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ORIGINAL PAPER

Comparison of clinical presentation of respiratory tract infections in H1N1/09-positive and H1N1/09-negative patients

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Abstract The true burden of influenza in children is difficult to assess and is probably underestimated as clinical signs are usually nonspecific, and formal viral identification is rarely searched. In this study, we compare the clinical features of infections related to the new H1N1/09 influenza virus with infections due to other respiratory viruses in children consulting in a tertiary care pediatric hospital in Geneva. Between October 1, 2009 and February 10, 2010, 109 patients were recruited, with a median of age of 7 years (range 0.1–18). There were 75 H1N1/09-positive patients (69%), and 32 (43%) had identified risk factors such as asthma or a history of wheezing. Fever (87%), cough (92%), and rhinitis (85%) were the most frequent reported presenting symptoms in both patient groups. H1N1/09-positive patients were significantly older (median of 8.2 vs. 4.6 years) and were more likely to have risk factors (43% vs. 24%) and myalgias (41% vs. 20%). H1N1/09-negative patients had more wheezing episodes (29% vs. 9%), higher rates of dyspnea (28% vs. 20%) and of hospital admissions (35% vs. 16%). *Conclusion:* Clinical signs cannot reliably differentiate H1N1/09-positive and H1N1/09-negative patients, although we found a higher proportion of myalgias in H1N1/09-positive patients. Severity of disease was lower in H1N1/09-positive than in H1N1/09-negative patients, mostly because of a higher proportion of asthma/wheezing episodes among H1N1/09-negative patients.

Keywords H1N1/09 · Influenza · Clinical presentation · Children

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Abbreviations

WHO	World Health Organization
RSV	Respiratory syncytial virus
ILI	Influenza-like illness
RT-PCR	Real-time polymerase chain reaction
NSAID	Non-steroidal anti-inflammatory drugs
PICU	Pediatric intensive care unit
PICO	Picornavirus
ADV	Adenovirus
PARA	Parainfluenza virus
OB	Obstructive bronchitis

Introduction

In spring 2009, an influenza A virus (H1N1/09) with a unique combination of human, avian, and porcine genes appeared in Mexico, and pandemia was declared on June

11, 2009 by the World Health Organization (WHO) [25]. In Switzerland, after a few imported cases during summer 2009, the epidemic threshold was reached during week 43, peaked on week 49, and lasted until the end of March 2010.

Seasonal flu clinical signs are usually nonspecific, and formal, laboratory-based, virological identification is rarely demanded [18]. However, some difference in clinical presentation can be recognized. For example, in a cohort of 186 hospitalized children (126 respiratory syncytial virus (RSV) and 60 influenza infections), Meury et al. found that RSV-infected patients appear to have a higher rate of lower respiratory tract infections than influenza A-infected patients [16]. In this same study, febrile seizures were more frequent among children admitted for influenza A and influenza B infection compared to RSV-infected patients [16]. For clinicians in emergency rooms and for general practitioners, there is a need to use clinical features as a basis for further use of specific diagnostic assays and to define any medical intervention. The H1N1/09 pandemia offered the ideal setting to evaluate the clinical presentation of this new virus since children admitted to the emergency room were systematically screened.

The aim of this study was to compare H1N1/09-positive and H1N1/09-negative patients presenting to our emergency department with an influenza-like illness (ILI) during the 2009 pandemia. Our secondary objective was to study the determinants for hospitalization among H1N1/09-positive patients and to compare H1N1/09-positive and H1N1/09-negative children presenting with wheezing or seizures.

Population and methods

Design and setting

This study is a prospective case–control study in a tertiary care pediatric hospital in Geneva (Hôpital des Enfants, University Hospitals of Geneva) during the epidemic wave of 2009–2010 H1N1/09 influenza pandemia. Children of equal or less than 18 years old consulting in the emergency department, during daytime (8:00 A.M.–8:00 P.M.) of week-days, presenting with ILI (fever ≥38° with signs of upper and/or lower respiratory tract infection, according to the WHO definition [24]), or a febrile seizure after H1N1/09 reached the epidemic threshold in the area were approached for participation in the study. Legal guardians—and the children, when appropriate—signed a written informed consent. Past medical history and current reason for the visit were recorded on a common case report form using the information in the medical charts and by interviewing the parents (and the child).

This study was approved by the institutional ethics committee, and conducted in accordance with the principles of the Declaration of Helsinki, the standards of Good Clinical Practice, and Swiss regulatory requirements.

H1N1/09 diagnosis and treatment

Enrolled children had a nasopharyngeal swab to perform an influenza real-time polymerase chain reaction (RT-PCR) to confirm either pandemic, seasonal (non-pandemic) influenza A, or influenza B infection. RT-PCR result was obtained within two working days. In addition, wheezing patients also had a PCR to detect the presence of other viral infections, such as RSV, picornavirus, adenovirus, or parainfluenza virus. RT-PCR assays for influenza and other respiratory viruses' detection were performed according to standardized protocols running in our virology laboratory [10, 20], which is also a WHO referral center for influenza. The primers and probes used for the H1N1/09 detection targeted the N1 gene and were specifically adapted to the circulating strains (forward primer 5′-AGACCTTGCTTCTGGGTTGA-3′, reverse 5′-ACCGTCTGGCCAAGACCA-3′, probe 5′-FAM-ATCTGGACTAGCGGGAGCAGCAT-TAMRA). This assay was used in parallel of another PCR targeting the M genes of human seasonal influenza A viruses [10, 20].

According to national recommendations published in August 2009 [19], oseltamivir was used to treat possibly infected patients at risk of complications (including infants below 12 months of age), those with severe manifestations, or in close contact with at-risk patients [22]. Patients were considered at risk if they had a cardiopathy, a chronic pneumopathy (such as asthma, recurrent obstructive bronchitis/bronchiolitis, cystic fibrosis, or bronchodysplasia), a neuromuscular disease affecting the pulmonary function, an immunodeficiency (congenital or acquired, including sickle-cell disease), a metabolic disease (affecting the heart, the lungs, the kidney, or the immune system), or prematurity (less than 33 weeks of gestation or 1,500 g at birth in children less than 2 years of age). Children were treated with oseltamivir twice a day for 5 days if H1N1/09 was positive by PCR or stopped in case of a negative PCR result.

Statistical analysis

Statistical analyses were performed with SPSS (SPSS version 15.0; SPSS Inc., Chicago, IL, USA). Demographics, other basic characteristics, and outcome measures between the groups were compared with chi-square test for categorical variables and with Mann–Whitney *U* test or Student's *t* test for continuous variables, as appropriate. Two-sided p value <0.05 was considered statistically significant.

Results

Description of the population

Between October 1, 2009 and February 10, 2010, 109 patients were included in the study (Fig. 1). Their median age was 7 years (range 0.1–18 years). The majority of patients (95%) presented with signs of respiratory tract infection, and less than 20% had a wheezing episode. Only five patients (5%) presented with a febrile seizure. Seventy-five children (69%) tested positive for H1N1/09 infection. There was no positive result for seasonal influenza.

Characteristics of the population

H1N1/09-positive patients were significantly older (median age of 8.2 years old, range 0.1–18) than H1N1/09-negative patients (4.6 years old, range 0.1–15; $p=0.002$; Table 1). There was no difference in gender and ethnicity between the H1N1/09-positive and H1N1/09-negative groups. H1N1/09-positive children had a greater proportion of high-risk medical condition (43% vs. 24%, $p=0.04$) than H1N1/09-negative children and were more likely to have received seasonal flu immunization the same year (20% vs. 3%, $p=0.02$). Overall, 7% of our population received H1N1/09 vaccine, without any difference between H1N1/09-positive and H1N1/09-negative patients. The main risk factor in both groups was a past history of asthma or wheezing (62% of all risk factors in H1N1/09-positive and 44% in H1N1/09-negative patients). In the H1N1/09-positive group, immunosuppression was the second most frequent medical condition (31%) followed by hemoglobinopathy (10%), neuropathy (9%), chronic pneumopathy (3%), and prematurity (3%). In the H1N1/09-negative group, the second most frequent medical condition was neuropathy (25%), followed by cardiopathy (13%). There was no significant difference in the overall distribution of risk factors among groups. Median delay for consultation after onset of symptoms was not significantly different between groups with an overall median of 1 day (range 0–9).

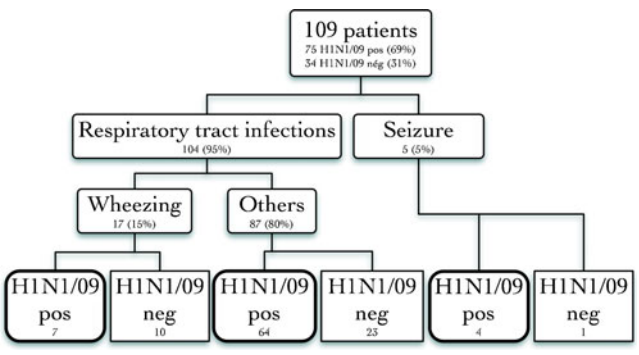

Fig. 1 Description of the population

Clinical presentation

When we compared the three clinical presentations (respiratory tract infections without wheezing, wheezing, and seizure), we found that wheezing episodes were more frequent in H1N1/09-negative patients (Table 2).

Cough (92%), fever (87%), and rhinitis (85%) were the most commonly reported symptoms in both groups without significant difference between H1N1/09-positive (93%, 91%, 87%, respectively), and H1N1/09-negative patients (88%, 79%, and 82%, respectively) (Fig. 2). The 13% of patients who did not report fever as symptom had temperature equal to or more than 38 C measured in the emergency room. Myalgias were more frequent in H1N1/09-positive patients (41% vs. 20%, $p=0.04$), and dyspnea were more frequent in H1N1/09-negative patients (28% vs. 20%, $p=0.05$). H1N1/09-positive patients used more non-steroidal anti-inflammatory drugs (NSAIDs) than H1N1/09-negative patients (48% vs. 27%, $p=0.04$). At enrollment, there were 18 patients (17%), which already had received oseltamivir with no significant difference between H1N1/09-positive (13/75, 17%) and H1N1/09-negative (5/29, 15%) patients.

Management

Fifty-one (68%) H1N1/09-positive patients were prescribed with oseltamivir before influenza PCR results were available, compared to 8 (24%) H1N1/09-negative patients ($p<0.001$). Of these patients, 12/51 H1N1/09-positive and 3/8 negative children began their treatment before enrollment. Subsequently, treatment was stopped in three H1N1/09-positive patients. Among clinical and basic characteristics (age, ethnic group, clinical presentation, risk factor), risk factor appears to be the only significant determinant of oseltamivir prescription before reception of H1N1/09 PCR result in the entire population and in H1N1/09-positive patients ($p<0.001$). Two at-risk patients (one asthmatic child and one patient with an immunosuppressive treatment for Crohn's disease) out of 32 H1N1/09-positive patients (6%) did not receive oseltamivir. The hospitalization rate was higher among H1N1/09-negative patients (12 (35%) vs. 12 (16%), $p=0.04$). Suspected bacterial complications were present in 12% of patients (nine cases of pneumonia, three cases of acute otitis media, and one case of sinusitis) and were similar in both groups. Seventeen patients (16%) received antibiotics, without any differences between H1N1/09-negative and H1N1/09-positive patients.

Table 1 Characteristics of 109 children with influenza-like illness at the emergency department during the H1N1/09 pandemia

Characteristic	Total n=109	H1N1/09 PCR positive n=75	H1N1/09 PCR negative n=34	P value
Age at consultation, median, in years (range)	7 (0.1–18)	8.2 (0.1–18)	4.6 (0.1–15)	0.002
Gender, male, n (%)	64 (58%)	40 (53%)	24 (71%)	NS
Caucasian ethnicity	66 (62%)	43[a] (59%)	23 (67%)	NS
Risk factor, n (%)	40 (37%)	32 (43%)	8 (24%)	0.04
Vaccination				
General vaccinations up-to-date	99 (93%)	68 (93%)	31 (94%)	NS
Seasonal flu 2009 vaccine	16 (15%)	15 (20%)	1 (3%)	0.02
H1N1/09 vaccine	8 (7%)	7 (10%)	1 (3%)	NS

Risk factors (% H1N1/09+/H1N1/09−), asthma/wheezing (44/62), immunosuppression (31/0), sickle-cell disease (10/0), neurologic disease (9/25), chronic pneumopathy (3/0), cardiopathy (0/13), prematurity (3/0)

[a] Two patients: unknown ethnicity

Hospitalization among H1N1/09-positive patients

Twelve H1N1/09-positive patients (16%) were hospitalized. Nine hospitalized patients had risk factors (75%) compared to 23 outpatients (37%) (p=0.02). There were more wheezing episodes among hospitalized patients (25% vs. 6%, p = NS). Four hospitalized patients were prescribed oseltamivir before enrollment compared to nine not hospitalized patients (14%) (p = NS). The main reason for hospitalization was a respiratory tract infection (8/12). One patient was admitted for surveillance because of underlying sickle-cell disease. Three patients had a nosocomial H1N1/09 influenza infection: one was hospitalized for a neurosurgical intervention, the second for an exacerbation of Crohn's disease and the third was a premature neonate. The source of their infection was not identified. Half of the hospitalized H1N1/09-positive patients developed a bacterial infection (five pneumonias (four radiologically confirmed) and one clinical sinusitis). All hospitalized patients received oseltamivir (either prescribed at or before admission) and 6/12 needed oxygen therapy for a median duration of 2.5 days (range 1–12 days). Four patients were admitted in the pediatric intensive care unit (PICU): two for a severe pneumonia, one for a respiratory surveillance of a pneumonia because of a risk factor (sickle-cell disease), and one was already in the PICU for a post-neurosurgery management. No patient needed mechanical ventilation. Median duration of hospitalization for non-nosocomial cases was 3 days (range 2–37 days).

Table 2 Clinical presentation and treatment of 109 children with influenza-like illness with or without positive H1N1/09 infection confirmed by PCR

Characteristic	Total n=109	H1N1/09+ n=75	H1N1/09 n=34	P value
Duration of symptoms				
Median (range)—days	1 (0–9)	1 (0–7)	2 (0–9)	NS
Clinical category				0.02
Wheezing	17 (15%)	7 (9%)	10 (29%)	
Respiratory (non-wheezing)	87 (80%)	64 (86%)	23 (68%)	
Seizure	5 (5%)	4 (5%)	1 (3%)	
Treatment received before enrollment				
Antibiotics	11 (10%)	7 (9%)	4 (12%)	NS
Oseltamivir	18 (17%)	13 (17%)	5 (15%)	NS
Paracetamol	83 (76%)	59 (79%)	24 (71%)	NS
Non steroidal anti-inflammatory drugs	45 (41%)	36 (48%)	9 (27%)	0.04
Vital signs at enrollment				
Temperature—mean (range)	37.65 (36.3–40.4)	37.7 (36.3–40.4)	37.45 (36.3–39.9)	NS
Respiratory rate mean/min (range)	28 (10–56)	26 (12–54)	31.5 (10–56)	0.06
Heart rate pulse/min (range)	120 (52–190)	117 (52–190)	124 (80–181)	NS

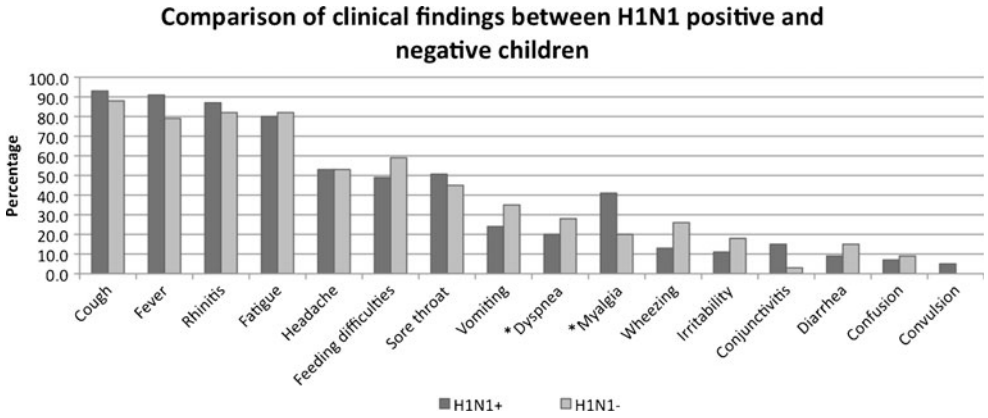

Fig. 2 Comparison of clinical findings in 109 children with influenza-like illness with or without positive H1N1/09 infection confirmed by PCR. *Asterisks* indicate significant difference ($p \leq 0.05$)

Wheezing

Seventeen patients presented with wheezing episodes (Table 3). Seven patients (41%) were H1N1/09 positive and ten (59%) H1N1/09 negative. Median age was 5.8 years (range 0.1–15). H1N1/09-positive patients were older (median age 5.8, range 1.4–15) than H1N1/09-negative patients (median age 4, range 0.1–10.3) (p=0.06). All H1N1/09-positive wheezing patients had a risk factor (all with a past history of recurrent wheezing episodes), unlike the H1N1/09-negative patients (4/10; p= 0.03). Among these, three patients also had a history of recurrent wheezing episodes, and one had a chronic neurological disease. There was no difference in the presenting symptoms, vital signs or management, except for oseltamivir prescription (100% for H1N1/09-positive patients compared to 20% for H1N1/09-negative patient, p=0.002). Only one H1N1/09-positive patient and no H1N1/09-negative patient developed pneumonia. Eleven (65%) wheezing patients were hospitalized: 8 H1N1/09-negative patients (80%) compared to 3 H1N1/09-positive patients (43%; p = NS). One H1N1/09-positive patient had a viral co-infection (H1N1/09+picornavirus+adenovirus). Among H1N1/09-negative patients, picornavirus was the most prevalent viral etiology (60%) followed by RSV (40%), adenovirus (20%), and parainfluenza virus (10%). Three patients had co-infections (RSV + adenovirus, RSV + picornavirus, and adenovirus + parainfluenza).

Febrile seizures

Five patients presented with a febrile seizure at a median age of 3.5 years (range 2–13.6). Four out of five were H1N1/09 positive. Two children (one H1N1/09 positive and

Table 3 Characteristics of children presenting with wheezing during the study period

Age (years)	Preexisting condition	Clinical presentation	Length of hospital stay (days)	PCR result
0.1	None	Bronchiolitis	6	RSV
0.4	None	Bronchiolitis	8	RSV+ADV
0.4	None	Bronchiolitis	3	RSV
1.4	Wheezing	OB	3	H1N1/09+PICO+ADV
1.5	None	OB	3	ADV+PARA
2.6	None	OB	2	PICO
5.2	Wheezing	OB	0	H1N1/09
5.3	Wheezing	Asthma	0	PICO
5.8	Wheezing	OB	0	H1N1/09
5.8	Wheezing	OB	3	H1N1/09
5.9	Wheezing	Bronchitis	0	PICO
7.7	Wheezing	Asthma	4	PICO
7.8	Cerebral palsy	OB	4	RSV+PICO
10.3	None	Asthma	0	PICO
13.5	Wheezing	Asthma	6	H1N1/09
13.7	Wheezing	Asthma	0	H1N1/09
15	Wheezing	Asthma	0	H1N1/09

RSV respiratory syncytial virus, *PICO* picornavirus, *ADV* adenovirus, *PARA* parainfluenza virus, *OB* obstructive bronchitis

one H1N1/09 negative) had a chronic neurological disease. One H1N1/09-positive patient was hospitalized.

Discussion

Our study confirms that clinical presentation cannot reliably differentiate ILI of influenza etiology from other viral causes, as it was already described for seasonal influenza [18]. However, H1N1/09-positive patients appear older, are more likely to have a risk factor, and complain more frequently of myalgias, which can explain a greater use of NSAID. The clinical course of new H1N1/09 influenza virus in children was more benign in our community than expected for a new pandemic virus. Moreover, in our epidemiological context, respiratory tract infections from causes other than H1N1/09 appeared more severe, as shown by a greater proportion of dyspnea, and a higher hospitalization rate in H1N1/09-negative children, associated with a greater proportion of wheezing episodes.

H1N1/09 was recently associated with severe clinical syndromes in children, such as hypoxemic syndrome requiring mechanical ventilation [9], organ failure pattern [14], or even neurologic complications [2, 21]. However, in other reports, when compared to seasonal influenza, pandemic H1N1/09 influenza did not appear to have a more severe course [1, 3, 17]. Differences in studied populations and in screening and treatment strategies could explain differences in reported severity. Jouvet et al. described that severe illness was common among aboriginal children [9]. Farias et al. found a positive effect of oseltamivir on survival when it was administered within 24 h of admission to PICU [7], and Hiba et al. demonstrate that early (<48 h) administration of oseltamivir could protect hospitalized adults from H1N1/09 complications [8]. Our patients consulted rapidly after the first symptoms (median of 1 day) and could receive oseltamivir promptly, which could have a protective effect. Moreover, H1N1/09-positive patients received oseltamivir more frequently before PCR result than H1N1/09-negative patients. The higher proportion of risk factors in this population dictated the prescription of antiviral treatment. Thus, only 2/32 at-risk H1N1/09-positive patients did not receive oseltamivir.

Risk factors have a predominant role in the severity of the disease. In our study, the prevalence of risk factors was significantly higher in H1N1/09-positive patients than in H1N1/09-negative patients and two thirds of our hospitalized H1N1/09-positive patients had a risk factor compared to only one third among outpatients. Similarly, in case series of hospitalized patients, risk factors—lung diseases being the most prevalent—were highly prevalent [12] and associated with a greater risk of severe disease [5], including that of being admitted to PICU [9]. In an outpatient setting, Mahut et al. showed that ILI and severe exacerbation are significantly and strongly associated in the H1N1 influenza pandemic in asthmatic children [15]. Finally, in the USA, Cox et al. found that the majority of pediatric deaths from H1N1/09 were in older children with high-risk medical conditions [6]. As a prevention strategy, vaccination could have offered an important protection to our vulnerable population. Unfortunately, H1N1/09 vaccines were only available at or after the epidemic peak. It explains why only 7% of our population received this vaccine.

Libster et al., in a hospitalized series in Argentina, report wheezing in 16% (39/251) of their patients [13]. This is higher than the percentage of wheezing in our H1N1/09 population but lower than the proportion in our hospitalized population. This confirms that wheezing increases the risk of hospitalization. Interestingly, these authors also describe a subset of 47 patients who had H1N1/09 influenza with a viral coinfection. In this subpopulation, when compared with H1N1/09 infection alone, proportions of wheezing, oxygen supply, admission to PICU, and use of mechanical ventilation were higher. These findings are in concordance with the results of our study. However, in another study, Tresoldi et al. reported a higher proportion (66%) of wheezing among hospitalized H1N1/09-positive patients when compared to H1N1/09-negative patients (52%, p = NS) [23]. In this same study, clinical course appeared more severe for H1N1/09-positive patients according to a higher proportion of PICU admission (47% vs. 11%, p=0.002) and three deaths among the 15 H1N1/09-positive patients. So, conclusions of this study appear to be different from ours. Nevertheless, comparisons seem to be difficult according to difference in study population and setting (Brazil, only hospitalized patients), in screening strategies (no research of viral co-infection in wheezing patients), and longer delay for consultation (median of 4 days).

The source of nosocomial infections could not be traced, but as H1N1/09 vaccination rates were 50% among healthcare workers in our center, and 14% in the general national population at the end of the pandemic, it is likely that the virus was transmitted via the hospital staff or visitors.

Our study has a major limitation. In our recruitment strategy, we did not include patients, who consulted during evening, night, and weekend hours, but enrolled them next day if they were admitted. Consequently, the calculated hospitalization rate may be overestimated. For comparison, in two outpatient studies, hospitalization rate of H1N1/09-positive patients was 4% and 11% [4, 11]. However, we believe that this bias affected similarly H1N1/09-positive and H1N1/09-negative children and did not have a major impact on our results. Another limitation was the selection of at-risk patients. They were advised to consult immediately in case of ILI to receive oseltamivir treatment. Most of the other patients did not consult at all or were seen in

private practice. Nevertheless, our institution is the only center in our area to hospitalize pediatric patients. One more limitation was that only wheezing patients had in addition PCR for other respiratory viruses. Some H1N1/09-positive patients could have had viral co-infections. However, as only one H1N1/09 positive wheezing patient had a co-infection, we hypothesize that prevalence of co-infection in H1N1/09 was not significantly high. Higher prevalence of co-infection in H1N1/09-negative patients may also have increased severity in this population. This cannot be excluded.

This is the first prospective study comparing the clinical features of H1N1/09 influenza with those of other seasonal respiratory viruses that include a comparison of risk factors and wheezing episodes. Thus, we were able to demonstrate that risk factors have a greater role in H1N1/09-positive population, which should motivate us to achieve a much better immunization rate, and that wheezing is more prevalent in H1N1/09-negative patients, which is related to a relative greater severity of disease in our setting. Oseltamivir was rapidly given to our at-risk patients and could have contributed to the relative benignity of H1N1/09 infections in our setting. Finally, we confirm that clinical signs do not reliably differentiate ILI caused by H1N1/09 from other viral etiology in children.

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Conflicts of interest The authors declare that they have no conflict of interest.

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