Original Article

Clinical Predictors for Diagnosing Pandemic (H1N1) 2009 and Seasonal Influenza (H3N2) in Fever Clinics in Beijing, China*

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Abstract

Objective Symptomatic predictors of influenza could assess risks and improve decisions about isolation and outpatient treatment. To develop such predictors, we undertook a prospective analysis of pandemic (H1N1) 2009 and seasonal influenza (H3N2) in patients attending fever clinics.

Methods From 1 May 2009 to 1 January 2010, all adult patients admitted to fever clinics for suspected influenza, confirmed by real time RT-PCR, were enrolled. Predictors of influenza virus infection were selected with logistic regression models. Measures of sensitivity, specificity, positive and negative likelihood ratios (LRs) were calculated to identify the best predictors.

Results The clinical features and routine blood test results of influenza (H1N1) 2009 and seasonal influenza were similar. The positive and negative LRs of current US CDC influenza-like illness (ILI) criteria were modest in predicting influenza infection. Our modified clinic predictors improved the ability of the positive and negative LRs to recognize pandemic (H1N1) 2009 and seasonal influenza. The revised criteria are: fever ⩾38 °C accompanied by at least one of the following—cough, arthralgia or relative lymphopenia.

Conclusion Patients with symptoms and signs that meet the new criteria are likely to have influenza and timely antiviral therapy may be appropriate. In addition, physicians should ascertain if influenza is circulating within the community or if there is a contact history of influenza and combine this information with the newly developed criteria to clinically diagnose influenza.

Key words: Diagnosis; Fever; Influenza A, H1N1; H3N2; Signs, Symptoms

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INTRODUCTION

The seasonal recurrence of influenza is a major public health concern all over the world, causing absenteeism from school and work, heavy loss of life, economic disruption, and other problems[1-5]. Clinical predictors for diagnosing influenza could help physicians and public health officers improve their decisions about prompt isolation, optimal management and effective treatment of influenza-infected patients during the regular influenza seasons. In China, patients with

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a body temperature ≥37.5 °C or patients with suspected pandemic influenza were asked to visit Fever Clinics (FCs) located in the local general hospitals.

As the signs and symptoms of pandemic influenza are largely indistinguishable from those of many common infectious diseases, physicians often do not suspect influenza virus infection nor do they carry out testing for confirmation of the disease[6]. From the public health point of view, it is impractical to test every person who presents with symptoms of influenza, even during the peak season, because of the high cost or unavailability of the test. The diagnosis of influenza, therefore, is usually based on clinical symptoms and signs, a routine blood test and the local epidemiologic situation.

For a patient with influenza-like illness (ILI) admitted to a FC during an influenza epidemic, the probability of them having influenza as opposed to other infections must be accurately estimated by a physician. However, without definitive real-time reverse transcriptase polymerase chain reaction (rRT-PCR) results, the differentiation between an infection caused by the influenza virus and an infection caused by other respiratory pathogens is difficult, given its non-specific clinical presentation. Knowledge of the clinical presentation of the patients may help physicians in carrying out further diagnostic testing and treatment. To be effective against pandemic (H1N1) 2009 and seasonal influenza, antiviral therapy, which can prevent the progression of severe diseases and reduce its mortality, must be initiated as soon as possible after the onset of the symptoms[7-8]. Accurate and prompt clinical diagnosis will benefit both the individual patient and the society, because the patients can be isolated quickly and control measures can be initiated.

Several studies of the clinical characteristics of pandemic (H1N1) 2009 in adults have been performed[9-16] and clinical prediction rules for diagnosing seasonal influenza have been[17-19]. However, almost all of the studies have concentrated on clinical predictors of pandemic (H1N1) 2009 and have not included those of contemporary seasonal influenza. Also, these studies, based mainly on clinical characteristics, have focused on inpatients[9,20], patients in acute care outpatient settings[16,21], patients in military settings[22], or students from a university campus[12]. Until now, no comprehensive studies into the accuracy of the clinical diagnosis of pandemic (H1N1) 2009 and seasonal influenza in the FC where most influenza patients in China were treated, have been carried out. One prospective study of the predictive clinical signs of pandemic (H1N1) 2009 was carried out but the sample size was relatively small[23]. Despite the rapid spread of the pandemic (H1N1) 2009 virus, for the majority of patients the symptoms were clinically mild and hospitalization was not required[20,24]. Under these circumstances, in the FCs, the early diagnosis and intervention appeared to be quite critical. Hence, we have performed a prospective study of patients to determine the association between the clinical manifestation and the presence of influenza virus infection and to assess the predictive accuracy of using clinical grounds alone.

MATERIALS AND METHODS

Study Design

The present prospective study was conducted between 1 May 2009 and 1 January 2010. The study sample included all patients from two FCs, one based at the Third Hospital, Peking University and the other at the Civil Aviation General Hospital in Beijing, China. The inclusion criteria included: patients with fever and at least one of the following symptoms coryza, cough, sore throat or myalgia. Fever was defined as a body temperature higher than or equal to 37.5 °C measured at the FC or having had a similar temperature within the previous 24 h.

All patients suspected of having an influenza infection were enrolled. They were sampled and tested by real-time reverse transcriptase PCR (rRT-PCR). During each examination, a standardized data collection form was completed by the physician for each patient enrolled in our study. If a patient presented with symptoms of severe acute respiratory illness (ARI), they were hospitalized and treated with oseltamivir. If no symptoms of severe ARI were identified, the patient returned home and symptomatic treatment with self-isolation for 7 days was recommended. When the rRT-PCR returned a positive result, the patient was informed by telephone and treated with oseltamivir.

Data Collection

Clinical data, including demographic characteristics, histories of exposure and influenza vaccination, comorbid conditions, clinical features, blood routine examination, were collected prospectively. Written informed consent was obtained from each subject

for the study which was approved by the Human Research Ethics Committees at the Peking University Health Science Center.

Laboratory Confirmation

Pharyngeal or nasopharyngeal swabs from all enrolled patients were collected for virus detection using real-time RT-PCR assays performed at the laboratories of the Beijing Center for Disease Prevention and Control (CDC), the Haidian district of Beijing CDC and the Chaoyang district of Beijing CDC. All the suspected influenza samples from patients visiting the FCs of the hospitals were transported to those three laboratories. To detect the influenza virus, real-time RT-PCR testing was done in accordance with the guidelines published by the United States Centers for Disease Control and Prevention (US CDC), as recommended by the World Health Organization (WHO)[16,25].

Statistical Analysis

The EpiData software program (version 3.0, www.epidata.dk) was used for data management. Statistical analyses were performed with SPSS software (version 16.0, SPSS). All data were double-entered into a computer and verified for accuracy.

Continuous variables of normal distributions were summarized as means and standard deviations. When the variables did not follow a normal distribution, they were summarized using the medians and interquartile ranges (IQRs). For qualitative variables, percentages and number of cases were analyzed. Differences in the means of normally distributed variables were compared with the Student's *t* test and the non-normally distributed variables were compared with the Mann–Whitney test. Comparison of qualitative variables was determined using the x^2 test. *P* values<0.05 (two sided) were considered statistically significant.

Detection of clinical symptoms and signs to predict the occurrence of influenza was made under multivariate logistic regression analysis. Measures of sensitivity, specificity, positive likelihood ratio (LR), negative LR and their 95% confidence intervals (CI)[26] were calculated to further identify the best predictors of influenza. Using the results from the real-time RT-PCR assays as the benchmark, the clinical diagnostic accuracy of the predictors of influenza was evaluated.

RESULTS

Epidemiologic Findings

From 1 May 2009 to 1 January 2010, a total of 465 patients suspected of contracting influenza, attended the two FCs and swab samples from them were tested by the rRT-PCR influenza assay. Of the 465 cases, 318 tested positive for influenza virus with the real time RT-PCR test. The positive cases included 165 pandemic (H1N1) 2009 and 153 seasonal influenza A (H3N2) cases (Figure 1). Pandemic (H1N1) 2009 began on 7 June and continued through a period of comparative stability from early June to late September. It reached its peak in 13 December and then sharply reduced at the end of December. Seasonal influenza (H3N2) began on 5 July, increased in early October and peaked in November before falling off.

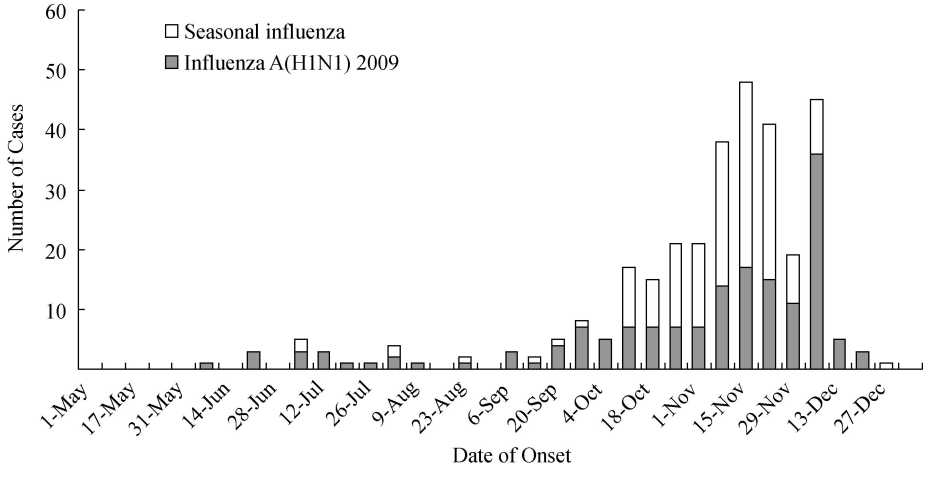

Figure 1. The numbers of cases of pandemic (H1N1) 2009 and seasonal influenza from data collected between 1 May 2009 and 1 January 2010 for patients attending two Fever Clinics in Beijing.

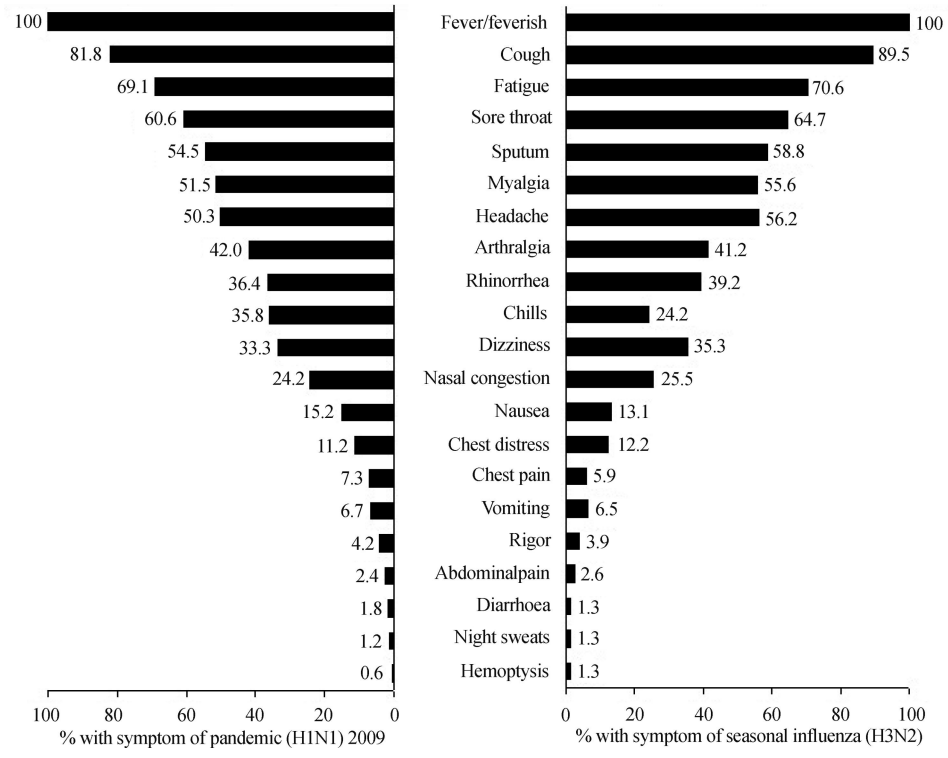

Figure 2. Symptoms and signs of patients with pandemic (H1N1) 2009 and seasonal influenza (H3N2) virus infections.

Demographic and Clinical Characteristics of Pandemic (H1N1) 2009 and Influenza A (H3N2) Virus Infections

Patients were categorized into two groups: (i) those with pandemic (H1N1) 2009 virus infection (*n*=165) and (ii) those with seasonal influenza (H3N2) (*n*=153).

Compared with the patients with the influenza A (H3N2) virus infection, the patients with the new H1N1 virus infection were more likely to have had contact with the H1N1 virus infection (20.6% *vs* 2.0%, *P*<0.001), but they were less likely to have had contact with ILI (1.8% *vs* 21.6%, *P*<0.01) (Table 1). Other demographic characteristics did not significantly differ between the two groups.

Clinical and Laboratory Characteristics of Pandemic (H1N1) 2009 Virus Infection and A (H3N2) Virus Infection

As shown in Figure 2, the most common presenting symptoms and signs of pandemic (H1N1) 2009 and seasonal influenza (H3N2) patients were fever, cough, fatigue, sore throat, and exuberant sputum production.

Compared with patients with the influenza A (H3N2) virus infection, patients with the new pandemic H1N1 virus infection were more likely to report chills (35.8% *vs* 24.2%, *P*=0.025). The other documented characteristics did not significantly differ between the two groups (Table 2).

Multivariate Logistic Regression Analysis

Multivariate logistic regression analysis identified body temperatures of ⩾38 °C, chills, cough, arthralgia and relative lymphopenia (lymphocytes ⩽ 20% of leukocytes) as clinical predictors of pandemic (H1N1) 2009 (the Hosmer-Lemeshow goodness-of-fit test, *P*=0.75) (Table 3).

For influenza A (H3N2), the data through multivariate analysis showed that body temperatures of ⩾38 °C, chills, cough and arthralgia were likely to be clinical predictors (The Hosmer-Lemeshow Goodness-of-Fit Test, *P*=0.56) (Table 3).

Predictive Ability of the Clinical Criteria for Diagnosing the Suspected Pandemic (H1N1) 2009 and Seasonal Influenza (H3N2)

We evaluated clinical case definitions for their abilities to distinguish pandemic (H1N1) 2009 and seasonal influenza (H3N2) in the FCs (Table 4). For

the participating patients with seasonal influenza A(H3N2), the sensitivity, specificity and positive LR of the clinical diagnosis were higher than for those with pandemic (H1N1) 2009, but the negative LR were lower.

Compared with the WHO criteria (sudden onset of fever of >38 °C and cough or sore throat in the absence of other diagnoses) (Table 5)[27] , the US CDC criteria (fever ⩾37.8 °C accompanied by at least one of the following respiratory symptoms: cough, sore throat, headache or muscle ache) (Table 5)[28] and the Chinese CDC ILI criteria (a temperature ⩾38 °C and cough or sore throat), our clinical diagnostic criteria (fever ⩾38 °C with at least one of the following: cough, arthralgia or relative lymphopenia) had higher sensitivity in diagnosing both H1N1(2009) (90.30%) and seasonal influenza (92.16%) and had lower negative LRs (0.37 and 0.62 respectively).

Table 1. Demographic and Epidemiologic Characteristics of Patients with (H1N1) 2009 Virus Infection and Patients with Seasonal Influenza (H3N2)

Characteristic	Pandemic (H1N1) 2009 (*n*=165)	Seasonal Influenza (H3N2) (*n*=153)	*P* Value
Age			
Median years (IQR)*	30(20-32)	30(20-34)	0.854
Sex, *n* (%)			0.850
Male	63/165(38.2)	60/153(39.2)	
Female	102/165 (61.8)	93/153 (60.8)	
Ethnicity, *n* (%)			0.498
Ethnic Chinese	162/165 (98.2)	153/153 (100.0)	
White	2/165 (1.2)	0/153 (0.0)	
Southeast Asian	1/165 (0.6)	0/153 (0.0)	
History of Exposure, *n* (%)			
Contact with H1N1 virus infection	34/165 (20.6)	3/153 (2.0)	<0.001
Contact with ILI	3/165 (1.8)	33/153 (21.6)	<0.001
Comorbid Conditions, *n* (%)			
Hypertension	10/165 (6.1)	5/153 (3.3)	0.241
Cardiovascular disease	6/165 (3.6)	3/153 (2.0)	0.574
Diabetes	6/165 (3.6)	1/153 (0.7)	0.153
Asthma/bronchitis /tuberculosis/COPD*	7/165 (4.2)	9/153 (5.9)	0.504
Others	10/165 (6.1)	14/153 (9.2)	0.297
Influenza vaccination history, *n* (%)			
Received seasonal influenza vaccination	4/165 (2.4)	3/153 (2.0)	1.000
Received pandemic (H1N1) vaccination	4/165 (2.4)	7/153 (4.6)	0.294

Note. *COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

Table 2. Clinical and Laboratory Characteristics of Patients with (H1N1) 2009 Virus Infection and Patients with Seasonal Influenza (H3N2)

Characteristic	Pandemic H1N12009 (*n*=165)	Seasonal Influenza (H3N2) (*n*=153)	*P*-value
Signs and Symptoms			
Fever, in °C			
Mean±SD	38.7±0.65	38.7±0.68	0.718
Chills, *n* (%)	59/165 (35.8)	37/153 (24.2)	0.025
Rigor, *n* (%)	7/165 (4.2)	6/153 (3.9)	0.885
Fatigue, *n* (%)	114/165 (69.1)	108/153 (70.6)	0.771
Night sweats, *n* (%)	2/165 (1.2)	2/153 (1.3)	1.000
Cough, *n* (%)	135/165 (81.8)	137/153 (89.5)	0.050
Sputum, *n* (%)	90/165 (54.5)	90/153 (58.8)	0.442
Hemoptysis, *n* (%)	1/165 (0.6)	2/153 (1.3)	0.948
Sore throat, *n* (%)	100/165 (60.6)	99/153 (64.7)	0.450
Nasal Congestion, *n* (%)	40/165 (24.2)	39/153 (25.5)	0.797
Rhinorrhea, *n* (%)	60/165 (36.4)	60/153 (39.2)	0.600
Chest distress, *n* (%)	19/165 (11.2)	19/153 (12.2)	0.793
Chest pain, *n* (%)	12/165 (7.3)	9/153 (5.9)	0.618
Dizziness, *n* (%)	55/165 (33.3)	54/153 (35.3)	0.713
Headache, *n* (%)	83/165 (50.3)	86/153 (56.2)	0.292
Myalgia, *n* (%)	85/165 (51.5)	85/153 (55.6)	0.470
Arthralgia, *n* (%)	71/165 (42.0)	66/153 (41.2)	0.889
Nausea, *n* (%)	25/165 (15.2)	20/153 (13.1)	0.595
Vomiting, *n* (%)	11/165 (6.7)	10/153 (6.5)	0.963
Abdominal pain, *n* (%)	4/165 (2.4)	4/153 (2.6)	1.000
Diarrhea, *n* (%)	3/165 (1.8)	2/153 (1.3)	1.000
Laboratory Findings			
Leukocyte count, *n* (%)			0.787
$<4.0\times10^9$/L	11/165 (6.7)	8/153 (5.2)	
$4.0\text{-}10.0\times10^9$/ L	146/165 (88.5)	139/153 (90.8)	
$>10.0\times10^9$ / L	8/165 (4.8)	6/153 (3.9)	
Neutrophils percentage*, %			0.438
<50%	2/163 (1.2)	5/151 (3.3)	
50%-70%	50/163 (30.7)	42/151 (27.8)	
>70%	111/163 (68.1)	104/151 (68.9)	
Lymphocyte percentage*, %			0.584
⩽20%	116/159 (73.0)	98/145 (67.6)	
21%-40%	41/159 (25.8)	44/145 (30.3)	
>40%	2/159 (1.3)	3/145 (2.1)	

Note. *The data for a few of the patients was unavailable. The reported percentage is calculated based on the data available.

Table 3. Logistic Regression Analysis of Predictors of Pandemic H1N1 and Seasonal Influenza (H3N2)

Characteristic	Pandemic (H1N1) 2009				Seasonal Influenza (H3N2)			
	β	OR* (95% CI)	Wald x^2	*P*	β	OR* (95% CI)	Wald x^2	*P*
Fever†	0.75	2.13 (1.06-4.27)	4.49	0.03	0.93	2.52 (1.22-5.23)	6.19	0.01
Chills	0.54	1.71 (1.09-2.68)	5.48	0.02	-0.50	0.61 (0.38-0.99)	3.97	0.046
Cough	0.77	2.16 (1.32-3.56)	9.26	0.002	1.49	4.44 (2.47-7.96)	24.97	<0.001
Arthralgia	0.66	1.94 (1.26-2.98)	9.03	0.003	0.71	2.03 (1.30-3.18)	9.59	0.002
Diarrhea	-2.03	0.13 (0.03-0.60)	6.90	0.009	-2.41	0.09 (0.01-0.69)	5.36	0.02
Relative ymphopenia‡	0.46	1.58 (1.01-2.48)	3.94	0.05		…§ …		…

Note. *In the multiple logistic regression models, the OR for each clinical variable were adjusted for age and sex. †Measured body temperatures ⩾38 °C. ‡Relative lymphopenia defined as lymphocytes being ⩽20% of the leukocytes. §Ellipses indicate characteristic was not selected in stepwise procedure.

Table 4. Multivariate Predictors of Pandemic H1N1 and Seasonal Influenza (H3N2) with Sensitivity, Specificity, and Likelihood Ratio (LR) Analyses

Clinical Diagnostic Criteria	Pandemic (H1N1) 2009				Seasonal Influenza (H3N2)			
	Sensitivity	Specificity	Positive LR*	Negative LR	Sensitivity	Specificity	Positive LR	Negative LR
Fever (⩾37.8 °C)+Cough/Relative lymphopenia†	93.33%	20.00%	1.17	0.33	96.73%	21.15%	1.23	0.15
Fever (⩾37.8 °C)+Cough/Arthralgia/ Relative lymphopenia	93.94%	19.33%	1.16	0.31	97.39%	20.51%	1.23	0.13
Fever (⩾38 °C)+Cough/Relative lymphopenia	89.70%	27.00%	1.23	0.38	91.50%	27.24%	1.26	0.31
Fever (⩾38 °C)+Cough/Arthralgia/ Relative lymphopenia	90.30%	26.33%	1.23	0.37	92.16%	26.60%	1.26	0.29

Note. *LR, likelihood ratio. †Relative lymphopenia defined as lymphocytes being ⩽20% of leukocytes.

Table 5. Sensitivities, Specificities, Positive LR, and Negative LR of the Current Clinical Predictors for Pandemic H1N1 and Seasonal Influenza (H3N2)

		Pandemic (H1N1) 2009			
		Sensitivity, % (95% CI)*	Specificity, % (95% CI)	Positive LR† (95% CI)	Negative LR (95% CI)
Pandemic (H1N1) 2009	WHO	72.12 (64.84-78.40)	44.67 (39.14-50.32)	1.30 (1.13-1.50)	0.62 (0.47-0.82)
	US CDC	84.24 (77.91-89.01)	28.33 (23.53-33.68)	1.18 (1.07-1.30)	0.56 (0.37-0.83)
	Chinese CDC	80.61 (73.91-85.91)	35.33 (30.14-40.90)	1.25 (1.11-1.40)	0.55 (0.39-0.78)
	Criteria from this study	90.30 (84.83-93.94)	26.33 (21.67-31.59)	1.23 (1.13-1.33)	0.37 (0.22-0.61)
Seasonal Influenza(H3N2)	WHO	75.16 (67.76-81.34)	45.51 (40.08-51.06)	1.38 (1.20-1.58)	0.55 (0.40-0.74)
	US CDC	90.85 (85.23-94.47)	31.09 (26.21-36.43)	1.31 (1.21-1.44)	0.29 (0.17-0.50)
	Chinese CDC	85.62 (79.19-90.31)	37.18 (32.00-42.67)	1.36 (1.22-1.52)	0.39 (0.26-0.58)
	Criteria from this study	92.16 (86.79-95.46)	26.60 (22.01-31.77)	1.26 (1.16-1.36)	0.29 (0.17-0.52)

Note. *CI, confidence interval. †LR, likelihood ratio.

DISCUSSION

Acute respiratory illnesses, especially influenza, are the leading cause of medical visits for outpatients in the FCs. For most influenza patients, establishment of the specific viral cause is neither necessary nor cost-effective. Thus, timely clinical diagnosis is critical for reducing the spread of disease and for the management of individual cases.

The most common presenting symptoms among individuals with pandemic (H1N1) 2009 in this cohort included fever, cough and sore throat, and this is consistent with most of the information published to date[9-10,13,22-23]. In our analysis, diarrhea was noted in a low percentage (2.4%) of the cases, consistent with the results of Bin Cao et al.[9] in China. Compared with this, patients in the United States[16], Mexico and other countries[29], had higher incidences of diarrhea. Relative lymphopenia was found, in laboratory tests, to be an early and sensitive indicator of adult seasonal influenza A and pandemic (H1N1) 2009[30-31]. As a result, arthralgia and relative

lymphopenia were highly predictive for the diagnosis of pandemic (H1N1) 2009. When of the symptoms of adult patients with seasonal influenza were compared, we found that the clinical presentation of pandemic (H1N1) 2009 did not significantly differ from that of contemporary seasonal influenza A (H3N2). Chills were an exception. Overall, the presenting symptoms, signs and routine blood test results for the two infections were largely similar.

In addition to the comparative study of the clinical presentation of patients with pandemic (H1N1) 2009 and seasonal influenza, we also used logistic regression models to select predictors of the two influenza virus infections. Of all the clinical symptoms and signs that were studied, a body temperature of ⩾38 °C, chills, cough, arthralgia and relative lymphopenia were identified as predictors of a positive diagnosis of pandemic (H1N1) 2009 infection by the multivariate analysis. Diarrhea had an unexpected negative association with pandemic (H1N1) 2009. In the multivariate logistic regression, most of the factors that predicted influenza (H1N1) 2009 infection were also relevant to seasonal influenza. We found that a body temperature of ⩾38 °C, chills, cough and arthralgia all appeared to be predictive of seasonal influenza (H3N2). Sore throat, which is classically associated with influenza (H1N1) 2009 and seasonal influenza, was not identified as a clinical predictor in our or other[10] multivariate analysis models.

On the basis of the multivariate logistic regression analysis, we evaluated various clinical predictors for their predictive abilities to distinguish pandemic (H1N1) 2009 and seasonal influenza using the LR indicators. The best test result is based on maximized positive LR and minimized negative LR. For body temperature, as the temperature increased both the positive and negative LRs gradually increased. No single clinical symptom or sign had a sufficiently high positive LR as along with a low negative LR. However, by a careful compromise based on sensitivity, specificity, positive LR and negative LR, we may have succeeded in developing treasonably good clinical predictors for pandemic (H1N1) 2009 and seasonal influenza (H3N2): fever ⩾38 ℃ accompanied by at least one other feature (cough, arthralgia or relative lymphopenia).

We compared the predictive power of the Chinese CDC screening criteria with those of WHO[27] and the US CDC[28]. The WHO clinical diagnostic criteria had the highest negative LR in screening influenza H1N1 (2009) and seasonal influenza. When compared with the WHO screening criteria, the criteria set by the US CDC added headache and muscle ache to the WHO symptoms, plus a body temperature of ⩾37.8 °C was used. These criteria resulted in the reduction of both positive LR and negative LR. When using the Chinese CDC screening criteria, the balance between the positive and negative LRs became more appealing. Comparing to the WHO, US CDC and Chinese CDC criteria, the clinical diagnostic criteria from our study had the highest sensitivity and the lowest negative LR. Thus, the clinical prediction rule including fever ⩾38 °C accompanied by at least one of the following features: cough, arthralgia or relative lymphopenia, could improve the accuracy for physicians in clinically diagnosing influenza in febrile adults during an influenza.

However, even using the best clinical predictors from this study, the positive LR was not high enough to accurately diagnose influenza, nor was the negative LR low enough to effectively eliminate influenza. Because the data used in this study were prospectively collected from all the patients who visited the two FCs between 1 May 2009 and 1 January 2010, some of the patients who had close contact with influenza infected patients but did not have typical ILI symptoms (e.g., low grade fever, slight cough, mild headache) were also enrolled in our study. Interestingly, some cases confirmed to have pandemic (H1N1) 2009 and seasonal influenza infection did not fully fit the current ILI criteria. This strongly suggests that both clinical and epidemiologic data are important for the effective control of influenza epidemics in the early stages. Another study had earlier suggested that clinical manifestations are not particularly useful in the diagnosis of influenza[32]. To help physicians more accurate recognize influenza virus infections, it would be very useful if a link could be established between the clinical situation and the epidemiologic history.

There may be some limitations to the widespread use of the clinical criteria identified in our study to diagnose influenza: (i) the data were collected in tertiary care hospitals, and the results might not fit all the patient populations; and (ii) patients with mild symptoms but did not visit the FCs in the hospitals, were not included in our study.

In summary, a practical but easy-to-handle clinical prediction rule for diagnosing influenza is needed for health care workers at the FCs. Based on the results of this study, we have suggested that, for febrile adults during influenza seasons, good predictors of pandemic H1N1 (2009) and seasonal influenza (H3N2) should include the following two important components: patients with fever ⩾38 °C

accompanied by at least one of the following features—cough, arthralgia or relative lymphopenia. In particular, to clinically diagnose influenza, physicians should use epidemiologic information to ascertain if there is contact history of influenza or if influenza is circulating in their communities and combine this information with clinical manifestations using the predictors described above. We believe that the combined use of the newly developed criteria and epidemiological contact history can improve the early identification and treatment for infected patients, shortening the duration of symptoms and reducing human-to-human transmission.

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REFERENCES

1. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA, 2004; 292(11), 1333-40.
2. Nichol KL. Cost-benefit analysis of a strategy to vaccinate healthy working adults against influenza. Arch Intern Med, 2001; 161, 749-59.
3. Presanis AM, De Angelis D, Hagy A, et al. The severity of pandemic H1N1 influenza in the United States, from April to July 2009: a Bayesian analysis. PLoS Med, 2009; 6, e1000207.
4. Hadler JL, Konty K, McVeigh KH, et al. Case Fatality Rates Based on Population Estimates of Influenza-Like Illness Due to Novel H1N1 Influenza: New York City, May-June 2009. PLoS One, 2010; 5, e11677.
5. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA, 2003; 289(2), 179-86.
6. WHO (2009). Comparing deaths from pandemic and seasonal influenza. World Health Organisation, Geneva.
7. Zarocostas J. WHO recommends early antiviral treatment for at risk groups with suspected swine flu[J]. Bmj, 2009; 339, b4831.
8. Falagas ME, Vouloumanou EK, Baskouta E, et al. Treatment options for 2009 H1N1 influenza: evaluation of the published evidence. International Journal of Antimicrobial Agents, 2010; 35(5), 421-30.
9. Cao B, Li XW, Mao Y, et al. Clinical Features of the Initial Cases of 2009 Pandemic Influenza A (H1N1) Virus Infection in China. N Engl J Med, 2009; 361(26), 2507-17.
10. Ong AK, Chen MI, Lin L, et al. Improving the clinical diagnosis of influenza--a comparative analysis of new influenza A (H1N1) cases. PLoS One, 2009; 4(12), e8453.
11. Komiya N, Gu Y, Kamiya H, et al. Clinical features of cases of influenza A (H1N1)v in Osaka prefecture, Japan, May 2009. Euro Surveill, 2009; 14(29).
12. Iuliano AD, Reed C, Guh A, et al. Notes from the Field: Outbreak of 2009 Pandemic Influenza A (H1N1) Virus at a Large Public University in Delaware, April–May 2009. Clinical Infectious Diseases, 2009; 49(12), 1811-20.
13. Hackett S, Hill L, Patel J, et al. Clinical characteristics of paediatric H1N1 admissions in Birmingham, UK. Lancet, 2009; 374(9690), 605.
14. Gianella A, Walter A, Revollo R, et al. Epidemiological analysis of the influenza A(H1N1)v outbreak in Bolivia, May-August 2009. Euro Surveill, 2009; 14(35).
15. Gerrard J, Keijzers G, Zhang P, et al. Clinical diagnostic criteria for isolating patients admitted to hospital with suspected pandemic influenza. Lancet, 2009; 374(9702), 1673.
16. Dawood FS, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med, 2009; 360(25), 2605-15.
17. Monto AS, Gravenstein S, Elliott M, et al. Clinical signs and symptoms predicting influenza infection. Arch Intern Med, 2000; 160(21), 3243-7.
18. Boivin G, Hardy I, Tellier G, et al. Predicting influenza infections during epidemics with use of a clinical case definition. Clin Infect Dis, 2000; 31(5), 1166-9.
19. Carrat F, Tachet A, Rouzioux C, et al. Evaluation of clinical case definitions of influenza: detailed investigation of patients during the 1995-1996 epidemic in France. Clin Infect Dis, 1999; 28(2), 283-90.
20. Centers for Disease Control and Prevention. Hospitalized patients with novel influenza A (H1N1) virus infection - California, April-May, 2009. MMWR Morb Mortal Wkly Rep, 2009; 58(19), 536-41.
21. Lee TC, Taggart LR, Mater B, et al. Predictors of pandemic influenza infection in adults presenting to two urban emergency departments, Toronto, 2009. CJEM, 2011; 13(1), 7-12.
22. Crum-Cianflone NF, Blair PJ, Faix D, et al. Clinical and epidemiologic characteristics of an outbreak of novel H1N1 (swine origin) influenza A virus among United States military beneficiaries. Clin Infect Dis, 2009; 49(12), 1801-10.
23. Brouqui P, Vu Hai V, Nougairede A, et al. Improving the diagnostic efficiency of H1N1 2009 pandemic flu: analysis of predictive clinical signs through a prospective cohort. PLoS Curr Influenza, 2009; RRN1120.
24. Yang P, Deng Y, Pang X, et al. Severe, critical and fatal cases of 2009 H1N1 influenza in China. J Infect, 2010; 61(4), 277-83.
25. Deng Y, Pang XH, Yang P, et al. Serological survey of 2009 H1N1 influenza in residents of Beijing, China. Epidemiol Infect, 2011; 139(1), 52-8.
26. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. J Clin Epidemiol, 1991; 44(8), 763-70.
27. WHO. Human infection with pandemic (H1N1) 2009 virus: updated interim WHO guidance on global surveillance. World Health Organisation, Geneva, 2009.
28. CDC. Centers for Disease Control and Prevention. Interim Guidance on Infection Control Measures for 2009 H1N1 Influenza in Healthcare Settings, Including Protection of Healthcare Personnel. CDC, Atlanta, 2009.
29. Human infection with new influenza A (H1N1) virus: clinical observations from Mexico and other affected countries, May 2009. Wkly Epidemiol Rec, 2009; 84(21), 185-9.
30. Cunha BA, Pherez FM, Schoch P. Diagnostic importance of relative lymphopenia as a marker of swine influenza (H1N1) in adults. Clin Infect Dis, 2009; 49(9), 1454-6.
31. Mohan SS, McDermott BP, Cunha BA. The diagnostic and prognostic significance of relative lymphopenia in adult patients with influenza A. The American Journal of Medicine, 2005; 118(11), 1307-9.
32. Call SA, Vollenweider MA, Hornung CA, et al. Does this patient have influenza? JAMA, 2005; 293(8): 987-97.