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# Feasibility of diagnosing influenza within 24 hours of symptom onset in children 1-3 years of age

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Running title:

Early diagnosis of influenza in young children

## ABSTRACT

### Purpose

Diagnosing influenza at an early stage of illness is important for the initiation of effective antiviral treatment. However, especially in young children, influenza often commences with an abrupt onset of fever, with full-blown respiratory symptoms developing only later. We determined the feasibility of diagnosing influenza in young children already during the first signs of the illness.

### Methods

During confirmed influenza activity, we obtained nasal swabs from children aged 1-3 years who presented as outpatients within 24 hours of the onset of fever ( $\geq 38.0^{\circ}\text{C}$ ). The specimens were tested for influenza viruses with viral culture, antigen detection, PCR, and a rapid point-of-care test (Actim Influenza A&B, Medix Biochemica, Finland). In addition, follow-up specimens were obtained from a proportion of children 3-7 days later.

### Results

Influenza virus was detected already within 24 hours of symptom onset in 56 of 61 (92%; 95% CI, 82-97%) children in whom influenza was eventually confirmed in the laboratory. A total of 158 rapid tests performed within 24 hours of symptom onset yielded a sensitivity of 90% (95% CI, 74-98%) for influenza A viruses but only 25% (95% CI, 3-61%) for influenza B viruses

( $P < 0.001$ ), resulting in an overall sensitivity of 77% (95% CI, 61-89%) and specificity of 99% (95% CI, 95-100%) for any influenza viruses.

### Conclusions

In most young children, influenza can be accurately diagnosed already within 24 hours of symptom onset. The rapid point-of-care test used was sensitive and specific for diagnosing influenza A, but its sensitivity for influenza B was limited.

### KEYWORDS:

Influenza

Children

Diagnostic methods

Rapid test

## INTRODUCTION

The burden of influenza is substantial in children [1, 2]. The attack rates are highest in this age group [3], and young children are hospitalized at rates similar to those for adults with high risk conditions [4]. Further, influenza predisposes children to bacterial complications such as acute otitis media [1]. Neuraminidase inhibitors oseltamivir and zanamivir can be used for treating influenza in children from 1 and 5 years of age, respectively [5]. These drugs reduce the duration and severity of symptoms when started within 48 hours of symptom onset [6, 7]. The mechanism of action of neuraminidase inhibitors and the results of a previous study in adults [8] suggest that the clinical benefits could be greater if the treatment were initiated at an earlier stage of illness. According to CDC recommendations, the antiviral treatment should be started as quickly as possible after the onset of symptoms [5].

Distinguishing influenza from other viral respiratory infections is difficult in young children because of the nonspecific signs and symptoms of influenza [9], children's inability to describe their subjective symptoms, and high frequency of other viral infections even during an influenza outbreak [2, 10, 11]. In a previous study among children, the overall sensitivity of the clinical diagnosis of influenza was only 38% and the positive predictive value 32% [12]. Therefore, virological methods are needed to optimize the use of antiviral drugs in children. For clinical decision-making, rapid point-of-care tests that provide almost immediate results are most useful. Previous studies have demonstrated that these tests are generally specific, but their sensitivity has varied greatly [13-19].

Infants and young children are frequently brought for clinical examination during an early stage of influenza illness. The clinician's dilemma is that influenza often commences with an abrupt onset of fever and ill appearance, with full-blown respiratory symptoms developing only later. Occasionally, febrile convulsion is the first sign of influenza in young children [20]. There are scarce data on whether influenza in children can be reliably diagnosed from upper respiratory specimens during the early stage of the illness, and limited data exist on the performance of influenza rapid tests in this clinical situation. We determined the feasibility of diagnosing influenza in outpatient children 1-3 years of age who presented within 24 hours of the onset of fever. In addition, we evaluated the diagnostic accuracy of influenza rapid testing performed in this setting.

## MATERIALS AND METHODS

### **Study design**

This study was conducted as part of a randomized placebo-controlled trial assessing the effectiveness of oseltamivir treatment started within 24 hours of the onset of symptoms in children (ClinicalTrials.gov; NCT00593502) during the influenza seasons of 2007-08 (predominance of A/H1N1 strains) and 2008-09 (predominance of A/H3N2 strains) at a single site in Turku, Finland [21]. Before each influenza season, children 1-3 years of age were recruited into follow-up cohorts (N=631 in 2007-08 and N=554 in 2008-09). No exclusion

criteria were employed for enrollment. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland. Written informed consent was obtained from the parents of the participating children.

### **Study procedures**

When local surveillance indicated that influenza was circulating in the area, a study clinic was opened. The parents were asked to bring their child to the study clinic within 24 hours if the child developed fever or any signs of respiratory infection. During each visit (n=764), the child was examined by a study physician, and nasal swabs were obtained for virological analyses. Rapid influenza tests (n=188) were routinely performed (according to the study protocol of the oseltamivir trial) during the first visit to all febrile children without respiratory symptoms, but also to any other children according to the decision by the attending physician who considered e.g. time constraints for performing the rapid tests during the busy hours of the influenza epidemic. A follow-up visit was scheduled on day 5-8 for all children who received the study medication. In addition, the parents were invited to bring their child to the study clinic whenever they deemed it necessary. Nasal swabs were obtained during all follow-up visits if the child was symptomatic. All visits were free of charge to the parents.

### **Virological methods**

Three flocked swab specimens (Copan, Italy) were obtained from a depth of 2-3 cm in the nostrils in non-standardized order. The specimens were refrigerated at +6°C until analyzed in the virological laboratory next working day. The samples were subjected to viral culture in Madin-Darby canine kidney cells followed by immunoperoxidase staining with monoclonal antibodies [22] and antigen detection using time-resolved fluoroimmunoassay (TR-FIA) [23]. All samples that remained negative for influenza viruses with these methods were further tested with reverse-transcriptase polymerase-chain-reaction (RT-PCR) assays for influenza A and B viruses.

After collection of specimens for the virological laboratory, another nasal swab specimen for rapid testing was obtained from a proportion of children (as described earlier in “Study procedures”) using the polyester swabs provided with the kit (Actim Influenza A & B, Medix Biochemica, Finland). The manufacturer of these rapid tests was not involved in this study; the authors purchased the test kits at market price. The rapid test was performed at the point of care immediately after the sampling according to the manufacturer’s instructions. All samples were obtained and the rapid tests performed by one of four trained study nurses who also interpreted the results. The personnel performing the other virological analyses were unaware of the rapid test results.

## **Data analysis**

*Detection of influenza virus within 24 hours of symptom onset*

In this analysis, we included all children in the placebo arm of the treatment trial in whom influenza was eventually confirmed by any of the conventional laboratory methods (viral isolation, TR-FIA, or RT-PCR) at any time within 8 days of the onset of symptoms. Children who had received oseltamivir were excluded from this analysis because the treatment might have decreased the viral load in the children and consequently led to increased numbers of negative test results during the follow-up visits. The sensitivity of detecting influenza virus within 24 hours of symptom onset was determined as the percentage of children (among all influenza-positive children) in whom influenza could be diagnosed in the nasal swabs collected during the first 24 hours of symptoms.

#### *Performance of the influenza rapid test*

The sensitivity, specificity, and predictive values of the rapid tests were assessed by comparing the results of the rapid tests obtained within 24 hours of symptom onset (i.e. before the start of any study medication) to those of the simultaneously obtained reference test samples. A reference test was considered positive if any of the methods (viral isolation, TR-FIA, or RT-PCR) yielded a positive result for influenza viruses.

#### *Statistical analysis*

Sensitivities, specificities, and predictive values and their binomial 95% confidence intervals were calculated for any influenza virus and for influenza A and B viruses separately. Fisher's exact test was used to compare proportions. Two-sided P values <0.05 were considered statistically significant. All analyses were performed using StatsDirect (version 2.7.7) software.

## RESULTS

### *Detection of influenza virus within 24 hours of symptom onset*

Of 409 children randomized to receive the study medication, influenza was eventually confirmed by any of the conventional laboratory methods (viral isolation, TR-FIA, or RT-PCR) in 98 children. Thirty-seven children who had received oseltamivir were excluded from this analysis. Of the remaining 61 placebo-treated children included in the analysis, 50 (82%) had influenza A and 11 (18%) influenza B. The diagnosis was based on viral culture in 54 (89%) children; antigen detection (TR-FIA) provided the diagnosis in 2 (3%) children with negative viral culture, and RT-PCR in 5 (8%) children in whom both viral culture and antigen detection were negative. In 57 (93%) children, nasal swabs were collected also during the follow-up visits. The mean age of the children was 2.5 (SD±0.8) years, and the median time from the onset of fever to the collection of the first nasal swab specimen was 6.5 hours (interquartile range, 3.4-13.3 h). Influenza virus was detected within 24 hours of the onset of fever in 56 of the 61 children, yielding a sensitivity of 92% (95% CI, 82-97%). The sensitivity was 94% (95% CI, 83-99%) for influenza A virus and 82% (95% CI, 48-98 %) for influenza B virus (P=0.2). There were no

statistically significant differences in the detection of the virus between children presenting <12 hours and 12-24 hours from the onset of symptoms ( $P>0.9$ ); between vaccinated and unvaccinated children ( $P=0.5$ ); or between children <2 years and 2-3 years of age ( $P>0.9$ ).

#### *Performance of the influenza rapid test*

Among a total of 764 visits to the study clinic for new respiratory symptoms or fever, rapid tests were performed in 188 (25%) cases. The results of 30 rapid tests were excluded from this analysis because of the following reasons: absence of fever (18); duration of fever >24 h (3); absence of reference samples (4); rapid test expired (5). Among the remaining 158 children, influenza virus was detected with one or more of the reference methods in 39 (25%) children (Table 1). The rapid test was positive in 31 children (including one false positive), resulting in an overall sensitivity of 77% (95% CI, 61-89%) and specificity of 99% (95% CI, 95-100%) for any influenza virus. The sensitivity of the rapid test was 90% (95% CI, 74-98%) for influenza A virus and 25% (95% CI, 3-61%) for influenza B virus ( $P<0.001$ ).

#### DISCUSSION

In children in whom influenza was eventually confirmed, 92% of nasal swab specimens that were obtained within 24 hours of the onset of fever were positive by at least one of the conventionally used laboratory methods. This suggests that children shed viruses in their nasal secretions in sufficient amounts to be detected already during the first day of illness. This

finding is clinically important because accurate diagnosis of influenza during the early stage of illness enables the rational use of antiviral drugs [6, 7] and proper cohorting of hospitalized patients to prevent nosocomial infections [24]. Rapid influenza diagnosis has also been associated with reduced use of antibiotics and shorter duration of hospitalization [25, 26].

The influenza rapid test that we used had an overall sensitivity of 77% and specificity of 99%. Our results are concordant with several previous studies in children, in which the sensitivities of different rapid tests have ranged from 63% to 85% and the specificities from 97% to 99% [13-15, 27]. Two previous studies assessing the performance of the same rapid test that we used found sensitivities of 65% [16] and 53% [17] in children. There are, however, reports of significantly lower sensitivities (ranging from 20% to 33%) for various rapid tests in populations consisting mainly of adults [28, 29]. Lower sensitivities (27-44 %) have been observed also in some studies with mainly pediatric populations [18, 19].

There are several potential explanations for the great variability between the sensitivities observed in different studies. Children shed influenza viruses in larger amounts and for longer periods than adults [30-32], which may account for the increased sensitivity observed in children [17, 32-34]. Also, the delay between the onset of symptoms and the collection of the specimen may affect the sensitivity of the rapid test. In experimental volunteer studies in adults, the viral load peaked on the second day after virus inoculation, and the shedding lasted for approximately 5 days [35]. In children, the viral shedding has been described to peak 1-3 days after the onset of illness and to last for 6-7 days [30, 31, 36]. In a Japanese pediatric study

in which most samples were obtained within 24 hours of the onset of fever, the overall sensitivity of an influenza rapid test was the same as in the present study (77%) [37]. In that study, the sensitivity of the rapid test was lower for specimens collected within 9 hours (64-69%) compared with specimens collected within 9-24 hours (83 -100%) of the onset of fever. A study conducted in Nicaraguan children found a higher sensitivity (74-75%) of influenza rapid tests for samples obtained 2-3 days after symptom onset, compared with samples obtained either 1 or 4 days after symptom onset (52-58%) [38]. In a recent study from Greece, the sensitivity of a rapid test was 76% when performed within 2 days of symptom onset and 65% when performed later during the course of the illness [27].

Presumably the most important factor affecting the yield of influenza virus is the quality of the sample, which, in turn, is dependent on the site and method of collection. A nasopharyngeal aspirate is often considered as the specimen of choice for everyday clinical purposes in children. The sensitivity of a nasal swab is, however, 91-92% when compared with a nasopharyngeal aspirate for the detection of influenza viruses in children, and the method is more pleasant for the patient and easy to perform in any setting [39, 40]. The sensitivity of nasal swabs may be further enhanced by using flocced swabs [41, 42] or collecting the swab from the nasopharynx [15].

We found the sensitivity of the rapid test to be high for influenza A virus but significantly lower for influenza B virus. Such significant differences were not seen in another study with Actim Influenza A&B rapid test, in which the sensitivities for influenza A and B viruses were 69% and

60%, respectively [16]. There are, however, previous reports of a lower sensitivity for influenza B virus with other rapid tests performed at different stages of illness. [13, 43, 44]. One potential explanation for the varying sensitivities of rapid tests for influenza A and B viruses was provided by a recent study from Hong Kong that demonstrated that viral shedding in naturally acquired influenza A infections peaked already at the time of symptom onset, whereas in influenza B infections the peak was reached only 3 days after the onset of symptoms [45]. Besides varying rates of viral replication, different assay methods and immunological differences might potentially interfere with the detection of influenza B viruses. In our study, however, the total number of children infected with influenza B viruses was too low for any firm conclusions to be made, and further studies in this area are warranted.

The main strength of the present study is that it was performed in real-life conditions. The patients were unselected young children who were examined at a primary care clinic during the acute phase of their illness. The rapid tests were performed immediately at the point of care by trained nurses, which reflects the actual situation in most clinical settings. In many previous studies, the rapid tests have been evaluated by using stored specimens in controlled laboratory conditions.

Our study has some limitations. We used flocked swabs for obtaining samples for the virology laboratory but a polyester swab included in the kit for the rapid test. This might have resulted in better-quality reference samples and thus underestimation of the sensitivity of the rapid test. However, using the exact swabs provided with the kit more likely represents the test's true

performance in the clinical practice. A total of three or four nasal swab specimens were obtained from the children during each visit, and consequently the representativeness of the samples may have varied. In addition, most of the follow-up samples were collected on study days 6-7. At that time, the viral load may have already been declining, and therefore we may have missed some children who actually had influenza. However, all samples that remained negative with viral culture and TR-FIA were further tested with RT-PCR and therefore we believe that potential variations in the quality of the samples or in the concentrations of viruses in the specimens are unlikely to have significantly affected our results. Finally, due to practical reasons, we obtained specimens for rapid testing only in approximately one-fourth of all cases. However, we have no reason to believe that this would have resulted in any major selection bias because the decisions to perform the rapid tests were made independently by several study physicians who worked at varying times, and there were no recommendations about which children should be preferably sampled for rapid testing.

In conclusion, our results indicate that influenza can be reliably diagnosed in children 1-3 years of age already during the first 24 hours of illness. Further, the influenza rapid test had a high specificity and sensitivity for diagnosing influenza A viruses, but its sensitivity for influenza B viruses was poor.

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**TABLE 1.** Sensitivity, specificity, and predictive values, according to influenza virus type, of 158 rapid influenza tests performed within 24 hours of the onset of symptoms.

Influenza virus type	Rapid test positive	Reference methods positive <sup>a</sup>	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (PPV)	Negative Predictive value (NPV)
Influenza A	29 <sup>b</sup>	31	90 % (74 – 98 %)	99 % (96 – 100 %)	97 % (82 – 100%)	98 % (93 – 100 %)
Influenza B	2	8	25 % (3 – 61 %)	100 % (98 – 100 %)	100% (16 – 100 %)	96 % (92 – 99 %)
Any influenza	31 <sup>b</sup>	39	77 % (61 – 89 %)	99 % (95 – 100 %)	97% (83 – 100 %)	93% (87 – 97 %)

<sup>a</sup> Composite of viral culture, antigen detection and RT-PCR was used as the reference test. The reference test was considered positive if influenza was detected by any of these methods.

<sup>b</sup> Including one false positive that remained negative with all reference methods.