Catching the common cold
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Chapter 3

Evaluation of a rapid antigen detection point-of-care test for respiratory syncytial virus and influenza in a pediatric hospitalized population in the Netherlands


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ABSTRACT

This pilot study evaluates the diagnostic performance of Sofia RSV Fluorescent Immunoassay Analyzer (FIA) and Sofia Influenza A+B FIA for rapid detection of respiratory syncytial virus and influenza A and B. Sofia had a lower-than-expected sensitivity for all viruses and a high rate of false-positive results for influenza B virus.
Respiratory viral infections are a serious public health concern and the most common cause for hospital admission of children in developed countries (1). Rapid and sensitive diagnosis of respiratory infections is needed to initiate timely and specific treatment, prevent misuse of antibiotics, and avoid infection transmission by optimizing infection control measures (2, 3). Due to its high sensitivity and high specificity, polymerase chain reaction (PCR) has become the reference method for diagnosing viral infections. However, performance of PCR is relatively expensive and may delay treatment as it requires technical expertise, and highly skilled laboratory personnel and equipment are not always directly available. As a result, rapid antigen detections tests or ‘point-of-care tests’ (POCT) are a promising alternative as a time saving method for viral detection (4). Sofia Fluorescent Immunoassay Analyzer (FIA) (Quidel, San Diego, CA) is a rapid fluorescence-based lateral flow immunoassay in which results are analyzed by a compact instrument (Sofia Analyzer). Sofia FIA is designed to be operated by both trained laboratory staff as well as bedside pediatric residents.

In this pilot study, we evaluated the performance of Sofia FIA for detection of respiratory syncytial virus (RSV) and influenza viruses compared to routinely used PCR and Binax blot, a rapid in vitro immunochromatographic assay for detection of RSV. Based on previously published results and information provided by the company, we expected sensitivity and specificity of Sofia FIA for RSV and Influenza in the order of 80% compared to PCR, which would be valued as acceptable (5). Secondly, we evaluated practical implementation and forthcoming clinical consequences of Sofia FIA testing.

The study was conducted at the pediatric intensive care unit (PICU) and infant ward (IW) of the Academic Medical Center (AMC), a university hospital located in Amsterdam, The Netherlands. After laboratory validation, samples were collected from children (aged 0-16 years old) with symptoms of respiratory illness admitted to either PICU or IW from December 2013 until February 2014. Nasopharyngeal swabs (Copan) were collected at the PICU and nasopharyngeal aspirates were taken at the IW. After collection, samples were immediately tested for RSV using Sofia RSV FIA and Binax and for Influenza using Sofia Influenza A+B FIA. An internally controlled multiplex real-time PCR was performed within 24 hours after sample collection using the same material (6). Two Sofia analyzers were provided by the manufacturers during study period for evaluation. Binax and PCR facilities were already operational at the AMC. Sofia testing was performed in accordance with the manufacturer’s instructions. Study sites were instructed to follow the package insert, and the Sofia analyzer was used in compliance with the manufacturer’s user manual. After diagnosis, pediatric residents and laboratory staff were asked to fill in a questionnaire to evaluate the practical benefits and limitations of Sofia
FIA. Influence of diagnosis on changes in isolation measures, discontinuation of antibiotics and initiation of antiviral agents were monitored.

Sixty-six samples were tested for RSV. Twenty-five were positive for RSV by PCR, 19 were positive by Sofia and 20 were positive by Binax. One sample (2.5%) was false positive using Sofia, and 1 was invalid. As compared to PCR results, Sofia had a sensitivity of 75% (95% confidence interval [CI]: 57.7-92.3%) and a specificity of 97.5% (95% CI: 92.7-100%), and Binax had a sensitivity of 80% (95% CI: 64.3-95.7%) and a specificity of 100% (Table 1).

Seventy-three samples were tested using Sofia Influenza A+B FIA. For Influenza A, 10 were positive by PCR and 8 were positive by Sofia. 2 samples (3.4%) were false positive using Sofia, and 5 were invalid. Compared to PCR, Sofia had a sensitivity of 66.7% (95% CI: 35.9-97.5%) and a specificity of 96.6% (95% CI: 92.0-100%) for Influenza A. For Influenza B, 11 of the 73 samples tested were positive by PCR, and 10 were positive by Sofia. Six samples (10.2%) were false positive for Sofia, and 5 were invalid. Compared to PCR, Sofia had a sensitivity of 40% (95% CI: 9.6-70.4%) and a specificity of 89.7% (95% CI: 81.8-97.5%) (Table 2).

Thirty questionnaires on clinical benefits and limitations were completed by pediatric residents. In 8 (26.6%), test result had consequences on isolation measures. In 1 case (3.3%) duration of administering antibiotics was reduced.

Our results show that performance of Sofia FIA, above all for sensitivity, is poorer than expected from other studies (7). Furthermore, rate of false positives is high, in particular for Influenza B. As mentioned by Olsen et al (2014) and Dunn et al (2014) the manufacturer of Sofia issued a recall on specific lots on December 3, 2012, due to issues with false-positive results (8-10). Despite that we used lots that were produced after the recall, our results demonstrate there still might be problems. Evaluation of Sofia by laboratory technicians showed as main limitation the numerous and time-consuming proceedings to perform the test, in contrast to Binax. Furthermore, additional material needed for on-site test implementation, e.g. vortex, clock and tube container, not routinely present on a medical ward, was not supplied. According to pediatric residents who were instructed by the company to perform the tests, Sofia was time consuming and difficult to perform. However, availability of a POCT was highly appreciated.
Table 1. Sensitivity and specificity calculations for Sofia FIA and Binax Blot, RSV.

<table>
<thead>
<tr>
<th>RSV</th>
<th>PCR+</th>
<th>PCR−</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofia+</td>
<td>18</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Sofia−</td>
<td>6</td>
<td>39</td>
<td>45</td>
</tr>
<tr>
<td>Sofia invalid</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>41</td>
<td>66</td>
</tr>
</tbody>
</table>

Sensitivity Sofia: \( \frac{18}{18 + 6} = 75\% \) (95% CI: 57.7–92.3%)

Specificity Sofia: \( \frac{39}{39 + 1} = 97.5\% \) (95% CI: 92.7–100%)

Table 2. Sensitivity and specificity calculations for Sofia FIA, Influenza A + B.

<table>
<thead>
<tr>
<th>Influenza</th>
<th>PCR+</th>
<th>PCR−</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofia+</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Sofia−</td>
<td>3</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>Sofia invalid</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>63</td>
<td>73</td>
</tr>
</tbody>
</table>

Sensitivity Sofia: \( \frac{6}{6 + 3} = 66.7\% \) (95% CI: 35.9 – 97.5%)

Specificity Sofia: \( \frac{57}{57 + 2} = 96.6\% \) (95% CI: 92.0 – 100%)

POCTs are a promising alternative as a simple, potentially time-saving, and cheaper method for viral testing. However, due to insufficient performance, POCT testing with Sofia FIA is not yet implemented at our center. For implementation of a POCT at a medical ward or emergency room, several logistic difficulties have to be overcome. Our advice for future implementation of POCTs is 3-fold. First, when implementing a POCT, a laboratory validation of the POCT is necessary. Second, it is strongly advised to provide sufficient training moments for both laboratory staff as well as other personnel involved in using the test to prevent problems with performing and interpreting test results. Third, confirmation of negative POCT results by more sensitive methods such as PCR would be a recommendable practice, and awareness for false-positive-results is necessary.
Conflict of interest

During the study period two Sofia analyzers were provided by the distributor (ITK Diagnostics) for evaluation. ITK Diagnostics had no involvement in the study design, data interpretation, or preparation of the manuscript.
REFERENCES


10. Administration UFD. Class 2 recall Sofia influenza A + B FICA, Kit#2028;2013.