BMJ Open

Influenza and morbidity and mortality risk in patients in Mexico with systemic arterial hypertension alone or with comorbidities: a retrospective, observational, cross-sectional study from 2014 to 2020

Alejandrina Malacara-Villaseñor,[1] Hermes Ilaraza-Lomeli,[2] Roberto Tapia-Conyer,[3] Elsa Sarti [1]

For numbered affiliations see end of article.

Correspondence to
Dr Elsa Sarti;
elsa.sarti@sanofi.com

ABSTRACT

Objectives In Mexico, patients with systemic arterial hypertension (SAH) are excluded from the influenza vaccination programme despite their risk of cardiovascular events as influenza-related complications. We investigated the impact of influenza on morbidity and mortality in patients with SAH.

Design This was a retrospective cross-sectional study that analysed data from early 2014 to mid-2020.

Setting Data were obtained from the Influenza Epidemiological Surveillance System in Mexico database.

Participants 32 663 cases of influenza in people aged ≥20 years with a confirmed case of influenza-like illness, severe respiratory infection and/or influenza death were investigated.

Primary and secondary outcome measures Influenza deaths, hospitalisation frequency and the impact on hospitalisation and/or death due to influenza by the SAH variate alone and in combination with diabetes, obesity, chronic obstructive pulmonary disease, cardiovascular disease and/or smoking, and by vaccination status were assessed.

Results The hospitalisation frequency increased with age. Notably, 46.0% (15 033/32 663) of confirmed influenza cases had at least one comorbidity, with SAH (19.2%; 6260/32 663) and obesity (18.7%; 6106/32 663) being the most prevalent. Most confirmed SAH cases (80.8%; 5057/6260) were in those who had not been vaccinated against influenza. There were 3496 deaths due to influenza (mortality rate, $0.69 \times 100\,000$ inhabitants), with the highest rates seen in those aged ≥80 years (80–89 years, 2.0%; ≥90 years, 3.6%). The case fatality rate due to influenza and SAH was significantly higher than those due to influenza without SAH in those aged <50 years, but not in the other age groups (20–29 years, 9.8%, p<0.0005; 30–39 years, 8.2%, p<0.035; 40–49 years, 17.8%, p<0.0005; vs 15.1%–20.0%, p=0.31–0.99 for those aged ≥50 years).

Conclusions Our findings support the need to include SAH in public policies of influenza vaccination as a secondary prevention measure to avoid fatal outcomes.

Strengths and limitations of this study

► Our study helped clarify the risk–benefit balance of excluding patients with systemic arterial hypertension (SAH) from the influenza vaccination programme in Mexico.
► This large-scale retrospective study included data of over 30 000 influenza patients.
► We assessed the impact of SAH (among other comorbidities) on various outcomes related to influenza infection, such as death and hospitalisation frequency.
► The study was limited in that the database from which influenza morbidity data were obtained covers <10% of the health units throughout Mexico.
► A further limitation was that vaccination history was obtained by questioning the patient, which is likely to be less reliable than official paper or electronic documentation.

INTRODUCTION

Influenza, which is caused by an RNA virus, is a public health problem affecting approximately 5%–10% of adults and 20%–30% of children worldwide, with 3–6 million cases reported each year and more than 640 000 deaths per year.[1 2] Additionally, influenza has a great potential to cause respiratory disease pandemics.[3 4]

Vaccination is one of the most cost-effective strategies for the prevention and control of many diseases. In the case of influenza, the implementation of vaccination campaigns worldwide has decreased mortality and morbidity.[5] Currently, the vaccination policy offered in Mexico covers children <5 years old; adults >60 years of age; those aged 5–60 years with risk factors such as asthma, heart

diseases, immunodeficiencies, haemoglobinopathies, asplenia, chronic kidney disease, diabetes, obesity and arthritis; and pregnant women and healthcare workers.[6 7] However, it excludes people diagnosed with systemic arterial hypertension (SAH), leaving patients with this chronic disease unprotected and at risk of having a cardiovascular disease (CVD) episode as a complication of influenza infection.[8 9]

During the last 20 years, SAH has been identified as one of the most important risk factors for morbidity and mortality globally.[10] According to the 2018 Mexican National Health and Nutrition Survey (ENSANUT), the prevalence of SAH in the population aged 20 years and older is 18.4% (women, 20.9%; men, 15.3%), representing at least 15.2 million Mexican people.[11 12] Although few studies focused on SAH and the impact of influenza vaccination are published,[13–16] the WHO recently recommended including patients with only SAH as a risk group to be vaccinated.[17]

Given that the prevalence of SAH in Mexico is steadily increasing, mainly in adults older than 20 years,[11 12] and that SAH by itself is not considered a risk factor for access to influenza vaccination in accordance with the public health policy of Mexico, this study was designed to determine the risk for each of the usual influenza outcomes (outpatient illness, hospitalisation and/or death) in patients with SAH in Mexico.

METHODS AND ANALYSIS
Study design and patients
The present study was a retrospective cross-sectional study using data from the Influenza Epidemiological Surveillance System in Mexico (SISVER). As this was an observational study with a secondary data source, it was not considered research with risk per article 17 of the Regulations of the General Health Law in the Field of Health Research.[18]

The SISVER sentinel surveillance system uses an influenza case definition as follows: (a) suspected cases include a clinical diagnosis of influenza-like illness (ILI) and/or an epidemiological association and (b) confirmed cases are diagnosed by real-time quantitative RT-PCR (qRT-PCR). The system collects biological samples and exhaustive clinical and epidemiological information on 10% of ILI cases and 100% of severe acute respiratory infection (SARI) cases and deaths due to influenza that occur in Mexico.[6 19] The sampling strategy for deciding which of the 10% of ILI cases were collected and analysed is as follows: in each health unit from SISVER, samples were to be taken from the first suspected case and sent to the laboratory for confirmation. Samples were not collected for the following nine cases and the process was repeated for every 10 cases.[6 19] Regarding the information collected, if the case was ambulatory, the clinical information was collected through patient interview, but if it was an in-hospital case, it was collected from medical chart review. A case was considered an in-hospital case if the patient spent at least 24 hours in hospital. In cases where the patient died, the information was also collected from the death certificate.

In this retrospective cross-sectional study, the SISVER database (Oficio de transparencia DGE-DGAE de la Secretaría de Salud con número 005533 referente a la Solicitud 0001200189920 del 4 de junio de 2020; the database was provided via a disk for the purpose of analysis and is not publicly available) entries from 1 January 2014 to 15 May 2020 were included. The analysis included all records of patients ≥20 years old who were diagnosed with a laboratory confirmed influenza infection of ILI or SARI by qRT-PCR and who requested medical attention. A case of death by influenza included any deceased patient with ILI or SARI, who had a positive laboratory result for influenza, and whose death certificate contained a diagnosis of influenza or pneumonia as the basic cause of death. If something other than influenza or pneumonia was listed as the basic cause of death on the death certificate, that individual was not considered to be a case of death by influenza and was excluded from the present study. All influenza deaths were rectified or ratified by an influenza-specific governmental scientific committee. Deaths ratified by this committee were included in the present study.[19]

Outcomes and statistical analysis
A descriptive analysis of the variables studied was performed, as well as bivariate and stratified (by age group) analyses considering the impact on hospitalisation and/or death due to influenza by the SAH variate alone and/or combined with diabetes, obesity, chronic obstructive pulmonary disease (COPD), CVD and/or smoking, and by influenza vaccination status. ORs were calculated considering the comparison between confirmed influenza cases with SAH alone or with other comorbidities, versus confirmed influenza cases without SAH, diabetes, obesity, COPD, CVD or a smoking habit. However, they could have diseases or lesions other than those listed. Statistical significance was determined using the χ^2 test or Fisher's exact test. Incidence rates were estimated considering the total number of new confirmed influenza cases per 100 000 inhabitants of each specific age group and totalled for persons-years of observation. Similarly, case fatality rates were determined by calculating the cases with influenza-related death over the confirmed cases per 100 inhabitants. Although the incidence rate calculations did not take into account the sampling scheme, the mortality and hospitalisation calculations took into account 100% of influenza cases reported in Mexico. For statistical analyses, Microsoft Excel (Microsoft Corp, Redmond, Washington, DC, USA), SPSS-PC (IBM, Armonk, New York, USA) and Epi Info software (Centers for Disease Control and Prevention, Atlanta, Georgia, USA) were used.

Patient and public involvement
Patients or the public were not involved in the design, conduct, or reporting or dissemination plans of our research.

RESULTS

Cases

A total of 32 663 confirmed cases of influenza were analysed; most of them were women (56.0% (18 284/32 663) vs 44.0% (14 379/32 663) men), the mean and median ages for women were 46 and 44 years, and for men, 47 and 46 years, respectively. The years 2014 (21.1%, 6892/32 663), 2016 (21.9%, 7149/32 663) and 2017 (15.8%, 5147/32 663) had the highest number of confirmed influenza cases, which corresponded to the seasons that also had the highest rates.[20]

The highest proportion of cumulative cases was in the group aged 30–39 years (21.3%, 6952/32 663), followed by the group aged 40–49 years (20.8%, 6806/32 663); however, the highest incidence rate per 100 000 inhabitants corresponded to elderly patients, especially those aged ≥80 years. Among all confirmed influenza cases, 19 948/32 663 (61.1%) were inpatient cases, and 12 715/32 663 (38.9%) were outpatient cases. The highest proportion of hospitalised influenza cases was in patients aged ≥80 years, with the frequency of hospitalisation increasing with age. For each outpatient case of influenza, 1.56 persons were hospitalised (online supplemental table S1).

Among all confirmed influenza cases, 46.0% (15 033/32 663) of patients had at least one comorbidity. SAH and obesity were the most prevalent, at 19.2% (6260/32 663) and 18.7% (6106/32 663), respectively, followed by type 2 diabetes (17.7%, 5794/32 663), smoking (11.4%, 3711/32 663), COPD (6.5%, 2136/32 663) and CVD (4.9%, 1607/32 663). When comorbidities were broken down by age group, the burden of influenza disease and obesity was notable mainly in those <50 years of age, and among those aged ≥50 years, SAH and diabetes were

more prevalent (figure 1). The combination of SAH with another comorbidity of interest was more frequent for diabetes (8.8%, 2884/32 663) and obesity (6.6%, 2143/32 663) and less frequent for COPD (2.8%, 925/32 663), smoking (2.7%, 881/32 663) and CVD (2.4%, 772/32 663).

Regarding the vaccination history against influenza, 80.8% of those with a confirmed case of SAH (5057/6260) had not been vaccinated, and only 15.1% (944/6260) had been vaccinated. The percentages do not add up to 100% because the vaccination status was unknown for some patients.

Deaths

In total, 3496 deaths due to influenza (overall mortality rate of 0.69×100 000 inhabitants) were reported, with the group aged ≥80 years presenting the highest rates, followed by the group aged 60–69 years. Regarding case fatality rates, the overall rate was 10.7% (3496/32 663), with the group aged 60–69 years presenting the highest rate (19.4%, 690/3562), even when compared with the group aged ≥90 years (17.1%, 72/421).

Similar trends were observed with the mortality rates of influenza and SAH, where the higher the age group, the higher the mortality rate; however, in the case of fatality due to influenza and SAH, the groups aged <50 years had significantly higher rates in comparison with the same age groups but without SAH, showing that having influenza with SAH leads to worse outcomes in specific age groups (table 1).

The influenza case fatality rates found in patients with SAH (16.3%; 1020/6260) increased when data were analysed by pairs of SAH plus other comorbidities such as diabetes (19.5%; 534/2741), obesity (18.6%; 385/2068),
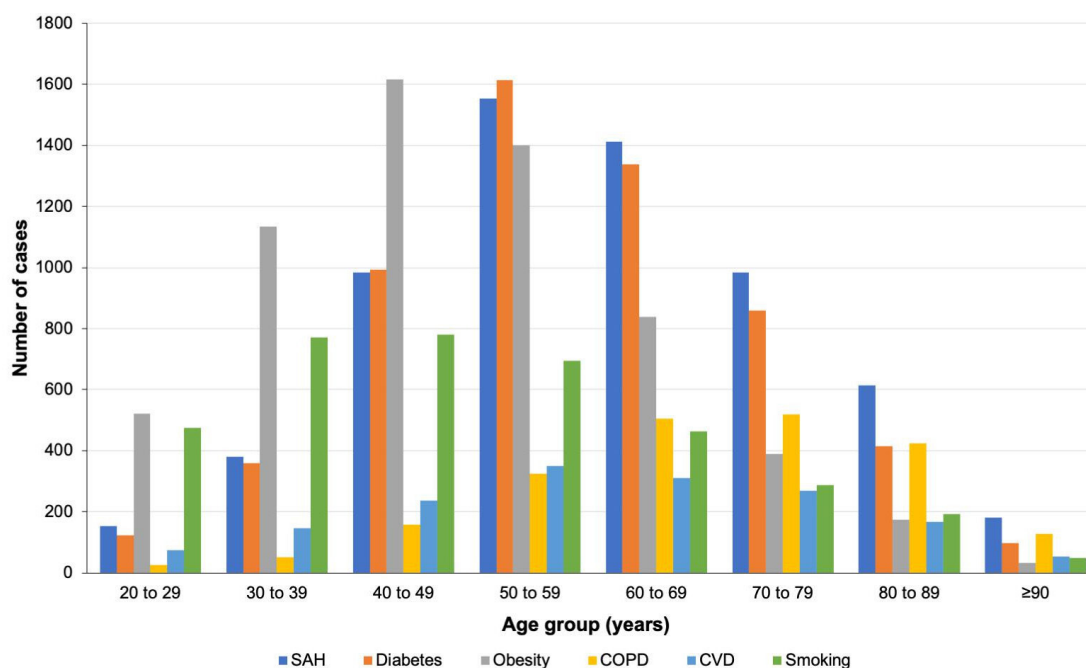

Figure 1 Cumulative influenza cases by age and comorbidity groups. COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; SAH, systemic arterial hypertension.

Table 1 Overall mortality and case fatality rates by influenza alone and combined with systemic arterial hypertension (SAH), by age group

| Age group, years	Confirmed influenza cases	Deaths from confirmed influenza cases (n)	Overall mortality rate*	Fatality rate of confirmed influenza cases†	Confirmed cases of influenza and SAH	Deaths from confirmed influenza and SAH (n)	Confirmed influenza and SAH mortality rate*	Fatality rate of confirmed influenza and SAH cases†	P value‡
20–29	5782	150	0.1	2.6	153	15	0.01	9.8	<0.0005
30–39	6952	380	0.3	5.5	380	31	0.03	8.2	<0.035
40–49	6806	784	0.8	11.5	984	175	0.2	17.8	<0.0005
50–59	5630	889	1.2	15.8	1553	247	0.3	15.9	0.92
60–69	3562	690	1.5	19.4	1412	273	0.6	19.3	0.99
70–79	2175	338	1.4	15.5	984	149	0.6	15.1	0.73
80–89	1335	193	2.0	14.5	614	94	1.0	15.3	0.52
≥90	421	72	3.6	17.1	180	36	1.8	20.0	0.31
Total	32 663	3496	0.7	10.7	6260	1020	0.2	16.3	–

*Per 100 000 person-years.
†Per 100.
‡χ² test.
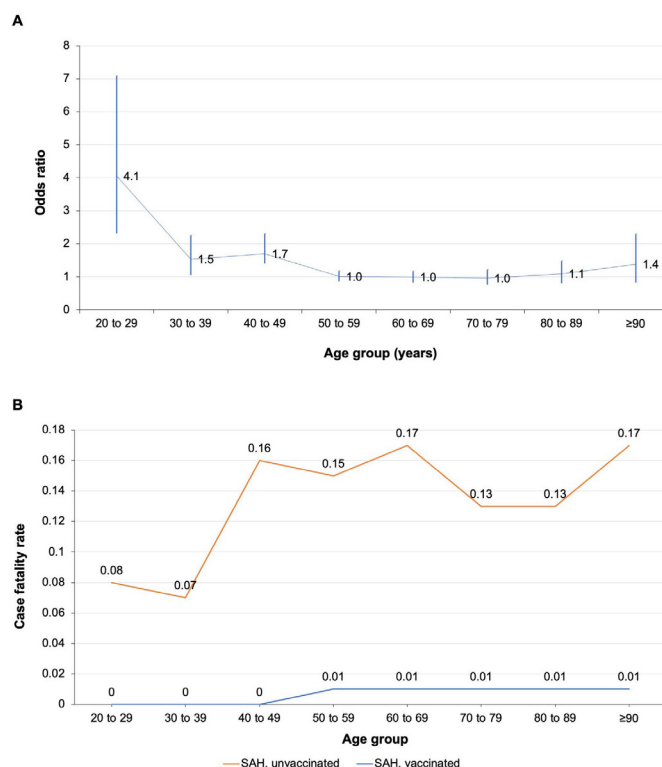
Figure 2 (A) ORs and CIs of case fatality rates by age group when compared between patients with and without SAH and (B) influenza case fatality rates in patients with SAH according to their age group and vaccination status. Error bars show 95% CIs in (A). SAH, systemic arterial hypertension.

CVD (19.1%; 138/721), COPD (16.8%; 146/871) and smoking (21.8%; 185/849) (online supplemental table S2).

When observing the influenza case fatality rates with the presence of SAH alone (figure 2A) compared with those who died without a history of SAH, a clear impact of this morbid condition was observed in those aged <50 years (mainly in those aged 20–29 years), but not in those aged ≥50 years, where it seems that the effect of age itself contributed to death.

When the analysis was performed considering the different SAH pairs, a greater risk effect was observed in the group of patients aged 30–39 years when combined with diabetes, obesity, COPD, CVD and smoking. Notably, in the combination of SAH with obesity, the greatest risk was found in the group aged 20–29 years (table 2).

Concerning vaccination history, age groups and the presence or absence of SAH, influenza-related deaths were notably lower among patients who were vaccinated (<2%) compared with unvaccinated patients (range 7%–17%) (figure 2B). Similar trends were observed in patients with SAH and other comorbidities.

The risk of hospitalisation (OR 3.3; 95% CI 3.1 to 3.5; p<0.0001) and death due to influenza (OR 1.9; 95% CI 1.8 to 2.1; p<0.0001) was shown in patients with SAH, and these risks increased more in the presence of other comorbidities (online supplemental table S2). The risks

Table 2 Case fatality rates of influenza and systemic arterial hypertension (SAH) combined with other comorbidities and ORs of these rates when compared with patients who died without comorbidities

Influenza+SAH and diabetes

Age group, years	Influenza deaths (n)/influenza cases (n) (with SAH and diabetes)	CFR with SAH and diabetes, %	Influenza deaths (n)/influenza cases (n) (without SAH and diabetes)	CFR without SAH and diabetes, %	OR	CI	P value
20–29	0/23	0.0	150/5759	2.6	–	0 to 6.6	0.43
30–39	10/91	11.0	370/6861	5.4	2.0	1.1 to 3.9	0.053
40–49	86/389	22.1	698/6417	10.9	2.0	1.6 to 2.6	0.0000001
50–59	141/770	18.3	748/4860	15.4	0.9	0.7 to 1.1	0.4
60–69	159/776	20.5	531/2786	19.1	1.1	0.9 to 1.3	0.49
70–79	88/529	16.6	250/1646	15.2	1.1	0.8 to 1.4	0.53
80–89	35/241	14.5	158/1094	14.4	1.0	0.7 to 1.5	0.97
≥90	15/65	23.1	57/356	16.0	1.4	0.8 to 2.7	0.32
Total	534/2884	18.5	2962/29 779	10.0	2.0	1.8 to 2.2	0.003

Influenza +SAH and obesity

Age group, years	Influenza deaths (n)/influenza cases (n) (with SAH and obesity)	CFR with SAH and obesity, %	Influenza deaths (n)/influenza cases (n) (without SAH and obesity)	CFR without SAH and obesity, %	OR	CI	P value
20–29	3/49	6.1	147/5733	2.6	2.4	0.7 to 7.7	0.29
30–39	18/172	10.5	362/6780	5.3	2.0	1.2 to 3.2	0.01
40–49	92/422	21.8	692/6384	10.8	2.0	1.6 to 2.6	0.00006
50–59	112/605	18.5	777/5025	15.5	1.2	1.0 to 1.5	0.11
60–69	99/494	20.0	591/3068	19.3	1.0	0.8 to 1.3	0.78
70–79	37/261	14.2	301/1914	15.7	0.9	0.6 to 1.3	0.64
80–89	21/121	17.4	172/1214	14.2	1.2	0.7 to 2.0	0.49
≥90	3/19	15.8	69/402	17.2	0.9	0.3 to 3.2	0.89
Total	385/2143	18.0	3111/30 520	10.2	1.7	1.6 to 2.0	0.001

Influenza+SAH and CVD

Age group, years	Influenza deaths (n)/influenza cases (n) (with SAH and CVD)	CFR with SAH and CVD, %	Influenza deaths (n)/influenza cases (n) (without SAH and CVD)	CFR without SAH and CVD, %	OR	CI	P value
20–29	0/12	0.0	150/5770	2.6	–	0 to 19.9	0.57
30–39	5/35	14.3	375/6917	5.4	2.6	1.0 to 6.8	0.036
40–49	13/71	18.3	771/6735	11.5	1.6	0.9 to 2.9	0.11
50–59	29/144	20.1	860/5486	15.7	1.3	0.9 to 1.9	0.27
60–69	42/195	21.5	648/3367	19.3	1.1	0.8 to 1.6	0.52
70–79	25/171	14.6	313/2004	15.6	0.9	0.6 to 1.4	0.76
80–89	18/109	16.5	175/1226	14.3	1.2	0.7 to 2.0	0.58
≥90	6/35	17.1	66/386	17.1	1.0	0.4 to 2.5	0.99
Total	138/772	17.9	3358/31 891	10.5	1.2	1.0 to 1.4	0.09

Influenza+SAH and COPD

Age group, years	Influenza deaths (n)/influenza cases (n) (with SAH and COPD)	CFR with SAH and COPD, %	Influenza deaths (n)/influenza cases (n) (without SAH and COPD)	CFR without SAH and COPD, %	OR	CI	P value
20–29	0/4	0.0	150/5778	2.6	–	0 to 58.7	0.74
30–39	4/22	18.2	376/6930	5.4	3.4	1.1 to 9.8	0.018
40–49	13/57	22.8	771/6749	11.4	2.0	1.1 to 3.7	0.02
50–59	14/115	12.2	875/5515	15.9	0.8	0.4 to 1.3	0.42
60–69	30/220	13.6	660/3342	19.8	0.9	0.5 to 1.5	0.68
70–79	36/237	15.2	302/1938	15.6	0.9	0.6 to 1.5	0.83
80–89	34/205	16.6	159/1130	14.1	1.2	0.8 to 1.8	0.48
≥90	15/65	23.1	57/356	16.0	1.4	0.8 to 2.7	0.32
Total	146/925	15.8	3350/31 738	10.5	1.1	0.9 to 1.4	0.35

Influenza+SAH and smoking

Age group, years	Influenza deaths (n)/influenza cases (n) (with SAH and smoking)	CFR with SAH and smoking, %	Influenza deaths (n)/influenza cases (n) (without SAH and smoking)	CFR without SAH and smoking, %	OR	CI	P value
20–29	0/19	0.0	150/5763	2.6	0	0 to 8.3	0.48

Influenza+SAH, diabetes and obesity

Age group, years	Influenza deaths (n)/influenza cases (n) (with SAH, diabetes and obesity)	CFR with SAH, diabetes and obesity, %	Influenza deaths (n)/influenza cases (n) (without SAH, diabetes and obesity)	CFR without SAH, diabetes and obesity, %	OR	CI	P value
20–29	0/12	0	136/5592	2.4	–	0 to 15.0	0.58

Continued

Table 2 Continued

Age group, years	Influenza deaths (n)/influenza cases (n) (with SAH and smoking)	CFR with SAH and smoking, %	Influenza deaths (n)/influenza cases (n) (without SAH and smoking)	CFR without SAH and smoking, %	OR	CI	P value	Influenza deaths (n)/influenza cases (n) (with SAH, diabetes and obesity)	CFR with SAH, diabetes and obesity, %	Influenza deaths (n)/influenza cases (n) (without SAH, diabetes and obesity)	CFR without SAH, diabetes and obesity, %	OR	CI	P value
				Influenza+SAH and smoking							Influenza+SAH, diabetes and obesity			
30–39	10/62	16.1	370/6890	5.4	3.0	1.5 to 5.9	0.002	7/50	14.0	314/6426	4.9	2.9	1.3 to 6.4	0.006
40–49	28/143	19.6	756/6663	11.4	1.7	1.1 to 2.6	0.012	38/186	20.4	530/5525	9.6	2.1	1.5 to 3.1	0.00001
50–59	40/201	19.9	849/5429	15.6	1.3	0.9 to 1.8	0.2	62/319	19.4	498/3693	13.5	1.4	1.1 to 1.9	0.015
60–69	50/209	23.9	640/3353	19.1	1.3	0.9 to 1.7	0.19	62/289	21.5	361/1995	18.1	1.2	0.9 to 1.6	0.25
70–79	26/128	20.3	312/2047	15.2	1.3	0.9 to 2.1	0.24	20/145	13.8	169/1184	14.3	1.0	0.6 to 1.6	0.99
80–89	22/93	23.7	171/1242	13.8	1.7	1.1 to 2.8	0.04	7/62	11.3	115/856	13.4	0.8	0.4 to 1.9	0.81
≥90	9/26	34.6	63/395	16.0	2.2	1.0 to 4.8	0.09	1/5	20.0	51/306	16.7	1.2	0.0 to 11.0	0.86
Total	185/881	21.0	3311/31 782	10.4	2.0	1.7 to 2.4	0.000001	197/1068	18.5	2174/25 577	8.5	2.2	1.9 to 2.5	0.0001

CFR, case fatality rate; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

of hospitalisation and death due to influenza were also high among unvaccinated patients, and these risks further increased in the presence of other comorbidities (online supplemental table S3).

DISCUSSION

Several studies have investigated the impact of influenza and vaccination against influenza on morbidity and mortality in patients with comorbidities such as CVDs, diabetes, obesity, COPD and cerebrovascular disease, among others.[6–9] However, few studies have been published regarding patients with only SAH and the impact of influenza vaccination. One Danish study showed that vaccination against influenza is associated with a reduction in the risk of all-cause mortality, cardiovascular mortality and myocardial infarction or stroke mortality in hypertensive patients without CVD.[13 14] Nevertheless, this study did not compare this population with non-hypertensive patients, as all patients studied had SAH. Others have reported alterations in circulation in patients with influenza and patients with hypertension,[8 15] and there is a high prevalence of hypertension (63%) and mortality due to myocardial infarction and influenza.[8 16] The present study is among the few in which an association was found that explains the impact of influenza on morbidity and mortality in patients having SAH only.

Regarding the cases of influenza and its epidemiological pattern, the present results are consistent with those reported by other authors: the greater the number of comorbidities, the greater the risk of hospitalisation and death from influenza, and the older the patient, the higher the incidence and hospitalisation rates.[21–23] Notably, the absolute number of cases was higher in the group aged 30–50 years (working-age population) who become a source of contagion in their work environment; the negative economic impact that this can have has been previously reported.[24] Regarding comorbidities, obesity and diabetes were the second and third most prevalent comorbidities in this study, after SAH. While a link between risk factors such as obesity, hypertension, diabetes and black/Hispanic ethnicity and the severity of influenza infection has been previously reported,[25 26] the presence of obesity has been suggested to be a possible confounding factor for these associations.[27] The mechanism through which these four risk factors are associated with the severity of influenza infection is not yet fully understood.

In the present study, most of the patients with confirmed cases of influenza presented associated comorbidities, and 19.2% of the entire population evaluated, including patients >20 years of age, had SAH. This percentage is very similar to that published by the ENSANUT,[11] which was 18.4% among a population >20 years of age. Therefore, despite the limitations of our study, we can infer that the results adequately reflect the situation in the country.

Regarding influenza fatality, most publications report that the older the age, the higher the death rate.[28–31] However, in our study, the group with the highest case fatality rate was the group aged 60–69 years, even when compared with the case fatality rate in the groups aged ≥70 years. This supports the vaccination programme in Mexico where vaccination is offered free of charge to the whole population aged >60 years.

However, it is worth reflecting on other age groups. For instance, in the group aged 50–59 years, the case fatality rate was similar to that of the group aged 70–79 years and was even higher than that of the group aged 80–89 years. This has already been recognised by the Mexican health authorities, and even though the recommendation by the collegiate bodies on vaccination includes this group (in those >50 years old),[7] the immunisation policy has yet to include this age group. A similar result was recently reported in a cross-sectional epidemiological study, in which the case fatality and mortality rate in this age group (50–59 years) was similar to that of patients >60 years old,[24] equivalent to an estimated range of 0.3–2.9 million cases per year. The same study also reported that vaccination of this population is cost-effective; thus, implementing vaccination in this age group would be a necessary step.

People with a diagnosis of SAH alone are not considered as a vulnerable or at-risk population in the official guidelines. In the present study, the highest ORs were found in groups <50 years of age, mainly in the group aged 20–39 years, and these are groups that are not considered in the vaccination recommendations either because of their age or because of a comorbidity with hypertension. In the last national health survey of the country,[12] it was reported that among adults aged 20–29 years, 5.6% had a previous diagnosis of SAH, in addition to 6.5% who were detected as hypertensive during the survey; in the group aged 30–39 years, these frequencies were 8.4% and 7.7%, respectively, and in the group aged 40–49 years, the frequencies increased to 16.8% for previous diagnosis and 12.1% by survey finding. Combining these results with our present findings, we found that 12.1% of those aged 20–29 years, 16.1% of the group aged 30–39 years and 28.9% of the group aged 40–49 years had a mortality risk from influenza that was 1.7 to 4 times higher than that in the population without a comorbidity with SAH. The population with SAH is not recommended for vaccination in the current policy in Mexico, which would lead to an increase in the risk of hospitalisation and death from influenza in unvaccinated patients with SAH especially when other comorbidities are present.

Conversely, the effect of SAH in younger age groups was not observed in those aged 60–79 years where the highest overall fatality was observed. A possible explanation is that because this group of patients is known to be hypertensive, they were hospitalised earlier and received a more careful medical supervision, thus avoiding a fatal outcome. Of note, the official

recommendations include this group among those recommended for vaccination.

It is essential to point out that hypertension alone is not the direct cause of death, but rather that influenza can lead to a cardiovascular event in a hypertensive patient.[32–34] In this regard, there is evidence indicating that in patients with coronary artery disease, it is advisable to vaccinate against influenza since it is associated with a decrease in all-cause mortality.[35] The same occurs with heart failure patients in whom this decrease in all-cause mortality is also shown.

Overall, findings from this study support the need to apply the vaccine recommendation to those >50 years of age and to include populations with SAH[17] in the influenza vaccination programme as a secondary prevention measure to avoid fatal outcomes. Specifically, we recommend the current guidelines be changed to replace 'Cardiovascular disease excluding SAH' with 'Cardiovascular disease including SAH'.[36] We expect that this new recommendation will benefit around 15 million people.

The present study has some limitations. Data for this study were obtained from a government database, and there are generally several limitations that must be considered for a correct interpretation of the results. For example, even though the results presented here give an epidemiological overview of the country, they do not represent the burden of disease (morbidity) because SISVER in Mexico operates under a sentinel model that covers less than 10% of the total number of health units in the country. This is not the case for deaths because according to official guidelines, 100% of influenza deaths should be reported to SISVER. Other possible reporting biases are related to vaccination history and comorbidities. Regarding the vaccination history, this is obtained by questioning the patient instead of via the submission of documents, so having an electronic vaccination system would objectively substantiate the vaccination status of any patient. As for the presence of comorbidities, this can be substantiated in inpatients, as opposed to outpatients, where it is only based on the information given by the patient. Additionally, we were not able to adjust for unknown potential risk factors because either the information was not requested from patients or may not have been listed in the clinical record and, as such, could not be reported in the database.

CONCLUSIONS

The present analysis of data from confirmed influenza cases collected by a sentinel system and 100% of deaths from influenza in Mexico during 2014 to week 20 of the year 2020 clearly shows the impact and risk that influenza has on morbidity, hospitalisation and death in patients with SAH (as the only comorbidity) as well as in those with SAH and other comorbidities. This publication adds value to the current literature in

that the data show that having SAH might represent an additional risk for complications in patients infected with influenza, highlighting the need for this group of patients to be vaccinated to reduce the morbidity and mortality risks. Therefore, we recommend that patients with SAH be included in the national recommendations for vaccination against influenza, per 2020 WHO recommendations.

Author affiliations
[1]Departamento Medico, Sanofi Pasteur Mexico, Ciudad de Mexico, Mexico
[2]Rehabilitacion Cardiaca, Instituto Nacional de Cardiologia Ignacio Chavez, Ciudad de Mexico, Mexico
[3]Facultad de Medicina, Universidad Nacional Autonoma de Mexico, Ciudad de Mexico, Mexico

ORCID iD
Elsa Sarti http://orcid.org/0000-0003-3112-2679

REFERENCES

1 World Health Organization. Up to 650 000 people die of respiratory diseases linked to seasonal flu each year, 2017. Available: https://www.who.int/news/item/13-12-2017-up-to-650-000-people-die-of-respiratory-diseases-linked-to-seasonal-flu-each-year [Accessed 09 Aug 2021].
2 Iuliano AD, Roguski KM, Chang HH, *et al*. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2018;391:1285–300.
3 European centre for disease prevention and control fact sheet for health professionals. Available: http://ecdc.europa.eu/en/healthtopics/seasonal_influenza/basic_facts/Pages/factsheet_professionals_seasonal_influenza.aspx [Accessed 09 Aug 2021].
4 Centers for Disease Control and Prevention. Pandemic influenza. Available: http://www.cdc.gov/flu/pandemic-resources/basics/past-pandemics.html [Accessed 09 Aug 2021].
5 Wang C-S, Wang S-T, Lai C-T, *et al*. Impact of influenza vaccination on major cause-specific mortality. *Vaccine* 2007;25:1196–203.
6 Gobierno de México, Secretaría de Salud, Dirección General de Epidemiología. Lineamiento estandarizado para La vigilancia epidemiológica Y POR laboratorio de la enfermedad respiratoria viral. Mayo del, 2021. Available: https://www.gob.mx/cms/uploads/attachment/file/672708/Lineamiento_VE_y_Lab_Enf_Viral_20211008.pdf [Accessed 03 Dec 2021].
7 Centro Nacional para la Salud de la Infancia y Adolescencia. Vacuna Contra La influenza Estacional, 2015. Available: https://www.gob.mx/salud/articulos/vacuna-contra-la-influenza-estacional [Accessed 09 Aug 2021].
8 Kjeldsen SE. Hypertension and cardiovascular risk: general aspects. *Pharmacol Res* 2018;129:95–9.
9 MacIntyre CR, Mahimbo A, Moa AM, *et al*. Influenza vaccine as a coronary intervention for prevention of myocardial infarction. *Heart* 2016;102:1953–6.
10 Kokubo Y, Matsumoto C. Hypertension is a risk factor for several types of heart disease: review of prospective studies. *Adv Exp Med Biol* 2017;956:419–26.
11 Campos-Nonato I, Hernández-Barrera L, Pedroza-Tobías A, *et al*. Hipertensión arterial en adultos mexicanos: prevalencia, diagnóstico Y tipo de tratamiento. Ensanut MC 2016. *Salud Publica Mex* 2018;60:233–43.
12 Shamah-Levy T, Vielma-Orozco E, Heredia-Hernández O. Encuesta Nacional de Salud Y Nutrición 2018-19, 2020. Resultados Nacionales. Instituto Nacional de Salud Publica. Available: https://www.insp.mx/produccion-editorial/novedades-editoriales/ensanut-2018-nacionales [Accessed 23 Aug 2021].
13 Modin D, Jørgensen ME, Gislason G. Influenza vaccine in heart failure: cumulative number of vaccinations, frequency, timing, and survival: a Danish nationwide cohort study. *Circulation* 2019;139:575–86.
14 Modin D, Claggett B, Joergensen ME, *et al*. The flu vaccine and mortality in hypertension. a Danish nationwide cohort study. *Eur Heart J* 2019;40:Abstract 1347.
15 Bogomolov BP, Deviatkin AV, Efimov LL, *et al*. [Microcirculation, hemostasis, and hemorheology in influenza and acute respiratory viral infections in patients with hypertension]. *Ter Arkh* 2001;73:7–11.
16 Yedlapati SH, Khan SU, Talluri S, *et al*. Effects of influenza vaccine on mortality and cardiovascular outcomes in patients with cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc* 2021;10:e019636.
17 World Health Organization. Who SAGE seasonal influenza vaccination recommendations during the COVID-19 pandemic. Available: https://www.who.int/immunization/policy/position_papers/Interim_SAGE_influenza_vaccination_recommendations.pdf?ua=1 [Accessed 09 Aug 2021].
18 Diario Oficial de la Federación. Reglamento de la Ley General de Salud en Materia de Investigación para La Salud. Available: http://www.diputados.gob.mx/LeyesBiblio/regley/Reg_LGS_MIS.pdf [Accessed 09 Aug 2021].
19 Instituto de Diagnóstico y Referencia Epidemiológicos "Dr. Manuel Martínez Báez". *Lineamientos para La vigilancia POR laboratorio de la influenza Y otros virus respiratorios*. INDRE. México: secretaría de salud, 2017. https://www.gob.mx/cms/uploads/attachment/file/647390/LVL_Virus_respiratorios.pdf
20 Dirección General de Epidemiología. Informe semanal de la temporada de influenza estacional 2019-2020 (semana 40 a la 20)/semana 52. Available: https://www.gob.mx/cms/uploads/attachment/file/520496/20191226_archivo_INFLUENZA_SE52_2019.pdf [Accessed 09 Aug 2021].
21 Barnett K, Mercer SW, Norbury M, *et al*. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380:37–43.
22 Müller L, Pawelec G. Aging and immunity - impact of behavioral intervention. *Brain Behav Immun* 2014;39:8–22.

23 Centers for Disease Control and Prevention. Key facts about influenza (flu). Available: http://www.cdc.gov/flu/keyfacts.htm [Accessed 09 Aug 2021].
24 Betancourt-Cravioto M, Falcón-Lezama JA, Saucedo-Martínez R, *et al*. Public health and economic benefits of influenza vaccination of the population aged 50 to 59 years without risk factors for influenza complications in Mexico: a cross-sectional epidemiological study. *Vaccines* 2021;9:188.
25 Dietz W, Santos-Burgoa C. Obesity and its implications for COVID-19 mortality. *Obesity* 2020;28:1005.
26 Schoen K, Horvat N, Guerreiro NFC, *et al*. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. *BMC Infect Dis* 2019;19:964.
27 Miyazawa D. Why obesity, hypertension, diabetes, and ethnicities are common risk factors for COVID-19 and H1N1 influenza infections. *J Med Virol* 2021;93:127–8.
28 Centers for Disease Control and Prevention. Prevention and Control of Influenza Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR, 39, 1-15*, 1990. Available: https://www.cdc.gov/mmwr/preview/mmwrhtml/00001644.htm [Accessed 09 Aug 2021].
29 Centers for Disease Control and Prevention. Flu & people 65 years and older. Available: https://www.cdc.gov/flu/about/disease/65over.htm [Accessed 09 Aug 2021].
30 Centers for Disease Control and Prevention. Disease burden of influenza. Available: http://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm [Accessed 09 Aug 2021].
31 Centers for Disease Control and Prevention. Flu symptoms & complications. Available: https://www.cdc.gov/flu/symptoms/symptoms.htm [Accessed 09 Aug 2021].
32 Clar C, Oseni Z, Flowers N. Influenza vaccines for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2015;5:CD005050.
33 Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis* 2009;9:601–10.
34 Udell JA, Zawi R, Bhatt DL, *et al*. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA* 2013;310:1711–20.
35 Rodrigues BS, Alves M, Duarte GS, *et al*. The impact of influenza vaccination in patients with cardiovascular disease: an overview of systematic reviews. *Trends Cardiovasc Med* 2021;31:315–20.
36 México Gde, Salud Sde. Lineamientos de vacunación para La temporada de influenza estacional 2021–2022, 2021. Available: https://www.gob.mx/salud/censia/documentos/lineamientos-de-vacunacion-para-la-temporada-de-influenza-estacional-2021-2022 [Accessed 3 Dec 2021].