Lessons from the epidemiological surveillance program, during the influenza A (H1N1) virus epidemic, in a reference university hospital of Southeastern Brazil

Lições aprendidas pelo programa de vigilância epidemiológica, durante a epidemia pelo vírus da influenza A (H1N1), em um hospital universitário na região sudeste do Brasil

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ABSTRACT

Introduction: The case definition of influenza-like illness (ILI) is a powerful epidemiological tool during influenza epidemics. **Methods**: A prospective cohort study was conducted to evaluate the impact of two definitions used as epidemiological tools, in adults and children, during the influenza A H1N1 epidemic. Patients were included if they had upper respiratory samples tested for influenza by real-time reverse transcriptase polymerase chain reaction during two periods, using the ILI definition (coughing + temperature ≥ 38ºC) in period 1, and the definition of severe acute respiratory infection (ARS) (coughing + temperature ≥ 38ºC and dyspnoea) in period 2. **Results**: The study included 366 adults and 147 children, covering 243 cases of ILI and 270 cases of ARS. Laboratory confirmed cases of influenza were higher in adults (50%) than in children (21.6%) ($p < 0.0001$) and influenza infection was more prevalent in the ILI definition (53%) than ARS (24.4%) ($p < 0.0001$). Adults reported more chills and myalgia than children ($p = 0.0001$). Oseltamivir was administered in 58% and 46% of adults and children with influenza A H1N1, respectively. The influenza A H1N1 case fatality rate was 7% in adults and 8.3% in children. The mean time from onset of illness until antiviral administration was 4 days. **Conclusions**: The modification of ILI to ARS definition resulted in less accuracy in influenza diagnosis and did not improve the appropriate time and use of antiviral medication.

Keywords: Seasonal influenza. Influenza A H1N1. Epidemiological surveillance. Influenza-like illness. Acute respiratory syndrome.

RESUMO

Introdução: A definição de síndrome gripal é uma ferramenta epidemiológica importante durante epidemias de influenza. **Métodos:** Foi conduzido estudo de coorte prospectivo para avaliar o impacto das definições de síndrome gripal (SG) e doença respiratória aguda grave (DRAG) como ferramenta de vigilância epidemiológica, em adultos e crianças, durante a epidemia de influenza A H1N1. Os pacientes foram incluídos se tivessem coleta de secreção respiratória alta testada por PCR *real time* para o vírus da influenza. Os dados clínicos e epidemiológicos foram estudados comparando-se dois períodos: período 1: SG (tosse + temperatura ≥ 38ºC), e período 2: DRAG (tosse + temperatura ≥ 38 e dispnéia). **Resultados:** Foram incluídos 366 adultos e 147 crianças, em um total de 243 casos de SG e 270 DRAG. A confirmação laboratorial de influenza em adultos (50%) foi significativamente maior do que em crianças (21,6%) ($p < 0,0001$) e a definição de SG foi mais confirmatória de infecção por influenza (53%) do que DRAG (24,4%) ($p < 0,0001$). Adultos referiam mais calafrios e mialgias do que as crianças ($p = 0,0001$). *Oseltamivir* foi prescrito, respectivamente, em 58% e 46% dos adultos e crianças com influenza A H1N1. A letalidade por influenza A H1N1 foi de 7% em adultos e 8,3% em crianças. **Conclusões:** A mudança de definição do critério de vigilância epidemiologia de SG para DRAG resultou em redução significativa da acurácia do diagnóstico de influenza e não contribuiu para melhor indicação do antiviral como também para a sua prescrição no tempo apropriado.

Palavras-chaves: Influenza sazonal. Influenza A H1N1. Vigilância epidemiológica. Síndrome gripal. Síndrome respiratória aguda.

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INTRODUCTION

A novel influenza A (H1N1) virus of swine origin spread worldwide in 2009, causing the first influenza pandemic of the 21st century[1-4]. Unlike the situation in the Northern hemisphere, in Brazil the peak of the influenza season begins in late autumn (May) to early spring (September). From a public heath perspective, the case definition of influenza-like illness (ILI) is the most important surveillance tool for identifying influenza cases and other respiratory diseases. ILI definitions can improve individual case management, given the availability of safe and effective anti-influenza drugs and increase wider public health surveillance and mitigation measures. The clinical diagnosis of influenza is nonspecific. The use of symptoms complex for ILI in the public healthcare system can be predictive of influenza infection, especially in the setting of a community outbreak. However, the sensitivity and positive predictive value of ILI definition may vary according to the prevalence of the disease, the geographic area and the affected population.

The first laboratory-confirmed case of influenza A H1N1 in Brazil occurred on May 7th, 2009, and on July 16th, 2009 the Ministry of Health declared the sustained transmission of the virus[5]. Brazil was seriously affected by the H1N1 pandemic with a reported case-fatality rate of 11.2% among confirmed pandemic influenza[5].

The purpose of this study was to analyze the clinical presentations and the laboratory confirmation of influenza infections during the influenza A H1N1 epidemic, based on ILI and severe acute respiratory syndrome (SARS) definitions that required mandatory reporting to the public health care system, performed at the Hospital and Clinics of the State University of Campinas (HC-UNICAMP), Campinas, São Paulo, Brazil.

METHODS

The study was conducted at HC-UNICAMP, a 400-bed tertiary-care university hospital that provides all major medical services as the reference hospital for 5 million inhabitants, except for gynecology-obstetrics cases and neonates. HC-UNICAMP participated as one of the reference hospitals for assisting the severe cases of influenza A H1N1 cases for 42 cities located in the surrounding geographic area.

The study included all patients attended from April 28th to December 31st, 2009, whose case were identified as mandatory notification for ILI or ARS and for which swab samples from the upper respiratory tract were tested for real-time reverse transcriptase polymerase chain reaction (RT-PCR) for influenza. The hospital communicable surveillance team performed all the mandatory notifications. Influenza infections (influenza A H1N1 and seasonal influenza type A and B) were confirmed by RT-PCR, which was performed by the reference microbiology laboratory of the State of São Paulo (Adolfo Lutz Institute).

To analyze the mandatory notifications, this study was divided in two periods: period 1 from April 28th to July 15th and period 2 from July 16th to December 31st, 2009. During 2009, the Ministry of Health of Brazil established different protocols for managing the surveillance of and assistance for patients with influenza. In period 1, the government established a containment plan that consisted of mandatory notification, combined swab of nasal and throat for the molecular diagnosis of influenza by RT-PCR, and treatment with oseltamivir of all cases with the following ILI definition: acute respiratory disease + temperature ≥ 38°C + coughing, and returning from countries where influenza A H1N1 was established or individuals in direct contact with a confirmed case of influenza A H1N1. During period 2, ARS was defined as acute respiratory disease + fever ≥ 38°C + coughing and dyspnoea. All suspected cases of influenza with mild symptoms were attended in the primary or secondary healthcare systems and only the severe cases or patients with risk factors for complications of influenza were referred to our hospital.

Patients were evaluated for the presence of underlying conditions, outcome and the following clinical symptoms: fever ≥ 38°C, coughing, chills, dyspnea, sore throat, arthralgia, myalgia, nasal congestion, diarrhea, hospitalization and use of oseltamivir. The data were analyzed according to age (child < 15 years-old; adult ≥ 15-years-old) and the laboratorial RT-PCR result for influenza A H1N1, seasonal influenza, or influenza-negative cases.

Statistical analysis

Statistical analysis was performed using Epi Info (version 3.5.1, 2008; CDC, Atlanta, USA) software. Normally distributed continuous variables were analyzed by the Student t test or analysis of variance. For comparison of length of stay and age data, the nonparametric Mann-Whitney and Kruskal-Wallis methods were used. The X^2 test or Fisher exact test were used to compare categorical variables between groups and to test for heterogeneity among multiple proportions. For data that were not normally distributed, the Wilcoxon rank-sum test for continuous variables was used. A two-tailed p value of < 0.05 was considered statistically significant.

RESULTS

Considering the total period of study, 513 patients composed the study population; these patients consisted of 366 (71%) adults and 147 (29%) children. Influenza infections (influenza A (H1N1) + seasonal influenza) were confirmed in 161 (43.9%) adults and in 33 (22.4%) children. Influenza A (H1N1) was confirmed in 24 (16.3%) children and in 115 (31.4%) adults; 9 children and 46 adults presented seasonal influenza and the remaining population were negative for influenza infections (**Table 1**).

The number of confirmed cases of influenza infections differed according to each period of analysis, in adults and children. In period 1 (ILI), 107 (55.4%) of the 193 reported cases in adults and, 21 (42%) out of the 50 reported cases in children confirmed influenza infection. In period 2 (SARS), among 173 adults, only 54 (31%) were confirmed with influenza infection. Ninety-seven children were reported in period 2, 12 (12.3%) were confirmed with influenza infection and all 12 confirmed cases were influenza A (H1N1) (**Table 1**). The total number of confirmed cases of influenza infections, in adults (107 cases) + children (21 cases), was significantly higher in period 1, than in period 2 (54 cases in adults + 12 cases in children) (p < 0.0001) (**Table 1**), suggesting that the ILI definitions were significantly more confirmatory for influenza infection than SARS. Laboratorial confirmation of influenza infection

TABLE 1 - Distribution of the 513 reported cases of ILI and SARS in adults and children, according to the laboratory results (RT-PCR) for influenza, in the two different periods.

	Number of reported cases		Influenza A (H1N1)				Seasonal influenza				Total number of confirmed cases of influenza infections				Number of deaths			
			AD		CH		AD		CH		AD		CH		AD		CH	
	AD	CH	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Period 1 (ILI)*	193	50	72	37.3	12	24.0	35	18.0	9	18.0	107	55.4	21	42.0	-	-	-	-
Period 2 (SARS)**	173	97	43	24.8	12	12.3	11	6.3	0	0.0	54	31.0	12	12.3	16	9.2	4	4.1
Total	**366**	**147**	**115**	**31.4**	**24**	**16.3**	**46**	**12.5**	**9**	**6.1**	**161**	**43.9**	**33**	**22.4**	**16**	**4.4**	**4**	**2.7**

Period 1: 04/24 to 07/15/2009, period 2: 07/16 to 12/31/2009, AD: adult (≥15 years old), CH: children (≤14 years old). ILI: influenza-like illness, SARS: severe acute respiratory syndrome, RT-PCR: reverse transcription polymerase chain reaction.

*Laboratory-confirmed cases of influenza infection (influenza A (H1N1) + seasonal) was higher in period 1 (p < 0.0001).

**Laboratory-confirmed cases of influenza A (H1N1) was higher in period 1 (p = 0.0002).

p < 0.0001 (for comparing the total number of laboratory-confirmed cases of influenza infections in children *vs.* adults).

was significantly higher among adults (164/362; 50%) than among children (32/148; 21.6%) in both periods. (p < 0.0001) (**Table1**).

Considering the child population of both periods, the mean age was 5.45, 4.9 and 3.1 years-old for influenza A H1N1, seasonal influenza and influenza-negatives cases, respectively, and influenza A H1N1 was more prevalent in older children (p = 0.03). Seventy-five children were < 2 years-old and 72 children were > 2 years-old. Children < 2 years-old were more likely to present influenza-negative results (84%) than those > 2 years-old (70.8%) (p = 0.04). Twenty-four (16.3%) cases of influenza A H1N1 and 9 (6.1%) cases of seasonal influenza were confirmed among the 147 notifications that comprised the total child population (**Table 1**).

In the adult population, influenza A H1N1 was significantly more prevalent in younger adults (mean age 33.13; ±11.8 years-old) than seasonal influenza (39.4; ±14.9) and the negative groups (39.89; ±17.9) (p = 0.001). Laboratory confirmation of influenza infections was significantly higher in period 1 (55.4%; 107cases/193 notifications) than in period 2 (31.2%; 54 cases/173 notifications) (p < 0.0001) (**Table 1**).

The hospitalization of adults and children occurred predominantly in period 2 (adults: 139/173 (80.4%); children: 95/97 (98%)) compared with period 1 (adults: 13/193 (6.7%); children: 4/50(8%)) (p < 0.0001). In period 2, the mean time of hospitalization was significantly higher in children (14.3 ±25 days) than in adults (6.9 ±8.6 days) (p = 0.0009).

Comorbidities

Forty-four (30%) children presented no comorbidities. Lung disorders were present in 30 (20.4%) children, followed by neurological conditions in 8, and cardiovascular, renal, and hematological diseases in 8, 4, and 2 children, respectively (**Table 2**). Of note, 28 of the 30 children in the influenza-negative group presented lung diseases. Forty-seven children were ≤ 2 years-old. Considering the proportion of children with comorbidities in the influenza negative group and in the influenza infection groups (influenza A(H1N1) + seasonal influenza), the influenza-negative group presented 1.6 times more comorbidities than children with influenza infections, reflecting the severity of the cases.

In the adult population, 57.4% of the cases presented no comorbidities. Similar to the child population, the influenza-negative group presented 1.5 times more comorbidities than the influenza patients. Lung disorders were the main underlying disease in the three groups of patients followed by cardiovascular and metabolic diseases (**Table 2**).

Clinical symptoms

The following symptoms: fever, coughing and dyspnea, which composed the clinical definitions of ILI and SARS, were not included in the analysis of clinical symptoms. Adults with influenza A H1N1 reported chills more frequently (40%) than children (4.2%) (p = 0.0001). Reports of myalgia were also significantly greater in adults (70.4%) than in children (25%) (p = 0.0001). The presence of

TABLE 2 - Comorbidities associated with influenza A (H1N1), seasonal influenza, and influenza-negative groups of patients.

	Children (0 to ≤ 14 years old) n(%)				Adult (≥ 15 years old) n(%)			
	Influenza A (H1N1) n = 24 (16.3)	Seasonal influenza n = 9 (6.1)	Influenza negative n = 114 (77.5)	Total n = 147	Influenza A (H1N1) n =115 (31.4)	Seasonal influenza n = 46 (12.5)	Influenza negative n = 205 (56)	Total n = 366
Mean age (years old)	5.45 ±4.9	4.9±5.3	3.1±4	3.6±4.3	33.13±11.82	39.4±14.9	39.89±17.9	37.7±16.1
Gender male	13 (41.6)	4 (44.4)	61 (53.5)	78 (53.0)	55 (47.8)	25 (54.3)	84 (41.0)	164 (44.8)
Comorbidities*								
absence	12 (50.0)	5 (55.5)	27 (23.7)	44 (30.0)	78(67.8)	28(60.8)	104 (50.7)	210 (57.4)
age <2 years old (without comorbidity)	7 (29.1)	3 (33.3)	37 (32.4)	47 (32.9)				
age ≥65 years (without comorbidity)					0 (0.0)	0 (0.0)	2 (0.9)	2 (0.5)
lung disorder	1 (4.1)	1 (11.0)	28 (2.5)	30 (2.0)	7 (6.0)	5 (10.8)	21 (10.2)	33 (9.0)
cardiovascular disease	1 (4.1)		4 (3.5)	5 (3.4)	6 (5.2)	2 (4.3)	18 (8.7)	26 (7.1)
neurologic condition	2 (8.2)		6 (5.2)	8 (5.4)		2 (4.3)	2 (1.0)	4 (1.0)
renal disease	1 (4.1)		3 (2.6)	4 (2.7)	1 (0.8)	1 (2.1)	1 (0.5)	3 (0.8)
HIV (+)			1 (0.9)	1 (0.7)	1 (0.8)		9 (4.4)	10 (2.7)
metabolic or endocrinal disorder					7 (6)	3 (6.5)	14 (6.8)	24 (6.5)
morbid obesity					5 (4.3)		4 (2.0)	9 (2.4)
hematological malignancy			2 (1.7)	2 (1.3)	5 (4.3)		12 (5.8)	17 (4.6)
SOT					3 (2.6)	1 (2.1)	5 (2.4)	9 (2.4)
smoking					6 (5.2)	3 (6.5)	5 (2.4)	14 (3.8)
others			6 (5.2)	6 (4.0)	2 (1.7)	1 (2.1)	12 (5.8)	15 (4.0)
Total of comorbidities	**12 (50.0)**	**4 (44.4)**	**87 (76.3)**	**103 (70.0)**	**43 (37.3)**	**18 (39.0)**	**105 (51.0)**	**166 (45.3)**

*Lung disorder: asthma, chronic obstructive pulmonary disease COPD, cystic fibrosis; Cardiovascular disease: congestive heart failure or atherosclerotic disease, hypertension; Neurologic condition: neuromuscular, neurocognitive, seizure disorders; Renal disease: renal dialysis, chronic renal insufficiency; Metabolic or endocrinal disorders: diabetes, thyroid disorders; SOT: solid organ transplant (kidney, liver).

a sore throat occurred significantly more often in influenza-negative adults than in influenza-negative children (p = 0.0001). Children with influenza A H1N1 presented myalgia more frequently (25%; p = 0.008) than the other groups of children (**Table 3**).

The mean time between illness onset and nasopharyngeal swabs was higher in the influenza-negative patients (3.3 days; SD 2.5) than in influenza A H1N1 (2.5 days; SD 2) and seasonal influenza patients (2.8 days; SD 3) (p = 0.0005).

The use of oseltamivir in the adult and child populations was 57.8% and 45.8% in cases of influenza A H1N1, 43.5% and 22% in the cases of seasonal influenza, and 54.1% and 54% in the negative patients, respectively (p = 0.10) (**Table 3**).

Outcome

In this study population, 16 (4.4%) adults and 4 (2.7%) children died. Influenza A H1N1 was responsible for 8 (6.9%) deaths among 115 cases in adults and for 2 (8.3%) deaths in 24 cases in children. One (2.2%) in 46 cases in adults died due to seasonal influenza. In the influenza-negative group, 7 adults and 2 children died (**Table 4**). In the adults (8 cases) who died due to influenza A H1N1, only 5 (62.5%) received oseltamivir in a mean period of 3 days (0-7 days) from illness onset; comorbidities were verified in 7 (87.5%) patients. The time of hospitalization for adults who died of influenza A H1N1 was shorter (4.75; ± 6.8 days) than that of patients who died in the influenza-negative group (12.6 ± 7.5 days) (p = 0.02). One child died of influenza A H1N1, 13 days after hospitalization and received oseltamivir 12 days after onset (**Table 4**).

When the patients who died were compared with those who survived, the fatal outcomes were not related to the mean time of illness onset until medical assistance (death-2.8 days; cure-2.3 days; p = 0.5) and to the mean time of illness onset until the administration of oseltamivir (death-4 days; cure-4.9 days; p = 0.85); however, the proper time of oseltamivir administration was inadequate. Of note, 90% of the patients who died due to influenza A H1N1 presented comorbidities compared with 31% of those with a favorable outcome (p = 0.0003).

TABLE 3 - Symptoms reported by adults and children with influenza A (H1N1), seasonal influenza, and in influenza-negative patients, use of oseltamivir and the mean time, in days, from illness onset until nasopharyngeal swab.

	Influenza A (H1N1)						Seasonal influenza						Influenza negative					
	Adult (n = 115)		Child (n = 24)		Total (n =139)		Adult (n = 46)		Child (n = 9)		Total (n = 55)		Adult (n = 205)		Child (n = 114)		Total (n = 319)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Fever > 38°C	98	86.0	21	87.5	119	86.2	35	76.1	5	55.6	40	72.7	126	61.5	76	67.3	203	63.6
Coughing	109	95.8	23	95.8	132	95.0	43	93.5	7	77.8	50	91.0	183	89.3	105	92.9	288	90.3
Chills	46	40.0	1	4.2	47	34.0	25	54.3	2	25.0	27	49.0	76	37.1	13	11.5	89	27.9
																		§ (p = 0.0001)
Dyspnea	44	38.3	12	50.0	56	40.3	12	26.1	-	-	8	14.5	118	57.6	77	68.1	195	61.0
Sore throat	41	35.7	5	20.8	46	33.7	20	43.5	-	-	20	36.4	84	41.0	14	12.4	98	30.7
											§ (p = 0.05)							§ (p = 0.0001)
Arthralgia	30	26.0	2	8.3	32	23.0	8	17.4	-	-	8	14.4	38	18.5	3	2.7	41	12.9
Myalgia	81	70.4	6	25.0	87	62.6	29	63.0	1	11.0	30	54.5	123	60.0	6	5.3	129	40.0
					§ (p = 0.0001)						§ (p = 0.007)							§ (p = 0.0001)
Nasal congestion	35	65.2	19	79.2	94	67.6	37	80.4	5	55.5	42	76.4	109	53.2	61	54.0	171	53.6
Diarrhea	13	11.3	2	8.3	15	10.8	5	10.9	3	33.3	8	14.5	29	14.1	10	8.8	39	12.2
Use of oseltamivir	55	57.8	11	45.8	66	47.5	20	43.5	2	22.0	22	40.0	11	54.1	61	54.0	172	53.9
Mean time (days) from illness onset until nasopharyngeal swab#	2.5±2		2.5±1.7 (p = 0.97)		2.5±2		2.7±3		3±2.3 (p = 0.83)		2.±3		3.3±2.6		3.3±2.4 (p = 0.82)		3.3±2.5	

AD: (adult ≥ 15 years old), CH: child (≤14 years old). § Statistically significant p values comparing the presence of symptoms in adult *vs.* children with influenza A H1N1, seasonal influenza, and influenza-negative. # (p = 0.005 for comparison among the 3 groups)

TABLE 4 - Characteristics of the adults and children with fatal outcome.

	Mean age (years)(SD)	Use of oseltamivir	Mean days between onset and use of oseltamivir	Number of patients with comorbidities	Duration of hospital stay (in days)	Comorbidities (n of patients)
Adult (n=16)						
Influenza A H1N1 (n=8)	40 (±15)	5 (62.5%)	3 (0 to 7 days)	7 (87.5%)	4.75 (±6.8) (range 0 to 18)	obesity (2) endocrinal disorder(1) lung disease (2) hematological malignancy (2)
Seasonal influenza (n=1)	69	1	1 day	1 (100%)	26	> 65 years-old
Influenza negative(n=7)	52 (±18)	4 (57.1%)	11 (range 1 to 2days)	6 (85.7%)	12.6 (±7.5) (range 1 to 20)	cardiovascular (2) liver transplant (1) neurological disorder (1) obesity (1) lung disease (1)
Children (n=4)						
Influenza A (H1N1) (n=2)						
child 1	0	Yes	12 days	1	13	< 2 years old
child 2	2	Yes	1 day	1	3	neurological disorder
Influenza negative (n=2)						
child 1	0	Yes	1 day	1	0	< 2 years old+ neurological disorder
child 2	10	Yes	58 days	1	77	neurological disorder

SD: Standard deviation.

DISCUSSION

The definitions of ILI vary according to the epidemiological situation and public healthcare system policies, such as the sentinel programs, institutions and geographic areas. The impact of ILI definitions seemed to be of major importance during the influenza A H1N1 epidemic in our region. Many physicians diagnosed influenza infections based on the presence or absence of certain clinical symptoms and signs. Previous reports have indicated that during the influenza season, physicians can correctly diagnose the infection in 60% to 70% of cases on the basis of clinical symptoms alone[6,7].

In this study, two definitions were used during the two different periods, and they were directly correlated with the diagnosis of influenza infections. The ILI definition adopted in period 1 was significantly more predictive of influenza infections than that used in period 2. Laboratorial influenza confirmations (43.9%) were greater in the adult population than in the child population (22.4%) in both periods. Analysis of the data showed, however, that influenza infection was confirmed in 37.8% of the study population (513 notifications) compared to 16.7% of 34,506 notifications reported by the official data of the surveillance team of the Ministry of Health[5], suggesting that our team might have been stricter with the clinical definitions of ILI and ILI+ARS.

Previous studies have shown that the clinical presentation of the novel H1N1 (2009) in adults[8-10] and children[11] does not differ significantly from that of contemporary seasonal influenza. In our adult population, the clinical presentation of the patients with laboratory-confirmed influenza infections (161; 50%) was similar to that of the influenza-negative patients (**Table 4**), but was different from that of children with influenza infections and the influenza-negative group. Myalgia and chills were reported significantly more often by adults with influenza than children. The clinical presentation of influenza may differ from hospitalized adults to outpatients[12], and this might explain the high number of influenza-negative cases in our hospitalized patients with ILI+ARS symptoms. The influenza-negative adults and children presented significantly more comorbidities than did patients with influenza infections. This fact probably led to the increased number of hospitalizations and suspected diagnoses of influenza during the 2009 pandemic influenza season.

Analysis of the data showed that the number of influenza-negative results was significantly higher in children ≤ 2 years-old (64%) than in children ≥ 3 years-old ($p = 0.04$), suggesting that some other virus might have caused ILI[13]. In cases involving children, clinical signs and symptoms needed to be precisely collected from the child's mother. Among older children, coughing and fever together are known to have a positive predictive value of 79%[8], while a better definition needs to be designed and validated for younger children.

Defining the clinical predictors of influenza infection can help guide timely therapy and avoid unnecessary antibiotic use. During the influenza season, patients with ILI who present both coughing and fever >38°C within 48h of symptom onset are likely to have influenza and it may be appropriate to consider the administration of influenza antiviral therapy. In our study population, oseltamivir was prescribed similarly for adults and children against influenza A H1N1, seasonal influenza and influenza-negative patients, such that about 50% of the influenza-negative cases unnecessarily took oseltamivir.

At the early stages of the epidemic, the worldwide stock of oseltamivir distributed among countries was short. Brazil controlled the distribution of the antiviral, making it available only to patients

with ILI coming from countries where cases of influenza A H1N1 had been reported. After the Brazilian Ministry of Health declared the sustained transmission of the virus, oseltamivir was restricted to patients with ARS or with comorbidities, and the distribution of the drug occurred only at reference centers, such as our hospital, and the drug was not available for purchase in pharmacies. The restriction of oseltamivir to severe cases may have led doctors to include and notify a high number of cases that did not correctly correspond to the definitions and to sample nasopharynx secretions for influenza A H1N1 PCR test, so they could offer oseltamivir to their patients.

The overall case fatality rate in the symptomatic population with influenza A H1N1 was surprisingly high in adults (6.9%) and in children (8.3%). Data in the literature reported an overall range of estimates from 0.0004% to 1.47%[14]. The case fatality rate for symptomatic illness was estimated to be 0.048% in the United States[15] and 0.026% in the United Kingdom[16]. In Mexico[17], the general fatality rate was reported as 1.3 per 100 confirmed cases; in Argentina it was 2%[18]. Our hospital is a tertiary care reference hospital servicing the 100km surrounding area population (5 million inhabitants), such that patients with severe diseases were referred to our hospital for diagnosis and medical assistance. This might partly explain the high case fatality rate in population attended.

Recommendations have been made to start empirical antivirals to patients with suspected influenza A H1N1, and not to withhold the same because of a negative PCR result or delay treatment until RT-PCR results are available[19]. RT-PCR is known to be positive in 81% of cases[20] and the optimal clinical specimen for identification of the virus varies according to several factors, such as the concentration and duration of viral shedding[21], the specimen source and quality, the sensitivity of the test, etc. In our patients the mean time from illness onset until the nasopharyngeal swabs was higher in the influenza-negative group (3.3 ± 2.5days) than in influenza A H1N1 (2.5 ± 2 days) and seasonal influenza patients (2.8 ± 3 days) (p=0.005), suggesting that the delay in time to collect the swabs might have reduced the sensitivity of the RT-PCR and cases of influenza A H1N1 were misdiagnosed in the influenza-negative group.

Although Brazil is a tropical country, the State of São Paulo has milder temperatures and a stronger winter compared with the Northern, Northeaster and Central-Western regions of the country. State of São Paulo and Southern regions were seriously affected by the pandemic A (H1N1) influenza virus, exhibiting high attack rates and higher case fatality rates than those of countries from the Northern hemisphere. To study the clinical presentations and outcome of a new influenza virus was a major issue; it allowed us to better understand the epidemiology of the disease and to recognize that influenza can represent a very important public health disease, causing fatal outcomes in children and adults in tropical and subtropical countries. Of note, except for healthcare workers exposed to potentially infective biological samples housing the influenza A H1N1 virus, the Ministry of Heath did not recommend antiviral chemoprophylaxis. The initial declarations of WHO stating that fatality rates of influenza A H1N1 were similar to those of the seasonal influenza virus might have influenced healthcare workers and the public in general to under evaluate the real risk of the epidemic, especially in tropical countries. Further studies showed that the new virus differs in modest but subtle ways from seasonal H1N1 virus in its intrinsic virulence for humans, which is in agreement with the epidemiology of the pandemic to date[22]. Pathological evaluation of respiratory specimens from initial influenza-associated deaths suggested marked differences in viral tropism and tissue damage compared with seasonal influenza[23]. These findings are therefore relevant for understanding the transmission and therapy.

In conclusion, analysis of the data obtained in this work showed that, during the influenza A H1N1 epidemic, the definitions of ILI symptoms directly determined the medical assistance provided to the patients. Modifying the clinical symptoms of ILI to ARS to include patients with dyspnea resulted in the notification of a high proportion of influenza-negative patients and to an unexpected number of patients with confirmed influenza infections who did not receive appropriate antiviral therapy. The high case fatality rate in our study was multifactorial, including the referral of patients with severe comorbidities to our hospital and the delay in diagnosis and antiviral administration. This epidemic changed the paradigm of the influenza infection representing a commonplace viral infection, affecting the elderly, patients with immunosuppressant conditions or lung disorders, to an infection with high rates of case fatality.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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