Predicting Influenza Infections during Epidemics with Use of a Clinical Case Definition

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Combined pharyngeal and nasal swab specimens were collected from 100 subjects who presented with a flu-like illness (fever >37.8°C plus 2 of 4 symptoms: cough, myalgia, sore throat, and headache) of <72 hours' duration at 3 different clinics in the province of Quebec, Canada, during the 1998–1999 flu season. The rate of laboratory-confirmed influenza infection was 72% according to cell culture findings and 79% according to the results of multiplex reverse-transcription polymerase chain reaction (RT-PCR) analysis (85%, influenza AH3; 15%, influenza B). All subjects for whom these results were discordant (negative culture and positive PCR) presented with a temperature ⩾38.2°C as well as 3 or 4 of the symptoms in the clinical case definition. Stepwise logistic regression showed that cough (odds ratio [OR], 6.7; 95% confidence interval [CI], 1.4–34.1; $P = .02$) and fever (OR, 3.1; 95% CI, 1.4–8.0; $P = .01$) were the only factors significantly associated with a positive PCR test for influenza. The positive predictive value, negative predictive value, sensitivity, and the specificity of a case definition including fever (temperature of >38°C) and cough for the diagnosis of influenza infection during this flu season were 86.8%, 39.3%, 77.6%, and 55.0%, respectively.

Infections caused by influenza viruses lead to substantial morbidity and mortality, particularly among elderly subjects and persons with chronic pulmonary or cardiovascular conditions. It is important from a public health perspective to differentiate influenza viruses from other respiratory tract pathogens responsible for flu-like illnesses. Now that safe and effective anti-influenza drugs (e.g., the neuraminidase inhibitors zanamivir and oseltamivir) are available [1–3], such distinction is also important for individual case management.

Influenza infections can now be rapidly diagnosed with simple antigen detection kits [4–6], but such confirmatory tests are probably not always required in the context of an influenza outbreak. In this study, we validated the use of a clinical case definition for the diagnosis of influenza infections by sentinel physicians in the province of Quebec during the 1998–1999 epidemic. In addition, we sought to identify the best clinical predictors of influenza infections in that population.

Materials and Methods

Study protocol. Physicians at 3 outpatient clinics in Quebec City and Montreal were instructed to collect up to 8 nasal and pharyngeal swab specimens per week from subjects presenting with a flu-like illness of <72 h duration. The definition of a flu-like illness was the following: fever (temperature of ⩾37.8°C) and 2 of the following 4 clinical symptoms: headache, cough, sore throat, and myalgia. The study was initiated after the first 2 laboratory-confirmed influenza cases were identified in the aforementioned clinic area after 1 December 1998; it was terminated on 31 March 1999. Vaccinated subjects could be enrolled if they fulfilled the clinical case definition. Combined nasal and pharyngeal swab specimens were collected and a standardized questionnaire was completed by a physician for each participant.

Laboratory procedures. Upon collection, swab specimens were immediately placed in a virus transportation medium (VTM; Cellmatics, Difco Laboratories, Detroit) and kept at 4°C for a maximum of 48 h before cell inoculation. An aliquot of 200 μL of VTM was inoculated in a vial containing Madin-Darby canine kidney cells for viral growth and hemadsorption testing (performed on day 10). A positive cytopathic effect or hemadsorption test was confirmed by typing of virally infected cells with use of monoclonal antibodies for influenza A and B (Whittaker, Walkersville, MD). Viral RNA was extracted from 100 μL of VTM according to the guanidinium-based method described by Boom et al. [7]. Viral RNA was amplified with a nested multiplex PCR assay with sets of primers for subtypes AH1, AH3, and B, as previously reported [8].

Statistical analyses. Along with descriptive statistics, univariate and stepwise logistic regression analyses were performed to determine the best clinical predictors of laboratory-con-

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Table 1. Descriptive data for the study population of 100 subjects from 3 clinics in the province of Quebec.

Characteristic	*n*/*N* (%) of subjects	Mean	Median
Age, y		39.3	36.0
⩾55 y	21/99 (21.2)		
⩾65 y	10/99 (10.1)		
Male	42/99 (42.4)		
Duration of symptoms, h		44.5	48.0
Temperature, °C		38.3	38.3
⩾38.0°C	74/96 (77.1)		
⩾39.0°C	12/96 (12.5)		
Use of antipyretic in previous 6 h	60/95 (63.2)		
Influenza vaccination	9/98 (9.2)		
Underlying illness[a]	18/100 (18.0)		
Cough	90/99 (90.9)		
Sore throat	83/97 (85.6)		
Headache	89/98 (90.8)		
Myalgia	88/98 (89.8)		
Presence of 2 symptoms[b]	6/97 (6.2)		
Presence of 3 symptoms[b]	30/97 (30.9)		
Presence of 4 symptoms[b]	61/97 (62.9)		

[a] Asthma ($n = 8$), angina pectoris ($n = 7$), chronic obstructive pulmonary disease ($n = 2$), or both diabetes and chronic obstructive pulmonary disease ($n = 1$).

[b] A combination of the following symptoms: cough, myalgia, headache and/or sore throat.

firmed influenza infections. SAS software version 6.12 (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

Descriptive data. Over the study period (14 December 1998 through 31 March 1999), 100 subjects were recruited: 51 in clinic 1, 30 in clinic 2, and 19 in clinic 3. Demographic and clinical data for the study population are summarized in table 1. Nine (9%) of the subjects were vaccinated and 18 (18%) had an underlying disease (asthma, 8; angina pectoris, 7; chronic obstructive pulmonary disease [COPD], 2; or both diabetes mellitus and COPD, 1). The subjects generally were middle-aged adults (mean age, 39.3 years; median, 36.0 years; range, 6–84 years), were febrile (mean and median temperature, 38.3°C), and had had their symptoms for a mean of 44.5 h (median, 48 h).

Laboratory confirmation. The overall positivity rate for the 100 samples on the basis of cell culture was 72.0% (84.2% at clinic 1, 70.6% at clinic 2, and 66.7% at clinic 3). On the basis of PCR, the positivity rate for all sites combined was 79.0% (89.5% at clinic 1, 76.5% at clinic 2, and 76.6% at clinic 3). On the basis of the size of PCR fragments on gel, 67 (84.8%) of 79 positive samples were identified as influenza AH3 and 12 (15.2%) of 79 as influenza B. Eighty-three percent of the samples were collected over a period of 5 consecutive weeks from 25 January through 1 March 1999. This period included 68 (86.1%) of the 79 PCR-positive samples. None of the PCR-negative samples were found to be positive by culture. In contrast, 7 specimens were found to be positive by PCR (6 for influenza AH3 and 1 for influenza B) and negative by culture. All subjects with discordant test results had a temperature ⩾38.2°C, and all had 3 or 4 flu-related symptoms. None of these subjects had received antiviral drugs, although 2 of the 7 had been vaccinated.

Predictive model. Univariate logistic regression on baseline clinical symptoms and other variables revealed a significant association between a PCR-confirmed influenza infection and fever or cough (table 2). With stepwise logistic regression, the best model to predict influenza included both cough and fever; cough was associated with an OR of 6.7 for a positive PCR test (95% CI, 1.4–34.1; $P = .02$) and fever was associated with an OR of 3.1 (95% CI, 1.4–8.0; $P = .01$) (table 2). The probability of a positive PCR test was greater with increasing levels of temperature, reaching ~60% at 39.0°C in the absence of cough (figure 1). In the presence of cough, the probability of a positive PCR test increased to ~90% at 39.0°C. Moreover, a combination of temperature >38.0°C and cough was associated with a positive predictive value of 86.8%, a negative predictive value of 39.3%, sensitivity of 77.6%, and specificity of 55.0% for a positive PCR test. The only factor significantly associated with a positive influenza culture in multivariate analysis was cough, with an OR of 4.6 (95% CI, 1.1–20.6; $P = .03$).

Discussion

A flu-like illness can be caused by a variety of viral and nonviral pathogens, including influenza viruses, parainfluenza viruses, adenoviruses, respiratory syncytial virus, rhinoviruses, *Chlamydia pneumoniae,* and *Mycoplasma pneumoniae* [9, 10]. In the nursing home population, recent studies have shown that both influenza viruses and respiratory syncytial virus were associated with a flu-like illness and were among the leading causes of viral pneumonia [11, 12]. Differentiating influenza virus from the other respiratory viruses is of prime importance because the influenza virus is associated with higher morbidity

Table 2. Clinical symptoms and variables associated with a positive polymerase chain reaction test for influenza.

	Univariate analysis			Multivariate analysis		
Variable	OR	95% CI	*P*	OR	95% CI	*P*
Age ⩾65 y	1.01	0.23–7.10	.99			
Sex	0.61	0.21–1.65	.34			
Duration of symptoms	1.54	0.54–4.23	.41			
Temperature[a]	3.20	1.31–8.39	.01	3.06	1.35–8.02	.01
Antipyretic use	0.90	0.31–2.48	.85			
Cough	5.78	1.39–25.74	.02	6.68	1.40–34.13	.02
Sore throat	0.60	0.09–2.48	.53			
Headache	1.13	0.16–5.15	.89			
Myalgia	0.97	0.14–4.31	.97			
Influenza vaccination	0.30	0.07–1.30	.09			
Underlying disease	0.63	0.20–2.19	0.44			

[a] Analyzed as a continuous variable.

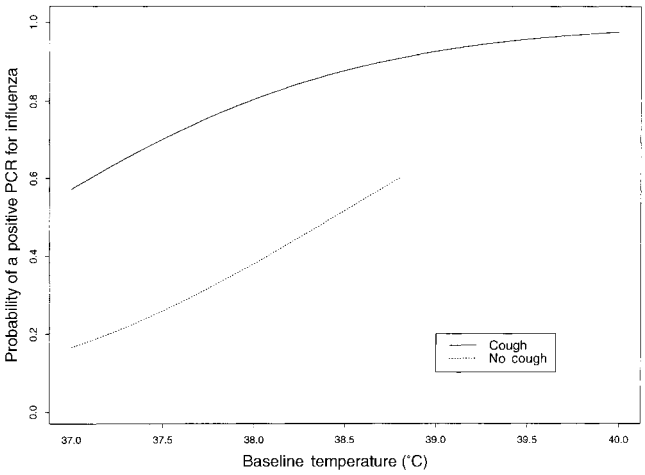

Figure 1. Probability of a positive polymerase chain reaction test for influenza, in relation to baseline temperature and cough.

and mortality, is potentially preventable by vaccination, and can now be managed with specific antivirals.

Two new antiviral agents, zanamivir and oseltamivir, are recently approved neuraminidase inhibitors active against all strains of influenza A and B viruses [13, 14]. When administered early (within 36–48 hours of the onset of symptoms), both drugs can reduce the median duration of flu-like symptoms by about 30% [1, 2, 15]. Because these drugs have no activity against other viruses and because of the short window of therapeutic opportunity for influenza infections, a rapid diagnosis is critical for appropriate individual management.

Classic laboratory diagnosis of influenza on the basis of viral culture or serology is of little interest in the context of individual treatment in outpatient clinics because of the time required to obtain results. New rapid antigen-detection tests for influenza viruses, with turnaround times of <15–20 minutes, are now available in clinics and can assist physicians in the management of this condition [4–6]. However, there are limitations to the general use of these tests, including their cost, their lower sensitivity in comparison with viral culture, and the fact that they may not be rapid enough for a busy physician's office.

At present, many practitioners diagnose influenza infections on the basis of the presence (or absence) of some clinical symptoms and signs. It has been reported that, with the knowledge that influenza is circulating in their community, physicians can correctly diagnose this infection in ⩾60%–70% of their patients on the basis of clinical symptoms alone [16]. Using a clinical case definition that included fever (temperature of ⩾37.8°C) and the presence of 2 of 4 symptoms (cough, sore throat, myalgia, and headache) of <72 h duration, we showed that general practitioners at 3 different clinics in the Province of Québec were usually accurate (72%, as confirmed by culture; 79%, as confirmed by PCR) in diagnosing influenza.

In stepwise logistic regression, cough and fever were the only factors significantly associated with a positive PCR test for influenza in our study. The positive predictive value of a modified case definition consisting of the presence of fever (temperature of ⩾38°C) and cough was 86.8%, with a negative predictive value of 39.3%. Other studies have identified the combination of fever, cough, and acute onset as the best predictors of influenza [10, 17, 18]. In contrast, by using the same clinical criteria for elderly people in the absence of a known influenza epidemic, Govaert et al. reported that physicians would have achieved a positive predictive value of only 44% [17]. This illustrates why such a clinical case definition would really help only when coupled with active surveillance indicating an influenza outbreak.

There are some limitations related to the widespread use of clinical criteria to diagnose influenza. As mentioned earlier, this practice requires an active virological surveillance system in a community and rapid diffusion of the results to the general practitioners. Also, because fever is an important component of the case definition, recent use of antipyretics could affect case management. Other factors that can potentially affect the accuracy of the clinical diagnosis are the vaccination rate of the study population (which was only 9% in our study), the circulating virus strain, the age of the subjects, underlying illnesses, and the duration of symptoms at the time of the consultation.

The small number of influenza B infections found during our study precluded analysis to discriminate between symptoms of influenza A and B infections. Our work also confirmed the slight increase in the sensitivity of the multiplex reverse transcription (RT) PCR assay for influenza virus, in comparison with that of traditional cell culture as originally reported by Ellis et al. [8]. In both studies, the increase in sensitivity was about 7% in favor of the former method. We believe that the discordant PCR-positive/culture-negative specimens are true-positives since they originated from very symptomatic subjects with high fever. Other advantages of the RT-PCR method over viral culture include its more rapid turnover, decreased requirements for rapid and adequate transportation of the samples, and the possibility of further analyzing the amplicon by sequencing or restriction enzyme digestion. An evaluation of the new rapid antigen-detection tests in comparison with the RT-PCR assay is warranted.

In conclusion, when influenza is circulating in a community, the presence of cough and high fever in a patient is likely to be associated with influenza. This association could be used by physicians to rapidly enact specific treatment with the new neuraminidase inhibitors of influenza viruses. However, because this clinical case definition is still imperfect (e.g., negative predictive value of ~40% in our study), cases with atypical presentations and cases occurring early in the flu season could benefit from rapid antigen-detection testing.

References

1. Hayden FG, Osterhaus AD, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. GG167 Influenza Study Group. N Engl J Med **1997**; 337:874–80.
2. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Lancet **1998**; 352: 1877–81.
3. Hayden FG, Treanor JJ, Fritz RS, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. JAMA **1999**; 282:1240–6.
4. Leonardi GP, Leib H, Birkhead GS, Smith C, Costello P, Conron W. Comparison of rapid detection methods for influenza A virus and their value in health-care management of institutionalized geriatric patients. J Clin Microbiol **1994**; 32:70–4.
5. Kramp WJ, Simpson D, Justewicz D. Sensitivity of the Quidel Rapid Vue influenza test to detect type A influenza virus strains [abstract H-280]. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **1999**.
6. Covalciuc KA, Webb KH, Carlson CA. Comparison of four clinical specimen types for detection of influenza A and B viruses by optical immunoassay (FLU OIA Test) and cell culture methods. J Clin Microbiol **1999**; 37: 3971–4.
7. Boom R, Sol CJ, Salimans MM, Jansen CL, Wertheim van Dillen PM, van der Noordaa J. Rapid and simple method for purification of nucleic acids. J Clin Microbiol **1990**; 28:495–503.
8. Ellis JS, Fleming DM, Zambon MC. Multiplex reverse transcription–PCR for surveillance of influenza A and B viruses in England and Wales in 1995 and 1996. J Clin Microbiol **1997**; 35:2076–82.
9. Monto AS. Studies of the community and family: acute respiratory illness and infection. Epidemiol Rev **1994**; 16:351–73.
10. Long CE, Hall CB, Cunningham CK, et al. Influenza surveillance in community-dwelling elderly compared with children. Arch Fam Med **1997**; 6: 459–65.
11. Falsey AR, Treanor JJ, Betts RF, Walsh EE. Viral respiratory infections in the institutionalized elderly: clinical and epidemiologic findings. J Am Geriatr Soc **1992**; 40:115–9.
12. Falsey AR, Cunningham CK, Barker WH, et al. Respiratory syncytial virus and influenza A infections in the hospitalized elderly. J Infect Dis **1995**; 172:389–94.
13. Woods JM, Bethell RC, Coates JA, et al. 4-Guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid is a highly effective inhibitor both of the sialidase (neuraminidase) and of growth of a wide range of influenza A and B viruses in vitro. Antimicrob Agents Chemother **1993**; 37:1473–9.
14. Calfee DP, Hayden FG. New approaches to influenza chemotherapy. Neuraminidase inhibitors. Drugs **1998**; 56:537–53.
15. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. JAMA **2000**; 283:1016–24.
16. Betts RF. Influenza virus. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and practice of infectious diseases. 4th ed. New York: Churchill Livingstone, **1995**:1546–67.
17. Govaert TM, Dinant GJ, Aretz K, Knottnerus JA. The predictive value of influenza symptomatology in elderly people. Fam Pract **1998**; 15:16–22.
18. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J, Freund B. Clinical predictors of an acute influenza epidemic with laboratory confirmation [abstract H-277]. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **1999**.