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Variability in the diagnostic performance of a bedside rapid diagnostic influenza test over four epidemic seasons in a pediatric emergency department

E. Avril [a], S. Lacroix [a], B. Vrignaud [a], A. Moreau-Klein [b], M. Coste-Burel [b], E. Launay [a,c], C. Gras-Le Guen [a,c,d,*]

[a] Pediatrics emergency department, University Hospital, Nantes, France
[b] Laboratory of Virology, University Hospital, Nantes, France
[c] Department of Pediatrics, University Hospital, Nantes, France
[d] Center of Clinical Investigation for Woman, Child and Adolescent, University Hospital, Nantes, France

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ABSTRACT

We wanted to determine the diagnostic performance of a rapid influenza diagnostic test (RIDT) used bedside in a pediatric emergency department (PED). This was a prospective study over four consecutive winters (2009-2013), comparing the results of a RIDT (QuickVue®) with RT-PCR in children admitted to a PED. Among the 764 children included, we did not observe any significant differences in the diagnostic performance of RIDT except during the H1N1 pandemic. The overall sensitivity of the test was 0.82; the specificity 0.98; the positive and negative likelihood ratios 37.8 and 0.19. The positive and negative post-test probabilities of infection were 98% and 17%. The diagnostic performance was increased for influenza B cases ($P = 0.03$). RIDTs are suitable for use every winter with few differences in its diagnostic value, except during specific pandemic periods. This test could limit unnecessary complementary exams and guide the prescription of antivirals during influenza epidemic periods in PEDs.

1. Introduction

Every winter, influenza infections cause numerous consultations in pediatric emergency departments (PEDs). During flu epidemics, clinicians have the task of distinguishing children with flu from children with serious bacterial infections. This is particularly difficult in children younger than five years of age because fever can be the only symptom during the first hours of a severe bacterial infection (reported in 7.2% of young children presenting with fever without a source) (Craig et al., 2010). Indeed, numerous studies have confirmed that clinical symptoms alone cannot accurately distinguish between these two sources of fever (Dagan et al., 1984; Peltola et al., 2005; Silvennoinen et al., 2012).

Rapid influenza diagnostic tests (RIDTs) can help clinicians to estimate the probability of an influenza infection in a young child quickly. RIDTs have been shown to reduce the length of stay in PEDs, cost of care, and use of antibiotics for influenza infections (Benito-Fernández et al., 2006; Jennings et al., 2009; Pierron et al., 2008; Poehling et al., 2006). It has also been established that the probability of a severe bacterial infection is very low when influenza is diagnosed with these tests (Krief et al., 2009; Smitherman et al., 2005).

Although the diagnostic value of RIDTs is poor in adults (Chartrand et al., 2012; Cho et al., 2013; Gao et al., 2012), their sensitivity increases with a decrease in patient age, and thus the use of RIDTs in children is of particular interest (Chartrand et al., 2012; Cho et al., 2013; Gao et al., 2012). Indeed, children have a maximum viral load that is 10–100 times higher than adults (Chartrand et al., 2012; Cheng et al., 2009) and increased viral shedding (Chartrand et al., 2012). However, some studies reported some variations in the diagnostic performance of RIDTs between years in relation to the epidemic season and viral serotype (Busson et al., 2014; Kok et al., 2010).

The objective of this study was to investigate whether the diagnostic value of a RIDT performed bedside varied during different epidemic seasons and to determine its appropriateness for use in pediatric emergency departments every winter.

2. Materials and methods

Patients with suspected influenza admitted to the pediatric emergency department of University Hospital Nantes, France over four consecutive epidemic seasons (defined by the Regional Groups Observation Flu (GROG) from December 2009–2012) were prospectively included in this study. The QuickVue RIDT (Quidel QuickVue® laboratory) was performed bedside by a clinician from the pediatric emergency department. Interpretation of the RIDT result was secondary

* Corresponding author. Tel.: +33-240087671.
E-mail address: christele.grasleguen@chu-nantes.fr (C. Gras-Le Guen).

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validated at the laboratory by biologists using real-time RT-PCR (reverse transcriptase polymerase chain reaction), according to the French National Influenza reference center protocol, to confirm the RIDT result obtained in the emergency department and recorded on an informatics system.

The indication for use of the RIDT in the PED was fever without a source in children under five years of age during the epidemic period. In the year of the pandemic (winter 2009–2010), the RIDT indications were different and focused on the at-risk population. All children and their contacts likely to develop severe influenza were tested (including those with underlying disease, age <3 months old, and the children of pregnant mothers). An information sheet about the RIDT was given to the child's parents and explained in detail, according to French law. No written consent was necessary due to the non-interventional study design.

3. Results

In total, 764 patients were included over the four-year study period (Table 1). The prevalence of influenza among the children included varied between 30–62% over the years (Table 1).

Table 1 reports the diagnostic values from the RIDT according to the year the test was performed and the strain of the virus (either A or B). No significant differences were observed in the diagnostic performance of the test over the years, except during the H1N1 pandemic. The main difference found for RIDTs performed during the period of the pandemic was the sensitivity of the test, which had decreased compared to those performed during other epidemic seasons. However, the post-test probability of having the flu and a positive test result was similar to the results for other years. There was a slight decrease in the negative post-test probability during the 2010–2011 season (7%). We also observed that the diagnostic performance was higher for influenza B, especially the negative post-test probability (12%, 95 CI 10–14 for influenza A versus 1%, 95 CI 1–3 for influenza B; $P = 0.03$).

The Fagan nomogram (Fig. 1) shows the post-test probability of infection based on the results from the RIDT. The global post-test probability of infection when the RIDT was positive over the four-year period was 98% (95% CI 95–99), but the post-test probability of infection when the test was negative remained high (17%, 95% CI 14–20). With a pre-test probability of 0.52 (prevalence), the probability of infection following a positive RIDT was increased by 1.9-fold; the probability of infection following a negative RIDT result was reduced by 3 fold.

Fagan nomogram for applying positive and negative likelihood ratios calculated from positive and negative RIDTs. This nomogram compares the pre-test likelihood of infection with the post-test likelihood. The pre-test probability was 52%, which corresponds to the incidence of influenza in the population studied. A positive RIDT result was associated with a 1.9-fold higher probability of flu infection; a negative RIDT was associated with a threefold reduced probability of flu infection.

4. Discussion

This study demonstrated that the variation in the diagnostic performance of the QuickVue RIDT used bedside in a pediatric emergency department was modest over four epidemic seasons, even though we observed significant differences during the year of the H1N1 pandemic, as previously reported (Cruz et al., 2010; Hurt et al., 2009; Kok et al., 2010). We observed differences between the A and B strains of influenza: the diagnostic performance was better for influenza B, with a negative post-test probability of 1%. However, because influenza B is documented in only a quarter of all flu cases, this has a minimal impact on the global diagnostic value of the test. But it could explain the better negative post-test probability in 2010–2011 season (7%) regarding the high prevalence of influenza B during this winter. Poehling et al. showed a similar diagnostic performance (sensitivity 82%, specificity 99%) in their 2006 study in a pediatric population from an emergency department and clinic (Poehling et al., 2006). A retrospective study by Eggers et al. (2015), which evaluated the performance of another RIDT in Germany, did not show a significant difference of diagnostic performance across seven seasons. However, RIDTs were not used in the year of the pandemic (Eggers et al., 2015). The sensitivities for the RIDT were lower than our study; however, they reported a lower sensitivity for influenza B than influenza A (23% versus 59%).

The performance of the QuickVue RIDT had already been studied in laboratories in small pediatric populations and showed similar results to those reported in this study (Agoritsas et al., 2006; Quach et al., 2002). Indeed, the sensitivities reported in the two small-scale studies ranged from 69% to 85% and the specificities from 82.6% to 98 %. The study by Agoritsas et al. also found positive predictive values (PPV) and negative predictive values (NPV) similar to those reported in this study (96–98% and 78–87% respectively, with the variations depending on the type of secretion collection) (Agoritsas et al., 2006).

While the large size of our cohort (764 children) provided precise confidence intervals for the diagnostic performance of the test, our

Table 1
Diagnostic performance of the QuickVue RIDT according to epidemic season and viral strain (results are presented with the 95% CI in square brackets).

	Winter 2009–2010	Winter 2010–2011	Winter 2011–2012	Winter 2012–2013	Total over four winters	Influenza A	Influenza B
Number of patients	94	294	156	220	764	764	764
Sensitivity	0.61 [0.42–0.76]	0.93 [0.88–0.96]	0.8 [0.71–0.87]	0.74 [0.65–0.81]	0.82 [0.78–0.85]	0.78 [0.73–0.83]	0.91 [0.84–0.95]
Specificity	0.99 [0.92–1]	0.98 [0.94–0.99]	0.98 [0.91–1]	0.97 [0.91–0.99]	0.98 [0.96–0.99]	0.987 [0.97–0.994]	0.997 [0.989–0.999]
Likelihood ratio +	40 [5.60–286.69]	45.67 [14.89–140.08]	47.44 [6.78–332.05]	24.1 [7.87–73.8]	37.8 [19–75.13]	62.4 [28.11–138.51]	267.63 [74.5–1189.1]**
Likelihood ratio −	0.4 [0.25–0.63]	0.07 [0.04–0.13]	0.2 [0.13–0.3]	0.27 [0.2–0.37]	0.19 [0.15–0.23]	0.22 [0.18–0.27]	0.093 [0.051–0.168]**
Post-test probability of flu with positive RIDT	94% [70–99]	98% [94–99]	99% [92–100]	97% [91–99]	98% [95–99]	97 % [94–99]	98% [92–99]
Post-test probability of flu with negative RIDT	15% [10–21]	7%* [4–12]	25% [18–33]	25% [20–32]	17% [14–20]	12% [10–14]	1% [1–3]
Percentage of influenza A	100%	55%	98%	66%	73%	-	-
Percentage of influenza B	0	45%	2%	34%	27%	-	-
Circulating serotypes	A(H1N1)pdm09	A(H1N1)pdm09 B	A(H3N2) B	A(H1N1)pdm09 A(H3N2) B	-	-	-
Prevalence	0.3	0.5	0.62	0.55	0.52	-	-

Prob = probability; PPV = positive predictive value; NPV = negative predictive value.
* $P < 0.05$ comparing winter 2011–2012 and winter 2012–2013.
** $P < 0.05$ versus Influenza A.

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