Community EM

Predictors of pandemic influenza infection in adults presenting to two urban emergency departments, Toronto, 2009

Todd C. Lee, BSc, MD[*]; Linda R. Taggart, MD[*]; Barbara Mater, RN, BA[†]; Kevin Katz, MD, MSc[*†]; Allison McGeer, MD, MSC[*‡]

ABSTRACT

Objective: Identifying features that differentiate patients with H1N1 influenza infection from those with other conditions may assist clinical decision making during waves of pandemic influenza activity.

Methods: From April 27 to June 15, 2009, nasopharyngeal swabs were obtained from all adults presenting to two urban emergency departments (EDs) with illness including fever or respiratory symptoms. H1N1 infection was detected by reverse transcriptase–polymerase chain reaction. Chart review was performed to compare cases of H1N1 influenza ($n = 117$) to matched controls.

Results: The median age of cases was 35 years versus 50 years for controls ($p < .001$). In those with pre-existing conditions, asthma was present in 31% of cases versus 14% of controls (OR 2.6, 95% CI 1.3–5.4). Cough (OR 7.8, 95% CI 3.2–19), fever (OR 3.0, 95% CI 1.7–5.4), headache (OR 2.0, 95% CI 1.2–3.2), and myalgias (OR 1.9, 95% CI 1.2–3.1) were significantly more common in H1N1 cases. The median white blood cell count was 5.7×10^9/mL versus 10.9×10^9/mL ($p < .001$). The combination of fever and cough had an OR of 5.3. Fever, cough, low white blood cell (WBC) count, and tachycardia had the highest OR at 11. The absence of both fever and cough had a negative predictive value of 99%, but this occurred in only 8% of controls.

Conclusion: In patients presenting to the ED, the combination of fever, cough, tachycardia, and WBC count $< 10 \times 10^9$/mL was suggestive of H1N1 influenza infection. However, clinical features could not reliably distinguish influenza from other acute respiratory illnesses in adult ED patients.

RÉSUMÉ

Objectif: Déterminer les caractéristiques différenciant les patients atteints de la grippe H1N1 de ceux ayant un autre problème de santé peut aider la prise de décision clinique pendant les vagues de pandémie de grippe.

Méthode: Du 27 avril au 15 juin 2009, des écouvillonnages nasopharyngés ont été effectués dans deux services d'urgence en zone urbaine auprès de tous les patients présentant des symptômes de fièvre ou de troubles respiratoires. Les infections à H1N1 ont été détectées à l'aide de la réaction en chaîne par polymérase après transcriptase inverse. Un examen des dossiers des patients a été effectué pour comparer les cas de grippe H1N1 ($n = 117$) aux témoins appariés.

Résultats: L'âge médian des cas était de 35 ans contre 50 pour les témoins ($p < 0{,}001$). Chez les patients ayant des troubles pré-existants, l'asthme était présent chez 31 % des cas contre 14 % des témoins (rapport de cotes [RC] de 2,6; intervalle de confiance [IC] à 95 %, de 1,3 à 5,4). La toux (RC de 7,8; IC à 95 %, de 3,2 à 19), la fièvre (RC de 3,0; IC à 95 %, de 1,7 à 5.4), les maux de tête (RC de 2,0; IC à 95 %, de 1,2 à 3,2) et les myalgies (RC 1,9; IC à 95 %, de 1,2 à 3,1) étaient significativement plus fréquents chez les cas de grippe H1N1. La numération leucocytaire médiane était de $5{,}7 \times 10^9$/ml contre$10{,}9 \times 10^9$/ml ($p < 0{,}001$). La combinaison fièvre et toux avait un RC de 5,3. La combinaison fièvre, toux, faible taux leucocytaire et tachycardie affichait le plus haut RC à 11. L'absence à la fois de fièvre et de toux avait une valeur prédictive négative de 99 %, mais cela ne s'est produit que chez 8 % des témoins.

Conclusion: Chez les patients se présentant à l'urgence, l'association de fièvre, de toux, de tachycardie et d'une numération leucocytaire inférieure à 10×10^9/ml était évocatrice d'une infection au virus H1N1. Toutefois, les manifestations cliniques ne permettaient pas de distinguer de façon fiable la grippe d'autres affections respiratoires aiguës chez les patients adultes à l'urgence.

Keywords: diagnosis, influenza, symptoms

From the *Division of Infectious Diseases, University of Toronto; †North York General Hospital; and ‡Department of Microbiology, Mount Sinai Hospital, Toronto, ON.

Presented at the Canadian Pandemic Planning Meeting, Toronto, ON, July 8, 2009.

Correspondence to: Dr. Todd C. Lee, 600 University Avenue, Room 1485, Toronto, ON M5G 1X5; todd.lee@utoronto.ca.

This article has been peer reviewed.

A global pandemic of a novel swine-origin H1N1 influenza virus has occurred.[1]

During pandemic activity, emergency departments and outpatient clinics may see large increases in visitor numbers. Diagnostic testing for influenza may be limited, and rapid testing is known to perform poorly in adults. Consequently, it is important to know whether symptoms, signs, and routine laboratory results can be used to inform clinical decisions about who requires further investigations, who should be isolated to prevent transmission, and who should be empirically treated for influenza. Previous studies have been conducted evaluating the use of clinical symptoms and simple laboratory investigations to diagnose influenza.[2–15] The majority of these studies have involved seasonal influenza, and only one has addressed adults presenting to the emergency department.[2]

In this study, we attempted to determine whether reported symptoms, signs, and routinely available laboratory test results could reliably distinguish between influenza and other diagnoses in adult patients presenting to our emergency departments with fever or acute respiratory symptoms.

METHODS

Study design

This was a retrospective case-control study with two controls for every case.

Setting

The study was conducted at Mount Sinai Hospital, a 472-bed tertiary care hospital, and North York General Hospital, a 420-bed urban community teaching hospital, both associated with the University of Toronto.

Selection of participants

From April 27, 2009, to June 15, 2009, it was the policy of the emergency departments of Mount Sinai Hospital and North York General Hospital to obtain nasopharyngeal (NP) swabs for influenza testing in all patients presenting with either fever or respiratory symptoms. Cases for this study were all adult (≥ 18 years of age) patients presenting to our emergency departments during this time who had influenza identified from their NP swab specimen. For each case, the next two adult patients registered in the same emergency department who had NP swabs obtained that were negative for influenza were selected as controls.

Specimen processing

NP swabs were obtained by trained emergency department nursing staff, as per routine. Samples were processed in the Mount Sinai Hospital laboratory by reverse transcriptase–polymerase chain reaction (RT-PCR) using the Canadian National Microbiology Laboratory (NML) protocol and primers and in the North York General Hospital laboratory using the Prodesse Proflu+ kit (Gene-Probe Prodesse, Waukesha, WI) according to the manufacturers' instructions, followed by influenza subtyping using the NML protocol.

Data collection and processing

Ethics approval was obtained from both institutional ethics review boards. Using a standardized form, the clinical information available in the emergency department chart, any relevant consultants' notes from the emergency department, and laboratory and imaging data that would have been available to the emergency physician on the date of the visit were collected by the study authors (L.R.T., T.C.L., A.M. at Mount Sinai Hospital and B.M. at North York General). Clinical features that were not charted were treated as not present. The reviewers were blinded as to the results of influenza testing.

Data analysis

Data were analyzed using *SPSS* version 17 (SPSS Inc., Chicago IL) and *SAS* version 9.2 (SAS Institute, Cary NC). Univariate comparisons between groups used chi-square or Fisher exact test for proportions and Mann-Whitney *U* tests for continuous variables. Cases were specifically compared to controls in terms of demographic data such as age, gender, and comorbidities, as well as clinical history, such as symptoms and duration of illness, and, finally, on any available laboratory information usually accessible during the emergency department visit. Multivariable analysis was performed using backward stepwise regression with proc logistic in *SAS* and including variables identified

https://doi.org/10.2310/8000.2011.100226 Published online by Cambridge University Press

by other studies and those with $p < .10$ in univariate analysis in the models.

RESULTS

There were 117 cases identified. Patient demographics are shown in Table 1. Cases were younger than controls (median age 35 [22–48] years v 50 [34–72] years for controls, $p < .001$) and less likely to have arrived by ambulance. Fifty-two of 117 (44%) cases and 131 of 236 (55%) controls had a chronic underlying illness ($p < .05$); H1N1 infection was more likely in those with asthma (31% vs 14%, $p < .001$).

The frequency of particular symptoms is shown in Table 2. Complaints of cough (OR 7.8, 95% CI 3.2–19), fever (OR 3.0, 95% CI 1.7–5.4), headache (OR 2.0, 95% CI 1.2–3.2), and myalgias (OR 1.9, 95% CI 1.2–3.1) were significantly more common in cases than in controls. The median maximum documented temperature of cases was 38.1 (37.4–38.8) versus 37.5 (36.8–38.6) degrees Celsius in controls ($p < .008$). The median triage heart rate (per minute) was 102 (87–114) versus 93 (80–108) in controls ($p < .003$). Fifty-six percent of cases had tachycardia (heart rate > 100 beats/min) at triage versus 36% of controls (OR 2.3, 95% CI 1.4–3.7). The oxygen saturation was normal in 91% of cases versus 78% of controls (OR 0.5, 95% CI 0.2–0.9).

Overall, 41 of 117 (40%) cases and 133 of 236 (60%) controls had a complete blood count requested ($p < .002$) with a median white blood cell count of 5.7×10^9/mL (5.2–8.6) versus 10.9×10^9/mL (7.6–14) ($p < .001$), respectively. Approximately half of cases and controls had chest radiographs taken; these were normal in 77% of cases versus 61% of controls ($p < .04$). Blood cultures and sputum cultures were rarely performed (approximately 20% and 3% for cases and controls, respectively). Electrocardiograms were performed in 10% of cases and 28% of controls ($p < .001$).

Cases were less likely to be referred to a consultant (10% vs 24%, $p < .01$), less likely to be admitted to hospital (7% vs 29%, $p < .01$), and less likely to be prescribed empiric antibiotics (15% vs 30%, $p < .03$) but more likely to be prescribed empiric oseltamivir (13% vs 2%, $p < .001$).

Various combinations of symptoms, signs, and laboratory complexes are presented in Table 3. Taken together, the combination of fever and cough had an odds ratio of 5.3 (95% CI 3.1–9.1). If the white blood cell count was also less than 10×10^9/mL, the odds ratio increased to 7.4 (95% CI 3.8–14). In combining fever, cough, tachycardia, and white blood

Table 1. Patient demographics

Demographic	Case (n = 117)	Control (n = 236)	OR (95% CI)/ p value if < .05
Median age, yr (IQR)	37 (22–48)	50 (34–72)	< .001
Age > 65 yr, n (%)	9 (8)	71 (31)	0.2 (0.1–0.4)
Male gender, %	39.5	48.7	
Ambulance to ED, n (%)	4 (3)	46 (20)	0.21 (0.08–0.55)
Arrival from home, n (%)	116 (99)	206 (88)	0.67 (0.60–0.74)
Median duration of illness prior to visit, d	2	3	
Previously healthy, n (%)	65 (56)	105 (45)	0.63 (0.4–0.98)
Of those with previous illness, n (%)			
Asthma	18 (31)	21 (14)	2.6 (1.3–5.4)
COPD	3 (5)	14 (10)	
Other lung disease	2 (3)	8 (6)	
Diabetes	8 (14)	28 (19)	
Cardiac disease	5 (9)	40 (28)	0.25 (0.09–0.66)
CRF (Cr > 150 mmol)	1 (2)	8 (6)	
Malignancy	3 (5)	16 (11)	
Pregnancy	2 (4)	0 (0)	
Would meet CDC guidelines for treatment	34 (29.6)	102 (44.9)	< .001

CDC = Centers for Disease Control and Prevention; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; ED = emergency department; IQR = interquartile range.

https://doi.org/10.2310/8000.2011.100226 Published online by Cambridge University Press

Table 2. Symptoms and signs documented in the emergency record

Symptom/sign	Case, *n* (%) (*n* = 117)	Control, *n* (%) (*n* = 236)	OR (95% CI)/ *p* value if < .05
Fever	100 (86)	156 (66)	3.0 (1.7–5.4)
Chills	30 (26)	55 (23)	
Cough	111 (95)	166 (70)	7.8 (3.2–19)
Sore throat	45 (39)	75 (32)	
Rhinorrhea	22 (19)	42 (18)	
Chest pain	21 (18)	28 (12)	
Dyspnea	34 (29)	79 (34)	
Myalgia	42 (36)	53 (23)	1.9 (1.2–3.1)
Fatigue	17 (15)	33 (14)	
Weakness	18 (15)	34 (14)	
Headache	38 (33)	46 (20)	2.0 (1.2–3.2)
Nausea	14 (12)	36 (15)	
Vomiting	11 (9)	34 (14)	
Abdominal pain	2 (2)	18 (8)	0.2 (0.05–0.92)
Diarrhea	8 (7)	16 (7)	
Documented T > 38.0°C	34 (53)	62 (41)	
Median maximum T (°C)	38.1	37.5	< .003
HR > 100 beats/min	54 (56)	72 (36)	2.3 (1.4–3.7)
O_2 saturation < 90%	71/78 (91)	122/156 (78)	0.5 (0.2–0.9)

HR = heart rate; T = temperature.

cell count less than 10×10^9/mL, the odds ratio for influenza increased to 11 (95% CI 3.4–35).

The absence of cough and fever had a negative predictive value of 99%.; however, only 8% of controls had neither fever nor cough.

Multivariable analysis revealed that only age, cough, and fever were associated with influenza. Fever (odds ratio 3.5, 95% CI 1.9–6.6) was consistently associated with influenza. There was an interaction between age and the presence of cough, with the odds ratio

Table 3. Symptom, sign, and laboratory complexes

Symptom complex	Case, *n* (%) (*n* = 117)	Control, *n* (%) (*n* = 236)	OR (95% CI) *p* value if < .05	PPV (%) (95% CI)
Symptoms alone				
Fever and cough	95 (81)	105 (44)	5.3 (3.1–9.1)	48 (40–55)
Fever and chest pain	18 (16)	19 (8)	2.1 (1.1–4.2)	49 (32–65)
Fever, cough, and HA	32 (27)	20 (9)	4.1 (2.2–7.5)	62 (47–74)
Fever or cough	116 (99)	217 (92)	10.1 (1.3–77)	35 (29–40)
Fever and HA	33 (28)	33 (14)	2.4 (1.4–4.2)	50 (38–62)
Symptoms and other data				
Fever and cough and HR < 100 beats/min	33/42 (79)	51/127 (40)	5.4 (2.4–12)	39 (29–51)
Fever and cough and HR > 100 beats/min	47/54 (87)	43/71 (61)	4.3 (1.7–11)	52 (41–63)
Fever and cough and WBC < 10×10^9/mL	31/55 (56)	29/196 (15)	7.4 (3.8–14)	52 (39–65)
With HR < 100 beats/min	9/18 (50)	17/104 (16)	5.1 (1.8–15)	35 (18–56)
With HR > 100 beats/min	14/22 (64)	8/78 (14)	11 (3.4–35)	64 (41–82)
Fever and cough and normal radiograph	33/40 (83)	38/78 (49)	5 (1.9–13)	46 (35–59)

HA = headache; HR = heart rate; PPV = positive predictive value; WBC = white blood cell count.

https://doi.org/10.2310/8000.2011.100226 Published online by Cambridge University Press

associated with cough decreasing with age such that in adults aged 18 to 44 years, the odds ratio was 13 (95% CI 2.9–60), whereas for adults aged 65 years and older, the odds ratio associated with cough was 1.7 (95% CI 0.3–9.4).

DISCUSSION

Although this study has identified several characteristics that increase the probability that an adult patient with fever or respiratory symptoms has influenza, the predictive value of any single characteristic or any combination of these characteristics is modest at best. Similarly, although it may be possible to exclude the diagnosis of influenza in young adult patients with neither fever nor cough, this may exclude only a small number of patients. Emergency departments will need to apply additional precautions to all patients with fever or respiratory symptoms if they wish to ensure that unprotected exposure to patients with influenza does not occur. If same-day laboratory testing by PCR is not available, physicians wishing to promptly treat patients with influenza at risk of complications will need to treat a substantial number of patients who do not have influenza, even when influenza activity is high. For instance, during the first wave of the pandemic in our emergency departments, if patients with fever and cough were selected for treatment, 81% of influenza patients would have been treated, but so would 44% of patients presenting with cough, fever, or any other respiratory symptom with an alternative diagnosis.

Our data describing symptom distribution differ somewhat from the initial description of the pandemic.[1] In that cohort of 642 cases, fever and cough featured prominently, as was seen in our population; however, sore throat, diarrhea, and vomiting were much more common than reported in our cohort. The reason for this is not immediately clear; however, their cohort was predominantly less than age 18 (60%); gastrointestinal symptoms may be more common in children than in adults.[16] This, and our finding that cough is less predictive of influenza in older compared to younger adults, underscores the importance of validating any clinical prediction algorithm for influenza for pediatric, adult, and elderly populations separately.

Although most previous studies of symptoms predictive of influenza have assessed clinic patients or inpatients rather than emergency department patients, seasonal rather than pandemic influenza, and influenza diagnosed by serology, culture, or rapid test rather than by PCR, their findings are similar to ours.[2–15] Fever and cough are the only two symptoms consistently associated with influenza; however, their reported performance characteristics are variable and clearly not optimal for diagnosis. In a study of younger adults during peak influenza season, Boivin and colleagues reported the highest positive predictive value for clinical symptoms and influenza at 87%.[17] However, even in that report, 23% of patients infected with influenza would have been missed if only patients with fever and cough were considered to have influenza. A number of other differences between cases and controls in our series (e.g., underlying cardiac illness) are likely a result of differences in age as older adults seem to be relatively protected from pandemic influenza. Asthma has previously been noted as an important association between younger persons and viral illnesses.[18]

The strength of our study is that our emergency departments were uniformly collecting specimens on all patients with fever or respiratory symptoms and any patients in whom the treating physician was significantly concerned about influenza. Our controls come from a cohort of patients with fever or respiratory symptoms, in whom the differential diagnosis of influenza would have been reasonable to entertain. Consequently, our data represent the "real-world" performance characteristics of the clinical history to detect influenza compared to other presenting illnesses, and our cases and controls are selected from the population in whom one would reasonably entertain the diagnosis of influenza.

Our study has several limitations. First, our cohort was limited to adults only, and there were very few older adults and immunocompromised patients who presented to our ED. There were also no cases of severe disease (ie, requiring intensive care unit admission), and such patients may also present differently. Although we recorded data as they appeared in the chart, systematic prospective histories were not taken, such that patients may have had symptoms that were not documented in the chart. These were taken as negative for the purposes of data analysis, potentially introducing bias if cases were, for some reason, more likely to have symptoms specifically documented compared to controls. For example, some symptoms, such as rapidity of onset and prostration, were

https://doi.org/10.2310/8000.2011.100226 Published online by Cambridge University Press

recorded too rarely to be useful. Similarly, whether cases or controls received the seasonal influenza vaccine, or whether they had personal contacts who were ill was rarely documented.

Additionally, although RT-PCR of the nasopharynx is considered the gold standard, it is recognized as being imperfect, with false–negative results caused by improper technique. Additionally, there have been cases that are positive on more invasive testing, such as bronchioalveolar lavage, which previously tested negative by NP swab. Such patients would not be captured in our study. Nevertheless, our results, with our highly trained cohort of nurses in the emergency departments and our laboratory expertise, are likely to represent close to the best possible real-world performance and, consequently, the best possible data.

Because we matched cases by date and time, we cannot assess the effect of variation in the prevalence of influenza in the community as a predictor of disease. Any clinical prediction algorithm for influenza is best served by recognizing the burden of illness that is present in the community at the time of presentation as the positive and negative predictive values of any algorithm are dependent on the pretest probability. Our pretest probability was 30%, which represents a fairly high level of influenza activity.

CONCLUSION

Our data suggest that the clinical history and preliminary investigations available in the emergency department have modest ability to diagnose influenza. In the absence of rapid, high sensitivity and specificity testing, the clinical diagnosis of influenza may lead to empiric treatment of many individuals who do not have such infection. This would be expected to become less important with higher levels of influenza activity in the community. Although the absence of both fever and cough will be seen infrequently in controls, perhaps the absence of these two symptoms will negate the need for isolation, testing, or empiric therapy, conserving resources for those who will require them.

Competing interests: None declared.

REFERENCES

1. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, 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;360:2605-15.
2. Monmany J, Rabella N, Margall N, et al. Unmasking influenza virus infection in patients attended to in the emergency department. *Infection* 2004;32:89-97.
3. Babcock HM, Merz LR, Dubberke ER, et al. Case-control study of clinical features of influenza in hospitalized patients. *Infect Control Hosp Epidemiol* 2008;29:921-6.
4. D'Heilly SJ, Janoff EN, Nichol P, et al. Rapid diagnosis of influenza infection in older adults: influence on clinical care in a routine clinical setting. *J Clin Virol* 2008;42:124-8.
5. van den Dool C, Hak E, Wallinga J, et al. Symptoms of influenza virus infection in hospitalized patients. *Infect Control Hosp Epidemiol* 2008;29:314-9.
6. Babcock HM, Merz LR, Fraser VJ. Is influenza an influenza-like illness? Clinical presentation of influenza in hospitalized patients. *Infect Control Hosp Epidemiol* 2006;27:266-70.
7. Call SA, Vollenweider MA, Hornung CA, et al. Does this patient have influenza? *JAMA* 2005;293:987-97.
8. Navarro-Mari JM, Perez-Ruiz M, Cantudo-Munoz P, et al. Influenza-like illness criteria were poorly related to laboratory-confirmed influenza in a sentinel surveillance study. *J Clin Epidemiol* 2005;58:275-9.
9. Ebell MH, White LL, Casault T. A systematic review of the history and physical examination to diagnose influenza. *J Am Board Fam Pract* 2004;17:1-5.
10. Thursky K, Cordova SP, Smith D, et al. Working towards a simple case definition for influenza surveillance. *J Clin Virol* 2003;27:170-9.
11. Walsh EE, Cox C, Falsey AR. Clinical features of influenza A virus infection in older hospitalized persons. *J Am Geriatr Soc* 2002;50:1498-503.
12. van Elden LJ, van Essen GA, Boucher CA, et al. Clinical diagnosis of influenza virus infection: evaluation of diagnostic tools in general practice. *Br J Gen Pract* 2001;51:630-4.
13. Zambon M, Hays J, Webster A, et al. Diagnosis of influenza in the community: relationship of clinical diagnosis to confirmed virological, serologic, or molecular detection of influenza. *Arch Intern Med* 2001;161:2116-22.
14. Monto AS, Gravenstein S, Elliott M, et al. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med* 2000;160:3243-7.
15. Govaert TM, Dinant GJ, Aretz K, et al. The predictive value of influenza symptomatology in elderly people. *Fam Pract* 1998;15:16-22.
16. Price DA, Postlethwaite RJ, Longson M. Influenzavirus A2 infections presenting with febrile convulsions and gastrointestinal symptoms in young children. *Clin Pediatr (Phila)* 1976;15:361-7.
17. Boivin G, Hardy I, Tellier G, et al. Predicting influenza infections during epidemics with use of a clinical case definition. *Clin Infect Dis* 2000;31:1166-9.
18. Azevedo AM, Durigon EL, Okasima V, et al. Detection of influenza, parainfluenza, adenovirus and respiratory syncytial virus during asthma attacks in children older than 2 years old. *Allergol Immunopathol (Madr)* 2003;31:311-7.