0.18, 0.71)	0.37 (0.31, 0.45)	0.38 (0.24, 0.96)
Center-North	16 067 520	45	19.1 (14.6, 22.6)	3 063 460	10 007	13 027	1.3	0.33 (0.28, 0.40)	0.33 (0.24, 0.56)	0.43 (0.36, 0.52)	0.43 (0.31, 0.73)
Center	12 386 608	46	25.5 (20.7, 29.6)	3 162 000	9287	13 559	1.5	0.29 (0.25, 0.34)	0.36 (0.23, 0.98)	0.43 (0.37, 0.50)	0.51 (0.33, 1.38)
Mexico City	9 191 022	39	19.6 (14.7, 23.8)	1 799 163	9606	17 742	1.8	0.53 (0.38, 0.64)	0.53 (0.38, 0.64)	0.99 (0.68, 1.19)	0.99 (0.68, 1.19)
State of Mexico	16 853 909	41	23.5 (18.3, 27.7)	3 960 427	12 139	24 274	2.0	0.31 (0.26, 0.37)	0.29 (0.20, 0.53)	0.61 (0.52, 0.73)	0.57 (0.41, 1.07)
Pacific South	16 041 051	46	24.3 (17.2, 30.2)	3 904 181	10 118	13 064	1.3	0.26 (0.22, 0.31)	0.29 (0.20, 0.69)	0.33 (0.29, 0.40)	0.36 (0.25, 0.87)
Peninsula	12 928 901	46	42.9 (36.3, 49.0)	5 544 874	8841	13 410	1.5	0.16 (0.14, 0.18)	0.18 (0.13, 0.27)	0.24 (0.22, 0.27)	0.26 (0.19, 0.41)

[a]Deaths due to COVID-19 (positive laboratory test result) registered in the national surveillance system named SISVER up to the epidemiological week of each region.

[b]COVID-19-specific mortality from all death records for which basic cause of death was coded as U07.1 and U07.2 according to the International Classification of Disease 10th revision (updated in 2020) up to the epidemiological week of each region.

[c]Mexico City was the reference population for sex and age standardization.

Table 3 Infection fatality rate by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by urbanity in Mexico 2020, using deaths for national surveillance system and excess of deaths attributed to COVID-19

Urbanity (residence size in inhabitants)	Population size	Seroprevalence ENSANUT 2020 Covid-19	Population with SARS-CoV-2 antibodies	Deaths in surveillance system[a]	COVID-19 deaths by death certificates[b]	Surveillance system		COVID-19 deaths by death certificates	
						Infection fatality rate	Sex- and age-adjusted infection fatality rate[c]	Infection fatality rate	Sex and age-adjusted infection fatality rate[c]
	N	% (95% CI)	*N*	*N*	*N*	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Rural	26 702 111	21.2 (16.8, 25.6)	5 641 001	8687	9670	0.15 (0.14, 0.18)	0.16 (0.13, 0.22)	0.17 (0.15, 0.20)	0.18 (0.15, 0.27)
Urban	37 465 353	27.1 (23.4, 30.8)	10 142 983	23 531	39 753	0.23 (0.21, 0.26)	0.23 (0.20, 0.30)	0.39 (0.36, 0.43)	0.44 (0.36, 0.60)
Metropolitan	60 782 815	25.2 (22.6, 27.8)	15 320 767	61 860	96 603	0.40 (0.37, 0.44)	0.40 (0.37, 0.44)	0.63 (0.58, 0.69)	0.63 (0.58, 0.69)

[a]Deaths due to COVID-19 (positive laboratory test result) registered in the national surveillance system named SISVER up to the epidemiological week of each region.

[b]COVID-19 specific mortality from all death records for which basic cause of death was coded as U07.1 and U07.2 according to the International Classification of Disease 10th revision (updated in 2020) up to the epidemiological week of each region.

[c]The metropolitan area was the reference population.

(95% CI 0.15, 0.20). Similar results were observed after sex- and age-standardization.

Sensitivity analysis

The surveillance- and certificate-based IFR estimates, considering deaths that occurred up to 1 month after the last survey date (rather than the survey midpoint date), were higher than the estimates from the main analysis (Supplementary Tables S1 and S2, available as Supplementary data at *IJE* online). Overall, the incorporation of this extended time lag into our analyses resulted in a 10% increase in COVID-19 IFR estimates. The estimates went from 0.30% to 0.33% for surveillance-based IFR and from 0.47% to 0.52% certificate-based IFR at the national level. The change in estimates was higher in regions where survey fieldwork took longer. The Center-North region had the largest increase in surveillance-based (IFR = 0.43; 95% CI 0.36, 0.52) and certificate-based (IFR = 0.60; 95% CI 0.36, 0.52) IFRs, which represent a change of 30% and 39%, respectively. Estimates for the State of Mexico and Mexico City remained unchanged.

Discussion

We aimed to estimate the overall and sex- and age-specific IFRs for SARS-CoV-2-related illness in Mexico, using national estimates of seroprevalence and death counts as registered in the national surveillance system and in death certificates. Overall, the COVID-19 IFR was 0.30% when using deaths based on the surveillance system and 0.47% when using death certificates; IFRs were higher for men than for women and increased with age. Urban and metropolitan areas experienced higher IFRs than rural areas, and important regional differences were observed, with the highest IFR in Mexico City and the lowest in the Peninsula.

Our study is the first to provide estimates of the COVID-19 IFR for Mexico. Prior analyses calculated that CFRs in Mexico ranged from 9.4% in April 2020[14] up to 20.2% at a major social security institution by November 2020.[15] Unlike these studies, which were conducted with administrative data and based largely on symptomatic cases, we used nationally representative data showing that one-quarter of the population (~31 million people) had been infected as compared with the 847 108 cases reported in official statistics by mid-October 2020.[16]

There is worldwide interest in estimating COVID-19 IFRs and identifying sources of variation. Supplementary Figure S1 (available as Supplementary data at *IJE* online) shows IFRs using national serosurveys conducted in 2020 from Luxembourg, Hungary, England, Spain and Brazil, in comparison with Mexico. The IFR in Mexico was smaller (0.47%) than the European estimates. Meyerowitz-Katz and Merone reported a 0.60% COVID-19 IFR in a meta-analysis based on serosurveys predominantly from Europe conducted from February to June 2020.[17] Differences across sites could be due to variations in age distribution. European countries have an average life expectancy of 81 years, whereas countries like Mexico and Brazil have life expectancies of 75 years. Therefore, with the same number of infections and healthcare capability, we would expect a higher IFR in European countries in comparison to Mexico.[18] Levin *et al.* estimated that 90% of the variation in IFRs across regions was attributable to age.[4] In the Levin *et al.* study, IFRs ranged from 0.5% to 2.7% using representative samples from four European cities and regions and 11 states of the USA, all conducted before September 2020.[4] Differences in methods, population age structures and time frames limit comparability across estimates.[4,19–21] Comparisons could also be affected by the epidemic dynamic experienced by each country. Many European countries experienced a sharp increase in COVID-19 cases during their first wave, which overloaded health services and could have led to a higher initial IFR. In contrast, Mexico experienced a more aggressive second wave from November 2020 to February 2021 that was not captured by our analysis.

To our knowledge, most IFR studies have used surveillance-based deaths. Only the Spanish study, by Pastor-Barriuso *et al.*, included excess deaths from all causes to estimate the IFR as an upper bound of IFR that includes both COVID-19 and non-COVID-19 deaths.[22] Compared with our death-certificate estimate (comprising only COVID-19 deaths), a higher IFR for excess deaths in Mexico would be expected using the methods of Pastor-Barriuso *et al.* That increase in overall IFR would be driven by the extent of non-COVID-19 deaths in Mexico, where excess deaths from all causes are ~30% higher than COVID-19 deaths from death certificates.[6] Notably, we found a higher IFR in Mexico than in Spain among adults aged 40–69 years (Supplementary Figure S2, available as Supplementary data at *IJE* online). The higher prevalence of chronic diseases such as diabetes and obesity at younger ages in Mexico could partially explain that difference, considering that one in four COVID-19 deaths among young adults is attributable to chronic co-morbidities.[23] Still, both studies concur on the high IFR in elderly people and provide a more encompassing estimate of the burden of the pandemic by including deaths that were not registered in the epidemiological surveillance system.

Our findings suggest that the COVID-19 IFR was higher in more urbanized regions, which could be related to population density and challenges in healthcare delivery.

With the certificate-based IFR, Mexico City experienced four times the COVID-19 mortality than the Peninsula (0.99% vs 0.26%). Mexico City has more healthcare facilities than any other region,[24] yet, during the first pandemic wave, it experienced one of the highest bed occupancies in the country (>70%).[25] The population density in Mexico City is higher (6163 inhabitants/km^2) than in cities in the Peninsula (from 16.1 in Campeche to 75.6 inhabitants/km^2 in Chiapas).[26] Crowded hospitals could increase the IFR by compromising the quality of care, limiting admissions or lacking the necessary resources.[27–29] According to a previous report in Mexico, inadequate availability of intensive care beds was associated with an increase of 45% in fatal outcomes.[27] Other factors could have also contributed to the high IFR observed in Mexico City. Evidence suggests that exposure to particulate matter is associated with higher COVID-19 mortality, likely related to chronic pollution exposure.[30] Additionally, overcrowding could increase the severity of COVID-19 outcomes, as a result of exposure to a higher viral load.[31] These factors could influence the IFR and explain some of the variability across regions; yet, studies analysing the causes behind IFR heterogeneity are needed.

Some limitations should be considered when interpreting our results. Estimating IFRs with the death-certificate database allowed us to capture a larger proportion of deaths than using only surveillance-based deaths. Mortality information from SEED has a delay of 3–5 months, thus we obtained the data set in February of 2021, when at least 4 months had passed since the end of ENSANUT 2020 Covid-19. Misclassification due to lack of testing could have occurred, particularly at the beginning of the pandemic; however, in April 2020, the Health Ministry published guidelines to include suspected COVID-19 cases through ICD-10 codes,[32] which should have reduced misclassification. In our sensitivity analysis, we observed a 10% variation in the IFR when including deaths that occurred 1 month after the end of ENSANUT's fieldwork, compared with the midpoint. Variation was higher in regions where fieldwork took longer to complete, where the gap between the mid and final dates of fieldwork completion was wider. This finding shows the variability in IFRs that can be introduced depending on selected dates; yet the range explored should cover most deaths, since >90% of people in Mexico died <25 days after symptom onset. Some subgroups at high risk of SARS-CoV-2 infection are not considered in ENSANUT 2020 Covid-19 since the survey does not include institutionalized people, such as those incarcerated (221 000 as of July 2021) or living in nursing homes (22 600 in 2015).[33,34] These groups have experienced high rates of infection and death, yet their size relative to the population is small, which could produce a small underestimation of seroprevalence. However, these deaths are represented in the numerator, since being institutionalized increases the probability of requesting and getting a death certificate. Finally, acknowledging that IFR is not a fixed metric, our results should be interpreted in the context of the first COVID-19 wave.

Having reliable epidemiological estimates to guide public policies is a fundamental step towards pandemic control. IFRs in Mexico show a different probability of death when compared with CFRs. They also show that the reported probability of dying upon infection after the first wave of COVID-19 in the country was highly heterogeneous across regions and age groups. IFR information is particularly useful to prioritize groups for non-pharmacological interventions and vaccination. Death certificates provide a more encompassing picture of COVID-19 fatality rates in Mexico, yet the administrative pathway of death certificates is long, making sentinel surveillance estimates a better option to track rapid changes in lethality. Strengthening the timeliness of death certificates through improved electronic records and simplified processes could help the country to produce complete and rapid fatality estimates. As vaccines and new drugs roll out, covering the groups with a higher risk of death upon infection will help to reduce the burden of COVID-19 and could provide much-needed relief for the health system. A closer look at the reasons behind the heterogeneity of IFR observed in the country is needed, including disparities in health system capacity and utilization, differences in the registries and the large social and economic inequalities that exist across the country.

Ethics approval

This analysis was conducted as part of the "System for the temporo-spatial analysis and quantitative visualization of the general situation of health problems, resources and costs, through linkage of big data from the health sector in Mexico" project, approved by the Institutional Review Board of the National Institute of Public Health of Mexico (No. CI-1706-2020). The ENSANUT 2020 Covid-19 study was approved by the Institutional Review Board of the National Institute of Public Health of Mexico No. CI-450–2021; written informed consent was obtained from the ENSANUT 2020 Covid-19 participants.

Data availability

The de-identified data from the seroprevalence study ENSANUT 2020 Covid-19 are publicly available at https://ensanut.insp.mx/encuestas/ensanutcontinua2020/descargas.php. The COVID-19 mortality data from the national surveillance system is publicly available at https://www.gob.mx/salud/documentos/datos-abiertos-152127. Death certificate data was obtained through a data use agreement with the General Direction of Information for Health

(www.dgis.salud.gob.mx). Aggregated and unidentified COVID-19 mortality data from death certificates used for this analysis are available in Torres, Leticia (2022): COVID-19 mortality data from death certificates SEED. figshare. Dataset. https://doi.org/10.6084/m9.figshare.19134959.v1

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

L.T.I. and T.B.G. were responsible for the study conceptualization and design. T.S.L. and J.A.R. were responsible for obtaining the funding for the ENSANUT 2020 Covid-19 seroprevalence study. L.T.I., A.B.A., M.C., R.S.T., F.R.S., L.P.M. and J.H.A. were responsible for data acquisition and were in charge of accessing and verifying the underlying data. L.T.I., A.B.A., M.C., R.T.A. and F.R.S. were in charge of statistical analyses. L.T.I., A.B.A., M.C. and T.B. were responsible for table and figure design as well as supervision of data analysis. L.T.I., A.B.A., M.C. and T.B.G. wrote the first draft of the manuscript. All authors contributed to data interpretation, critically reviewed the first draft and approved the final version of the manuscript, and agreed to be accountable for the work. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Conflict of interest

None declared.

References

1. Cao Y, Hiyoshi A, Montgomery S. COVID-19 case-fatality rate and demographic and socioeconomic influencers: worldwide spatial regression analysis based on country-level data. *BMJ Open* 2020;**10**:e043560.
2. Ghayda RA, Lee KH, Han YJ *et al.* Estimation of global case fatality rate of coronavirus disease 2019 (COVID-19) using meta-analyses: comparison between calendar date and days since the outbreak of the first confirmed case. *Int J Infect Dis* 2020;**100**: 302–08.
3. Murhekar M, Bhatnagar T, Selvaraju S *et al.* Prevalence of SARS-CoV-2 infection in India: findings from the national serosurvey, May-June 2020. *Indian J Med Res* 2020;**152**:48.
4. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. *Eur J Epidemiol* 2020;**35**: 1123–38.
5. Roser M, Ritchie H, Ortiz-Ospina E, Hasell J, *Coronavirus Pandemic (COVID-19)*. Published online at OurWorldInData.org. 2021. https://ourworldindata.org/coronavirus (4 April 2021, date last accessed).
6. Grupo Interinstitucional Para la Estimación del Exceso de Mortalidad. *Boletín Estadístico Sobre el Exceso de Mortalidad por Todas las Causas Durante la Emergencia por COVID-19. Número 11. Semana 6. Del 7 al 13 Febrero 2021*. Mexico, 2021. https://coronavirus.gob.mx/wp-content/uploads/2021/03/Boletín_XI_Exceso_Mortalidad_SE6_MX_19Mar2021.pdf (20 April 2021, date last accessed).
7. Romero-Martínez M, Barrientos-Gutiérrez T, Cuevas-Nasu L *et al.* Metodología de la Encuesta Nacional de Salud y Nutrición 2020 sobre Covid-19. *Salud Publica Mex* 2021;**63**:444–51.
8. Basto-Abreu A, Carnalla M, Torres-Ibarra L, *et al.* Nationally representative SARS-CoV-2 antibody prevalence estimates after the first epidemic wave in Mexico. *Nat Commun* 2022;**13**:589. https://doi.org/10.1038/s41467-022-28232-9.
9. National Institute of Statistics and Geography (INEGI). *Censo de Población y Vivienda 2020*. 2021. https://www.inegi.org.mx/programas/ccpv/2020/default.html#Tabulados (18 February 2021, date last accessed).
10. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)-WHO Version for;2019-covid-expanded*. 2019. https://icd.who.int/browse10/2019/en#/U07.1 (19 April 2021, date last accessed).
11. Secretaría de Gobernación. *Decreto por el que se reforman los artículos 314, 348 y 419; y se adicionan los artículos 348 Bis, 348 Bis 1 y 348 Bis 2 de la Ley General de Salud*. 2020. http://dof.gob.mx/nota_detalle.php?codigo=5584754&fecha=24%2F01%2F2020 (17 September 2021, date last accessed).
12. United Nations. *Demographic and Social Statistics: Civil Registration and Vital Satatistics*. 2021. https://unstats.un.org/unsd/demographic-social/crvs/index.cshtml (17 September 2021, date last accessed).
13. National Institute of Statistics and Geography (INEGI). *Catálogo Único de Claves de Áreas Geoestadísticas Estatales,*

Municipales y Localidades. 2021. https://www.inegi.org.mx/app/ageeml/ (20 January 2020, date last accessed).
14. Kammar-García A, de Vidal-Mayo JJ, Vera-Zertuche JM *et al.* Impact of comorbidities in Mexican SARS-CoV-2-positive patients: a retrospective analysis in a national cohort. *Rev Invest Clin* 2020;**72**:151–58.
15. Peña JE, de la Rascón-Pacheco RA, Ascencio-Montiel I de J *et al.* Hypertension, diabetes and obesity, major risk factors for death in patients with COVID-19 in Mexico. *Arch Med Res* 2020;**52**:443–49.
16. Secretaría de Salud. *Subsecretaria de Prevención y Promoción de la Salud. Informe Técnico Diario COVID-19 México. 17 Octubre 2020*. Mexico, 2020. https://www.gob.mx/cms/uploads/attachment/file/585919/Comunicado_Tecnico_Diario_COVID-19_2020.10.17.pdf (1 June 2021, date last accessed).
17. Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. *Int J Infect Dis* 2020;**101**:138–48.
18. The World Bank. *Life Expectancy at Birth, Total (Years)*. 2021. https://data.worldbank.org/indicator/SP.DYN.LE00.IN? (21 March 2020, date last accessed).
19. Sudharsanan N, Didzun O, Bärnighausen T, Geldsetzer P. The contribution of the age distribution of cases to COVID-19 case fatality across countries: a nine-country demographic study. *Ann Intern Med* 2020;**173**:714–20.
20. Williamson EJ, Walker AJ, Bhaskaran K *et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**:430–36.
21. Kim DH, Choe YJ, Jeong JY. Understanding and interpretation of case fatality rate of coronavirus disease 2019. *J Korean Med Sci* 2020;**35**:e137.
22. Pastor-Barriuso R, Pérez-Gómez B, Hernán MA *et al.*; ENE-COVID Study Group. Infection fatality risk for SARS-CoV-2 in community dwelling population of Spain: nationwide seroepidemiological study. *BMJ* 2020;**371**:m4509.
23. Reyes-Sánchez F, Basto-Abreu A, Torres-Alvarez R *et al.* Fraction of COVID-19 hospitalizations and deaths attributable to chronic diseases. *Prev Med* 2021;**155**:106917.
24. Secretaría de Salud. *Subsecretaría de Integración y Desarrollo del Sector Salud. Informe sobre la Salud de los Mexicanos 2016*. Mexico, 2016. https://www.gob.mx/cms/uploads/attachment/file/239410/ISSM_2016.pdf (20 May 2021, date last accessed).
25. Secretaría de Salud. *Sistema de Información de la Red IRAG*. Mexico, 2020. https://www.gits.igg.unam.mx/red-irag-dashboard/reviewHome (20 May 2021, date last accessed).
26. National Institute of Statistics and Geography (INEGI). *Densidad de Población por Entidad Federativa, 1990 a 2020. Datos. Tabulados Interactivos*. 2020. https://www.inegi.org.mx/app/tabulados/interactivos/?px=Poblacion_07&bd=Poblacion (27 March 2021, date last accessed).
27. Olivas-Martínez A, Cárdenas-Fragoso JL, Jiménez JV *et al.* In-hospital mortality from severe COVID-19 in a tertiary care center in Mexico City; causes of death, risk factors and the impact of hospital saturation. *PLoS One* 2021;**16**:e0245772.
28. De la Hoz-Restrepo F, Alvis-Zakzuk NJ, De la Hoz-Gomez JF, De la Hoz A, Gómez Del Corral L, Alvis-Guzmán N. Is Colombia an example of successful containment of the 2020 Covid-19 pandemic? A critical analysis of the epidemiological data, March to July 2020. *Int J Infect Dis* 2020;**99**:522–29.
29. Speciale A, Lepido D, Kresge N. *Virus Spread Pushes Italian Hospitals Toward Breaking Point*. Bloomberg. 2020 https://www.bloomberg.com/news/articles/2020-03-10/virus-spread-pushes-italian-hospitals-toward-breaking-point (7 May 2021, date last accessed).
30. Copat C, Cristaldi A, Fiore M *et al.* The role of air pollution (PM and NO2) in COVID-19 spread and lethality: a systematic review. *Environ Res* 2020;**191**:110129.
31. Ahmad K, Erqou S, Shah N *et al.* Association of poor housing conditions with COVID-19 incidence and mortality across US counties. *PLoS One* 2020;**15**:e0241327.
32. Secretaría de Salud. *Correcto llenado del Certificado De Defunción Muertes por Virus SARS-CoV2 (COVID-19)*. 2020. https://coronavirus.gob.mx/wp-content/uploads/2020/04/Correcto_llenado_del_certificado_de_defuncion_muertes_por_COVID-19.pdf (17 September 2021, date last accessed).
33. Secretaría de Seguridad y Protección Ciudadana. *Cuaderno Mensual de Información Estadística Penitenciaria Nacional*. 2021. https://www.gob.mx/cms/uploads/attachment/file/666317/CE_2021_07.pdf (17 September 2021, date last accessed)
34. Instituto Nacional de Estadística y Geografía. *Censo de Alojamientos de Asistencia Social (CAAS)*. 2015.https://www.inegi.org.mx/contenidos/programas/caas/2015/doc/caas_resultados.pdf (17 September 2021, date last accessed).