Accuracy of Clinical Diagnosis of Influenza in Outpatient Children

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In a prospective study, children ≤13 years of age with respiratory infections were examined. At each visit, a nasal swab specimen was obtained for the detection of influenza, and the physician recorded his or her opinion on whether the child had influenza. Among 2288 infections, the overall sensitivity of the clinical diagnosis of influenza was 38% and the positive predictive value was 32%.

Influenza causes a substantial burden of illness for children and their families in terms of morbidity, complications, treatment, and absenteeism [1–3]. The attack rates of influenza during annual epidemics are consistently highest in children, resulting in high frequencies of outpatient visits and hospitalizations for influenza-related illnesses [4–7]. Among children, the impact of influenza is greatest in the youngest ones, in whom the viral illness is frequently associated with bacterial complications, such as acute otitis media [1, 2, 8].

The availability of specific antiviral treatments for influenza has increased the need to distinguish influenza from infections caused by other viruses. Prompt initiation of oseltamivir treatment for children with influenza shortens the duration of illness significantly and reduces the incidence of acute otitis media developing as a complication of influenza by ~40% [9]. Because children are considered to have a key role in the transmission of influenza in the community [10], differentiation between influenza and other viral infections would also be important for surveillance purposes.

Several rapid diagnostic tests for influenza are currently available, but these are rarely used for outpatients [11]. The diagnosis of influenza is therefore usually made on the basis of patient history, clinical signs and symptoms, and knowledge of the local epidemiologic situation. Correct identification of influenza in children, however, is severely hampered by the frequent cocirculation of other respiratory viruses during influenza epidemics and by the lack of signs or symptoms specific for influenza. During a local outbreak, the combination of fever and cough was reported to increase the likelihood that respiratory disease in adults was influenza [12, 13], but the situation may be substantially worse for children. A large community-based study showed that in children ≤5 years of age presenting with influenza-like illness, respiratory syncytial virus was identified as the etiological agent in 35% of the cases, whereas influenza virus was found in only 29% of the cases [14].

Limited data exist on the prediction of influenza in children in the hospital environment [15], but there are virtually no studies of the accuracy of clinical diagnosis of influenza in children in the primary care setting, where most influenza-infected children are treated. We sought to determine whether influenza could be diagnosed reliably on clinical grounds alone in children who are outpatients.

**Methods.** This study was performed as part of a prospective cohort study of respiratory infections in children in Turku, Finland [2]. A total of 1338 children aged 0–13 years were monitored during the 2000–2001 respiratory-infection season. The parents were asked to bring their children to the study clinic for examination by a study physician whenever fever or signs of respiratory infection appeared. At each visit for a new episode of respiratory infection, the physician filled out a form recording his or her opinion on whether the child had influenza. Of the 11 study physicians, 8 were pediatricians or experienced residents in pediatrics, 2 were otolaryngologists, and 1 was a general practitioner. No formal criteria for the diagnosis of influenza were established, but the physicians were instructed to base their judgment on patient history, signs and symptoms, and clinical examination of the child, together with their knowledge of influenza as an illness. This part of the study was started after confirmation of influenza activity in the study population, and the physicians were aware of the local epidemiological situation throughout the study period.

Each time a child came to the study clinic with signs of a new respiratory infection, a nasal swab specimen was obtained from a depth of 2–3 cm in the nostril by means of a sterile cotton swab that was then inserted into a vial containing viral transport medium [16]. Influenza virus in the specimens was detected by viral culture in Madin-Darby canine kidney cells and subsequent immunoperoxidase staining with monoclonal
antibodies [17]. Rapid diagnostic tests for influenza were not used for any children.

The study protocol was approved by the ethics committee of Turku University Hospital. Written, informed consent was obtained from the parents of all participating children.

**Results.** Data on a total of 2288 visits for a newly acquired respiratory infection were available for analysis. The youngest participants included were 7 months of age. Influenza virus was confirmed as the etiological agent in 231 (10.1%) of 2288 infections (table 1). Among the children with proven influenza infection, the clinical diagnosis of influenza was made in 88 cases (38.1%). Conversely, of all 276 cases in which the clinical diagnosis of influenza was made, 88 cases (31.9%) had the diagnosis confirmed in the laboratory.

The overall sensitivity of the clinical diagnosis of influenza was 38%, with a positive predictive value of 32% throughout the study period (table 2). During the period of peak influenza activity (22 January through 25 March 2001), which accounted for 65% of all instances of influenza virus isolation, the sensitivity and positive predictive value increased to 45% and 41%, respectively. Sensitivity and positive predictive value were substantially lower during the early and late phases of the epidemic.

With regard to the age of the participants, the sensitivity and positive predictive value of the clinical diagnosis of influenza were highest in children aged 7–13 years (53% and 48%, respectively); in this age group, influenza accounted for 18.9% of all respiratory infections diagnosed (tables 1 and 2). The accuracy of the clinical diagnosis diminished with decreasing age of the children; the sensitivity and positive predictive value were lowest in children <3 years of age (21% and 16%, respectively); in this age group, only 6.3% of all respiratory infections were caused by influenza virus.

**Discussion.** This study demonstrates that the clinical diagnosis of influenza is extremely difficult in children in everyday clinical practice among outpatients. Fewer than 40% of all true cases of influenza were identified as such on the basis of patient history and clinical examination, and only approximately one-third of all clinically diagnosed influenza cases could be verified in the laboratory. Even during the peak weeks of the epidemic, the sensitivity and positive predictive value of the clinical diagnosis remained well below 50%, and the accuracy of diagnosis was considerably poorer during the early and late phases of the outbreak.

The clinical diagnosis of influenza was least accurate in children <3 years of age. This finding was discouraging, especially because the burden of influenza is greatest in this age group [1, 2], but our findings are in accordance with the clinical experience of diagnosis of respiratory infections in infants and young children. Most viral infections in these children present with varying degrees of fever [18], and infants and young children are unable to verbally describe their subjective symptoms such as headache, myalgias, or pharyngitis. However, it was surprising to find out that, even among school-aged children, the sensitivity of the clinical diagnosis was only ~50%. These findings suggest that, in many cases, the clinical presentation of influenza in children is different from the typical presentation described in textbooks and review articles.

### Table 1. Laboratory documentation and clinical diagnosis of influenza in a cohort of children aged ≤13 years.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Overall</th>
<th>Laboratory documented influenza</th>
<th>Clinically diagnosed influenza</th>
<th>Clinically diagnosed and laboratory documented influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 years</td>
<td>973</td>
<td>61 (6.3)</td>
<td>81 (8.3)</td>
<td>13 (1.3)</td>
</tr>
<tr>
<td>3–6 years</td>
<td>919</td>
<td>95 (10.3)</td>
<td>112 (12.2)</td>
<td>35 (3.8)</td>
</tr>
<tr>
<td>7–13 years</td>
<td>396</td>
<td>75 (18.9)</td>
<td>83 (21.0)</td>
<td>40 (10.1)</td>
</tr>
<tr>
<td>All ages</td>
<td>2288</td>
<td>231 (10.1)</td>
<td>276 (12.1)</td>
<td>88 (3.8)</td>
</tr>
</tbody>
</table>

### Table 2. Sensitivity, specificity, and predictive value of clinical diagnosis of influenza in 2288 respiratory infections in children.

<table>
<thead>
<tr>
<th>Category</th>
<th>Sensitivity, % (rangea)</th>
<th>Specificity, % (range)</th>
<th>Positive predictive value, % (range)</th>
<th>Negative predictive value, % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (rangea)</td>
<td>38 (20–53)</td>
<td>91 (86–92)</td>
<td>32 (17–37)</td>
<td>93 (88–96)</td>
</tr>
<tr>
<td>Phase of the epidemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>30</td>
<td>91</td>
<td>18</td>
<td>95</td>
</tr>
<tr>
<td>Peak</td>
<td>45</td>
<td>88</td>
<td>41</td>
<td>90</td>
</tr>
<tr>
<td>Late</td>
<td>19</td>
<td>95</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>Patient age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 years</td>
<td>21</td>
<td>93</td>
<td>16</td>
<td>95</td>
</tr>
<tr>
<td>3–6 years</td>
<td>37</td>
<td>91</td>
<td>31</td>
<td>93</td>
</tr>
<tr>
<td>7–13 years</td>
<td>53</td>
<td>87</td>
<td>48</td>
<td>89</td>
</tr>
</tbody>
</table>

a Range among those study physicians who examined at least 10 children with laboratory-documented influenza.
In the study by Friedman and Attia [15], the symptom triad of cough, headache, and pharyngitis was found to be a predictor of isolation of influenza virus in febrile children who were selected from emergency department patients at a tertiary pediatric center according to predetermined criteria indicating influenza infection. The mean age of the children in their study was 6 years. Despite the positive findings in that study, the difficulty of predicting whether an infection is caused by influenza virus was well illustrated by the fact that even in the selected group of children for whom suspicion of influenza was high, fewer than half of the children really had influenza infection.

It is obvious that the diagnostic skills of physicians differ, but we do not think that this could explain our results. Most of our study physicians were either pediatricians or pediatric residents with a considerable amount of clinical experience, and we could not find any correlation between the diagnostic accuracy of the physicians and the amount of their clinical experience.

Oseltamivir treatment of influenza has been shown to reduce the duration of illness and the rate of complications in children [9], but our findings demonstrate that institution of antiviral treatment on the basis of clinical diagnosis alone may result in poor targeting of the treatment in children. Further studies are needed to determine whether there are any combinations of signs and symptoms that could be used to predict whether an infection is influenza in children seen in primary care practice. Alternatively, rapid viral detection methods could be used to increase the accuracy of diagnosis of influenza in children.

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