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RAPID INFLUENZA TESTING IN INFANTS AND CHILDREN YOUNGER THAN 6 YEARS IN PRIMARY CARE

IMPACT ON ANTIBIOTIC TREATMENT AND USE OF HEALTH SERVICES

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Abstract: Influenza is often misdiagnosed in children because of the low sensitivity of clinical diagnosis because of nonspecific signs and symptoms. This can be overcome by using digital immunoassays or rapid molecular diagnostic tests with adequate sensitivity and specificity. When using these tests at the patient care site, antibiotic consumption and number of healthcare consultations were reduced.

Key Words: influenza, primary care, children, rapid influenza diagnostic test, point of care test

Accepted for publication January 8, 2019.
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This study was partially financed by an unrestricted grant from AstraZeneca Pharmaceutical Spain. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.
The authors have no funding or conflicts of interest to disclose.
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DOI: 10.1097/INF.0000000000002287

Influenza is a universal infection that affects all age groups and causes substantial morbidity and mortality globally. Particularly, the burden of influenza disease is high in infants and toddlers because of the lack of previous immunity. It is estimated that 20%–30% of the pediatric population in the United States and Europe gets infected during each annual season.[1] Attack rates are even higher (50%) in day-care attendees.[1] However, nonspecific signs and symptoms like fever and cough make the clinical diagnosis of influenza in this age group difficult.[2] In their study, Peltola et al[2] reported that both sensitivity and positive predictive value of clinical diagnosis were low (38% and 32%, respectively). Furthermore, children play a key role in the transmission of influenza as they act as primary vectors spreading the disease in the community shedding virus at higher viral titers and for more days than adults.[3]

In the absence of a confirmed influenza diagnosis using microbiologic tests, infants and young children may not get a correct diagnosis, and, as a consequence, they are more frequently admitted to hospital, submitted to redundant laboratory tests and receive unnecessary antibiotics because influenza can mimic a bacterial infection or sepsis.[4]

Rapid influenza diagnostic tests (RIDTs) used at the point of care, also known as influenza point-of-care tests (POCTs), can detect the presence of influenza A (IAV) and B (IBV) virus in respiratory specimens and display the result in a qualitative way (positive vs. negative). POCTs can yield results in a clinically relevant time frame, 15–20 minutes after sample collection, thus offering a rapid result to manage patients immediately. New molecular RIDTs, which detect the presence of nucleic acids from the virus, or digital immunoassays, which detect viral antigens, have improved the reliability in the diagnosis of IAV and IBV, with sensitivities >90% compared with traditional viral antigen detection by immunochromatographiy-based assays.[5]

The use of POCTs in primary care settings might be beneficial to improve diagnosis and reduce additional visits, unnecessary laboratory tests, antibiotic prescriptions and hospitalizations related to the unclear etiology of febrile patients. A microbiologic confirmation also supports antiviral treatment, if warranted.

The primary objectives of this study were the comparison of the use of antibiotics 10 days after diagnosis and the number of additional consultations to healthcare centers between children with POCT-confirmed influenza in the primary care office to those who had only been clinically diagnosed. Our secondary objective was the evaluation of the performance of 2 different POCTs by comparing them to real-time (RT) polymerase chain reaction (PCR), which is the current gold standard.

MATERIALS AND METHODS

We conducted a descriptive, prospective, longitudinal study during the 2016–2017 influenza season in 4 primary care centers of Barcelona, involving 15 pediatricians. The study was reviewed and approved by the ethics committee of IDIAP Jordi Gol in Catalonia (Spain) and conducted in compliance with the Declaration of Helsinki and the principles of Good Clinical Practices. Eligible participants included children 6 years of age or younger presenting either (1) axillary temperature ≥38°C or (2) axillary temperature between 37.2 and 38°C with rhinorrhea, nasal congestion, or cough within 72 hours from symptom onset. No exclusion criteria were established. Written informed consent was obtained from parents or legal guardians before enrollment into the study.

Nasopharyngeal swabs from enrolled patients were collected and resuspended in a vial containing viral transport medium. Respiratory specimens were tested in parallel using 2 rapid tests: Sofia Influenza A+B (Quidel), which is an immunofluorescence nucleoprotein antigen detection-based test, and Cobas Liat (Roche Diagnostics, Spain), an automated multiplex RT-PCR-based assay. Both assays were used according to the user's manual to provide results concerning influenza infection within 15–20 minutes. Residual volume of all respiratory specimens was kept frozen at −80°C until laboratory confirmation at the end of the season by a one-step, multiplex RT-PCR assay (Allplex; Respiratory Panel Assay, Seegene, South Korea), which is used in routine respiratory virus confirmation in the hospital's reference laboratory. Patients were asked to complete a diary for 10 days to assess clinical symptoms, antibiotic

TABLE 1. Comparison of Antibiotic Treatment and Additional Visits in Primary Care

	Group 1*	Group 2†	Group 3‡	*P*§ (Group 1 vs. Group 2)	*P*§ (Group 1 vs. Group 3)
Number of subjects	91	166	913	—	—
Age mean, (SD; range), mo	31.2 (16.5; 4–60)	34.0 (16.7; 6–60)	29.1 (17.2; 6–60)	0.23	0.24
Antibiotic treatment (%)	4.4	7.2	9.7	0.38	0.098
Additional visits in primary care	0.19	0.48	0.81	0.001	<0.001

*Group 1: Influenza-confirmed diagnosis.
†Control group 2: Influenza clinical diagnosis (J11).
‡Control group 3: Clinical diagnosis (J11, B34 and R50).
§$P < 0.05$ is significant.
International Classification of Diseases, 10th revision, 2016 coding is as follows: J11: influenza, virus, not identified; B34: viral infection of unspecified site; R50: fever of other and unknown origin.

treatment and the use of healthcare services. This information was gathered by a phone call, maximum 3 attempts, starting the first working day after the 10-day period.

Antibiotic treatment and use of primary care healthcare services for enrolled patients with a confirmed influenza test (group 1) were compared with data collected from electronic health records, including either patients diagnosed with code J11 (influenza virus not identified; group 2) or those with codes J11or B34 (viral infection of unspecified site) or R50 (fever of other or unknown origin; group 3). All these codes are included in the International Classification of Diseases, 10th revision, 2016 classification.

Statistical Analysis

Univariate methods were used to describe the sample. Comparison of antibiotic consumption and frequency of consultations at the healthcare center was performed by comparative statistics using bivariate analysis (χ^2 and Student *t* test). A $P < 0.05$ was considered to be significant.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and inter-rate agreement (Cohen κ) for both RIDTs in comparison with routine PCR assay were determined using MedCalc Statistical Software version 18.9.1 (MedCalc bvba, Belgium).

RESULTS

Overall, 189 nasopharyngeal samples were collected from patients with suspected influenza infection, of which 93 (49%) were positive for influenza virus, 92 (99%) for IAV and 1 (1%) for IBV. The final analysis in group 1 was performed on 91 children with confirmed influenza virus infection because 2 patients were older than 6 years and therefore excluded.

The mean age for influenza-confirmed patients (group 1) was 31.2 months, whereas the mean age for patients of group 2 was 34.0 months and 29.1 months for group 3.

As shown in Table 1, influenza-confirmed patients (ie, group 1) received fewer antibiotics during the 10 days after influenza diagnosis (4.4%) and had significantly lower revisit rate (0.19 additional visits per patient) compared with the groups having a clinical diagnosis of influenza without a microbiologic confirmation (group 2: 7.2% antibiotics, 0.48 additional visits per patient, $P = 0.001$; group 3: 9.7% antibiotics, 0.81 additional visits per patient, $P < 0.001$).

Cobas Liat showed a sensitivity of 97.5% (95% CI: 91.4–99.7), a specificity of 98.8% (95% CI: 93.5–100), PPV = 98.8% (95% CI: 91.8–99.8), NPV = 97.6% (95% CI: 91.3–99.4) and κ = 96.3% (95% CI: 92.2–100) when compared with Allpex RT-PCR. The values for Sofia when compared with Allpex RT-PCR were sensitivity 93.9% (95% CI: 86.3–98.0), specificity 100% (95% CI: 95.7–100), PPV = 100% (95% CI: 100–100), NPV = 94.3% (95% CI: 87.7–97.5) and κ = 93.9% (95% CI: 88.7–99.2).

DISCUSSION

Influenza, which affects a high percentage of the pediatric population every year, causes significant morbidity in infants and children.[1] Additionally, influenza disease has not only an impact on children's healthcare but also on society because of its spread to close contacts such as siblings, family members and day-care contacts.[3]

In the present study, the number of additional visits at primary care centers was significantly reduced, which has a positive impact on the healthcare system because it is usually under pressure because of the high number of consultations during the winter season. Antibiotic prescriptions were also reduced when patients had a confirmed influenza diagnosis using a RIDT, compared with those having a clinical diagnosis without microbiologic confirmation, although the differences were not statistically significant. Tillekeratne et al[6] showed a 20% decrease in the antibiotic prescription with an influenza POCT confirmation. Busson et al,[7] who evaluated the advantages of using a molecular POCT as a complement to the clinical diagnosis in the emergency department (ED), found comparable results to those obtained in our study. Rogan et al[8] studied the impact of using a molecular POCT for respiratory syncytial virus and influenza on real-time decision making in the pediatric ED and showed a decrease in the length of stay, fewer antibiotics on discharge and increased appropriate antiviral therapy if immediate results were available. Lacroix et al,[9] in a prospective study in children up to 5 years of age admitted in the ED because of fever without source, studied the estimation of the likelihood of influenza and serious bacterial infection before and after RIDT results. The study showed that RIDTs improved the accuracy of physicians' estimates of influenza and serious bacterial infection and significantly decreased the number of ordered chest radiographs and laboratory tests.[9]

One of the most prominent drawbacks of incorrect diagnosis is the prescription of antibiotics, because the symptoms might lead to the assumption of a bacterial infection. The decision-making process of an antibiotic prescription is vastly influenced by an accurate diagnosis.[8–10]

Both RIDTs used in our study have high sensitivity and specificity and are in excellent agreement with definitive results provided by routine PCR-based assay (gold standard), which is in line with previous work in children.[11,12] However, the nucleic acid-based RIDT (Cobas Liat) showed a slightly higher sensitivity than the antigen-based one (Sofia), and thus, the overall accuracy of diagnosis improved; although the difference was not statistically significant.

The most important limitation of our study was that the data from clinically diagnosed patients without influenza confirmation (groups 2 and 3) were extracted from electronic health records of patients of the same age and living in the same geographic area, while information for patients diagnosed using RIDTs (group 1) came from the direct follow-up within the study.

In conclusion, the use of RIDTs with high sensitivity and specificity in primary care settings can provide important benefits in terms of clinical management of cases, reduction in antibiotic prescriptions, rate of further consultations and families' trust in the diagnosis of influenza when confirmed using a POCT.

ACKNOWLEDGMENTS

The authors thank Roche Diagnostics (Spain) and Werfen (Spain) for their help with equipment and tests, Irene Farré and Beate Walter for providing medical writing support, Francesc Orfila for his statistical analysis and Miguel Angel Muñoz for his help as head of the Primary Care Research Unit of the Catalan Institute of Health. The authors are indebted to the other members of the BCN_FLU study group; study physicians: Josep Ferrer, Anna Bosch, María Angeles Ferrández, Montse Mas, Maria Bosch, Ulla Aguilera, Josep M. Linares, Rosa Piqué, Maria Teresa Fabregas, Sònia Burch and Cristina Andrés; study nurses: Israel Caro, Pilar Po, Ana Belen López, Raquel Casado Rosa Maria Castella, Celia Vázquez, Emma Vilaró, Rosario Álvarez, Mariona Castella and Mireia Diaz.

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