

Evaluating Case Definitions for Clinical Influenza Surveillance.

K Osaka MD., MPH.^{1,2}, Y Nagai MD³, M Syoji MD⁴, H Nishimura MD, PhD⁵

¹Infectious Disease Surveillance Center, National Institute of Infectious Diseases,
Tokyo, Japan.

²Department of Population and International Health, Harvard School of Public Health,
Boston, USA

³Nagai Children's Clinic, Sendai, Japan

⁴Shoji Clinic, Sendai, Japan

⁵Virus Research Center, Sendai National Hospital, Sendai, Japan

Corresponding author:

Ken Osaka MD, MPH

1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8640 Japan

Tel 81-3-5285-1111 Fax 81-3-5285-1129

E-mail: kosaka@nih.go.jp

Words count: abstract 121 words, text 2,055 words

Abstract

To evaluate case definitions for clinical influenza surveillance, we studied the relationship between various symptoms and virus isolation during the 2000-01 influenza season. We also calculated the sensitivity and predictive value positives of clinical case definitions used in various countries, adopting these case definitions to our data collected in Sendai city, Japan. Using logistic regression analysis, we found that the significant predicting symptoms were cough (OR 1.80, 95%CI 1.19-2.85) and myalgia (OR 1.80, 95%CI 1.16-2.79). In comparing case definitions used in various countries, we found a wide range of sensitivities (43-85%), but a narrow range and relatively low predictive value positives (48-54%). To effectively assess influenza epidemic and to compare the situation of various countries, the standardized case definitions is needed

Key words

Influenza, surveillance, case-definition, cough, myalgia, predictive value positive, sensitivity, virus isolation.

Introduction

Influenza causes substantial morbidity and mortality and its overall attack rates are estimated to be 10-20% during average epidemics, but in selected populations or age groups, attack rates of 40-50% are not unusual. Age-specific attack rates are reported to be highest in school children [1]. To monitor influenza infections, clinical surveillance has been implemented in many countries in which influenza is endemic. These surveillance data are also used to evaluate the morbidity and mortality of influenza within the country or district. The World Health Organization (WHO) is conducting a worldwide surveillance program named "FluNet", which allows for the monitoring the epidemic situation of influenza infection and the collection of data on circulating virus subtypes using data from multiple WHO collaboration centers [2]. These data provide the basic information of influenza activities of worldwide and the WHO uses the data when it recommends the seed viruses for influenza vaccine for the next season.

Infection with influenza typically gives rise to non-specific flu-like symptoms, and it is often difficult to distinguish between the symptoms of influenza and symptoms caused by other viruses such as respiratory syncytial virus (RSV), or adeno virus [3,4].

Effective drugs for the treatment of influenza, including neuramidase inhibitors have been recently approved in many countries. If administered in the early stage of the

illness (within 36-48 hours of the onset of symptoms), these drugs have been shown to reduce the length and severity of symptoms significantly [5, 6]. Since they are not effective against other viruses, rapid accurate diagnosis is critical for appropriate case management. Rapid tests for detection of influenza A and B viral antigens have recently been introduced in clinical settings [7, 8]. However, it is not feasible for practitioners to use these tests in all the cases, because they are relatively expensive, and the procedure further burdens the staff of busy clinics. In addition, we sometimes found that patients who initially tested negative for influenza antigens were positive for virus isolation. These false negative findings, particularly early in the course of the disease, would cause clinicians to miss the optimal window for initiating influenza treatment.

Therefore, a clinical case definition of influenza based on symptoms and observable signs is still important for the appropriate management of individual influenza patients, as well as to assure the quality of surveillance. However, there is no standardized case definition for the influenza, and we have found that various case definitions are used in different countries and areas [9, 10, 11, 12]. The variability of case definitions makes it difficult to compare data from different surveillance systems. This problem has surfaced within the EU, where the use of different case definitions has complicated the comparison of influenza data between countries [13].

In Japan, a new infectious disease surveillance system started in April 1999 and a new clinical case definition has been used since this time. In the new surveillance system, about 3,000 pediatricians and 2,000 physicians were selected as sentinels, based on the population and geographical districts [14]. They report the total number of influenza-like illnesses encountered in their daily practice every week. Additional information is gained from reports of school absences due to influenza. However, these data are surveyed in a different system, and further evaluation is needed to link this information with the new surveillance system. [15].

In the present study, we evaluated the choice of symptoms used for the clinical case definition by comparing the cases detected by the case definition with those detected by influenza virus isolation. We also evaluated the sensitivity and predictive value positive rate of the case definition used in selected countries.

Materials and Methods

Study protocol

Well-experienced physicians at 2 clinics (one pediatrician and one internal medicine physician) in Sendai city, Miyagi prefecture were instructed to collect pharyngeal swab specimens from subjects presenting with a influenza-like illness. When they suspected the influenza infection among their outpatients, a standardized questionnaire concerning

the nature of each patient's symptoms was completed by the physicians. Data collected in this study included: age, sex, days since onset, maximum body temperature, the presence or absence of cough, sputum, myalgia, runny or stuffy nose, pharyngitis, general malaise and the number of days between the collection of the sample and its isolation test. Upon collection, specimens were immediately placed in a virus-transportation medium and transferred to the Virus Research Center of Sendai National Hospital. There, virus isolations were attempted for influenza and other viruses that give rise to influenza-like illnesses. The study was conducted from Feb. 24 – April 3, 2001.

Laboratory procedure

Each throat swab specimen was collected in 3ml of transport medium consisting of MEM with 0.5% gelatin, 500µg of penicillin, and 500µg of streptomycin per ml. The specimens were kept for 0 to 3 days at 4°C until inoculation. Virus isolation was performed at the Virus Research Center at Sendai National Hospital using the microplate method to isolate several kinds of respiratory viruses [16, 17]. Briefly, clinical specimens were centrifuged at 3,000 rpm for 15 minutes. The supernatant was then inoculated directly onto a 96-well microtiter plate, on which five types of cells were cultured in each well: human embryo fibroblast, HEp-2, Vero, MDCK and HMV-II cells. The inoculated plates were incubated at 33°C in a CO₂ incubator, and

cytopathic effects (CPE) were observed for up to 10 days. The MDCK cultures showing characteristic influenza-like CPE were passed in the MDCK cultures in larger wells and the supernatants were applied to hemagglutinin inhibition test using anti-influenza A or B virus ferret serum against the following virus strains provided by the National Institute of Infectious Diseases, Tokyo, for identification of the isolated viruses: A/Moscow/13/98(H1N1); A/New Caledonia/20/99(H1N1); A/Panama/2007/99(H3N2); B/Shandong/07/97; B/Yamanashi/166/98.

Statistical analysis

Along with descriptive statistics, univariate and stepwise logistic regression analyses were carried out to determine the best clinical predictors of virus isolation. SPSS version 10.0 was used for all statistical analysis.

Evaluation

Using data from known cases of influenza, we calculated the sensitivity and predictive value of current case definitions devised by Japan and other countries.

Results

A total 385 specimens , along with records of clinical symptoms were collected. Two hundred and thirty-nine cases (62%) were found in children younger than 15 years old.

Just under half of the cases (179 out of 385; 46%) were in males. A total 175 (45%) influenza viruses were isolated; 97 were A (H1N1), 39 were A (H3N2) and 39 were B type of influenza. Adeno viruses (type3) were isolated in three specimens, which were negative for influenza. None of these subjects had received anti-viral drugs or vaccination before the specimens were collected.

Univariate logistic regression on baseline clinical symptoms and other variables are shown in Table 2. A significant association was observed between virus isolation and following symptoms, cough, malaise and myalgia. With stepwise logistic regression, the best model to predict influenza included both cough and myalgia. Cough was associated with an OR of 1.84, (95%CI [1.19-2.85], $p < 0.01$) for a positive influenza culture and myalgia was associated with an OR of 1.80 (95% CI [1.16-2.79], $p < 0.01$), as shown in Table 2.

We applied our data set to the current case definitions used by the USA, Canada, Italy, New Zealand and Japan and calculated the sensitivity and predictive value positive (Fig. 1). Two definitions used in Australia were excluded for the calculation due to lack of available data of one of criteria; influenza in close contacts. The most sensitive case definition was that of the USA (85%) followed by New Zealand (67%), Italy (66%) and Canada (49%). The Japanese case definition showed the lowest

sensitivity (43%). On the other hand, the highest predictive value positives were from the Japanese case definition (54%) followed by Canada (53%), New Zealand (49%) and USA (48%).

Discussion

Influenza-like illnesses can be caused by infection with various pathogens. A study of the epidemiology of RSV reported the prevalence of this virus in specimens submitted during the winter was 20-30% [18]. Adeno virus is estimated to be responsible for about 5-10% of pediatrics respiratory infections [19]. Infection with parainfluenza virus is thought to be associated with 2-10% of cases of upper respiratory tract infections, 25-50% of cases of croup and 5-20% of cases of pneumonia and bronchiolitis [20].

We collected our data during the 2000-2001 flu season. This flu season proved to be atypical, in that there was a relatively low incidence of influenza throughout Japan. Laboratory-confirmed influenza infections included equal proportions of three different viruses; A(H1N1), A(H3N2) and B [21]. The influenza season was also later than usual, with a peak at week 11 of 2001, rather than the usual peak at week 3-5

[21]. The unusual characteristics of the influenza season that we studied could have resulted in atypical data.

Among the symptoms included in case definitions of influenza, fever is not a significant predictor for influenza virus isolation. One previous study [22] on clinical symptoms in the elderly people reported that a fever of at least 38°C, coughing and malaise were significant predicting symptoms of influenza. In our study, we found 32 cases where the subject had fevers $\leq 38^\circ\text{C}$ whose specimens were shown to be positive for influenza. If our target population had been elderly people or compromised hosts, who tend to have dampened fever responses, we might have overlooked more cases.

Of all the symptoms we considered, coughing and myalgia were the only predicting symptoms for a positive influenza culture. Previous studies have also shown that coughing is a predicting symptom for influenza [22, 23]. Although, previous studies did not show generalized symptoms as positive predictive value for influenza, myalgia has been shown to be a significant predictor in this study. Influenza was considered to cause more severe generalized disease than other upper respiratory infection, so it seems reasonable that myalgia was shown as a predictor symptom.

When we adopted the case definitions currently in use for influenza-like illness surveillance in Japan, we found a relatively good predictive value positive of 54%, but

the sensitivity of the definition was low (43%). In considering the case definitions employed by various countries, there was a wide range of sensitivities (43-85%), but the predictive value positive were relatively low and within a narrow range (48-54%). If the purpose of clinical influenza-like illness surveillance is to detect even small epidemics, sensitivities should be prioritized over predictive value positive. There appears to be a trade off of these two indicators. It would be better to use comprehensive surveillance, which combines high sensitivity clinical surveillance, as is used in the USA, with laboratory confirmation of influenza infection. The data obtained from clinical surveillance can be modified using results of laboratory confirmation by virus isolation, PCR and serological tests. The rapid test kit for influenza A and B could also be used for crude but rapid modification of clinical surveillance data.

In the course of analyzing our data, we compared symptoms among the different virus types. There was a tendency for there to be fewer or milder symptoms in patients with influenza type B. However, these differences were not significant.

In the present study, we used virus isolation as our gold standard for influenza infection, and we isolated the viruses in the 175 cases out of 385 patients with upper respiratory symptoms. Virus isolation is widely recognized as a standard for confirmation of influenza virus infection. It might be possible, however, that we failed

to detect some influenza cases, which might be caused by possible inactivation of the virus in the specimens, and the sensitivity of the detection might be increased slightly by addition of both RT-PCR and serological methods. With the view of cost and effectiveness that it would not be realistic to perform the RT-PCR on the large number of specimens collected in this study or to collect the paired-serum from every patients of the out-patient clinics, for that level of increase.

In conclusion, we have shown that symptoms of coughing and myalgia are significant predictors for influenza isolation in this study. The clinical case definitions of various countries showed a wide range of sensitivities, but narrow ranges of predictive value positives. In order to compare the data from multiple countries more easily and to monitor the spread of influenza more accurately, standardization of these case definitions.

References

- 1) Glezen, W. P. Emerging infections: pandemic influenza. *Epidemiol Rev* 1996; 18: 64-76.
- 2) Flahault A., Dias-Ferrao V, Chaberty P, Esteves K, Valleron AJ, Lavanchy D. FluNet as a tool for global monitoring of influenza on the Web. *Jama* 1998; 280: 1330-2.
- 3) Tannock GA, Reid AL, Gillett SM, Herd R, Gillett RS, Hensley MJ. A set al. Study of respiratory infections in a healthy adult population during the 1987 Australian winter. *Fam Pract* 1993; 10: 378-86.
- 4) Long CE, Hall CB, Cunningham CK, Weiner LB, Alger KP, Gouveia M, et al. Influenza surveillance in community-dwelling elderly compared with children. *Arch Fam Med* 1997; 6: 459-65.
- 5) Dunn CJ, Goa KL. Zanamivir: a review of its use in influenza. *Drugs* 1999; 58: 761-84.
- 6) Silagy CA, Campion K. Effectiveness and role of zanamivir in the treatment of influenza infection. *Ann Med* 1999; 31: 313-7.
- 7) Ikematsu H, Nabeshima A, Nabeshima S, Kakuda K, Maeda N, Chong Y. et al. Evaluation of a rapid enzyme immunoassay for detection of influenza A virus among adult and elderly patients. *Kansenshogaku Zasshi* 1999; 73 : 1153-8.

- 8) Ueda M, Maeda A, Nakagawa N, Kase T, Kubota R, Takakura H. Application of subtype-specific monoclonal antibodies for rapid detection and identification of influenza A and B viruses. *J Clin Microbiol* 1998; 36: 340-4.
- 9) Anonymous. New influenza surveillance programme in Italy. *Eurosurveillance weekly* 1999;52.
- 10) Kong WM. A Review of the HongKong influenza surveillance system. *Public Health & Epidemiology Bulletin* 2000; 9: 37-41.
- 11) Kelly, H. Murphy, A. Leong, W. Leydon, J. Tresise, P. Gerrard, M. et al. Laboratory-supported influenza surveillance in Victorian sentinel general practices. *Commun Dis Intell* 2000 ;24: 379-83.
- 12) Jennings LC. Influenza surveillance in New Zealand. *Vaccine* 1999; 17 Suppl 1: S115-7.
- 13) Anonymous. Surveillance of influenza in Europe from October 1999 to February 2000. *Eurosurveillance* 2000; 5: 63-8
- 14) Anonymous . The National Epidemiological Surveillance of Infectious Diseases in compliance with the enforcement of the new Infectious Diseases Control Law. *Infectious Agent Surveillance Report* 1999;20: 3.
- 15) Takahashi H, Fujii H, Shindo N, Taniguchi K. Evaluation of the Japanese school

health surveillance system for influenza. *Jpn J Infect Dis* 2000; 54: 27-30.

16) Numazaki, Y., Oshima, T., Ohmi, A., Oizumi, Y., Komatsu, S., Takagi, et al. a microplate method for of viruses from infants and children with acute respiratory infections. *Microbiology and Immunology* 1987; 31:1085-1095.

17) Moriuchi, Y., Oshima, T., Nishimura, H., Nakamura, K., Katsushima, N. Numazaki, Y. Human malignant melanoma cell line (HMV-II) for isolation of influenza C and parainfluenza viruses. *J. Clin. Microbiol.* 1990; 28: 1147-1150.

18) Weigl A, Puppe W, Schmitt J. Incidence of respiratory syncytial virus-positive hospitalizations in Germany. *Eur J Clin Microbiol Infect Dis* 2001; 20: 452-9.

19) Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *Jama* 1999; 282: 1440-6.

20) Kajon AE, Wadell G. Molecular epidemiology of adenoviruses associated with acute lower respiratory disease of children in Buenos Aires, Argentina (1984-1988). *J Med Virol* 1992; 36: 292-7.

21) Anonymous. Influenza, 2000/01 season, Japan. *Infectious Agent Surveillance Report* 2001; 22: 1-2.

22) Boivin G, Hardy I, Tellier G, Maziade J. Predicting influenza infections during

epidemics with use of a clinical case definition. *Clin Infect Dis* 2000; 31: 1166-9.

23) Govaert M, Dinant J, Aretz K, Knottnerus A. The predictive value of influenza symptomatology in elderly people. *Fam Pract* 1998; 15: 16-22.

Acknowledgement

This study was financially supported by a grant from the Japanese Ministry of Health, Labour and Welfare, Japan.

Table 1: Case definitions from selected influenza-like illness (ILI) surveillance systems.

USA: U.S. Influenza Sentinel Physicians Surveillance Network

ILI is defined as fever (temperature of $\geq 100\text{F}(37.8\text{ C}^\circ)$) plus either a cough or a sore throat.

Canada:

ILI in the general population: Acute onset of respiratory illness with fever and cough and with one or more of the following - sore throat, arthralgia, myalgia, or prostration which could be due to influenza virus. In children under 5, gastrointestinal symptoms may also be present. In patients under 5 or 65 and older, fever may not be prominent.

Australia: (ASPREN, and the Victorian and Northern Territory schemes):

- viral culture or serological evidence of influenza virus infection; or
- influenza epidemic, plus four criteria listed below; or
- six of the following clinical criteria
 - sudden onset (within 12 hours),
 - cough,
 - rigours or chills,
 - fever,
 - prostration and weakness,
 - myalgia, widespread aches and pains,
 - no significant respiratory physical signs other than redness of nasal mucous membranes and throat,

-influenza in close contacts.

Australia (NSW)

- cough; and
- myalgia; and
- no abnormal respiratory physical signs other than redness of nasal mucous membranes and throat; and
- two of the following
 - sudden onset,
 - rigours or chills or fever,
 - prostration or weakness,
 - influenza in close contacts.

New Zealand:

an acute respiratory tract infection characterized by an abrupt onset of two of the following: fever, chills, headache and myalgia.

Italy:

acute respiratory infection with sudden onset and fever $>38^{\circ}\text{C}$, accompanied by at least one of the following systemic symptoms (headache, malaise, fatigue, shivering), and at least one of the following respiratory symptoms (cough, nasal congestion, sore throat).

Japan:

Cases of influenza have all of the following 4 symptoms:

1. Abrupt onset,
 2. Fever $>38^{\circ}\text{C}$,
 3. symptoms of upper respiratory inflammation,
 4. generalized symptoms such as malaise.
-

Table 2: Clinical symptoms and other factors associated with a positive isolation of influenza virus.

Variable	Univariate analysis			Multivariate analysis		
	OR	95%CI	p	OR	95%CI	p
Temperature	0.96	0.73 - 1.25	0.74			
Pharyngitis	1.12	0.75 - 1.67	0.59			
Headache	1.06	0.71 - 1.58	0.79			
Cough	1.58	1.05 - 2.40	0.30	1.84	1.19 - 2.85	<0.01
Sputum	0.87	0.54 - 1.40	0.55			
Malaise	1.53	1.02 - 2.30	0.04			
Myalgia	1.53	1.01 - 2.32	0.04	1.80	1.16 - 2.79	<0.01
Nasal discharge	0.46	0.78 - 1.75	0.46			
Days from onset	0.91	0.76 - 1.09	0.30			
Days for lab.tests	0.93	0.75 - 1.16	0.52			

Fig. 1: Sensitivity and Predictive Value Positive of Influenza Surveillance in Selected Countries.

In the case definition of various countries, there was a wide range in sensitivity (43-85%), but a relatively narrow range of predictive value positives (48-54%).