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Analytical performances of the BD Veritor™ System for the detection of respiratory syncytial virus and influenzaviruses A and B when used at bedside in the pediatric emergency department

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ABSTRACT

This study aims to evaluate the analytical performance of the BD Veritor™ rapid diagnostic assays (RDTs) for respiratory syncytial virus (RSV) and influenzaviruses when performed 24/7 at bedside by nurses in the pediatric emergency department (PED). The study was performed between 14/10/2015 and 19/03/2016 on nasopharyngeal aspirates (NPAs) collected from children consulting at the PED of the University Hospital of Saint-Etienne for bronchiolitis (RSV detection) or flu-like syndrome (influenzaviruses A/B detection). NPAs were tested 24/7 at the PED with the RDT and then sent to the Infectious Agents Department for routine analyses, first by immunofluorescence assay (IFA), then by nucleic acid amplification test (NAAT) considered as the gold standard in case of discrepancy between RDT and IFA results. For RSV detection, 205 NPAs was analyzed; the overall concordance between RDT and routine assays was of 97.6% (200/205). The sensitivity (Se), specificity (Sp), negative predictive value (NPV) and positive predictive value (PPV) were of 97.6% (160/164), 97.6% (40/41), 90.9% (40/44) and 99.4% (160/161), respectively. A total of 419 NPA was tested for influenzaviruses. For influenzavirus A, the overall concordance was of 98.8% (414/419); Se, Sp, NPV and PPV were of 100% (41/41), 98.7% (373/378), 100% (373/373) and 89.1% (41/46), respectively. For influenzavirus B, the overall concordance was of 97.9% (410/419); Se, Sp, NPV and PPV were of 96.6% (172/178), 98.8% (238/241), 97.5% (238/244) and 98.3% (172/175), respectively. Due to their excellent performances and their easy handle by non-laboratory personnel, these RDTs can be warmly recommended as point of care assays at the PED.

Respiratory syncytial virus (RSV)-associated bronchiolitis and flu-like syndromes represent a huge burden at the pediatric emergency department (PED) each year during the winter season. Identification of the etiological agent helps the triage of sick children and helps to the limitation of prescriptions (Lacroix et al., 2015), inappropriate use of antibiotics (Messacar et al., 2017), and health costs (Messacar et al., 2017). Rapid diagnosis tests (RDTs) based on the detection of viral antigens are easy to perform by non-laboratory personnel at bedside but the weak performances of most of them restrict their wide use (Dunn and Ginocchio, 2015). "Second-generation" RDTs including an objective reading of the result on a small digital instrument, such as the Veritor™ System (Becton Dickinson Diagnostics) and the Sofia® Fluorescence Immunoassay (Quidel), have been shown to exhibit improved sensitivity (Azar and Landry, 2018; Bruning et al., 2017; Koski and Klepser, 2017). The aim of this study was to assess the analytical performances and practicability of the BD Veritor™ System for the detection of RSV or influenzaviruses A/B when used 24/7 at the PED.

The commercial chromatographic immunoassays that were evaluated were the BD Veritor™ System for Rapid Detection of RSV that targets the RSV fusion protein nucleoprotein antigens, and the BD Veritor™ System for Rapid Detection of Flu A + B that targets the influenza A/B viral nucleoprotein antigens. The two devices are Clinical Laboratory Improvement Amendments (CLIA)-waived (Azar and Landry, 2018). They were used on nasopharyngeal aspirates (NPAs) collected between 14/10/2015 and 19/03/2016 from children admitted at the PED of the University Hospital of Saint-Etienne either for

Abbreviations: IFA, immunofluorescence assay; NAAT, nucleic acid amplification test; NPA, nasopharyngeal aspirate; PED, pediatric emergency department; RDT, rapid diagnosis test

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Table 1
BD Veritor™ rapid diagnosis tests (RDT) for respiratory syncytial virus (RSV) and influenzavirus (Flu) A/B detection compared to the routine assays used during the 2015–2016 winter season.

	RSV	Flu A	Flu B
Crude results (no.)			
-RDT + / IFA + / NAAT ND	150	24	154
-RDT- / IFA- / NAAT ND	12	329	201
-RDT- / IFA- / NAAT-	26	44	36
-RDT- / IFA + / NAAT-	2	0	1
-RDT + /IFA-/NAAT +	10	17	18
-RDT-/IFA-/NAAT +	3[a]	0	0
-RDT-/IFA + /NAAT +	1[b]	0	6[c]
-RDT + /IFA-/NAAT-	1	5	3
Total	205	419	419
Analytical performances expressed as %[d]			
Overall concordance	97.6 (200/205)	98.8 (414/419)	97.9 (410/419)
-Cohen kappa coefficient	0.93	0.94	0.96
-Sensitivity	97.6 (160/164)	100 (41/41)	96.6 (172/178)
-Specificity	97.6 (40/41)	98.7 (373/378)	98.8 (238/241)
-Negative predictive value	90.9 (40/44)	100 (373/373)	97.5 (238/244)
-Positive predictive value	99.4 (160/161)	89.1 (41/46)	98.3 (172/175)

IFA: immunofluorescence assay; NAAT: nucleic acid amplification test; ND: not done.
[a] Cycle threshold (Ct) values all > 34.
[b] Ct value of 32.
[c] Ct values comprised between 23.9 and 33.9.
[d] Except for kappa coefficient.

bronchiolitis (infants aged from 0 to 24 months) or for fever or other flu-like symptoms. The appropriate RDT was performed 24/7 by nurses of the PED who all received a short training by one of us (SP), according to the International Standard NF EN ISO 22,870 international standard. Immediately after NPA sampling, the swab included in the kit was inserted and rolled 5 times in the sample before being introduced into the reagent tube. The test was then performed as recommended by the manufacturer and objectively interpreted by using the digital BD Veritor™ reader. The result was available in less than 15 min.

Then, NPAs were sent to the Infectious Agents Department and kept at 4 °C before being tested with routine assays during the opening hours of the laboratory. NPAs were first analyzed by immunofluorescence assay (IFA) for the detection of RSV or influenzavirus A/B antigens, using specific murine monoclonal antibodies (Argene®, bioMérieux) as specified by the manufacturer. These antibodies are directed against the F0 and F1 subunits of the fusion protein for RSV, a nucleoprotein for influenzaviruses A and a group-specific antigen for influenzaviruses B. If discrepant result between RDT and IFA was observed, the sample was tested by nucleic acid amplification test (NAAT) and the latter result was considered as the gold standard. Commercial one-step reverse-transcription and real-time PCR-based assays (RSV/metapneumovirus Multi Well System r-gene™ and Influenza A/B Multi Well System r-gene™, bioMérieux) were used as previously described (Pillet et al., 2013). The subtype of influenzavirus A was determined by RT-PCR assay using primers and probes designed by the French National Reference Centre for Influenza.

A total of 217 patients (sex ratio M/F: 1.13; mean of age: 134 days, range [7–684 days]) and 477 patients (sex ratio M/F: 1.10; mean of age 3.5 years, range [12 days-14.9 years]) were included for RDT detection of RSV and influenzaviruses, respectively. The RDT was found not interpretable in 4 samples for RSV (1.9%) and in 6 samples for influenzaviruses (1.4%) because of test failure. No result was available for IFA in 8 and 52 samples for RSV and flu, respectively, because of cell absence on the slide or insufficient amount of specimen. The remaining specimens (n = 205 for RSV and 419 for influenzaviruses) were used to evaluate the analytical performances of both RDTs by comparison to the combination of IFA and/or NAAT used routinely in the laboratory at the time of the study. The detailed results are shown in Table 1. The distribution of the RDTs performed during the 2015–2016 winter season is depicted in Fig. 1.

Among the 41 specimens found positive with influenzavirus A by RDT, the strain could be subtyped in 34 cases (82.9%), including 23 H1N1 pdm09 and 11 H3N2 subtypes. For flu B, the virus was not subtyped, but the Victoria lineage was shown to be predominant one during the 2015–2016 winter season (European Centre for Disease Prevention and Control, 2017).

A special interest was given to discrepant results. Concerning RSV, in case of discordant result between IFA and RDT (n = 14), the RDT result was concordant with that of the NAAT in 12 samples (85.7%). Four samples gave a false negative result by RDT in comparison with NAAT; interestingly, the cycle threshold (Ct) value was 32 or more by NAAT, which corresponds to very low signals (Table 1). For flu A, from 22 discrepant results between RDT and IFA, 17 (77.3%) were arbitrated in favor of RDT by NAAT. For flu B, from 27 discrepant results between RDT and IFA, 18 (66.7%) were arbitrated in favor of RDT by NAAT; 6 samples gave a false negative result by RDT in comparison with NAAT, with Ct values comprised between 23.9 and 33.9, which could indicate a lower sensitivity of the RDT for this target than for RSV and influenzavirus A (Table 1).

The BD Veritor™ assays for the detection of RSV and influenzaviruses were compared to the routine techniques performed in our laboratory. At the time of the study, the first-line technique was IFA; this technique is cheap but lacks sensitivity and the result is dependent upon the reading of technicians. IFA was shown to be less sensitive than RDT in our study (a total of 48 false negative results for IFA against 10 for RDT, Table 1), the RDT giving closest results to NAAT for both RSV and influenzaviruses. The real-life design of the study did not allow the comparison between RDT and NAAT for all the specimens, the latter having been done mainly in case of discrepant result between RDT and IFA, which could have led to miss very low positive samples with high Ct values and found negative both by RDT and IFA. Despite these pitfalls, the analytical performances of the Veritor™ assays were shown to be very close to those described when these RDTs were compared to NAAT, for the detection of both RSV (Bell et al., 2014; Jonckheere et al., 2015; Jung et al., 2016; Kanwar et al., 2015; Schwartz et al., 2015) and influenzaviruses (Koski and Klepser, 2017; Mese et al., 2016; Ndegwa et al., 2017; Ryu et al., 2017). Of note, the sensitivity of RDT was slightly lower for influenzavirus B than for influenzavirus A, as already recorded (Bruning et al., 2017; Koski and Klepser, 2017; Mese et al., 2016; Ndegwa et al., 2017; Ryu et al., 2017). Importantly, the

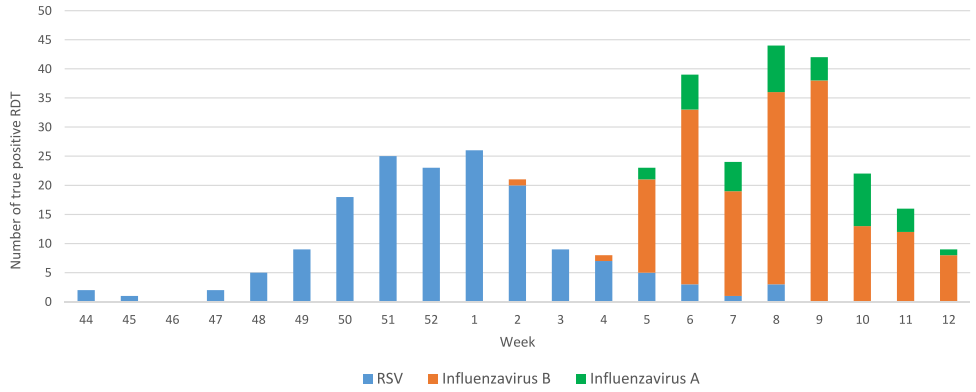

Fig. 1. Distribution of the BD Veritor™ rapid diagnosis tests (RDT) results during the 2015–2016 winter season. Only true positive results after comparison with routine assays are shown.

performances of RDTs are not affected when done at bedside by non-laboratory personnel (this study, (Mese et al., 2016; Ndegwa et al., 2017; Schwartz et al., 2015)). In our study, NPAs were preferred to swab specimens because of their common use for care of children exhibiting upper respiratory tract obstruction, thus limiting an additional invasive procedure; this practice has also been shown to increase the RDT sensitivity when compared to swabbing (Bell et al., 2014).

The Veritor™ assays for detection of respiratory viruses were shown to have excellent analytical performances in children, to be easy to perform by nurses at the PED with availability of the result 24/7 and to have limited cost. These qualities make them the choice as point-of-care assays in PED. The availability of the result within 15 min allows the rapid triage of children with cohorting of patients infected by the same virus in the same ward, prevention of nosocomial infections, limitation of unnecessary biological and radiological prescriptions, and rational use of antibiotic, meeting the criteria of diagnostic and antibiotic stewardship (Cantais et al., 2019; Messacar et al., 2017). After the study period, these assays were routinely implemented in the PED of our hospital during winter seasons and NAAT replaced IFA at the laboratory for respiratory specimens.

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Competing interests

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Ethical approval

The study received the approval of the Ethics Committee of the University-Hospital of Saint-Etienne under the code IRBN322016/CHUSTE.

Author contributions

Aymeric Cantais and Olivier Mory conceptualized and designed the study, selected the patients according to clinical criteria, collected the clinical and virological data, analyzed the results, drafted the initial manuscript, and approved the final version.

Bruno Pozzetto and Sylvie Pillet conceptualized and designed the study, collected the clinical and virological data, analyzed the results, and wrote the final version of the manuscript.

Aurélie Plat and Antoine Giraud participated to the clinical inclusion of patients, contributed to the collection of data and approved the final manuscript.

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