Influenza-like illness criteria were poorly related to laboratory-confirmed influenza in a sentinel surveillance study

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Influenza Surveillance Network in Andalusia

Abstract

Objective: To analyze the most related clinical data for influenza and the utility of influenza-like illness criteria as the clinical threshold for sampling in an influenza sentinel surveillance over a 3-year period.

Methods: Sentinel physicians collected throat specimens and data from outpatients with acute respiratory infection (≤72 hours duration). Laboratory-confirmed influenza infection was compared with independent symptoms and the influenza-like illness criteria, as defined by the Classification Committee of the World Organization of Family Doctors.

Results: From 1934 patients, 359 (18.56%) yielded positive results for influenza viruses. Only 199 (55.4%) of laboratory-confirmed cases fulfilled clinical criteria of influenza-like illness: positive and negative predictive value (PPV and NPV) of 0.36 and 0.88, respectively. Fever, cough, and rhinorrhea individually correlated with influenza infections (PPV: 0.30, 0.20, and 0.20, respectively; NPV: 0.92, 0.87, and 0.85, respectively). Multivariate analysis demonstrated that the correlation of influenza infection with the presence of fever and cough was similar to the correlation between influenza infection and influenza-like illness criteria (odds ratio 2.24 vs. 2.71, respectively).

Conclusion: Influenza-like illness criteria are poorly related to laboratory-confirmed influenza. For early detection of influenza viruses in surveillance systems, a less restrictive clinical criterion (specifically, acute respiratory infection) perhaps should be followed.

Keywords: Influenza; Sentinel surveillance; ICHPPC-2; Influenza-like illness; Acute respiratory infection

1. Introduction

Influenza illness is a highly contagious infectious disease, annual epidemics occurring typically in the Northern Hemisphere between December and April [1]. Major changes on influenza A viruses have led to periodic emergence of pandemics, during which the rates of morbidity and mortality increase [2].

Influenza disease is subjected to surveillance worldwide by national networks that predict the epidemic threshold by reporting clinical and virological data [3]. World Health Organization encourages reinforcing influenza surveillance systems, because they provide data about the occurrence of a new influenza A virus subtype [2]. In an influenza surveillance network, patients from whom throat and/or nasal samples are collected must fulfill a clinical case definition [3]. Sample collection in most surveillance systems is made by using the clinical criteria of influenza-like illness (ILI) or acute respiratory infection (ARI) [3], the later being a less restrictive definition than the ILI criteria. In Spain, sentinel physicians follow the clinical criteria of ILI [3]. ILI has been defined by the Classification Committee of the World

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0895-4356/05 - see front matter © 2005 Elsevier Inc. All rights reserved.
doi: 10.1016/j.jclinepi.2004.08.014
Organization of Family Doctors [4] (ICHPPC-2) by the presence of six of nine symptoms, though other authors have adopted the criteria of ILI as defined by the presence of fever plus two of the following four symptoms: headache, cough, sore throat, and myalgia [5,6].

The present study analyzes the most related clinical data for influenza and the utility of ILI as defined by the ICHPPC-2 criteria in the context of the sentinel surveillance network in Andalusia (Spain) during a 3-year period.

2. Methods

As part of the sentinel surveillance network for influenza disease in Spain, throat samples and clinical data from outpatients were collected by 20 sentinel physicians (17 general practitioners and 3 pediatricians) during three periods of influenza surveillance, October 2000 to May 2001 (Period 1), October 2001 to May 2002 (Period 2), and October 2002 to May 2003 (Period 3). Inclusion criteria comprised persons of all ages with clinical evidence of ARI over a duration of ≤72 hours. ARI was defined as any infection of sudden onset involving the respiratory tract, with or without fever. The upper limit of samples submitted by each sentinel physician was five per week.

Epidemiological and clinical data collected from each patient were name, age, sex, vaccination status, duration of the disease at consultation and the presence of specific symptoms: fever (body temperature ≥38.5°C), cough, rhinorrhea, sore throat, and gastrointestinal symptoms. Sentinel physicians also recorded if patients fulfilled clinical criteria of ILI according to the ICHPPC-2 definition [4]: (a) Influenza epidemic, plus 4 of the following 9 criteria: sudden onset (within 12 hours), cough, rigors and chills, fever, prostration and weakness, headache, myalgia, widespread aches and pain, no significant physical signs other than redness of nasal mucous membrane and throat, and influenza in close contact; or (b) in the absence of influenza epidemic, any 6 of the 9 criteria.

Throat samples were sent within the first 6 hours following collection to the laboratory at 4°C in minimal essential medium (MEM) supplemented with 1% bovine serum albumin. Specimens were inoculated in MDCK cells (Vircell, Granada, Spain) by means of shell-vial assay and traditional tube culture [7]. Shell-vial assay was performed in triplicate. After 48 hours incubation, cell monolayers were subjected to direct fluorescence assay with monoclonal antibodies against influenza A and B viruses (Dako Diagnostics, Ely, Cambridgeshire, UK). Influenza A positive samples were subtyped by means of indirect fluorescence assay (IFA) with monoclonal antibodies against H1 and H3 hemagglutinins (Light Diagnostics; Chemicon, Temecula, CA, USA).

The tube culture was examined daily for 14 days to observe the appearance of cytopathic effect (CPE). Before discarding negative results, tubes without CPE were subjected to hemagglutination test as previously described [8]. Positive tubes (CPE and/or positive hemagglutination) were confirmed for influenza viruses by means of direct fluorescence assay as just described.

Data were statistically analyzed with SPSS 11.0.1 software (SPSS, Chicago, IL, USA). Along with descriptive statistics, bivariate and multivariate analyses were performed to compare clinical and demographic characteristics with laboratory-confirmed influenza cases. Bivariate analysis included Student’s t test for quantitative variables and chi-square test for qualitative variables. Odds ratio (OR) and its 95% confidence interval (CI) and measures of positive predictive value (PPV) and negative predictive value (NPV) were calculated for each variable. Forward-stepwise logistic regression analysis was conducted only on the variables that reached statistical significance at the .10 level with the bivariate analysis. The OR and its 95% CI for each variable were also calculated.

3. Results

A total of 1,934 patients with ages ranging between 2 months and 96 years (mean age ± standard deviation = 25.09 ± 22.99) were studied: 541 in period 1, 668 in period 2, and 725 in period 3. Patient characteristics by age groups are shown in Table 1: sex, vaccination status, and influenza virus isolations. From the 1934 throat specimens processed, 359 yielded positive results for influenza viruses (18.56%), 173 influenza A viruses (48.2% of total isolations), and 186 influenza B (51.8% of total isolations). Subtyping of 94 influenza A isolates yielded 38 H1 and 56 H3.

Table 1
Demographic characteristics, vaccination status and influenza virus isolations of the study population

<table>
<thead>
<tr>
<th>Age, years</th>
<th>no. (%)</th>
<th>M/F, no.</th>
<th>Vaccinated, no. (%)</th>
<th>Influenza virus isolations, no. (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤14</td>
<td>930 (48.1)</td>
<td>478/452</td>
<td>37 (4.0)</td>
<td>85 (44) 108 (56)</td>
</tr>
<tr>
<td>15–49</td>
<td>646 (33.4)</td>
<td>308/338</td>
<td>31 (4.8)</td>
<td>69 (51.9) 64 (48.1)</td>
</tr>
<tr>
<td>50–64</td>
<td>169 (8.7)</td>
<td>73/96</td>
<td>48 (28.4)</td>
<td>12 (54.5) 10 (45.5)</td>
</tr>
<tr>
<td>≥65</td>
<td>189 (9.8)</td>
<td>85/104</td>
<td>124 (65.6)</td>
<td>7 (63.6) 4 (36.4)</td>
</tr>
<tr>
<td>Total</td>
<td>1,934 (100)</td>
<td>990/944</td>
<td>240 (12.4)</td>
<td>173 (48.2) 186 (51.8)</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; M, male.

a Percentages for influenza A and B are % of all positive results.
Bivariate analysis demonstrated that ICHPPC-2 criteria (OR [95% CI] = 4.34 [3.41–5.51]), fever (OR [95% CI] = 4.88 [3.75–6.34]), cough (OR [95% CI] = 1.76 [1.28–2.42]), and rhinorrhea (OR [95% CI] = 1.40 [1.08–1.82]) individually showed a positive correlation with the number of positive results. Vaccination showed a negative correlation with the number of positive results (OR [95% CI] = 0.32 [0.20–0.53]) (Table 2).

To evaluate whether clinical data could vary with age, further bivariate analyses were conducted by age group with statistically significant clinical parameters (ICHPPC-2 definition, fever, cough, and rhinorrhea). ICHPPC-2 criteria and fever showed statistically significant in all age groups; cough was significant in patients ≤50 years old (≤14 and 15–49 years old); rhinorrhea was significant only in patients ≤14 years old. The NPV of these variables in each age group did not vary substantially compared with those obtained in the whole population (data not shown). The PPV of the ICHPPC-2 criteria decreased to 0.23 in patients >50 years old, compared with 0.36 and 0.41 in patients ≤14 and 15–49 years old, respectively. Similarly, PPV of fever was lower in patients 50–64 (0.23) and ≥65 years old (0.15) compared with that obtained in patients ≤14 (0.29) and 15–49 years old (0.37).

For the stepwise logistic regression analysis, three symptoms (fever, cough, and rhinorrhea) were selected, along with the ICHPPC-2 criteria and age (Table 3). The combination of fever and cough (OR = 2.24, 95% CI = 1.44–3.50) gave similar results to those obtained for the ICHPPC-2 criteria (OR = 2.71, 95% CI = 2.08–3.52). Fever was the only independent symptom that reached statistical significance in the regression model. Age was also a multivariate predictor of influenza infection for patients ≤50 years old.

Comparison of demographic and clinical characteristics between influenza A- and B-infected patients, showed that cough (91.9 vs. 79.6 %, respectively; P = .001) and sex (55 vs. 46%, respectively; P = .032) were statistically different between both groups. No statistical differences were observed between H1 and H3 influenza A virus–infected patients.

From the 359 influenza-confirmed patients, only 199 (55.4%) fulfilled the ICHPPC-2 criteria: 95 of 193 (49.2%) patients ≤14 years, 86 of 133 (64.7%) patients aged 15–49 years, 11 of 22 (50%) patients aged 50–64 years, and 7 of 11 (63.6 %) patients older than 64 years.

4. Discussion

The distribution of the population in the present study shows that almost 50% correspond to a pediatric population. Although the percentage is high, it is not surprising, because children are the main reservoir of respiratory viruses and attack rates are higher in this population [9,10]. We note that the pediatric population was also attended by some general practitioners from the sentinel network (apart from the three pediatricians), which may have contributed in part to the increased number of children included in the present study.

Rates of influenza infection are highest among children [11]. Our results show that more than half of the laboratory-confirmed influenza cases were in patients <15 years old; elderly people had the lowest rates of influenza. An explanation for this may be the high vaccination coverage (65.6%) and/or the higher implication of other viruses on respiratory infections in the later group as recently reported [12].

All clinical data demonstrated a good NPV for influenza disease, but poor PPV. Fever was the most related independent symptom in laboratory-confirmed influenza cases with the bivariate analysis, showing similar results to those obtained for the ICHPPC-2 criteria. Rhinorrhea, sore throat, and gastrointestinal symptoms have been repeatedly associated with influenza illness [13–16], although they are not included in the ICHPPC-2 definition. Inclusion of these symptoms did not markedly improve the results.

Mean duration of the disease at consultation was lower in positive influenza cases than in the group with negative results (Table 2). The need for a rapid sampling of suspected cases has been previously reported [5,13]. Diagnosis of influenza infection with viral culture requires viable viruses in the specimen. Thus, early sampling is crucial to avoid

Table 2
Comparison of clinical data and laboratory results for influenza in the study population with bivariate analysis

<table>
<thead>
<tr>
<th>Data</th>
<th>Positive, n (%)</th>
<th>Negative, n (%)</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICHPPC-2 criteria</td>
<td>199 (55.4)</td>
<td>351 (22.3)</td>
<td>&lt;.001</td>
<td>4.34</td>
<td>3.41–5.51</td>
<td>0.36</td>
<td>0.88</td>
</tr>
<tr>
<td>Fever</td>
<td>273 (76.0)</td>
<td>621 (39.4)</td>
<td>&lt;.001</td>
<td>4.88</td>
<td>3.75–6.34</td>
<td>0.30</td>
<td>0.92</td>
</tr>
<tr>
<td>Cough</td>
<td>307 (85.5)</td>
<td>1213 (77.0)</td>
<td>.001</td>
<td>1.76</td>
<td>1.28–2.42</td>
<td>0.20</td>
<td>0.87</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>270 (75.2)</td>
<td>1077 (68.4)</td>
<td>.011</td>
<td>1.40</td>
<td>1.08–1.82</td>
<td>0.20</td>
<td>0.85</td>
</tr>
<tr>
<td>Sore throat</td>
<td>261 (72.7)</td>
<td>1096 (69.6)</td>
<td>.244</td>
<td>1.16</td>
<td>0.90–1.50</td>
<td>0.19</td>
<td>0.83</td>
</tr>
<tr>
<td>Digestive symptoms</td>
<td>54 (15.0)</td>
<td>215 (13.6)</td>
<td>.492</td>
<td>1.12</td>
<td>0.81–1.55</td>
<td>0.20</td>
<td>0.82</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>18 (5.0)</td>
<td>222 (14.1)</td>
<td>&lt;.001</td>
<td>0.32</td>
<td>0.20–0.53</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Durationb</td>
<td>1.64 ± 0.83</td>
<td>1.82 ± 0.83</td>
<td>&lt;.001</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ND, not determined; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

a Positive results, n = 359; negative results, n = 1,575. Percentages expressed as % of total results.

b Duration of the disease at consultation (days), mean ± standard deviation.
false negative results. The present study demonstrates that as the time of sampling increased from the onset of the symptoms, the number of laboratory-confirmed influenza cases was lower.

The best multivariate clinical predictor of influenza infection was the combination of fever and cough along with the ICHPPC-2 criteria. Fever and cough have already been considered the best symptoms to predict influenza infection [5,13,14,17,18]. Other reports, however, have shown better PPVs than ours for diagnosing influenza of the ICHPPC-2 criteria and independent symptoms [13,14]. The reason for this difference may be that all the studies cited involved RT-PCR. The use of molecular techniques such as RT-PCR would probably have yielded more positive results. RT-PCR requires a lower viral load than culture techniques, and does not depend on the ability of the virus to replicate [5,13]. On the other hand, most of the studies were conducted during influenza epidemics [13,14]. The present study evaluated the utility of clinical criteria in the context of a surveillance system. Thus, it included cases of influenza over the whole season each year, because one of the most important objectives of surveillance systems is the early detection of influenza at the beginning of the season. During the epidemic months of periods 2 and 3 (no epidemic took place in period 1 [3]), the PPV of both ICHPPC-2 criteria and fever increased to 0.49, which is similar to those described by other authors [13,14]; however, during the nonepidemic months of these periods, the PPV of ICHPPC-2 definition and fever were 0.26 and 0.23, respectively. No other symptom showed a statistical positive correlation with the number of positive results (data not shown).

The poor PPV of the ICHPPC-2 definition is especially relevant in the pediatric population and the elderly. In the former group, epidemics with respiratory syncytial virus and influenza virus usually coincide [19–21]. Thus, an etiological diagnosis becomes necessary in order to adopt the right measures of control and treatment [19,20]. Moreover, more sensitive criteria for sampling must be followed in elderly people, because 95% of deaths and most complications due to influenza occur in this group [22,23]. In our study, the PPV of the ICHPPC-2 definition in older adults (0.23) was lower than in the pediatric population and young adults, consistent with a previous report [18] which demonstrated a PPV of 18% in elderly people.

In conclusion, because clinical criteria are poorly related to laboratory-confirmed influenza cases, a less restrictive criterion (specifically, ARI instead of ILI), should perhaps be followed for sampling within a surveillance system, especially at the beginning of the annual season. Furthermore, rapid and easy-to-perform diagnostic methods for influenza antigen detection might be useful in primary care and emergency services, especially for high-risk patients susceptible of specific therapeutic measures.

Acknowledgments

Authors are indebted to María del Mar Rodríguez del Águila, Servicio de Bioestadística del Hospital Universitario Virgen de las Nieves, Granada, for helping in the statistical analysis of the data.

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