Major Article

The characteristics, clinical manifestations and outcomes of pandemic influenza A (H1N1) 2009 in the elderly

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ABSTRACT

Introduction: The objetctive of this study was to evaluate the 2009 Pandemic Influenza A (H1N1) in the elderly and identify the clinical characteristics, mortality and prognostic factors of the infection in these patients. **Methods:** This was an observational, retrospective study. Data were collected from the National Notifiable Diseases (SINAN), from the Brazilian Ministry of Health. Only patients 60 years old or more that had laboratory confirmed infections were included. The socio-demographic and clinical variables and outcomes were evaluated to compare mortality rates in the presence or absence of these factors. **Results:** We included 93 patients in the study, 16.1% of whom died. The symptoms of cough and dyspnea, the use of the antiviral oseltamivir, influenza vaccine and comorbidities influenced the outcomes of cure or death. Chest radiography can aid in diagnosis. **Conclusions:** Although relatively few elderly people were infected, this population presented high lethality that can be justified by the sum of clinical, physical and immunological factors in this population. Treatment with oseltamivir and vaccination against seasonal influenza have significantly reduced rates of hospitalization and mortality.

Keywords: Pandemic influenza A (H1N1). Elderly. Clinical characteristics.

INTRODUCTION

Influenza, also known as the flu, is an acute, infectious disease that affects the respiratory system, has a universal distribution and causes a higher number of cases during the winter months[1-3]. The importance of influenza stems from its ability to spread throughout the population and the resulting morbidity and mortality in specific population groups[1,4].

Seasonal influenza usually has a higher incidence in elderly populations, children less than 2 years old and individuals with chronic disease, with the highest mortality rate being observed in the elderly[4]. However, in epidemic or pandemic periods, the highest rate of mortality occurs in populations under 65 years of age[5].

There is a broad clinical spectrum for Influenza[6]. Evolution of the disease is usually benign and self-limiting, and a reduction in symptoms usually occurs in an average of three days[7-11]. However, in the elderly, very young children, and individuals at high risk, with comorbidities or who are pregnant, the clinical symptoms of seasonal influenza can evolve to be serious[7,9,10,12]. Complications that can occur are sinusitis, otitis, pneumonia, dehydration or worsening of chronic diseases such as heart failure, asthma or diabetes[9].

Over the past 20 years, respiratory diseases have been the third leading cause of death among the 60 and older population in Brazil[13]. To reduce mortality and decrease the cost of hospitalization and treatment of secondary infections, one of the public health measures adopted in Brazil to prevent influenza and its severe complications is the annual campaign for influenza vaccination[14]. Each year, the composition of the vaccine strains are reviewed and updated by the epidemiological surveillance services based on the main circulating viruses[15].

Currently, have been few studies conducted on the 2009 Pandemic Influenza A (H1N1) in the elderly, including its impact on the rates of hospitalizations and deaths. The objective of this study was to determine the clinical profile of the disease in an elderly Brazilian subpopulation and to explore data about the mortality of the disease according to the presence or absence of potential risk factors. The results of this study could contribute to the knowledge of the epidemiology of influenza in elderly patients.

METHODS

This is a retrospective, observational study using data from structured questionnaires pertaining to registration information pandemic influenza A (H1N1) 2009 of the national information system for notifiable diseases (SINAN), from the Ministry of Health. Data were obtained from disease notification records of patients from the state of Paraná that had a diagnosis of influenza A (H1N1) during the year of 2009, provided by the Health Secretary of the State of Paraná.

The study population consisted of elderly individuals aged 60 years old or more. All cases confirmed as the

2009 Pandemic Influenza A (H1N1) by RT-PCR (reverse-transcription polymerase chain reaction) were included in the analysis. After collection, the data were individually inspected for any inconsistencies or missing information.

The included variables were age, hospitalizations, immunizations, the presence of any risk factors for worsening of influenza highlighted in the SINAN (yes or no, separately), test results of chest radiography, the use of oseltamivir, and the dates of symptom onset, initiation of treatment with oseltamivir (when treated) and death.

In the statistical analysis, we compared mortality associated with Pandemic Influenza A (H1N1) infection among the elderly in 2009 according to the presence or absence of traits measured by the variables. Descriptive statistics included the calculation of mean and standard deviation for continuous variables and absolute numbers and proportions for categorical variables. The study of risk factors was performed by comparing the distribution of variables based on the outcomes of cured, death and hospitalization. These comparisons were performed using the z-test comparison of proportions, the chi-square test (categorical variables), Student's t-test (continuous variables) and measures of central tendency. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 17.0 software, and values of $p < 0.05$ were considered statistically significant.

Ethical considerations

This project complies with the principles contained in the Declaration of Helsinki, meets the specific legislation of Brazil and was approved by the Ethics and Research Committee from Universidade Federal do Paraná, by number: 0038.0.091.000-10.

RESULTS

In the State of Paraná 121,513 suspected cases of influenza A (H1N1) 2009 were reported in 2009. Of these, 72,776 were considered of new viral subtype, 364 have been identified as other infectious agents (295 seasonal flu; and the rest divided into adenovirus, pneumonia, tonsillitis, influenza B, parainfluenza, rhinovirus or respiratory syncytial virus), 27,768 were discarded and 20,605 did not record the final result. Among the cases of the new virus subtype, 5,695 were laboratory confirmed by RT-PCR, 66,954 were diagnosed by clinical-epidemiological criteria and 127 did not contain this information.

Among patients diagnosed by RT-PCR and who had no missing or inconsistent data, 6.8% were aged up to 2 years, 16% aged 3 to 10 years, 21.1% 11 to 19 years, 25.8% 20 to 29 years, 14.1% 30 to 39, 8.3% 40 to 49 and 6% 50 to 59. Ninety-three patients over the age of 60 years with a Pandemic Influenza A (H1N1) infection during the pandemic of 2009 were included in this study, representing 2% of cases. These individuals were included in this study.

All of the patients had an influenza A infection that was confirmed in the laboratory by RT-PCR. The first laboratory-confirmed case of the disease in the elderly population occurred on June 20, 2009 in a 60-year-old woman. **Figure 1** shows the temporal distribution of the 2009 Pandemic Influenza A (H1N1) laboratory-confirmed cases occurring in the elderly population

during 2009. The period with the highest incidence of cases coincided with the seasonality of the disease during the winter months.

Fifteen deaths, representing 16.1%, were recorded from complications of Pandemic Influenza A (H1N1) in 2009. The average time between the date of symptom onset and death was 13.9 days (3-37). Only one patient died at home without hospitalization. All of the other cases of death occurred in a hospital.

As illustrated in **Figure 2**, there are differences in mortality rates when the patients are divided into age groups. The age groups 60-69 years and ≥ 80 years had mortality rates higher than the average total of 16.1%. The highest mortality rate was observed in patients over the age of 80 years. Two patients of the seven patients in this age group died.

Among the subjects included in the study, 38 (40.9%) patients had been previously vaccinated against seasonal influenza, two (5.3%) of which died. Comparing among the 15 patients who died, only 2 (13.3%) of these patients had been previously vaccinated. Therefore, 86.7% of the deaths occurred in unvaccinated elderly patients, suggesting that vaccination may reduce the number of influenza-associated deaths. The mortality rate observed in unvaccinated patients was 15% (6/40) and was significantly ($p < 0.05$) higher than that observed among the vaccinated patients, which was 5.2% (2/38). Similarly, the hospitalization rate among unvaccinated patients, which was 62.5% (25/40), was significantly higher than that observed among those who received the influenza vaccine, which had a rate of 44.7% (17/38).

Table 1 lists the patient characteristics compared with disease outcome.

In this sample of elderly people who contracted the disease, 50.5% were male and 78.5% were white. There were two illiterate patients and six patients who received higher education. Regarding the presence of comorbidities, 61.3% of patients had at least one underlying medical condition. Among the comorbidities reported, the main comorbidities were heart disease and diabetes, and none of these characteristics showed a significant relationship with cure or death rates. The z-test comparison of proportions indicated that in relation to the characteristic color / ethnicity, although not significant, there was a higher cure rate in white patients and a higher proportion of deaths among non-white patients.

Only 44 patients provided information regarding whether they had used the antiviral oseltamivir. Of those that responded, 88.6% were treated with oseltamivir. The median time to initiation of treatment after symptom onset was 2.6 (0-8) days in patients who progressed to healing and 4.6 (0-12) days in patients who subsequently died. All untreated patients subsequently died. However, among the treated patients, only one quarter progressed and died from the disease. Treatment with oseltamivir was significantly correlated with outcome (p=0.001).

With regard to hospitalization, 58.1% of the elderly were hospitalized as a result of the disease. Hospitalization was also significantly correlated with outcome (p=0.003), with an increased rate of death being observed in those that were hospitalized. The need for hospitalization was observed in the
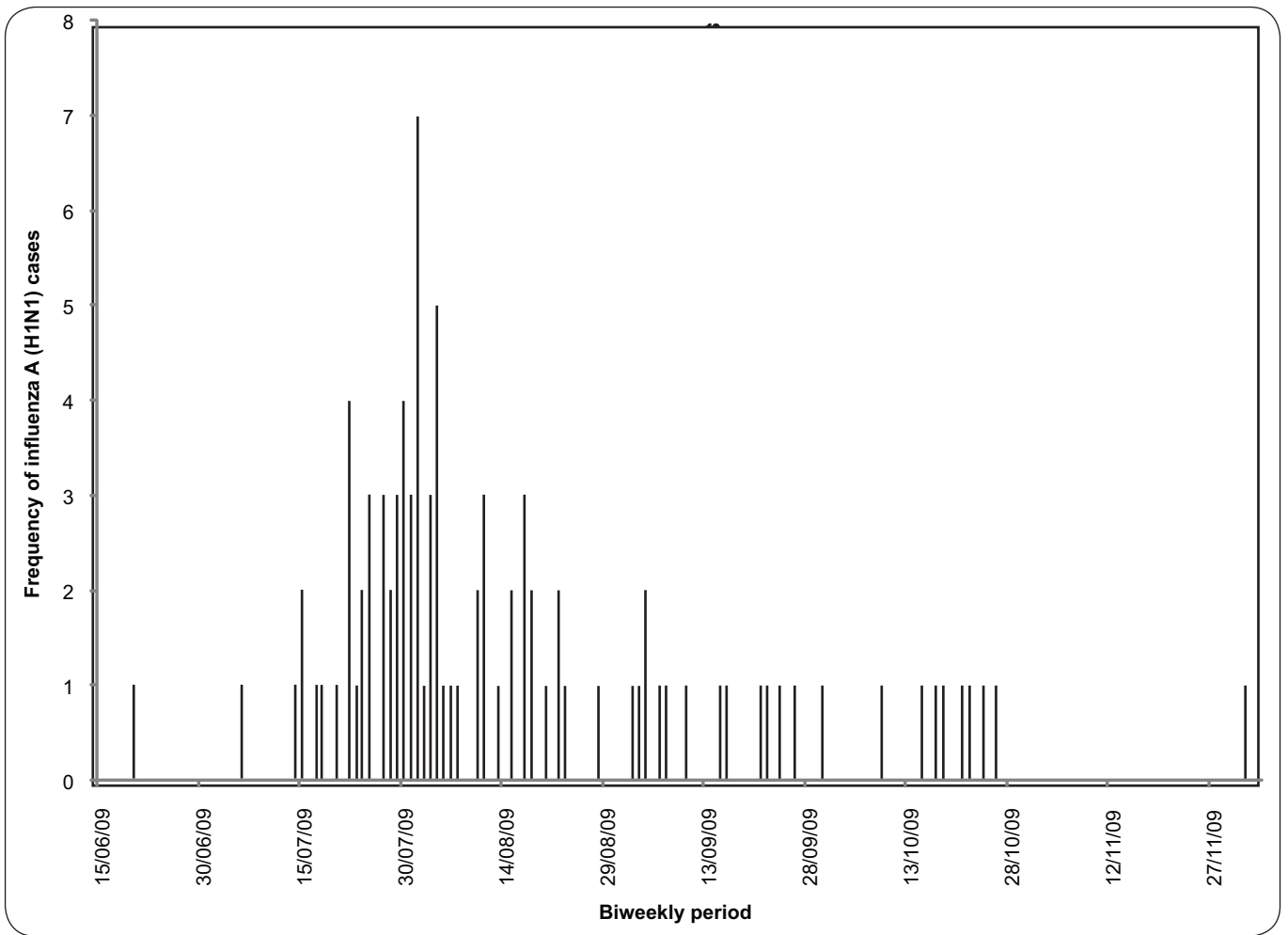
FIGURE 1 - The temporal distribution of laboratory-confirmed cases of influenza A (H1N1) in the elderly.
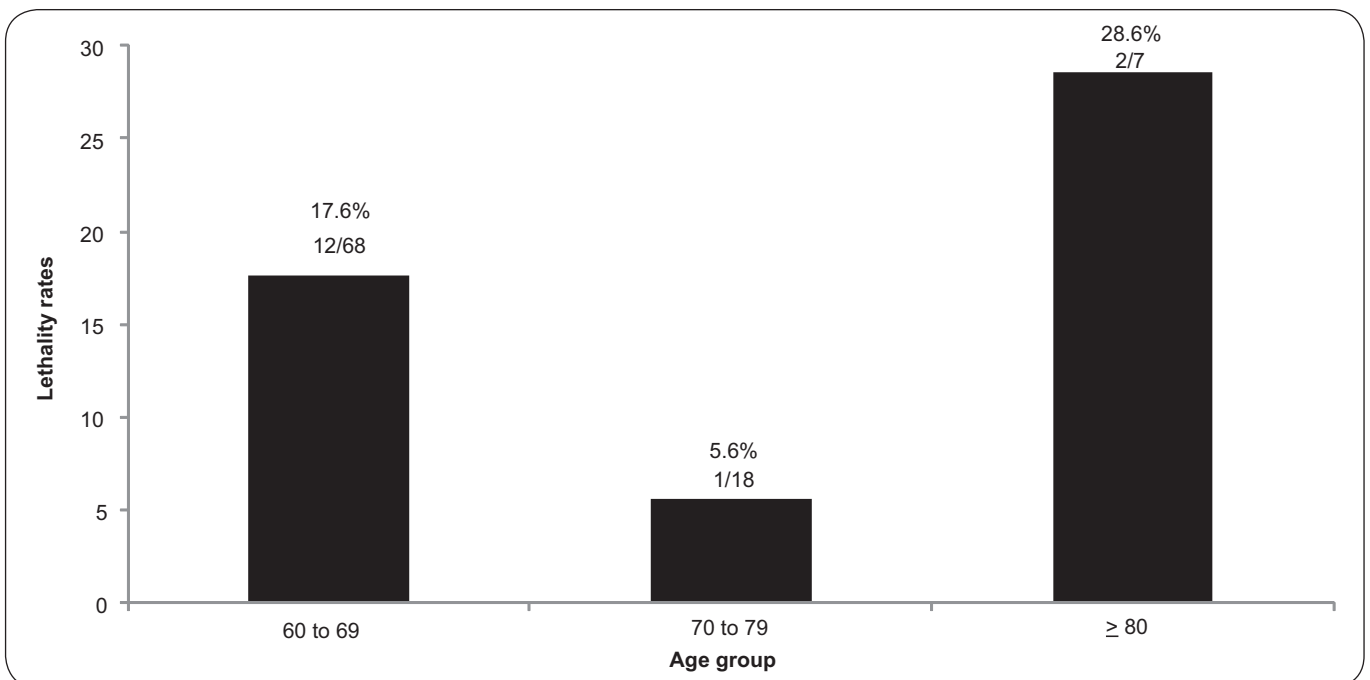

FIGURE 2 - A comparison of the mortality rates in the elderly according to their age.

TABLE 1 - Main characteristics of 2009 pandemic influenza A (H1N1) on Brazilian elderly people

Characteristics	Cases		Cure		Death		p	Z-test
	n	%	n	%	n	%		
Gender								
male	47	50.5	40	85.1	7	14.9	0.743	
female	46	49.5	38	82.6	8	17.4		
Color/ethnic								
white	73	7.5	65	89.0	8	11.0		C > D
black	1	1.1	1	100.0	0	0.0		
Asian	2	2.2	1	50.0	1	50.0		
brown	12	12.9	7	58.0	5	41.7	0.089	D > C
Indian	1	1.1	1	100.0	0	0.0		
NR	4	4.3	3	75.0	1	25.0		
Education								
illiterate	2	2.2	2	100.0	0	0.0		
primary level	24	25.8	21	87.5	3	12.5		
secondary level	7	7.5	6	85.7	1	14.3	0.612	
high school	7	7.5	7	100.0	0	0.0		
superior level	6	6.5	6	100.0	0	0.0		
NR	47	50.5	36	76.6	11	23.4		
Comorbidities								
without comorbidities	36	38.7	29	80.6	7	19.4	0.490	
with comorbidities	57	61.3	49	86.0	8	14.0		
heart disease	23	24.7	21	91.3	2	8.7	0.264	
pneumopathy	10	10.8	9	90.0	1	10.0	0.577	
nephropathy	4	4.3	4	100.0	0	0.0	0.370	
imunosupression	7	7.5	6	85.7	1	14.3	0.890	
smoking	12	12.9	10	83.3	2	16.7	0.957	
diabetes	14	15.1	12	85.7	2	14.3	0.839	
hypertension	12	12.9	10	83.3	2	16.7	0.957	
obesity	3	3.2	2	66.7	1	33.3	0.410	
Oseltamivir								
not treated	5	11.4	0	0.0	5	100.0	0.001	
treated	39	88.6	29	74.4	10	25.6		
Hospitalization								
no	39	41.9	38	97.4	1	2.6		C > D
yes	54	58.1	40	74.1	14	25.9	0.003	D > C

D: death; C: cure; NR: not related; Z-test: compare column proportions.

clinically more severe cases, thus justifying the higher frequency of deaths in this group. We observed that patients who died had a median hospital stay of 11.4 days (1-32). However, death occurred despite drug treatment and intensive care during hospitalization, emphasizing the need for disease prevention. Of the 15 deaths observed, 14 (93.3%) occurred in patients who required hospitalization.

In **Table 2**, the results of the observed clinical manifestations of the disease compared to disease outcome are shown.

The main signals and symptoms of the disease were cough, fever, dyspnea, myalgia, chills and coryza, and greater than 50% of the patients experienced these symptoms. No patients contracted pneumonia, and one patient had orotracheal bleeding, which later progressed and resulted in death. Cough and dyspnea

TABLE 2 - Clinical manifestations of the 2009 influenza A (H1N1) virus in elderly people

Clinical manifestations	Cases		Cure		Death		p	Z-test
	n	%	n	%	n	%		
Signals and symptoms								
fever	79	84.9	66	83.5	13	16.5	0.839	
cough	88	94.6	76	86.4	12	13.6	0.006	C > D
chill	54	58.1	47	87.0	7	13.0	0.329	
dyspnea	62	66.7	48	77.4	14	22.6	0.017	D > C
sore throat	37	39.8	34	91.9	3	8.1	0.087	
arthralgia	29	31.2	26	89.7	3	10.3	0.307	
myalgia	61	65.6	51	83.6	10	16.4	0.924	
conjunctivitis	5	5.4	5	100.0	0	0.0	0.313	
coryza	48	51.6	40	83.3	8	16.7	0.884	
diarrhea	12	12.9	12	100.0	0	0.0	0.104	
vomiting	6	6.5	6	100.0	0	0.0	0.267	
nausea	3	3.2	3	100.0	0	0.0	0.440	
headache	19	20.4	18	94.7	1	5.3	0.149	
chest pain	1	1.1	1	100.0	0	0.0	0.659	
hemoptysis	1	1.1	1	100.0	0	0.0	0.659	
pneumonia	0	0.0	-	-	-	-	-	
orthotracheal bleeding	1	1.1	0	0.0	1	100.0	0.659	
Results of chest radiography								
normal	7	22.6	7	100	0	0.0		
interstitial infiltrate	19	61.3	15	78.9	4	21.1	0.014	
consolidation	2	6.4	1	50.0	1	50.0		
mixed	3	9.7	0	0.0	3	100.0		

D: death; C: cure; Z-Test: compare column proportions.

were the only symptoms that showed a significant relationship with outcomes. Dyspnea occurred in greater proportion among patients who subsequently died, indicating that it is related to clinical severity and higher mortality rate. However, a cough occurred in a higher proportion among those who experienced cure. The main symptoms of the patients who died, in decreasing order of frequency, were dyspnea, coryza, fever, myalgia and chills.

One of the tests performed during the clinical consultation was a chest radiograph. The results of the exam were obtained from 31 patients and showed that the highest death rates were found among patients with interstitial infiltrate and a mixed pattern (interstitial infiltrate and consolidation).

DISCUSSION

The mortality rate among the elderly in this study was higher than the rate observed in the general population, showed by laboratory diagnosis, whose value was found to be 5.8%, as described by Lenzi et al[16]. The elderly in this study, divided by age, showed mortality rates lower than those found in other studies conducted in California, which showed rates of 37.8%, 42.3% and 36% for ages 60-69, 70-79 and over 80 years of age, respectively[17]. Nevertheless, other studies have reported mortality rates of 2.2%[18] and 1.7%[19]. The variations between these results can be justified by differences in the clinical severity of disease according to geographical region, climate and host adaptation[6]. The average time from symptom onset to death in our study was 13.9 days, which was similar to the time period of 14 days observed in California[17].

The rate of oseltamivir treatment was 88.6% in our study and was similar to the treatment rate of 80% observed in another study[17]. Early treatment within 2 days after the onset of symptoms was significantly associated with a lower risk of emergency admissions and death in hospitalized patients who contracted the 2009 Pandemic Influenza A (H1N1)[20,21]. Our results agree with other studies suggesting that oseltamivir treatment is beneficial[21,22].

Our results suggest benefits that elderly persons may receive from vaccination. However, despite the reduction in hospitalization and mortality rates observed among vaccinated patients, the overall effectiveness of vaccination in the elderly is uncertain[17]. A large, randomized, controlled trial using

vaccinated subjects slightly older and with higher prevalence rates of all the baseline medical conditions except dementia or stroke, found that vaccination for seasonal flu was associated with a 27% reduction in the risk of hospitalization for pneumonia or influenza (adjusted odds ratio, 0.73; 95% confidence interval [CI], 0.68 to 0.77) and a 48% reduction in the risk of death (adjusted odds ratio, 0.52; 95% CI, 0.50 to 0.55)[23]. Reliable estimates of the benefits of vaccination are important for establishing informed policies regarding resource allocation for the immunizations and identifying the need for new vaccines and strategies for the prevention and control of influenza in this group.

The absence of association between comorbidity and outcomes can be explained by the prevalence of other risk factors, such as age. About age, the risk attributed to the presence of comorbidity seems to be neutralized, since all individuals belong to the same age group. Another study with patients of all age groups showed an association between death and age over 50 years (OR: 11.521, 95% CI 5.804-22.869) and the number of comorbidities (OR: 1.367, 95% CI 1.122-1.664)[24]. This evidence confirms the hypothesis suggested that the risk factor age exceeded the risk of comorbidities, making them no significant between individuals in the same age range.

The 2009 pandemic, despite antigenic changes in the virus, shared similarities with the Group A (H1N1) viruses that were circulating in the twentieth century[25]. Adults over 60 years old may have presented with fewer cases of infection compared to other age groups (children, youth and adults) because of the presence of pre-existing immunity. However, once infected, hospitalization and mortality rates were high. The symptoms were mild and similar to seasonal influenza and may also be mistaken for other diseases such as the common cold and dengue. No underlying medical conditions (comorbidities) significantly increased the rate of death. There were no differences in the rates of death among patients with comorbidities compared to that of previously health (no comorbidity) patients. Thus, it was not possible to identify specific risk factors for complications and death among these elderly patients.

This study has some limitations. These limitations include underreporting and inaccuracy of data collected from retrospective records. Furthermore, the temporal information was collected in days, which prevented the reporting of time from symptom onset to treatment initiation in hours.

The elderly accounted for the lowest percentage of cases among the total number of laboratory-confirmed patients; however, among the sick elderly patients, the percentage of deaths was high. However, the data failed to isolate any characteristic as a risk factor for death from the 2009 Pandemic Influenza A (H1N1) in the elderly population. The sum of the clinical, physical and immunological characteristics may explain the high rates of mortality in this population. In addition to treatment with oseltamivir, which significantly reduced the mortality from the disease, vaccination against seasonal influenza was shown to reduce the rates of hospitalization and mortality. Like seasonal flu, pandemic data suggest that the elderly constitute a high-risk group, thus requiring the adoption of preventive measures. The vulnerability of the elderly to severe illness should not be underestimated.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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