Pandemic influenza A (H1N1) 2009: risk factors for hospitalization*

Influenza pandêmica A (H1N1) 2009: fatores de risco para o internamento

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Abstract

Objective: To evaluate pandemic influenza A (H1N1) 2009 in hospitalized patients in order to identify risk factors for hospitalization and, consequently, for the worsening of the disease. **Methods:** This retrospective observational study was conducted between March and December of 2010. The data were collected from the Brazilian Ministry of Health National Case Registry Database. We included only patients (inpatients and outpatients) in whom H1N1 infection was confirmed (via laboratory testing) during the study period. The variables regarding demographic and clinical characteristics were statistically evaluated in order to compare the hospitalization rates in the presence or absence of these factors. Risk factors were identified by logistic regression analysis. **Results:** We included 4,740 patients with laboratory confirmation of H1N1 infection. Of these, 1,911 individuals were hospitalized, and 258 (13.5%) died. The risk factors for hospitalization were age (20-29 years), African or Indigenous ethnicity, presence of specific comorbidities (heart disease, lung disease, kidney disease, hemoglobinopathy, immunosuppression, diabetes, obesity, puerperium, and smoking), a high number of comorbidities, and specific symptoms (dyspnea, diarrhea, vomiting, chest pain, hemoptysis, pneumonia, and wheezing). Higher levels of education and early use of oseltamivir were found to be protective factors. Hospitalization contributed to an increase in survival. **Conclusions:** Knowledge of the epidemiological characteristics that can be associated with hospitalization, disease severity, and mortality can be helpful in the adoption of preventive measures, as well as in the early diagnosis and treatment of disease, which might contribute to the reduction in the numbers of hospitalizations and deaths.

Keywords: Influenza A virus, H1N1 subtype; Hospitalization; Risk factors; Oseltamivir.

Resumo

Objetivo: Avaliar os aspectos da influenza pandêmica A (H1N1) 2009 em pacientes hospitalizados a fim de identificar os fatores de risco para o internamento e, consequentemente, para o agravamento da doença. **Métodos:** Estudo observacional e retrospectivo realizado entre março e dezembro de 2010. Os dados foram coletados a partir do Sistema Nacional de Agravos de Notificação do Ministério da Saúde. Foram incluídos somente os pacientes hospitalizados e não hospitalizados com confirmação laboratorial da infecção durante o período de estudo. As variáveis referentes às características demográficas e clínicas foram avaliadas estatisticamente a fim de comparar as taxas de internamento na presença ou na ausência desses fatores. Os fatores de risco foram identificados por regressão logística. **Resultados:** Foram incluídos no estudo 4.740 pacientes com confirmação laboratorial da infecção. Desses, 1.911 foram internados, e 258 (13,5%) foram a óbito. Os fatores de risco para o internamento foram idade (faixa etária de 20 a 29 anos), etnia negra ou indígena, presença de algumas comorbidades (cardiopatias, pneumopatias, nefropatias, hemoglobinopatia, imunodepressão, diabetes, obesidade, puerpério e tabagismo), número alto de comorbidades associadas, e alguns sintomas (dispneia, diarreia, vômito, dor torácica, hemoptise, pneumonia e sibilos). Níveis maiores de escolaridade e uso precoce do oseltamivir foram relacionados a fatores de proteção. A hospitalização contribuiu para o aumento da sobrevida. **Conclusões:** O conhecimento das características epidemiológicas que podem estar associadas a internação, gravidade da doença e mortalidade podem ser úteis na adoção de medidas preventivas e no diagnóstico e tratamento precoce da doença, colaborando para a diminuição dos óbitos e da necessidade de hospitalização.

Descritores: Vírus da influenza A subtipo H1N1; Hospitalização; Fatores de risco; Oseltamivir.

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Introduction

Influenza has a worldwide distribution, usually being seasonal or endemic, with localized outbreaks.[1] However, because of the ability of the virus to mutate frequently, when the population comes into contact with a new variant of the virus, there can be epidemics or pandemics.[2] The ability of the virus to spread and disseminate is high and can impact morbidity and mortality in specific groups of the population.[3,4]

In general, influenza presents as an asymptomatic or oligosymptomatic viral infection with a benign, self-limiting course. However, the severity of the disease can be affected by different geographic contexts and seasonal conditions, and can also vary depending on whether or not the virus will adapt to its new host.[5-9] The leading causes of mortality are related to respiratory impairment, which increases the clinical severity of the infection. The significant respiratory impairment associated with severe cases of influenza is described as severe acute respiratory syndrome.[10,11]

At the end of the outbreak, the new variant of the virus begins to circulate in the population, concomitantly with the seasonal virus.[12] For this reason, there is a need for detailed knowledge of the disease, its clinical course, and the risk factors for complications and death. Epidemiological and clinical studies performed to data indicate that the characteristics of the influenza A (H1N1) 2009 pandemic were significantly different from those of seasonal flu infection. Therefore, it is of great importance to obtain information about the clinical spectrum of the manifestations and the risk factors for the severe form of the disease, as well as about treatment and disease course in patients with pandemic influenza A (H1N1) 2009.[13]

On the basis of the knowledge that more severe cases were hospitalized and on the basis of the knowledge of the characteristics of these inpatients and of the relationship of these characteristics with the need for hospitalization, it is possible to investigate the risk factors for disease-related complications and, consequently, for disease-related deaths.

Methods

This was a retrospective observational study conducted between March and December of 2010. The data source used was the pandemic influenza A (H1N1) 2009 Report Records of the Brazilian Ministry of Health *Sistema Nacional de Informação de Agravos de Notificação* (SINAN, National Case Registry Database).[14] The database searches were performed via the internet and by direct evaluation of the disease report forms, which were made available by the Center for Strategic Health Surveillance Information of the Paraná State Department of Health.

The study population consisted of patients from the state of Paraná who were hospitalized for pandemic influenza A (H1N1) 2009 virus infection and in whom the diagnosis was based on reverse transcriptase followed by polymerase chain reaction.

To study the factors that showed a relationship with hospitalization, we included the following variables: age; ethnicity; level of education; comorbidities; major signs and symptoms; outcomes (cure and death); treatment with oseltamivir; date of symptom onset; date of hospitalization; time to treatment initiation after symptom onset; chest X-ray findings; and influenza vaccination. Individuals who selected "yes" in the "influenza vaccination" field were considered vaccinated, regardless of the date of vaccination. Major symptoms were defined as those addressed on the report form, recorded as "yes" or "no" separately, and as those entered by the patient ("others" field) and showing a significant relationship with the hospitalization outcome among the patients included in the study.

The differentiation between inpatients and outpatients was based on the "yes" or "no" response collected from the "hospitalization" field on the SINAN report form. The information about treatment with oseltamivir was obtained from the "observations" field (information entered by the patient). We considered only the information on the patients who started the treatment before hospitalization, for the sake of comparisons with outpatients.

In the statistical analysis, we sought to compare the hospitalization rates in the patients, who were categorized by the presence or absence of each of the study variables. Categorical variables were compared by the chi-square test, and continuous variables were compared by the Student's t-test. The Z-test was used for determining the proportion of distribution of the variables in each group (inpatients and outpatients). Risk factors for

hospitalization were identified by logistic regression analysis, and OR and 95% CI were used as the measure of association. This analysis included the variables that were significant in relation to hospitalization and that showed the highest proportions of this outcome according to the Z-test. The Kaplan-Meier method was used for comparing survival between the inpatients and outpatients who died. Statistical analyses were performed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA), and values of $p < 0.05$ were considered significant.

This study conformed to the principles of the Declaration of Helsinki and to specific Brazilian legislation, as well as being approved by the local research ethics committee (Protocol no. 938.063.10.06 and CAAE 0038.0.091.000-10).

Results

During the 2009 pandemic, there were 4,740 patients with laboratory confirmation of influenza A (H1N1) 2009 infection in the state of Paraná, there being no inconsistencies or lack of data on the report forms. Of those 4,740 patients, 1,911 were hospitalized, and of those 1,911 inpatients, 258 (13.5%) died. Among the 2,829 patients who were not hospitalized, there were 15 deaths (0.5%), 6 of which occurred before reaching a health care facility, and the diagnosis was confirmed by laboratory testing of material collected after death. The mean age of the inpatients who died was 37.7 years (range, 0-90 years). The mean time to treatment initiation after symptom onset was 2.9 days (range, 0-39 days).

Among the inpatients, 88.5% were under 50 years of age, most being in the 20-29 age bracket. Only 2.8% of the inpatients were 60 years of age or older.

The hospitalization rates in each age group can be measured by the proportions of hospitalization, which were obtained by calculating the ratio between the number of inpatients and the total number of patients in each age group. This analysis made it possible to obtain the graph shown in Figure 1.

Table 1 shows the characteristics of the patients and the relationship of these characteristics with the hospitalization outcome. We sought to determine which subject-related characteristics could be defined as risk factors for hospitalization.

Figure 2 shows the Kaplan-Meier curve comparing survival times between the inpatients and outpatients who died. The mean survival times and their respective 95% CIs are given.

On the report forms of 1,704 patients, there was information about influenza vaccination. Of those patients, 131 had been vaccinated, 7 (5.3%) of whom died, and 1,573 had not received the vaccine, 203 (12.9%) of whom died. There were significant differences ($p = 0.011$) in the mortality rates between the groups, the highest proportion of deaths having occurred among the unvaccinated patients. In addition, there were significant differences ($p < 0.001$) regarding the hospitalization rates and influenza vaccination. Of the vaccinated patients, 29.6% required hospitalization, compared with 41.0% of the unvaccinated patients.

We also sought to determine whether the clinical manifestations of the disease are risk factors for hospitalization, and the results are shown in Table 2.

The subject-related and disease-related variables that showed a significant relationship with hospitalization were analyzed by multiple regression analysis in order to identify the potential risk factors for hospitalization. The results are shown in Table 3.

Level of education and use of oseltamivir were found to be protective factors against hospitalization, reducing the OR for the occurrence of this outcome. The remaining variables were classified as risk factors for hospitalization.

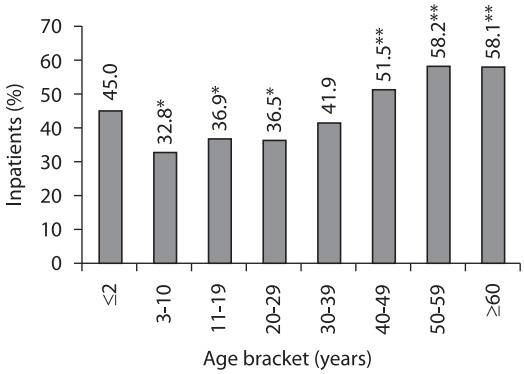

Figure 1 - Distribution of the patients by age brackets in relation to the hospitalization outcome. *Lower proportions of hospitalization. **Higher proportions of hospitalization.

Table 1 - Characteristics of the patients and relationship of these characteristics with the hospitalization outcome.[a]

Characteristic		Group		p	Z
		Inpatients	Outpatients		
Age, years[b]		25.8 (0-90)	22 (0-83)	< 0.001	---
Gender	Male	865 (45.3)	1,348 (47.7)	0.106	---
	Female	1,046 (54,7)	1,481 (52.3)		
Ethnicity	Caucasian	1,530 (80.1)	2,348 (83.0)	0.004	< 1
	African	49 (2.6)	41 (1.4)		> 1
	Asian	22 (1.1)	40 (1.4)		---
	Mulatto	191 (10.0)	244 (8.6)		---
	Indigenous	30 (1.6)	23 (0.8)		> 1
	No data	89 (4.6)	133 (4.7)		---
Level of education	Literate	1,076 (56.3)	1,733 (61.2)	< 0.001	< 1
	Illiterate	17 (0.9)	9 (0.3)		> 1
With comorbidities		610 (28.3)	566 (20.0)	< 0.001	> 1
Healthy (with no comorbidities)		1,301 (71.7)	2,263 (80.0)		< 1
Comorbidity	SAH	66 (3.4)	59 (2.1)	0.004	> 1
	Obesity	32 (1.7)	16 (0.6)	< 0.001	> 1
	Heart disease	94 (4.9)	50 (1.8)	< 0.001	> 1
	Lung disease	209 (10.9)	208 (7.3)	< 0.001	> 1
	Kidney disease	28 (1.5)	19 (0.7)	0.007	> 1
	Hemoglobinopathy	18 (0.9)	9 (0.3)	0.005	> 1
	Immunosuppression	64 (3.3)	37 (1.3)	< 0.001	> 1
	Smoking	136 (7.1)	123 (4.3)	< 0.001	> 1
	Diabetes	72 (3.8)	36 (1.3)	< 0.001	> 1
Number of comorbidities	None	1,301 (68.1)	2,263 (80.0)	< 0.001	< 1
	One	326 (17)	351 (12.4)		> 1
	Two	217 (11.3)	178 (6.3)		> 1
	Three	48 (2.5)	33 (1.2)		> 1
	Four	13 (0.5)	2 (0.1)		> 1
	Five	4 (0.2)	2 (0.1)		> 1
	Seven	2 (0.1)	0 (0.0)		> 1
Oseltamivir	Treated	943 (49.3)	884 (31.2)	< 0.001	< 1
	Untreated	69 (3.6)	21 (0.7)		> 1
Time to treatment initiation, days[b]		2.9 (0-49)	2.0 (0-20)	< 0.001	
Pregnancy		162 (8.5)	190 (6.7)	0.071	
Outcome	Cure	1,653 (86.5)	2,814 (99.5)	< 0.001	< 1
	Death	258 (13.5)	15 (0.5)		> 1

SAH: systemic arterial hypertension; < 1: lower proportions of hospitalization; and > 1: higher proportions of hospitalization. [a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as mean (range).

Discussion

The epidemiological characteristics of influenza A (H1N1) 2009 that are related to hospitalization, disease severity, and mortality have been intensively investigated since the beginning of the pandemic.

According to the results obtained, the epidemiological profile of pandemic influenza differs from that of seasonal influenza. Most of the patients affected by the former were young adults, whereas the highest incidence of the latter occurs in elderly subjects (over 65 years of age) and in children under 2 years of age.[1,3,6,10,12,15]

The results indicated higher percentages of cases among young adults and a low incidence among elderly subjects, suggesting that there are differences between the age group of the patients hospitalized for influenza A (H1N1) 2009 infection and the age group of the population in the state

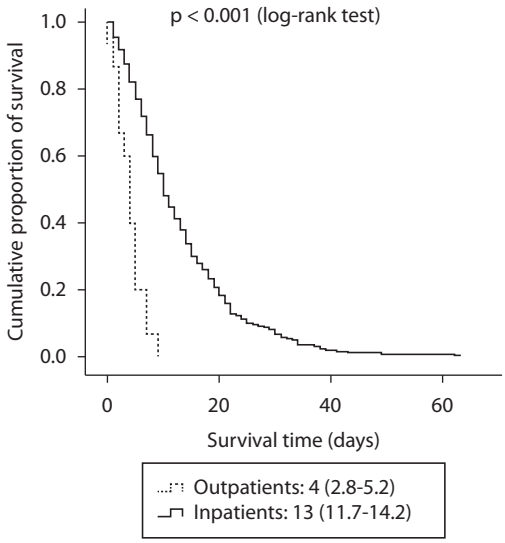

Figure 2 - Kaplan-Meier curve comparing survival times between the inpatients and outpatients who died. The mean survival times and their respective 95% CIs are given.

of Paraná and in the rest of the country. According to data obtained from the Brazilian Institute of Geography and Statistics,[16] subjects under 50 years of age represented 84.1% and 78.4% of Brazilians and of residents of the state of Paraná, respectively, and most of these populations were in the 11-19 age bracket. In contrast, subjects aged 60 years or older represented 8.6% and 11.2% of the Brazilian population and of residents of the state of Paraná, respectively. This result suggests that the distribution of cases of increased clinical severity, and which therefore required hospitalization, did not coincide with the distribution of the general population, and this reinforces the observation that age is a risk factor in this infection.

The mean age of the inpatients was significantly higher than was the mean age of the outpatients, which is in agreement with the findings of other studies.[17-19] The subjects over 40 years of age showed higher hospitalization rates

Table 2 - Relationship of symptoms and chest X-ray findings with hospitalization.[a]

Variable	Group		p	Z
Symptoms	**Inpatients**	**Outpatients**		
Fever	1,828 (95.6)	2,706 (95.6)	0.994	
Cough	1,813 (95.0)	2,685 (94.9)	0.953	
Chills	1,154 (60.4)	1,735 (61.3)	0.514	
Dyspnea	1,247 (65.2)	1,049 (37.1)	< 0.001	> 1
Sore throat	1,004 (52.5)	1,663 (58.8)	< 0.001	< 1
Arthralgia	691 (36.2)	1,080 (38.2)	0.159	
Myalgia	1,215 (63.6)	1,871 (66.1)	0.070	
Conjunctivitis	161 (8.4)	269 (9.5)	0.203	
Rhinorrhea	1,072 (56.1)	1,834 (64.8)	< 0.001	< 1
Diarrhea	259 (13.5)	318 (11.2)	0.017	> 1
Vomiting	189 (9.9)	194 (6.9)	< 0.001	> 1
Nausea	54 (2.8)	99 (3.5)	0.198	
Headache	424 (22.2)	790 (27.9)	< 0.001	< 1
Abdominal pain	26 (1.4)	32 (1.1)	0.481	
Chest pain	45 (2.3)	28 (1)	< 0.001	> 1
Hemoptysis	12 (0.6)	3 (0.1)	0.002	> 1
Pneumonia	15 (0.8)	4 (0.1)	0.001	> 1
Wheezing	9 (0.5)	3 (0.1)	0.014	> 1
Chest X-ray findings				
Normal	175 (22.9)	166 (42.2)	< 0.001	< 1
Interstitial infiltrate	464 (60.7)	197 (50.1)		> 1
Consolidation	64 (8.4)	16 (4.1)		> 1
Mixed	61 (8)	14 (3.6)		> 1

< 1: lower proportions of hospitalization; and > 1: higher proportions of hospitalization. [a]Values expressed as n (%).

Table 3 - Identification of risk factors for hospitalization by logistic regression analysis.

	Risk factor	OR	95% CI	p
Age (continuous, years)		1.016	1.012-1.020	< 0.001
Ethnicity	Caucasian	1.000	---	0.004
	African	1.834	1.205-2.791	0.005
	Asian	0.844	0.500-1.426	0.526
	Mulatto	1.201	0.984-1.467	0.072
	Indigenous	2.002	1.158-3.459	0.013
Level of education		0.815	0.724-0.917	0.001
Comorbidity	Having a comorbidity	1.894	1.648-2.178	< 0.001
	Number of comorbidities	1.471	1.361-1.591	< 0.001
	Heart disease	2.875	2.030-4.073	< 0.001
	Lung disease	1.547	1.265-1.893	< 0.001
	Kidney disease	2.199	1.225-3.949	0.008
	Hemoglobinopathy	2.979	1.336-6.646	0.008
	Immunosuppression	2.615	1.737-3.936	< 0.001
	Smoking	1.686	1.311-2.167	< 0.001
	Diabetes	3.038	2.027-4.551	< 0.001
	Obesity	2.994	1.638-5.472	< 0.001
	Puerperium	10.397	1.278-84.573	0.029
Clinical manifestation	Dyspnea	3.187	2.823-3.597	< 0.001
	Diarrhea	1.238	1.039-1.475	0.017
	Vomiting	1.491	1.209-1.838	< 0.001
	Chest pain	2.412	1.500-3.881	< 0.001
	Hemoptysis	5.953	1.678-21.122	0.006
	Pneumonia	5.587	1.852-16.861	0.002
	Wheezing	4.457	1.205-16.486	0.025
Treatment	Oseltamivir	0.325	0.198-0.534	< 0.001
	Time to treatment initiation (days)	1.171	1.120-1.224	< 0.001

and, therefore, higher risk than did the patients in the remaining age groups (Figure 1), as well as showing higher frequencies of comorbidities, which were found to be risk factors for the worsening of the disease. This is in agreement with the findings of the three aforementioned studies, since the more severe forms of the disease were found in these subjects. In contrast, the higher incidence in young subjects could be explained by the greater exposure of these subjects to the pandemic influenza A (H1N1) 2009 virus.[20-23] These results suggest that subject demographic characteristics, such as age, may play a role as a risk factor in this infection.

There were no differences in terms of patient gender. In terms of ethnicity, the results suggest that African-Brazilian and Indigenous patients showed higher hospitalization rates, in contrast to Caucasian patients, who showed a significantly lower rate. This finding might be associated with characteristics related to access to health care facilities, living conditions, and lifestyle.

The analysis of hospitalizations by level of education revealed that the illiterate patients showed a significantly higher proportion of hospitalization than did those who had some years of schooling. The relationship between level of education and disease severity can be associated with the social class of the subjects. This result suggests that habits, living conditions, and knowledge of the disease have a relationship with the clinical severity of the infection.

The patients infected with the pandemic influenza A (H1N1) 2009 virus who had one or more comorbidities showed significantly higher proportions of hospitalization than did those who were considered healthy, i.e., who had no comorbidities. All comorbidities or other associated clinical conditions investigated showed significant relationships with hospitalization, occurring in greater proportion in the inpatients. In addition, some patients were found to have more than one comorbidity. When assessing patients for number of comorbidities, we found that the proportion

of hospitalizations was lower only in the group of patients with no comorbidities, whereas, in the remaining groups, in which the patients had one to seven comorbidities, the proportion of inpatient cases was significantly higher than that of outpatient cases. The comorbidities found to be risk factors are in agreement with findings of other studies.[24,25]

The patients who were treated with the antiviral drug oseltamivir showed lower hospitalization rates than did the untreated patients. In addition, time to treatment initiation after symptom onset was found to be higher in the patients who required hospitalization. Regarding time to treatment initiation, delayed antiviral therapy can affect disease severity and mortality in patients with pandemic influenza A (H1N1) 2009, which is in agreement with the results of other studies.[13,25]

The results obtained for the subjects included in the present study do not suggest significant differences in the need for hospitalization among pregnant women. The fact that pregnancy was not found to be a risk factor for hospitalization in this population sample differs from the results reported in other studies[26-28] and from what is observed in seasonal influenza, in which pregnant women are more susceptible to the risk of worsening of the disease and hospitalization.[18,29]

The death outcome was significantly more common among the inpatients. However, the Kaplan-Meier curve of the patients who died revealed that the inpatients had higher survival times than did the outpatients. This result suggests that the intensity of care provided to the severe cases that were hospitalized contributed to a significant increase in survival (Figure 2). The increase in survival times observed among the inpatients can allow the adoption of measures to improve the prognosis for cure of patients exhibiting a worsening of the clinical profile.

Diarrhea and pneumonia were the most common clinical manifestations of the infection, whereas dyspnea, vomiting, chest pain, hemoptysis, and wheezing were the most common symptoms. All of these clinical manifestations and symptoms showed significant relationships with the hospitalization outcome, occurring in greater proportion among the inpatients. The symptoms headache and sore throat occurred in greater proportion among the patients who did not require hospitalization. In addition, the chest X-ray findings obtained during the investigation of the disease showed a direct relationship with hospitalization. The hospitalization rates were higher among the patients who presented with radiological abnormalities than among those whose X-ray findings were normal.

Regarding the mean time to hospitalization after symptom onset, other studies reported values ranging from 1 to 4 days.[17,19] These results, which are in agreement with those obtained in the present study, suggest that, despite the low severity and lethality levels of this infection, disease progression is rapid in patients exhibiting a worsening of the clinical profile.

Influenza vaccination seems to reduce the lethality of the infection with this endemic strain, as well as the hospitalization rates. Studies have suggested potential cross-immunity between the pandemic strain and strains previously circulating in the population. This preexisting immunity conferred by prior contact with strains that are antigenically similar to the pandemic strain and are used in the composition of vaccines might have contributed to a reduction in the clinical severity of the disease, thereby explaining the lower death and hospitalization rates found among the vaccinated patients.

According to the results presented, the inpatients had a higher number of risk factors for death (comorbidities, older age, and no treatment with oseltamivir), therefore having a more severe clinical profile. The large number of variables responsible for the increased risk for worsening of the disease and consequent death from the infection explain the increased number of inpatients.

The risk factors for hospitalization were age, presence of specific comorbidities (heart disease, lung disease, kidney disease, hemoglobinopathy, immunosuppression, diabetes, obesity, puerperium, and smoking), a high number of comorbidities, and presence of specific symptoms (dyspnea, vomiting, chest pain, hemoptysis, and wheezing) and specific clinical manifestations (diarrhea and pneumonia). Higher levels of education and early use of oseltamivir were found to be protective factors. Hospitalization contributed to an increase in survival, and influenza vaccination seemed to reduce the clinical severity of the infection with this pandemic strain, resulting in lower rates of hospitalization and death.

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