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Differences in clinical predictors of influenza in adults and children with influenza-like illness

Research Article

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Abstract: Influenza contributes significantly to morbidity and mortality in the winter season. The aim of the study was to identify clinical signs and symptoms most predictive of influenza infection in children and adults with influenza-like illness. A prospective systematic sampling analysis of clinical data collected through sentinel surveillance system for influenza in 32 primary care centers and one tertiary care hospital in Slovenia during two consecutive influenza seasons (2004/2005 and 2005/2006) was carried out. Children and adults who had influenza-like illness, defined as febrille illness with sudden onset, prostration and weakness, muscle and joint pain and at least (cough, sore throat, coryza) were included and tested for influenza A and B virus, adenovirus, respiratory syncytial virus and enterovirus by RT-PCR. Clinical data were evaluated in statistical models to identify the best predictors for the confirmation of influenza for children (under age of 15) and adults. Of 1,286 patients with influenza-like symptoms in both seasons 211 were confirmed to have influenza A or B alone and compared to 780 influenza-negative patients. A fever over 38ºC, chills, headache, malaise and sore eyes revealed a significant association with positive RT-PCR test for influenza virus in children. In adults, only three symptoms were significantly related to PCR-confirmed influenza infection: fever, cough and abnormal breath sounds. The stepwise logistic regression analysis showed that four symptoms predicted influenza in children: fever (38ºC or more) ($p=0.010$), headache ($p=0.030$), cough ($p=0.044$) and absence of abnormal breathing sounds ($p=0.015$) with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 5.1%, 98.1%, 57.1% and 80.1%, respectively. For adults, the strongest impact on influenza positivity was found for fever ($p=0.008$) and cough ($p=0.085$). The model for adults had less favorable characteristics, with sensitivity, specificity, PPV and NPV of 0%, 100%, 0% and 76.4%, respectively. Differences in clinical predictors of influenza in children compared to adults were found. The model for adults was acceptable but not a good one. The model for children was found to be more reliable than the prediction model for adults.

Keywords: *Influenza-like illness • Prediction model • Surveillance • Multiplex reverse transcription polymerase chain reaction for influenza virus*

1. Introduction

Influenza is a communicable disease that contributes significantly to morbidity and mortality during the winter season. The circulation of influenza virus is associated with increased general practice consultation rate, hospital admissions and excess death [1-3]. During season where the rate of influenza peaks, school and work absenteeism increases, and health care services are put under additional pressure [4]. Influenza is an important public health problem and early detection of influenza virus in the community is essential. To establish whether a patient with febrile illness is suffering from influenza, viral isolation or PCR should be conducted. Nevertheless, the laboratory tests cannot be performed in every patient consulted for acute febrile respiratory illness resembling influenza.

The difficulties in identifying influenza virus infection on the basis of clinical characteristics have been well documented [5-9]. Several studies have shown that

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a high fever and cough represent best predictors for influenza infection in adults while influenza virus circulates in any given community [10-12]. The data on clinical predictors of influenza in pediatric populations are scarce [6,13,14]. Children play a primary role in influenza transmission, given their increased tendency to acquire and shed influenza. Children are timely sentinels for the beginning of influenza circulation in the community and contribute its spreading more so than adults [15]. Improved knowledge of clinical signs and symptoms of influenza infection in children is indispensable. In clinical practice, knowledge of the most predictive symptoms of influenza would be very useful in daily work – not only to detect influenza virus for surveillance purposes, but also to start treatment with neuraminidase inhibitors if necessary.

The aim of our study was to identify clinical signs and symptoms most predictive of influenza infection in children and adults with influenza-like illness.

2. Material and Methods

2.1.Study design and population studied

The study was a prospective, systematic sampling study. We collected clinical and virological data for surveillance purpose as part of National Program for Communicable Disease Surveillance, yearly approved by Ministry of Health in accordance with the Helsinki Declaration. Inclusion criteria were based on clinical data. Patients suspected of having influenza based on predetermined criteria were enrolled. The patients elected for influenza testing presented with influenza-like illness characterized by the sudden onset, presence of fever, prostration and weakness, muscle and joint pain and at least one symptom of respiratory tract affection (cough, sore throat, coryza). A standardized data collection form was completed by the physician for each patient. Demographic data (age and sex), presence of signs and symptoms (fever ≥38°C, chills, malaise, headache, joint/muscle pain, cough, hoarseness, coryza, earache, sore eyes or throat, presence of conjuctivitis, pharyngitis, otitis media or abnormal breathing sound on pulmonary auscultation) were recorded on the same form. We did not collect data on hospitalisation rate. Patients with incompletely fulfilled standard forms were excluded from the study.

2.2. Study setting

Patients were recruited from 32 primary care centers participating in the influenza surveillance network and from the Department for Infectious Diseases (a tertiary care hospital) in Ljubljana. The primary care centers are dispersed all over the country to cover all geographical areas of Slovenia. The primary care physicians are trained to collect nasal and throat swabs. Eight hundred sixteen patients were recruited from sentinel surveillance system and 470 patients from the department of tertiary care centre.

2.3. Study period

The patients with influenza-like illness were enrolled during two consecutive influenza seasons: 2004/2005 and 2005/2006. There were 793 patients enrolled in the season 2004/2005 and 493 in the season 2005/2006, in total 1286 (602 male and 684 female) patients. Children and adolescents less then 15 years of age accounted for 49.6% of the patients included. The mean age of the patients was 21.8 years with standard deviation 20.1. The minimum age of the patients was less then one year and the maximum 91 years.

In the first season, data collection started in the 42nd week of 2004 and finished in week 17 of the next year. Influenza virus was confirmed for the first time in week 48, and for the last time in week 15. The peak influenza activity was found in week 5 of year 2005. In the next season, data collection began a month earlier – the first swabs for surveillance purposes were taken in week 38 of the year 2005 and the last in week 18 of the following year. In season 2005/2006, influenza virus was confirmed for the first time in week 45 and for the last time in week 16. The peak influenza activity was late and reached its peak in week 13.

2.4. Laboratory procedure

One throat and one nasal swab sample was collected from each patient. Multiplex reverse transcription polymerase chain reaction (RT-PCR) was used as a method for influenza A and B virus, respiratory syncytial virus (RSV), adenovirus and enterovirus detection. The specimens collected were stored in an Eagle's minimum essential medium (EMEM) transport medium and sent to the laboratory. Ribonucleic acid (RNA) was immediately extracted from each 200 µl sample. The QIAamp Viral RNA Mini Kit (QIAGEN, USA) was used according to the manufacturer's instructions. RT-PCR was performed on the same or on the following day. RT-PCR method combines five pairs of primers in a single reaction, which enables the simultaneous amplification of target sequences of the genome of five different viruses (multiplex PCR). The primers for detecting the RNA of influenza A and B viruses, RSV, adenoviruses and enteroviruses cover highly conserved regions of the genome, allowing the detection of a broad

range of viruses from these groups. The primers and the temperature conditions for reverse transcription and PCR were described previously [16]. The reaction mixture was modified from two steps to one step PCR, using the AccessQuick RT-PCR System reagents (Promega, USA). PCR products were analysed by electrophoresis in a 2% agarose gel using an UV transiluminator. Nested multiplex RT-PCR method was used to determine the types of haemglutinins and neuraminidases in samples where the nucleic acid of influenza A was found, and to determine the RSV subtype when RSV nucleic acid was found [17,18].

In order to prevent cross contamination, the RNA extraction procedures, preparation of the master mix for RT-PCR, and work with the PCR products were conducted in separate rooms, in compliance with applicable safety measures. All reactions were examined by the use of positive and negative controls.

2.5. Data Analyses

The data collected were entered into a computer. Unrecorded variables were coded as missing. The analysis was carried out on children (under 15 years of age) and adults separately. A group of influenza positive patients was compared to patients with no viral pathogen confirmed.

The aim of the statistical analysis was to find the best clinical predictors of influenza infection for children and adults. Along with descriptive statistics, univariate and multivariate logistic regression analyses were done. Backward stepwise logistic regression was performed to determine the best clinical predictors of influenza virus infection. The predictors obtained with models should help to distinguish between influenza-positive and influenza-negative children and adults.

P-value less then 0.05 (two sided) was considered statistically significant. The goodness of fit of the logistic regression models was tested with the Hosmer-Lemeshow test. To assess the model discrimination the area under the ROC curve was used. A value of 0.5 means that the model is useless for discrimination and values near 1 mean that higher probabilities will be assigned to influenza-positive than to influenza-negative patients.

SPSS version 12.0 and R 2.4.0 were used for all statistical analyses.

Table 1. Demographics and virological results in children and adults with and without influenza virus infection.

Characteristic	Children	Adults
Number	476	515
Mean age, years	7.4	36.3
Sex, % male	50.0	41.7
Influenza positive, %	18.7%	23.7%

3. Results

Influenza A virus was found in 128 (9.9%) of eligible patients, influenza B virus in 92 (7.2%), enterovirus in 162 (12.6%), RSV in 32 (2.5%) and adenovirus in 28 (2.2%) patients. Twenty-nine (2.2%) patients had two viruses in nasal/throat swabs simultaneously. On the basis of RT-PCR, none of the viruses tested could be found in 815 (63.4%) patients.

For analysis, patients with uncompleted forms and those with double infection were excluded. Ten patients with confirmed influenza A or B infection were excluded as they had double infection. Thirty-five patients from influenza-negative group could not be included because their forms were incompletely fulfilled and few forms were missing.

Finally, data from 911 patients were analysed - 211 RT-PCR-confirmed influenza patients were compared to 780 virus-negative patients. The patients were separated into two groups according to their age: from 0 to 14 years (476 children) and 15 years or more (515 adults). Demographics and virological data are presented in Table 1. Higher positivity rate was observed in school children aged 7–14 years (24.6%) than in pre-school children (11.8%).

In children, history of fever ≥38°C, chills, headache, malaise and sore eyes revealed a significant association with influenza-positive PCR test. Earache, acute otitis media and abnormal breathing sounds were less common in influenza positive children. In adults, only three symptoms and signs were significantly related with a PCR-confirmed influenza infection: fever ≥38°C, cough and abnormal breathing sounds. The results of univariate logistic regression are presented in Table 2.

3.1. Multivariate analysis

Two different models are presented: one for adult patients and the other for children.

For adults, three symptoms/signs were included in the model: fever ≥38◦C, cough and abnormal breathing sounds. These symptoms/signs were statistically significant in univariate logistic regression modelling. Hosmer and Lemeshov goodness of fit test statistic

Table 2. Univariate logistic regression of clinical symptoms and signs of influenza-positive children and adults.

	Children			Adult		
Symptom and signs	OR*	95% CI	p-value	OR*	95% CI[2]	p-value
Fever ≥38°C	8.266	1.982 – 34.48	0.004	2.638	1.389 – 5.01	0.003
Cough	1.450	0.710 – 2.959	0.308	3.096	1.378 – 6.98	0.006
Chills	2.938	1.807 – 4.777	0.000	1.296	0.831 – 2.02	0.253
Headache	2.850	1.643 – 4.941	0.000	0.940	0.521 – 1.67	0.838
Malaise	1.984	1.030 – 3.822	0.040	1.015	0.364 – 2.83	0.978
Myalgia	1.279	0.794 – 2.061	0.311	1.361	0.802 – 2.31	0.253
Sore eyes	1.717	1.058 – 2.786	0.029	0.941	0.626 – 1.42	0.771
Nasal discharge	0.926	0.536 – 1.600	0.784	1.419	0.872 – 2.31	0.159
Sore throat	1.550	0.949 – 2.532	0.080	0.938	0.589 – 1.49	0.785
Earache	0.277	0.084 – 0 .916	0.035	0.787	0.476 – 1.30	0.353
Hoarseness	1.195	0.699 – 2.041	0.515	0.994	0.66 – 1.498	0.978
Conjunctivitis	1.009	0.592 – 1.720	0.974	0.775	0.49 – 1.225	0.276
Pharyngitis	0.687	0.394 – 1.197	0.815	1.125	0.67 – 1.886	0.654
Otitis media	0.370	0.154 – 0.888	0.026	2.188	0.87 – 5.488	0.095
Abnormal breathing sounds	0.181	0.064 – 0.508	0.001	1.743	1.069 – 2.84	0.026

OR - odd ratio, CI[2] - confidence interval*

Table 3. Multivariate predictors of influenza infection in adults.

	Significance	Stepwise Analysis Odds Ratio	95.0% CI*	
			Lower	Upper
Fever ≥38°C	0.008	2.395	1.250	4.588
Cough	0.021	2.623	1.153	5.965
Abnormal breathing sounds	0.085	1.557	0.941	2.576

CI - confidence interval*

(χ^2=8.4' p=0.30) is not statistically significant, which means that the prediction model fits the data at an acceptable level.

Fever ≥38◦C (Wald=6.933' p=0.008) has the strongest impact on influenza positivity for adults, followed by the impact of cough (Wald=5.293' p=0.021) (Table 3). Abnormal breathing sounds (Wald=2.974' p=0.085) have a marginal statistical significance. If the probability of 0.5 is taken as the threshold value for predicting that the subject has influenza, then the sensitivity of the model is 0%, specificity 100%, positive predictive value (PPV) 0% and negative predictive value (NPV) 76.4%. The area under the ROC curve is 0.614. This means that in almost 62% of all possible pairs of patients in which one has influenza and the other is not infected, this model will assign a higher probability to the subject with influenza. The model is acceptable, but it is not a good one.

Fever ≥38◦C, absence of abnormal breathing sounds and headache were important symptoms for predicting influenza in children, with p-values of 0.010, 0.015 and 0.030, respectively (Table 4). Presence of fever compared to absence of fever is 6.8 (95% CI 1.6 – 29.4) times more likely in children with influenza. Like fever, headache is also a positive predictor for influenza, while abnormal breathing sound is a negative predictor. Also, cough with p-value of 0.044 is an important symptom of influenza in children. The prediction model fits the data since Hosmer and Lemeshov goodness of fit test statistic was not statistically significant (χ^2=10.6' p=0.150). If the probability of 0.5 is taken as the threshold value for predicting that the subject has got influenza, then the sensitivity of the model is 5.1% and the specificity 98.1 % with a positive predictive value of 57.1% and a negative predictive value of 80.1%. The ROC area for the model of children was found to be 0.73. It means that in 73% of all possible pairs of children in which one has influenza and the other does not, this model will assign a higher probability to a child with influenza. The model for children was found to be more reliable than the prediction model for adults (Figure 1).

4. Discussion

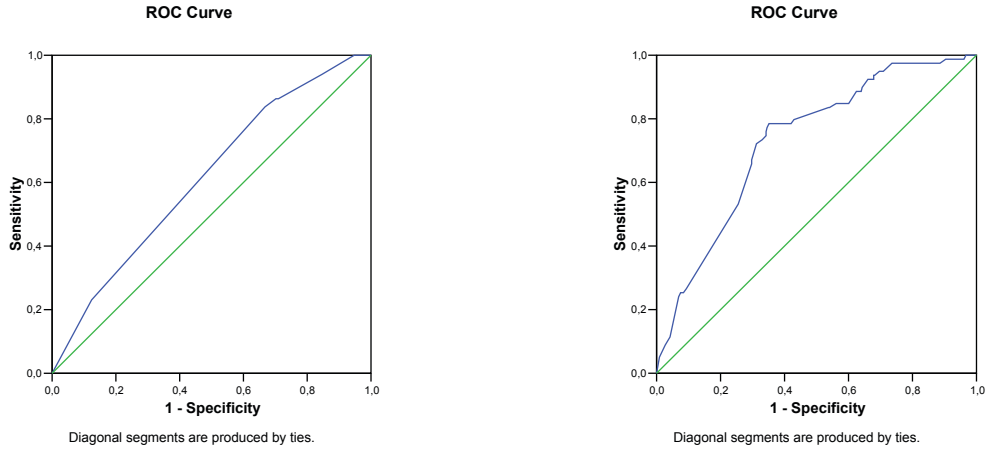
Analysis of the clinical data of patients seen by primary care physicians and specialists for infectious diseases during influenza season with influenza like-illness demonstrated that symptoms and signs predicting influenza in children differed from those in adults. The presence of fever and cough in adult patients is likely to

Table 4. Multivariate predictors of influenza infection in children.

	Significance	Stepwise Analysis Odds Ratio	95.0% CI*	
			Lower	Upper
Fever ≥38°C	0.010	6.823	1.581	29.448
Chills	0.067	1.753	0.961	3.201
Headache	0.030	2.117	1.076	4.165
Joint and/or muscle pain	0.072	0.577	0.316	1.051
Cough	0.044	2.257	1.022	4.984
Pharyngitis	0.066	0.556	0.297	1.041
Abnormal breathing sounds	0.015	0.254	0.084	0.762

CI -confidence interval*

Figure 1. ROC (Receiver Operating Characteristics) curves displaying the relationship beetwen sensitivity and specificity that defined influenza in adults (left figure) and children (right figure).



be associated with influenza. Fever (≥38°C), headache, cough and absence of abnormal breathing sounds are significant predictors of influenza in children with positive predictive value (PPV) 57.1%.

There were several studies aiming to determine symptoms with the highest predictive value for influenza virus infection, mainly in adults. In some studies children were included but not analysed separately from adults [10,19,20]. Yet, influenza infection is a considerable cause of morbidity and health care utilisation in paediatric population. Attack rates in healthy children are estimated to be between 10% and 40% [21]. There is a wide range of clinical symptoms associated with influenza in infants and toddlers, making the clinical management difficult. Owning to influenza unspecific presentation, laboratory tests are done to exclude bacterial infections. Even more often, antimicrobial agents are used empirically without confirming bacterial infection. Identifying the symptoms which correlate considerably well with influenza infection would be very useful in every day practice at least to guide a decision for ancillary diagnostic testing and may have an impact on unjustified antibiotic usage.

A similar study, focused on children, found that those children who had higher temperature, cough, headache, abdominal pain/nausea and signs of pharyngitis were more likely to have influenza virus infection [13]. The clinical triad of cough, headache, and Pharyngitis accurately predicted an influenza infection in children with fever when influenza virus was circulating in the community with an NPV value similar to that found in our study (app. 80%) though PPV was much higher (77%). The dissimilarity could be attributed to different patient's recruitment. Our study included children seen by a primary care physician and clinicians in tertiary care department and not only children examined at the emergency department of a tertiary paediatric hospital. The virological method used differed, as viral isolation was the confirmatory method in abovementioned study [13]. Influenza A virus is detected at higher rates and for more extended time periods by RT-PCR than by cell cultures [2]. Sentinel physicians are instructed to collect swabs from patients presenting on the first or second day of their illness, but it is possible that influenza-positive children included in our study were seen later during the course of influenza. The second comparable study

included children from zanamivir and oseltamivir trials [14]. Fever and cough predicted influenza in children from five to twelve years of age in zanamivir trial with PPV of 83%, but not in oseltamivir trial. In oseltamivir trial only cough predicted influenza infection. In the same study, there was no symptom found which could predict influenza in children from one to four years of age.

Headache was one of the influenza predictors found in our study. Our study included small children and adolescents to 15 years of age. The spectrum of ages probably influenced the influenza predictors identified. Very small children cannot complain about headache - a symptom which quite often accompanies high fever in older preschool children, school children and adolescents. Therefore, headache might be a useful predictor in these groups only.

Children in comparative group (influenza negative children with no virus confirmed) probably suffered from infection caused by microbes which have a tendency to provoke obstructive signs or other auscultatory abnormalities (e.g. human metapneumovirus, human bocavirus para-influenza virus etc.) more often then influenza virus as absence of abnormal breathing sounds predicted influenza. Human metapneumovirus, as respiratory syncytial virus, causes wheezing, actelectasis and lower respiratory infection more frequently then influenza virus [23]. Two other clinical symptoms, fever and cough, were predictors of influenza in children as found in most adult studies.

Fever, cough and acute onset were found to be most useful predictors of influenza infection in adults [17,20,21]. In the present study, univariate analysis showed that adult patients with fever ≥38°C, cough and abnormal breathing sounds were 2.6, 3.09, and 1.7 times more likely to have influenza. Two clinical features, i.e. fever ≥38°C and cough, were identified by stepwise logistic method as independent predictors of influenza, but the PPV of the model was 0%. If a lower prediction probability (0.3 instead of 0.5) had been taken, PPV would have reached 36.5%. Govaert also found a relatively low PPV (30.3%) of symptom complex including fever, cough, and acute onset in the elderly with influenza in the primary care setting [11]. Two predictive models, which included only fever ≥38.2°C and cough, were found to have much higher PPV (86.8% and 79%) [10,12]. The reason of low PPV for adults in our study it difficult to explain as inclusion criteria were not basically different from previous studies [10-12]. One of previous studies used pooled data from eight phase 2 and 3 clinical trials designed to evaluate zanamivir vs. placebo. The different study setting might have an influence on the results as our patients were recruited through sentinel surveillance system for influenza. The PPV found in our study, hampers the value of clinical signs and symptoms to be used in clinical practice.

There are several limitations regarding the study presented. The first limitation of our study is that it was conducted during two seasons only. Influenza A predominated in one season and influenza B in the other. In most of the studies (as in ours) both viruses were taken as one. One study presented segregated prediction model for influenza A/H3 and A/H1 subtypes [24]. It was found that different clinical variables predict infection with influenza H3 and H1 subtypes: high fever, myalgia, rhinorrhea and cough predicted influenza A H3N2 infection, while fatigue, conjunctivitis and absence of myalgia predicted influenza A H1N1 subtype. Data on clinical presentation regarding different subtypes are limited and at present we do not know if the clinical presentation of influenza depends on type or subtype.

Patients were recruited from two settings – primary care and referral hospital. Those two cohorts might vary – referred patients are usually more seriously ill or have a predisposing condition for complicated course of illness. As a result of two different cohorts of patients being combined, important features of one cohort may become blurred.

An inherent limitation of the study was that high fever is part of influenza-like illness definition. Physicians are instructed that only patients with influenza-like illness should be swabbed. Nevertheless, lower temperature elevations above the normal value (e.g. ≥37.5°C) were not an impediment for specimen collection. In both, children and adults, higher fever (≥38°C) correlated with influenza. According to the previous studies, the likelihood of influenza increases with higher temperature.

Respiratory infections are one of the most common reasons for consultation especially in small children. Influenza-like illness is a syndrome caused by various pathogens such as adenovirus, parainfluenza virus, respiratory syncytial virus, some enteroviruses, are clinically almost impossible to differentiate from influenza. In daily practice, all patients with acute respiratory symptoms can not be swabbed and tested for influenza virus – it would be too expensive and time consuming [4]. There is an ongoing discussion who is the right patient to swab, when and how often collect swabs to get an optimal results from public health perspective i.e. to detect influenza virus as it starts circulating. Sentinel surveillance systems were set up to detect the influenza virus in the community by combining epidemiological, clinical and virological information [25]. Sentinel surveillance systems usually use a case definition for influenza-like illness and recommend more frequent swabbing at the beginning of the season to identify the predominant type and subtype of influenza virus. It is

also recommended that swabs should be collected less often during full-blown epidemic to avoid work overload in virological laboratories. Definition of influenza-like illness varies from country to country. Most definitions include fever, feverishness, myalgia, general weakness, headache and respiratory symptoms [26,27]. The definition we use in our sentinel surveillance system is also relatively broad and comprises fever, general symptoms of ill health (malaise, myalgia) and at least one respiratory symptom. It is interesting that almost all influenza-like illness case definitions of European Influenza Surveillance Network include myalgia [26]. Myalgia is one of the symptoms physicians traditionally associate with influenza infection and yet no such correlation could be found with influenza infection in the study presented. Our finding is in accordance with the estimated likelihood ratios for myalgia found to be near 1.0 – and therefore of no diagnostic value [28].

Differentiating influenza virus from the other respiratory viruses is of prime importance because the influenza virus is associated with higher morbidity and mortality, is potentially preventable by vaccination, and can now be managed with specific antivirals. In practice, many physicians diagnose influenza infections on the basis of the presence (or absence) of some clinical symptoms and signs. However, because this clinical case definition is still imperfect, cases will be missed. As shown in our study, clinical symptoms and signs in children predicting influenza are not the same. Further studies in primary care setting should be encouraged including patients with influenza-like illness to develop sensitive clinical definition which may not be the same for children and adults.

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