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How critical is timing for the diagnosis of influenza in general practice?

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Summary

Questions under study: The diagnostic significance of clinical symptoms/signs of influenza has mainly been assessed in the context of controlled studies with stringent inclusion criteria. There was a need to extend the evaluation of these predictors not only in the context of general practice but also according to the duration of symptoms and to the dynamics of the epidemic.

Principles: A prospective study conducted in the Medical Outpatient Clinic in the winter season 1999–2000. Patients with influenza-like syndrome were included, as long as the primary care physician envisaged the diagnosis of influenza. The physician administered a questionnaire, a throat swab was performed and a culture acquired to document the diagnosis of influenza.

Results: 201 patients were included in the study. 52% were culture positive for influenza. By univariate analysis, temperature >37.8 °C (OR 4.2; 95% CI 2.3–7.7), duration of symptoms <48 hours (OR 3.2; 1.8–5.7), cough (OR 3.2; 1–10.4) and myalgia (OR 2.8; 1.0–7.5) were associated with a diagnosis of influenza. In a multivariable logistic analysis, the best model predicting influenza was the association of a duration of symptom <48 hours, medical attendance at the beginning of the epidemic (weeks 49–50), fever >37.8 and cough, with a sensitivity of 79%, specificity of 69%, positive predictive value of 67%, negative predictive value of 73% and an area under the ROC curve of 0.74.

Conclusions: Besides relevant symptoms and signs, the physician should also consider the duration of symptoms and the epidemiological context (start, peak or end of the epidemic) in his appraisal, since both parameters considerably modify the value of the clinical predictors when assessing the probability of a patient having influenza.

Key words: influenza; clinical predictors; clinical diagnosis; epidemic time

Introduction

The recent marketing of antiviral drugs against influenza has changed the diagnostic approach to this disease. Indeed, there is a need to make the diagnosis as quickly as possible so that the new drugs can be used appropriately [1–3]. The general practitioner needs epidemiological, clinical and/or laboratory tools to improve the reliability of the diagnosis of influenza at first attendance.

The diagnostic performance of clinical symptoms/signs of influenza has mainly been assessed in the context of controlled studies (clinical trials of new antiviral drugs) often using stringent inclusion criteria. A temperature >37.8 °C, cough and sudden onset of symptoms have been identified as indicators of influenza [4–11]. In the present study, we wanted to assess these predictors in the context of general practice and more importantly, the magnitude of their variation according to the duration of symptoms and the dynamic of the epidemic (start, peak and end).

Methods

Microbiological diagnosis was supported by the Swiss surveillance national programme of infectious diseases "Sentinella". Conflict of interest: none declared.

Design

Prospective study conducted during the winter season 1999–2000 at the Medical Outpatient Clinic, University Hospital of Lausanne, Switzerland, a primary care centre that serves an urban population of approximately 150,000 inhabitants. The study was conducted within a national surveillance programme of influenza epidemics in Switzerland called Sentinella [12]. Throughout the year, naso-pharyngal swabs are collected and tested for influenza and other infectious diseases from several institutions (outpatient clinics) and private practices in Switzerland, in order to detect and monitor epidemic outbreaks. The proportion of medical consultations for influenza-like illness (% MC-ILI) is also reported, and is used to describe the dynamics of the influenza epidemic (by definition the threshold for an epidemic is 1.5%).

Patients and procedure

Patients were recruited into the study by the physician on duty, if he/she felt that the symptoms or signs were compatible with a diagnosis of influenza.[1] There were no specific criteria for inclusion or exclusion (such as those of Sentinella surveillance in Switzerland, for example) in order to avoid selection bias (patient with a high pre-test probability) and to reflect the real practice. Following oral consent, the physician administered a questionnaire to the patient to collect demographic (i.e. age, sex) and clinical data (i.e. symptoms of cough, sore throat, rhinitis, myalgia, headache, fatigue, chills/sweating, as well as the duration of symptoms from onset to medical attendance and signs, mainly axillary temperature). A threshold value of 37.8° was used to define fever as in most comparable studies [3]. A throat-swab was performed and sent in medium (Leibowitz, BSA, bicarbonate, hybrimax and gentamycin) to the reference laboratory for the Sentinella Surveillance Program (IKMI, St-Gallen, Switzerland) for a MDCK culture in order to identify influenza A and B viruses.

1 This study was conducted within the Swiss national surveillance program of infectious diseases "Sentinella" and therefore no ethical approval was required. The patients agreed to have a throat swab taken and that the results be reported to the medical and scientific community.

Data analysis

To measure the association between the explanatory variables (duration of the symptoms, the period of the consultation, axillary temperature of >37.8 °C, cough, sore throat, rhinitis, myalgia, headache, fatigue, chills/sweating), and the outcome variable (presence of influenza A or B in throat swab culture), we estimated the odds ratio with the program CIA SOFTWARE version 2.0.0 from BMJ using univariate analysis. For each of these variables, we estimated the sensitivity (Se), specificity (Sp), positive and negative predictive values (PPV/NPV).

We then built a multivariable logistic model using STATA 8.2 software, starting with a simple model including only duration of symptoms and period of consultation. The categories for the duration of symptoms were <24 h, 24–48 h and >48 h. The categories for the time-period of consultation were: week 49–51 (pre-epidemic), 52–1 (peak of the epidemic) and >1 (post-epidemic) [based on the proportion of medical consultations due to flu-like syndromes estimated by the Swiss infectious disease surveillance system (Sentinella)]. We added step by step those clinical variables with odds ratio higher than one. We retained in the model variables for which the estimated odds ratio was >1 (p-value <0.05). Working backwards, we proceeded to a simplification in the definition of the categorical variables, using the deviance statistic to judge the loss of diagnostic power. The ROC curves of both the initial and the final models were computed, as well as the sensitivity, specificity, PPV and NPV.

Results

This study was conducted from December 1999 to February 2000. 222 patients were included in the study and 21 patients with incomplete data or where no throat-swab had been done were excluded from the analysis, 201 patients remained. 104 of 201 (52%) had a positive throat-swab for influenza, of which 103 were positive for influenza A and one for influenza B. The mean age was similar in the group with positive culture (mean = 34.3 years, SD = 13) and with negative culture (mean = 34.3, SD = 12). Patients at the height of the epidemic were older than 60 years and half of them tested positive for influenza. The demographical characteristics as well as the prevalence of symptoms and signs among cases of influenza vs controls are summarised in table 1.

By univariate analysis, temperature >37.8 °C, cough, duration of symptoms <48 hours before consultation and myalgia were associated with a diagnosis of influenza.

Table 2 shows the diagnostic performance (PPV, NPV, sensitivity and specificity) of clinical variables for the diagnosis of influenza.

We started to construct the multivariable logistic model with the two variables: time-period of consultation and duration of symptoms before

Table 1

Demographical characteristics and prevalence of symptoms and signs among cases of influenza (culture +) vs controls (culture –).

Characteristics	% (number) of patients with positive culture (n = 104)	% (number) patients with negative culture (n = 97)	Odds Ratio*	CI 95%
Female sex	53 (55)	46 (44)	1.3	0,8–2.3
Duration of symptoms before medical attendance <48 h	66 (69)	38 (37)	3.2	1.8–5.7
Time-period of consultation				
weeks 49–50 (pre-epidemic)	26 (27)	28 (27)	2.3	1.2–4.5
weeks 51–5 (epidemic and post-epidemic)	74 (77)	72 (70)	ref	
Temperature >37.8 °C	74 (77)	40 (39)	4.2	2.3–7.7
Cough	96 (100)	89 (86)	3.2	1.0–10.4
Temperature >37,8 °C and cough	72 (75)	37 (36)	4.4	2.4–7.9
Sore throat	75 (78)	75 (73)	1	0.5–1.9
Myalgia	94 (98)	86 (83)	2.8	1.0–7.5
Rhinitis	81 (84)	81 (79)	1	0.5–1.9
Headache	85 (88)	84 (81)	1.1	0.5–2.3
Fatigue	91 (95)	92 (89)	1	0.4–2.6
Chills/sweating	88 (91)	77 (75)	2.1	1.0–4.4

* by univariate analysis

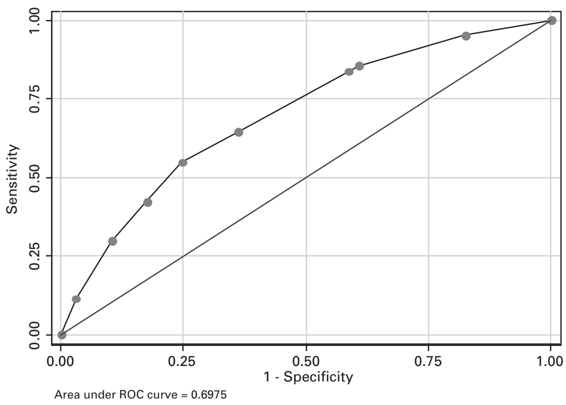
Table 2

Diagnostic performance: Positive Predictive Value (PPV), sensitivity (Se) and specificity (Sp)) of clinical variables for the diagnosis of influenza.

Symptoms and signs	PPV	NPV	Se	Sp
Cough	54	73	96	11
Sore throat	52	48	75	25
Rhinitis	52	47	81	19
Myalgia	54	70	94	14
Headache	52	50	85	17
Fatigue	52	47	91	8
Duration of symptoms <48 h	65	63	66	62
Chills/sweating	55	63	88	23
Temperature >37,8 °C	66	68	74	60
Cough + Temp. >37,8 °C	68	68	72	63

Figure 1

ROC curve, model with the two variables: time-period of consultation (weeks 49–51, 52–1 and >1) and duration of symptoms before first medical attendance (<24 h, 24–48h, >48h).



first medical attendance, each divided into three categories as described in the data analysis section. In this situation the area under the ROC curve was 0.69 with a prediction rule of 0.5, Se was 64% (IC 95% 54–74), Sp 64% (54–73), PPV 66% (56–75) and NPV 63% (52–72) (see figure 1). We then added step by step the variables with an estimated OR >1, temperature >37.8, cough, and myalgia. The latter symptom added nothing to the power of the model and was thus withdrawn. Following this, we replaced temperature >37.8° by continuous temperature measurement. We then simplified the three time-period categories into two (week 49–50 and week 51–5) and also the three categories of duration of symptoms into two (<48 h and >48 h) without changing the power of our model. Finally, the model with two categories for time-period of consultation and duration of symptoms, continuous temperature and cough had an area under the ROC curve of 0.76 with a Se of 74% (65–82), Sp of 69% (59–78), PPV of 72% (62–80) and NPV of 71% (61–80) (see figure 2). When we replaced continuous temperature by categorical temperature >37.8, the area under the ROC curve was 0.74 with a Se of 80% (70–87), Sp of 59% (48–69), PPV of 67% (58–76) and NPV of 73% (62–82) (see figure 3).

Figure 2

ROC curve, model with the four variables: time-period of consultation (weeks 49–50, 51–5), duration of symptoms before first medical attendance (<48h, >48h), continuous temperature and cough.

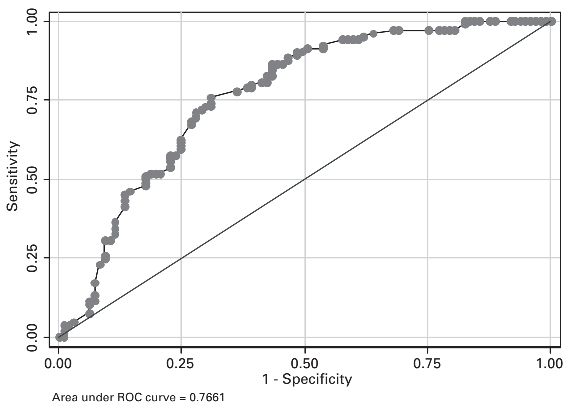
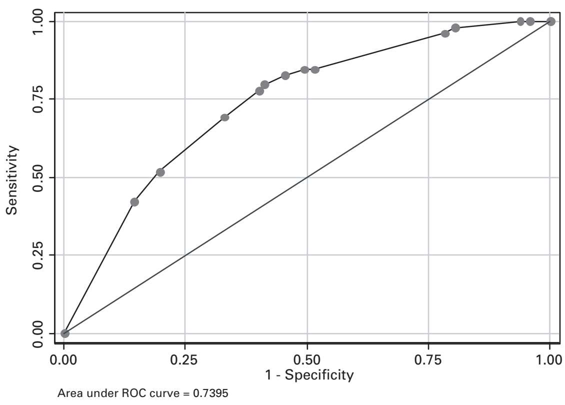


Figure 3

ROC curve, model with the four variables: time-period of consultation (weeks 49–50, 51–5), duration of symptoms before first medical attendance (<48h, >48h), temperature >37.8 °C and cough.



Discussion

The present study shows that the best model for the prediction of influenza in clinical practice is the association of a duration between symptom onset and first medical consultation of <48 hours, medical attendance at the beginning of the epidemic, a temperature >37.8 °C, and cough. The model was even better when we used temperature as a continuous measurement, meaning that the higher the temperature peaked, the better the prediction. However in practice it is much easier to use a fixed threshold (>37.8 °C).

Temperature >37.8 °C and cough were good clinical predictors of influenza, which is in line with the results described in previous studies conducted in selected populations aimed at assessing the safety and efficacy of antiviral drugs [4–11, 13]. This means that primary care physicians can also safely use these predictors to guide their practice.

According to our results, the timing of the consultation must also be considered in the presence of clinical signs and symptoms suggesting influenza. Indeed, duration of symptoms less than 48 hours, and first medical attendance at the beginning of the epidemic were also good predictors for the positive diagnosis of influenza in the presence of fever and cough. The primary care physician should therefore consider the duration of symptoms and the point of time during the epidemic when assessing the probability that his/her patient has a diagnosis of influenza in the presence of a known clinical predictor.

In summary, the probability of having influenza is highest when the patient attends rapidly after symptom onset, at the beginning of the epidemic and in the presence of a temperature >37.8 °C and cough. At the peak of the epidemic, almost all patients have influenza, irrespective of their symptoms and signs. The clinical predictors, as well as the rapid diagnostic tests (due to the important variability of specificity of these assays [14–16]) thus lose their usefulness at that time. The fact that the point of time of the consultation during the epidemic influences the prediction of influenza, highlights the necessity for the clinician to consider the epidemiological context at the time of consultation, when estimating the probability of his/her patient having influenza.

The identification of clinical predictors of influenza, as well as a fair estimation of their variability in time, should help to establish clinical scores that could be used by the general practitioner to optimise the care of patients in terms of rapid diagnostic tests use and antiviral therapy initiation.

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References

1 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.
2 Nicholson KG, Aoki FY, Osterhaus ADME, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomized controlled trial. Lancet 2000;355:1845–50.
3 Lalezari J, Campion K, Keene O, Silagy C. Zanamivir for the treatment of influenza A and B in high-risk patients. Arch Intern Med 2001;161:212–7.
4 Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. Arch Intern Med 2000;160:3243–7.
5 Monmany J, Rabella N, Margall N, Domingo P, Gich I, Vázquez G. Unmasking influenza virus infection in patients attended to in the Emergency Department. Infection 2004;32: 89–97.
6 Carrat F, Tachet A, Rouzioux C, Housset B, Valleron AJ. Evaluation of Clinical Case Definitions of Influenza: Detailed Investigation of Patients During the 1995–1996 Epidemic in France. Clin Infect Dis 1999;28:283–90.
7 Zambon M, Hays J, Webster A, Newman R, Keene O. Diagnosis of influenza in the community: relationship of clinical diagnosis to confirmed virological, serological, or molecular detection of influenza. Arch Intern Med 2001;161:2116–22.
8 Boivin G, Hardy I, Tellier G, Maziade J. Predicting influenza during epidemics with use of a clinical case definition. Clin Infect Dis 2000;31:1166–9.
9 van Elden LJR, van Essen GA, Boucher CAB, et al. Clinical diagnosis of influenza virus infection: evaluation of diagnosis tools in general practice Br J Gen Pract 2001;51:630–4.
10 Hulson TD, Mold JW, Scheid D, et al. Diagnosing influenza: the value of clinical clues and laboratory tests. J Fam Pract 2001;50:1051–6.
11 Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does this patient have influenza? JAMA 2005;293: 987–97.
12 Swiss Sentinel Surveillance Network, Swiss Federal Office of Public Health, CH-3003 Bern.
13 Friedman MJ, Attia MW. Clinical Predictors of influenza in children. Arch Pediatr Adolesc Med 2004;158:391–4.
14 Ruest A, Michaud S, Deslandes S, Frost HF. Comparison of the Directigen flu A+B test, the QuickVue influenza test, and clinical case definition to viral culture and reverse transcription-PCR for rapid diagnosis of influenza virus infection. J Clin Microbiol 2003;41:3487–93.
15 Rodriguez WJ, Schwartz RH, Thorne M. Evaluation of diagnostic tests for influenza in a pediatric practice. Pediatr Infect Dis J 2002;21:193–6.
16 Boivin G, Hardy I, Kress A. Evaluation of a rapid optical immunoassay for influenza viruses (FLU OIA test) in comparison with cell culture and reverse transcription-PCR. J clin Microbiol 2001;39:730–2.

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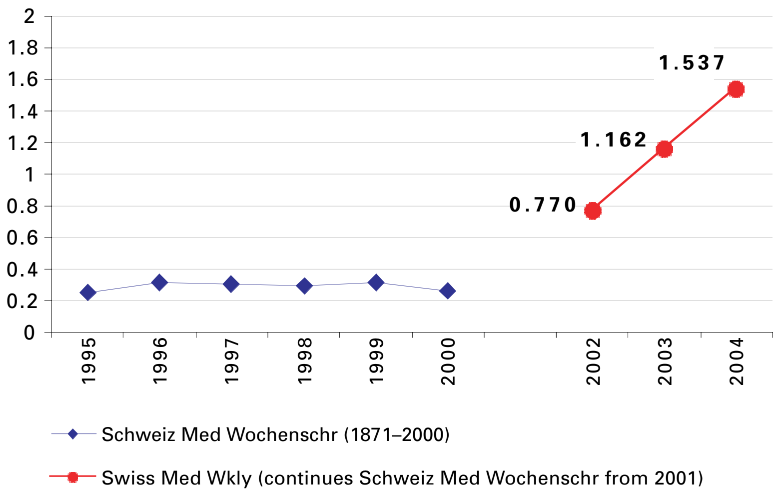

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