

ORIGINAL ARTICLE

Severe Respiratory Disease Concurrent with the Circulation of H1N1 Influenza

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ABSTRACT

BACKGROUND

In the spring of 2009, an outbreak of severe pneumonia was reported in conjunction with the concurrent isolation of a novel swine-origin influenza A (H1N1) virus (S-OIV), widely known as swine flu, in Mexico. Influenza A (H1N1) subtype viruses have rarely predominated since the 1957 pandemic. The analysis of epidemic pneumonia in the absence of routine diagnostic tests can provide information about risk factors for severe disease from this virus and prospects for its control.

METHODS

From March 24 to April 29, 2009, a total of 2155 cases of severe pneumonia, involving 821 hospitalizations and 100 deaths, were reported to the Mexican Ministry of Health. During this period, of the 8817 nasopharyngeal specimens that were submitted to the National Epidemiological Reference Laboratory, 2582 were positive for S-OIV. We compared the age distribution of patients who were reported to have severe pneumonia with that during recent influenza epidemics to document an age shift in rates of death and illness.

RESULTS

During the study period, 87% of deaths and 71% of cases of severe pneumonia involved patients between the ages of 5 and 59 years, as compared with average rates of 17% and 32%, respectively, in that age group during the referent periods. Features of this epidemic were similar to those of past influenza pandemics in that circulation of the new influenza virus was associated with an off-season wave of disease affecting a younger population.

CONCLUSIONS

During the early phase of this influenza pandemic, there was a sudden increase in the rate of severe pneumonia and a shift in the age distribution of patients with such illness, which was reminiscent of past pandemics and suggested relative protection for persons who were exposed to H1N1 strains during childhood before the 1957 pandemic. If resources or vaccine supplies are limited, these findings suggest a rationale for focusing prevention efforts on younger populations.

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IN EARLY APRIL 2009, A SHARP INCREASE IN reports of patients requiring hospitalization for pneumonia and an unusual series of deaths were reported to the Mexican Ministry of Health. The National Epidemiological Surveillance System (SINAVE), a nationwide interagency system led by the Directorate General of Epidemiology,¹ noted a particular increase among adults between the ages of 20 and 40 years and an increase in cases of laboratory-confirmed influenza. Typically, in Mexico, seasonal influenza is observed from October through March,² with an appreciable increase in the rate of death among the elderly,³ similar to the pattern observed in other temperate climates, such as the United States.^{4,5} The concurrent finding of a swine-origin influenza A (H1N1) virus (S-OIV)⁶ from infected children in the United States⁷ prompted a rapid response from the Mexican public health emergency system.

From March 24 through April 29, 2009, there were reports of 2155 cases of severe pneumonia, including 100 deaths, to the SINAVE system in response to requests for data on patients who had required hospitalization for severe pneumonia. During this period, of the 8817 nasopharyngeal specimens that were submitted to the National Epidemiological Reference Laboratory, 3664 (42%) tested positive for influenza subtype A; of these specimens, 2582 (70%) were confirmed as S-OIV by reverse-transcriptase–polymerase-chain-reaction (PCR) assay.

In this article, we evaluate the reported case series of severe pneumonia and compare the age patterns with respect to morbidity and mortality with patterns from recent influenza epidemics in Mexico. Crucial epidemiologic factors, such as the age pattern of morbidity and mortality during the 2009 epidemic, are inferred because of the limited availability of diagnostic tests and data. Given the relatively rapid global spread of this newly described pathogen,⁸ early identification of groups at risk for severe pneumonia can aid in prioritizing the use of vaccines and antiviral drugs in the face of limited supplies.

METHODS

EPIDEMIOLOGIC SURVEILLANCE

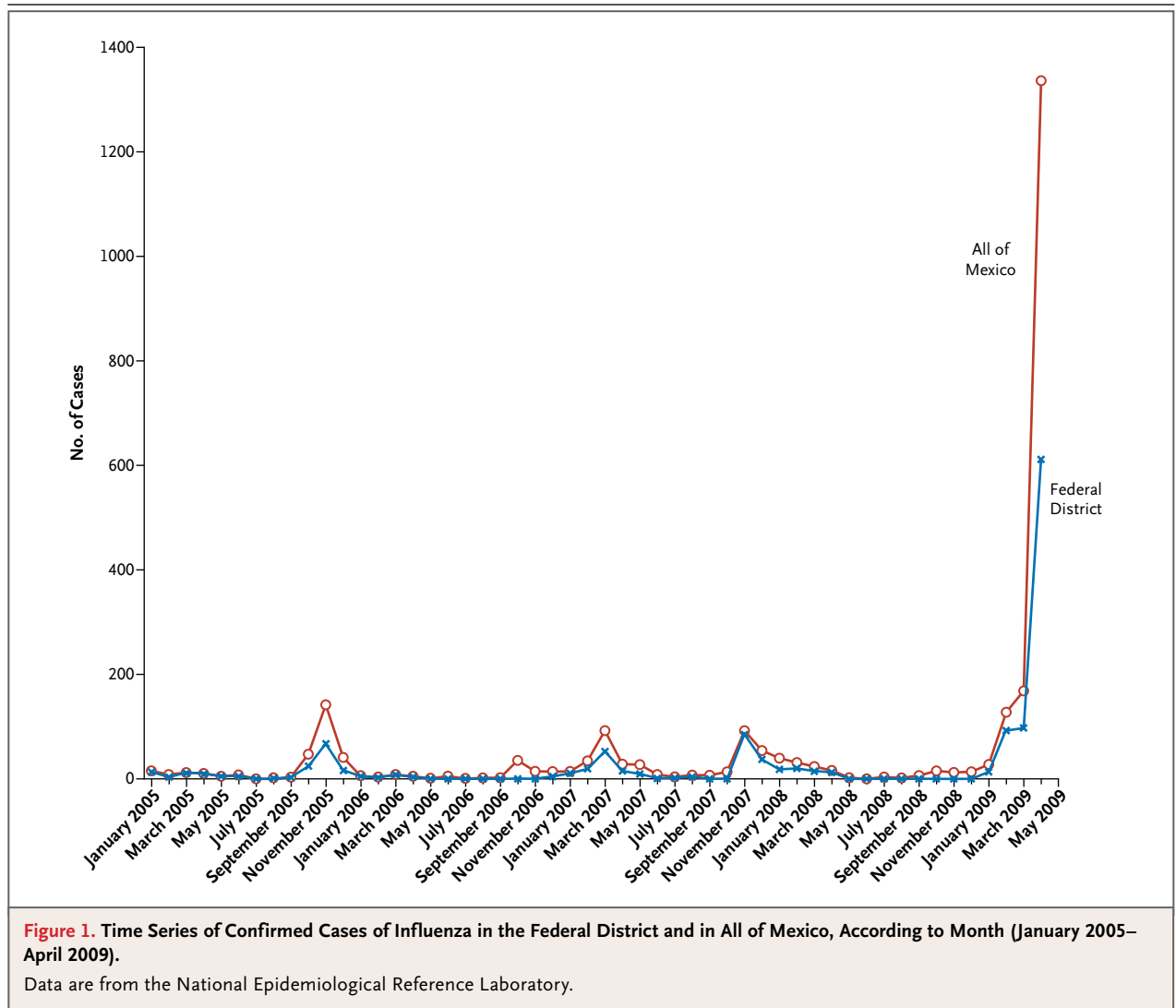
The SINAVE was established in September 1995 to harmonize surveillance procedures nationally. SINAVE receives weekly reports of 117 notifiable conditions from 19,715 of 20,472 (96%) public and private primary care clinics and hospitals in Mex-

ico. Since 2006, surveillance of influenza-like illness with testing for influenza virus has been conducted in sentinel units in all 32 states, increasing from 380 sentinel units in 2006 to 520 in 2008. Influenza-like illness is defined as fever, cough, and headache, accompanied by one or more of the following signs or symptoms: rhinorrhea, coryza, arthralgia, myalgia, prostration, odynophagia, chest pain, abdominal pain, and nasal congestion. Nasopharyngeal swabs are taken from a proportion of patients and processed with the use of an immunofluorescence assay for influenza. Positive specimens are then sent to the National Epidemiological Reference Laboratory for PCR testing. The proportion of specimens that are confirmed as positive typically ranges from 7.5 to 9.0% during influenza season.

On April 14 and April 15, 2009, the Mexican Ministry of Health received notification from several cities of cases of severe pneumonia affecting mostly young persons, coupled with an increase in the number of cases and outbreaks of seasonal influenza observed since February. Responding to this situation, on April 17, the Ministry of Health issued an epidemiologic alert and requested that medical institutions in all Mexican states intensify notification regarding patients requiring hospitalization for pneumonia through an Internet-based platform. Individual case records were reported online to the SINAVE, including the date of the onset of symptoms, the date of hospitalization, the institution reporting the case, and the patient's age, sex, and state of residence. Since influenza season normally ends in March, few of the original samples from patients during this period had undergone laboratory testing to diagnose influenza.

STUDY PERIOD

Without knowing when the index case of S-OIV infection occurred, we defined the study period as the interval from the date of the onset of symptoms in the patient with the earliest suspected case of atypical pneumonia (March 24) to April 29, when selective reporting of severe pneumonia ceased. We reviewed the records of 2155 patients with severe pneumonia in the database. Of these records, 821 (38%) indicated a date of hospitalization for pneumonia, and 100 (5%) involved deaths of patients. Although the SINAVE system captured only a portion of all hospitalizations for pneumonia, it provided the best data currently available on the rate of increase in severe pneumonia during this period.



From national registries we obtained data on age-specific cases of pneumonia and influenza and corresponding deaths during the peak of seasonal influenza periods from 2005 through 2008.⁹ Since there may be underreporting in the SINAVE and we do not expect systematic reporting bias according to age, we compared the proportion of patients in each age group between the study period and the previous periods of seasonal influenza.

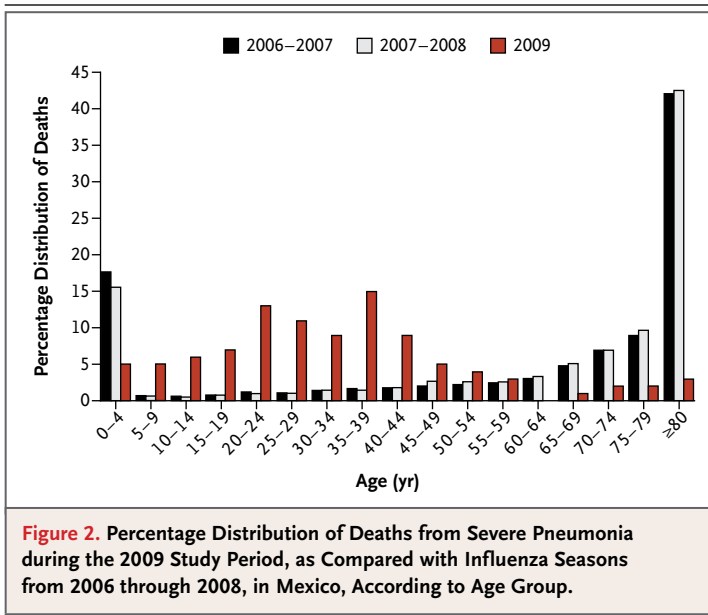
RESULTS

The time series of laboratory-confirmed influenza for the Federal District and all of Mexico from 2005 through April 2009 is shown in Figure 1. Peak epidemic periods that were used as a base-

line occurred in November and December, January through March, and November through February during three preceding influenza seasons (2005 through 2008). The influenza season in the Federal District coincided with the rest of the country for the greater part of that period.

The percentage age distributions for mortality (Fig. 2) and morbidity (Fig. 3) for all patients with severe pneumonia during the 2009 outbreak show a marked shift to persons between the ages of 5 and 59 years, as compared with distributions observed during previous periods of epidemic influenza. Similar results were observed for the data restricted to the Federal District.

The reported shift in the proportion of young adults who died from pneumonia is readily observed in the data for the study period, as compared with previous influenza seasons (Fig. 2).



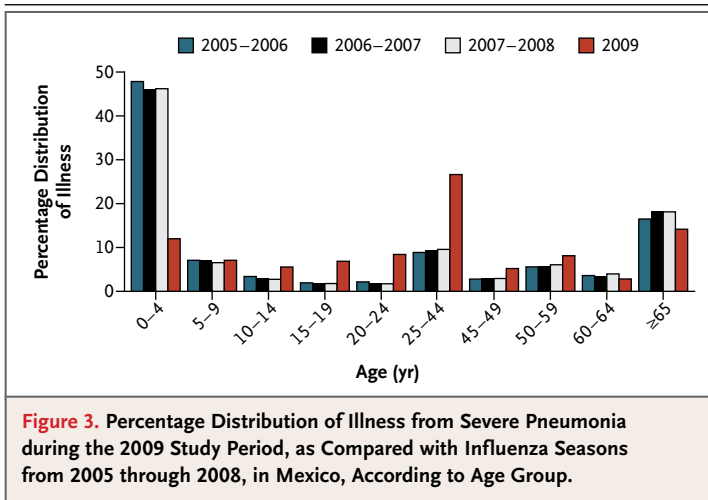
DISCUSSION

These data show a sudden increase in the rate of severe pneumonia and a shift in the age distribution of patients with such illness, which were concurrent with person-to-person circulation of S-OIV infection in Mexico. Although the epidemiologic, clinical, and virologic characteristics of this outbreak are evolving, this wave of pneumonia is reminiscent of the initial phase of pandemics from the last century.¹⁰ These factors include the documentation of a novel pathogenic influenza virus and a shift in the ages of patients who become ill or die.¹¹ Early waves of respiratory illness in young adults were observed before the 1918 influenza pandemic in New York,¹² Copenhagen,¹³ the United Kingdom,¹⁴ and Geneva,¹⁵ as well as among members of the U.S. military.¹⁶ The apparent population effect of S-OIV infection has several signature features¹⁷ of previous pandemics, including atypical timing and age shifts in disease severity.

Case ascertainment for the specific diagnosis of S-OIV infection has been limited, given the lack of commercially available tests for this virus and the scarcity of reagents in the setting of an evolving global epidemic. We address this challenge through analyses of data before, during, and after the initial acceleration of reporting activities, as well as through stratification according to region. We have also compared the data with those obtained during periods of seasonal epidemic influenza. Given variable underreporting, we have based our comparisons on proportionate distributions. Unless there are systemic biases in reporting according to age group, this approach provides a reasonable approach for comparison.

Although many cases of severe pneumonia have not yet been confirmed as S-OIV infection through laboratory diagnoses, given the limited availability of specific assays for the new pathogen, the proportional increase in incidence among younger adults and the high proportion of patients with confirmed S-OIV infection (44%) lead us to believe that a large proportion of the reported cases are probably associated with this novel pathogen. A similar study that was performed in Denmark during the 1918 outbreak indicated that during a wave of atypical pneumonia, there was an increase by a factor of 20 in incidence, as compared with that in preceding years, which implied that influenza was the putative agent.¹³

Influenza A (H1N1) viruses were in circulation from 1918 through 1957, and genetically similar



Percentage increases in death were seen in subgroups of patients between the ages of 5 and 59 years, representing 87% of deaths from severe pneumonia during the study, as compared with 17% on average during previous epidemic periods. Percentage increases ranged from a factor of 1.2 to a factor of 11.7, with percentage decreases in the subgroup of patients under 4 years of age (0.3) and in subgroups of patients 60 years of age or older (0 to 0.3) (Table 1). Shifts in morbidity were pronounced, with 71% of cases of severe pneumonia occurring in patients between the ages of 5 and 59 years, as compared with an average of 32% of cases in that age group during the referent periods (Fig. 3).

isolates, most likely representing a laboratory escape, reemerged in 1977 to periodically cocirculate with A (H3N2) subtypes. In 1976, a limited number of swine-influenza cases set off a massive vaccine campaign to control a potential pandemic, which fortunately never occurred. However, unlike the situation in 1976, epidemiologic evidence from this outbreak indicates that there were continuous chains of person-to-person transmission for several viral generations. Since the discovery of influenza viruses, the past two influenza pandemics have been characterized by novel subtypes. Although humans have previously been exposed to the influenza A (H1N1) subtype, this novel virus has made a host-species jump with sustained human-to-human transmission.

In 1918, patients who were documented with illness during the early waves of severe pneumonia in Denmark and among members of the U.S. military were less likely to be ill in the later wave of the pandemic,^{13,16} which suggests the possibility of natural infection with a less virulent but antigenically similar virus in the general population. It is unclear whether this circulating virus would have a similar effect if it recirculated after the initial wave. Likewise, childhood exposure to influenza A (H1N1) viruses in persons who were born before 1957, when these viruses circulated widely, may have conferred some level of protection.

Of note, during the study period, there was proportionately lower morbidity among persons who were 60 years of age or older, the age group in which all persons were born before the 1957 pandemic. With an annual influenza incidence of 15 to 20%, most of these persons would have been first exposed to influenza A (H1N1) strains, which disappeared from circulation after the 1957 A (H2N2) influenza pandemic. Francis described the concept of "original antigenic sin," in which the immune response is greatest to antigens to which first exposure occurred in childhood.¹⁸ According to this concept, persons born before 1957 who were exposed in childhood to influenza A (H1N1) viruses might be better protected against this viral subtype than those who were first exposed to other influenza A subtypes, H2N2 and H3N2, at a later date. Age shifts in mortality to younger populations during pandemics have been described from the reemergence of a subtype.¹⁹ Although persons who were born after 1977 may have been first exposed to an influenza A (H1N1) subtype virus, such strains rarely predominate. In this data series, persons who were 60 years of age or older

Table 1. Proportion of Mortality from Severe Pneumonia According to Age Group during the 2009 Study Period, as Compared with Influenza Seasons from 2006 through 2008, in Mexico.*

Age Group <i>yr</i>	Mortality		
	2006–2008 Influenza Seasons <i>percent</i>	March 24 to April 29, 2009	Ratio, Study Period to Referent Period
0–4	17	5	0.3
5–9	1	5	7.6
10–14	1	6	10.7
15–19	1	7	8.6
20–24	1	13	11.7
25–29	1	11	10.3
30–34	1	9	6.0
35–39	2	15	9.4
40–44	2	9	4.8
45–49	2	5	2.1
50–54	2	4	1.6
55–59	3	3	1.2
60–64	3	0	0.0
65–69	5	1	0.2
70–74	7	2	0.3
75–79	9	2	0.2
≥80	42	3	0.1

* Data were reported by the National System of Health Care Information and the National Epidemiological Surveillance System (SINAVE).

were proportionately less likely to have severe pneumonia, a consideration for future strategies for vaccine allocation.²⁰

An early wave of influenza in northern England during the 1951 influenza season was documented with even higher mortality than that of the 1918 pandemic, but the situation never evolved into a pandemic.²¹ Similarly, the public health community acted swiftly to develop a vaccine in response to human cases of swine influenza in 1976, and a pandemic did not occur.²² During the early phase of this epidemic, the rapid identification of persons who are likely to have severe disease, as compared with those who are likely to have mild disease, can guide epidemic or pandemic response strategies. Our outline of the age-stratification profile of risk provides a possible foundation for control strategies on the basis of the biologic plausibility of partial protection from earlier exposure. Further studies are under way in Mexico to elucidate other potential risk factors

for severity of S-OIV infection to guide targeted control efforts.

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REFERENCES

1. Sistema Nacional de Vigilancia Epidemiológica (SINAVE). Mexico City: Mexico Ministry of Health. (Available at <http://www.dgepi.salud.gob.mx/sinave/index.htm>.)
2. Viboud C, Alonso WJ, Simonsen L. Influenza in tropical regions. *PLoS Med* 2006;3(4):e89.
3. Chowell G, Viboud C, Wang X, Miller M. Evaluating vaccination strategies against pandemic influenza in Mexico. Geneva: World Health Organization, 2008.
4. Serfling RE. Methods for current statistical analysis of excess pneumonia-influenza deaths. *Public Health Rep* 1963;78:494-506.
5. Reichert TA, Simonsen L, Sharma A, Pardo SA, Fedson DS, Miller M. Influenza and the winter increase in mortality in the United States, 1959-1999. *Am J Epidemiol* 2004;160:492-502.
6. A/Texas/04/2009(H1N1) gene sequence. Bethesda, MD: National Center for Biotechnology Information, 2009. (Accessed June 17, 2009, at <http://www.ncbi.nlm.nih.gov/nuccore/229299531?report=genbank>.)
7. Swine influenza A (H1N1) infection in two children — Southern California, March–April 2009. *MMWR Morb Mortal Wkly Rep* 2009;58:400-2.
8. Epidemic and Pandemic Alert and Response (EPR): influenza A(H1N1). Geneva: World Health Organization, 2009. (Accessed June 17, 2009, at <http://www.who.int/csr/disease/swineflu/en/index.html>.)
9. Sistema Nacional de Información en Salud [National System of Health Care Information]. Mexico City: General Directorate of Health Care Information. (Accessed June 17, 2009, at <http://sinais.salud.gob.mx/>.)
10. Simonsen L, Olson DR, Viboud C, Taylor RJ, Miller MA, Reichert T. Pandemic influenza and mortality: past evidence and projection for the future. In: Knobler SL, Mack A, Mahmoud A, Lemon SM, eds. *The threat of pandemic influenza: are we ready?* Washington, DC: National Academy Press, 2005:89-114.
11. Simonsen L, Clarke MJ, Schonberger LB, Arden NH, Cox NJ, Fukuda K. Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. *J Infect Dis* 1998;178:53-60.
12. Olson DR, Simonsen L, Edelson PJ, Morse S. Epidemiological evidence of an early wave of the 1918 influenza pandemic in New York City. *Proc Natl Acad Sci U S A* 2005;102:11059-63.
13. Andreasen V, Viboud C, Simonsen L. Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implications for pandemic control strategies. *J Infect Dis* 2008;197:270-8.
14. Chowell G, Bettencourt LM, Johnson N, Alonso WJ, Viboud C. The 1918-1919 influenza pandemic in England and Wales: spatial patterns in transmissibility and mortality impact. *Proc Biol Sci* 2008;275:501-9.
15. Chowell G, Ammon CE, Hengartner NW, Hyman JM. Estimation of the reproductive number of the Spanish flu epidemic in Geneva, Switzerland. *Vaccine* 2006;24:6747-50.
16. Barry JM, Viboud C, Simonsen L. Cross-protection between successive waves of the 1918-1919 influenza pandemic: epidemiological evidence from US Army camps and from Britain. *J Infect Dis* 2008;198:1427-34.
17. Miller MA, Viboud C, Balinska M, Simonsen L. The signature features of influenza pandemics — implications for policy. *N Engl J Med* 2009;360:2595-8.
18. Francis JT. On the doctrine of original antigenic sin. *Proc Am Philos Soc* 1960;104:572-8.
19. Simonsen L, Reichert TA, Miller MA. The virtues of antigenic sin: consequences of pandemic recycling on influenza-associated mortality. In: *Options for the control of influenza V. International Congress Series* 2004;1263:791-4.
20. Miller MA, Viboud C, Olson DR, Grais RF, Rabaa MA, Simonsen L. Prioritization of influenza pandemic vaccination to minimize years of life lost. *J Infect Dis* 2008;198:305-11.
21. Viboud C, Tam T, Fleming D, Miller MA, Simonsen L. 1951 Influenza epidemic, England and Wales, Canada, and the United States. *Emerg Infect Dis* 2006;12:661-8.
22. Neustadt R, Fineberg H. *The epidemic that never was: policy-making and the swine flu affair.* New York: Vintage Books, 1983.

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