

Comparing the Cobas Liat Influenza A/B and respiratory syncytial virus assay with multiplex nucleic acid testing

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Influenza virus and respiratory syncytial virus (RSV) detection with short turn-around-time (TAT) is pivotal for rapid decisions regarding treatment and infection control. However, negative rapid testing results may come from poor assay sensitivity or from influenza-like illnesses caused by other community-acquired respiratory viruses (CARVs). We prospectively compared the performance of Cobas Liat Influenza A/B and RSV assay (LIAT) with our routine multiplexNAT-1 (xTAG Respiratory Pathogen Panel; Luminox) and multiplexNAT-2 (ePlex-RPP; GenMark Diagnostics) using 194 consecutive nasopharyngeal swabs from patients with influenza-like illness during winter 2017/2018. Discordant results were reanalyzed by specific in-house quantitative nucleic acid amplification testing (NAT). LIAT was positive for influenza virus-A, -B, and RSV in 18 (9.3%), 13 (6.7%), and 55 (28.4%) samples, and negative in 108 samples. Other CARVs were detected by multiplexNAT in 66 (34.0%) samples. Concordant results for influenza and RSV were seen in 190 (97.9%), discordant results in 4 (2.1%), which showed low-level RSV (<40 000 copies/mL). Sensitivity and specificity of LIAT for influenza-A, -B, and RSV were 100%, 100% and 100%, and 100%, 99.5% and 100%, respectively. The average TAT of LIAT was 20 minutes compared to 6 hours and 2 hours for the multiplexNAT-1 and -2, respectively. Thus, LIAT demonstrated excellent sensitivity and specificity for influenza and RSV, which together with the simple sample processing and short TAT renders this assay suitable for near-patient testing.

KEYWORDS

influenza virus, nucleic acid amplification testing, point-of-care test, respiratory syncytial virus, turn-around time

1 | INTRODUCTION

Influenza virus and respiratory syncytial virus (RSV) detection with short turn-around-time (TAT) is pivotal for rapid decisions regarding treatment and infection control.^{1,2} Current diagnostics for the detection of influenza virus and RSV include direct antigen detection (DAD), virus isolation by cell culture (VIC), and nucleic acid amplification testing (NAT). DAD is rapid, but had been shown to be of limited sensitivity compared to VIC.^{3,4} In the past, VIC has been the gold standard for sensitive and specific identification of community-acquired respiratory viruses (CARVs) including influenza

virus and RSV. However, VIC requires skilled technicians, dedicated cell culture equipments, and a TAT of several days, which limits the use of this technique to specialized laboratories.⁵ By contrast, NAT has the advantage of a shorter TAT of approximately 6 to 8 hours, and the detection of multiple pathogens by parallel testing in a semiquantitative format and as multiplexNAT. More recently, NAT platforms became available for detecting influenza virus as point-of-care tests (POCTs).^{3,6,7} Besides short TAT of less than 2 hours, cartridge-based POCTs are simple to operate, which permit their use in near-patient settings without extensive laboratory training. However, negative results are difficult to interpret since POCT

may have a limited sensitivity or the influenza-like illnesses in question may be due to other CARVs not covered by the POCT. For this reason, comparison with a multiplexNAT assay is of considerable advantage.³ In fact, a number of centres are exploring deep-sequencing to detect other CARVs.⁸ The Cobas Liat Influenza A/B and RSV real-time assay (LIAT) is of interest, since both influenza virus-A, -B as well as the RSV-A and -B are targeted, all of which cause significant morbidity in younger children and older adults during the cold season, and can therefore guide initial decisions regarding antiviral therapy as well as infection control measures.⁹⁻¹²

2 | MATERIALS AND METHODS

In a first phase, eight external quality assurance samples covering influenza virus-A, -B, and RSV were tested by the LIAT and by our in-house tests.^{4,13} Then, the limit of detection was estimated by using twofold serial dilutions in virus transport medium (VTM) of patient samples that had tested positive for either influenza or RSV in our in-house quantitative nucleic acid amplification (QNAT) assays.^{4,13}

For a prospective parallel study, 194 consecutive nasopharyngeal swabs had been submitted for routine testing between November 2017 and January 2018. The swabs were compared using the LIAT and two Food and Drug Administration (FDA)-cleared multiplex-NATs. Discordant results between the LIAT and the multiplexNATs were resolved by in-house real-time QNAT. Briefly, nasopharyngeal samples were collected using Copan swabs for adults or for infants and submersed in 2 mL VTM. For the LIAT, 200 μ L of respiratory specimen was transferred into the single-use, disposable assay tube using a sterile transfer pipette. The tube was capped and directly inserted into the LIAT analyzer.

For multiplexNAT-1, the FDA-cleared xTAG Respiratory Pathogen Panel (RPP) assay was used (<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K152386>; Luminex Molecular Diagnostics Inc, MV-Hertogenbosch, The Netherlands), total nucleic acids were extracted from 200 μ L of 150 respiratory specimens on the MagNa-Pure-96 using the Viral NA Small Volume Kit (Roche Diagnostics AG, Rotkreuz, Switzerland) according to the manufacturer's instructions. The nucleic acids were collected in 100 μ L elution buffer and 25 μ L were used for multiplexNAT-1 according to the manufacturer's instructions. The multiplexNAT-1 covers 22 targets consisting of adenovirus, coronavirus (229E, HKU1, NL63, and OC43), human bocavirus, human metapneumovirus, human rhinovirus/enterovirus, influenza-A, influenza-A H1, influenza-A H1-2009, influenza-A H3, influenza-B, parainfluenza 1 to 4, RSV-A, RSV-B, *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*.¹⁴

For multiplexNAT-2 (ePlex-RPP; GenMark Diagnostics, Carlsbad, CA), 200 μ L of 44 respiratory samples were mixed with an equal volume of 200 μ L ePlex sample buffer on a vortex for 10 seconds, and 350 μ L were transferred to the RPP cartridge followed by insertion into the ePlex System. The multiplexNAT-2 covers 23 targets consisting of adenovirus, coronavirus (229E, HKU1, NL63, and OC43), human bocavirus, human metapneumovirus, human rhinovirus/enterovirus,

influenza-A, influenza-A H1, influenza-A H1-2009, influenza-A H3, influenza-B, Middle East respiratory syndrome coronavirus, parainfluenza 1 to 4, RSV-A, RSV-B, *B. pertussis*, *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*. Recently, the ePlex-RPP has received conformit  europ enne (CE)-in vitro diagnostica (IVD) and FDA clearance.^{15,16}

In-house QNATs for influenza virus and RSV were performed as previously described.^{3,4,13,14} Briefly, after reverse transcription, influenza virus-A was identified by amplifying specific sequences of the matrix protein M1, whereas specific hemagglutinin sequences were targeted for identifying influenza virus-B. RSV-A and -B were detected by a duplex QNAT amplifying specific sequences of the nonstructural protein 1C. QNAT reactions were incubated at 50°C for 10 minutes and at 95°C for 5 minutes, followed by 45 cycles of 95°C for 30 seconds and 60°C for 1 minute. The reaction mix had a total volume of 25 μ L after adding 5 μ L extracted nucleic acids for one-step reverse transcription and amplification. All samples were tested in duplicates. An additional replicate was spiked with 1000 copies of the respective plasmid to detect amplification inhibition. The viral load of patient samples was determined by our in-house QNAT. For quantification, a plasmid that contains the corresponding region of the pathogen genome is used in triplicate at 1e6, 1e4, and 1e2 copies to generate a standard curve. External quality assurance programs testing different types at different dilutions of influenza and RSV are used for validation.

Statistical analyses were performed by Prism software (version 7.0, (GraphPad Software Inc., La Jolla, CA) or GraphPad software (GraphPad Software Inc., La Jolla, CA). Two-sided $P < 0.05$ were regarded as statistically significant.

3 | RESULTS

The eight external quality assurance samples correctly identified influenza virus-A ($n = 2$), influenza virus-B ($n = 1$), RSV-A ($n = 3$), and RSV-B ($n = 2$), all of which were concordant with the multiplexNAT-1 and the intended quality assurance result. The LIAT and the multiplexNAT results were directly entered into the laboratory information system for electronic documentation and validation. The detection limit of the LIAT was evaluated using twofold serial dilutions of patient samples containing influenza virus-A, -B, or RSV. For influenza virus-A, the LIAT detected a dilution corresponding to 5000 copies/mL, for influenza virus-B a dilution of 1250 copies/mL, and for RSV a dilution containing 2500 copies/mL.

The prospective study consisted of 194 respiratory samples consecutively submitted for routine testing of 194 patients presenting with influenza-like illness between November 2017 and January 2018 (Figure 1). The majority of patients was 16 years or younger (167; 86.1%) and approximately half of them were male (104; 53.1%). The median age of the patients was 1 year (25th percentile [Q1], 2 months; 75 th percentile [Q3], 7 years; range, 2 weeks to 87 years) (Table 1).

By LIAT, 86 of 194 (44.3%) samples were positive consisting of influenza virus-A in 18 (9.3%), influenza virus-B in 13 (6.7%), and RSV in 55 (28.4%) cases. One hundred fifty of 194 samples were analyzed

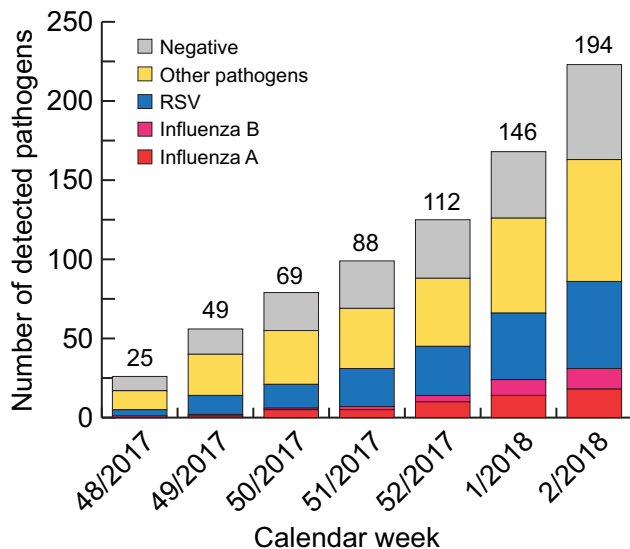


FIGURE 1 Respiratory pathogen detection in nasopharyngeal swabs of 194 patients by LIAT (influenza-A, -B, and RSV) and multiplexNAT (other pathogens). The columns show the cumulative number of pathogens detected from calendar week 48 in 2017 to week 2 in 2018. Above the columns, the cumulative number of tested samples is indicated. x-Axis: time period in weeks; y-axis: cumulative number of pathogens detected, including negative results. LIAT, Liat influenza-A/B and RSV real-time assay

by multiplexNAT-1 and the remaining 44 by multiplexNAT-2. The combined multiplexNAT assays identified 18 of 194 (9.3%) influenza virus-A, 12 of 194 (6.2%) influenza virus-B, and 52 of 194 RSV (26.8%) positive specimens (Table 2). RSV-A was identified in 29 (55.8%) cases, whereas RSV-B in 23 (44.2%) samples. Thus, concordant results were obtained in 190 cases; discordant results for four samples consisting of RSV detected in three cases and confirmed by QNAT with 6000, 30 800, and 34 600 copies/mL, respectively. The fourth discordant sample reported influenza virus-B by LIAT, but was negative in the influenza-specific QNAT.

Taken together, the LIAT showed a sensitivity and specificity for influenza virus-A of 100% and 100%, for influenza virus-B 100% and 99.5%, and for RSV 100% and 100%, respectively. The positive predictive value, negative predictive value, and κ values (interobserver agreement) were high for all three pathogens (Table 2).

The multiplexNAT detected 77 additional pathogens (Figure 1), which were present either alone in 43 cases, or as coinfections in 23 cases (Table 3). Single infections included adenovirus (3), human

TABLE 1 Demographic characteristics of patients

Characteristic	Number
Patients	194 (100%)
Male	104 (53.6%)
Children (≤ 16 y)	167 (86.1%)
Median (25th percentile; 75th percentile) age	1.0 (2 mo; 7.0 y)
Age range	2 wk-87 y

bocavirus (4), coronaviruses (5), human metapneumovirus (6), parainfluenza viruses (6), and rhinovirus/enterovirus (19).

The median age of patients with single infections was 1 year (25th percentiles [Q1], 2 months; 75th percentile [Q3], 3 years) and 38 (88.4%, $P = 0.804$) of the 43 cases were found in children. Among the patients with single infections, 29 individuals were male (median age, 1 year, 25th percentiles [Q1], 6 months; 75th percentile [Q3], 9 years) and thus a strong trend was seen for male gender but did not reach statistical significance, $P = 0.056$. This observation is solely based on the demographics, and would require dedicated clinical-diagnostic studies. However, it has been reported by others that children of male gender may be more susceptible for severe respiratory disease manifestations.¹⁷⁻²⁰

In 17 of 23 (73.9%) coinfections, RSV (13), and influenza virus-A (4) were found together with other pathogens, but influenza virus-B was not found in coinfections (Table 3). Median age of the patients with coinfections was 1 year (25th percentiles [Q1], 1 month; 75th percentile [Q3], 2 years) and 22 (95.7%, $P = 0.21$) of 23 coinfections were detected in pediatric patients. For both single and coinfections, median age of the patients was 1 year, but Q1 and Q3 were lower in coinfections.

4 | DISCUSSION

The results of the prospective evaluation of the LIAT during the winter season 2017/2018 (Figure 1) indicate excellent sensitivity and specificity for detection of influenza virus and RSV when compared to routine diagnostic multiplexNAT. The LIAT showed a sensitivity of 100% for all three pathogens. The specificity reached 100% for influenza virus-A, 99.5% for influenza virus-B, and 100% for RSV when compared with multiplexNAT and QNAT. Only four discordant results were encountered, which concerned RSV in three cases and influenza virus-B in one case among 194 samples (Table 2). For the influenza virus-B case, the sample was negative by multiplexNAT-1 and tested twice negative by in-house QNAT.¹³ Repeat testing by LIAT was not possible due to lack of sample material.

For the RSV cases, the LIAT scored three samples positive that tested negative by multiplexNAT (multiplexNAT-1: two samples, multiplexNAT-2: one sample). These discordant results were resolved by our in-house QNAT with viral loads of 6000, 30 800, and 34 600 copies/mL of VTM, respectively. This suggested a limited sensitivity of the multiplexNAT possibly due to multiplexing or target sequence issues.²¹ The detection of 6000 copies/mL of VTM by QNAT in one LIAT RSV-positive sample is in line with the results from our where 5000 copies/mL of VTM of RSV were detectable. The sensitivities for influenza virus-A (2500 copies/mL of VTM) and influenza virus-B (1250 copies/mL of VTM) were in a similar range, thereby permitting detection of acutely ill patients having typically much higher viral loads.^{4,13}

In previous studies, the LIAT was compared to other commercial NAT.^{6,7,22,23} The results of these studies suggest that LIAT has superior sensitivity compared to other POCT. However, the samples

TABLE 2 Performance of Cobas Liat real-time PCR assay

Pathogens	TP	FP	TN	FN	Total ^a	Sensitivity (95% CI) ^b	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	κ
Influenza-A	18	0	176	0	194	100 (81.5-100)	100 (97.9-100)	100 (81.5-100)	100 (97.9-100)	1.0
Influenza-B	12	1	181	0	194	100 (73.5-100)	99.5 (97.0-100)	92.3 (64.0-99.8)	100 (98.0-100)	0.96
RSV	55	0	139	0	194	100 (91.9-100)	100 (96.6-100)	100 (91.9-100)	100 (96.6-100)	1.0

Abbreviations: CI, confidence interval; FN, false negatives; FP, false positives; NPV, negative predictive value; PPV, positive predictive value; TN, true negatives; TP, true positives; κ , interobserver agreement.

^aAs reference method, 150 (77.3%) samples were tested by multiplexNAT-1 and 44 (22.7%) by multiplexNAT-2.

^bFor calculations, both multiplexNATs were combined.

were mostly obtained from adult patients, which is now complemented by our study, where the majority was symptomatic children (Table 1).

From week 52 in 2017 to week 2 in 2018, influenza virus-A and -B cocirculated among our predominately pediatric population (Figure 1), whereas mostly influenza virus-B dominated among adults during January and February 2018.²⁴ In Switzerland, influenza is a reportable disease and epidemiological evaluation is performed by the Sentinella surveillance network that is based on weekly notifications by physicians and the mandatory reporting of influenza subtypes by diagnostic laboratories.

The LIAT generated a valid result in 194 of 195 (99.5%) samples. In our laboratory, the LIAT was easy to handle including inexperienced personnel and features like barcode reading and direct transfer of the results into the laboratory information system saved time and eliminated error-prone manual procedures. A hands-on time of less than 5 minutes plus an assay time of 15 minutes resulted in a TAT of 20 minutes that can be reached even for personal with minimal training. Thus, the LIAT permits rapid responses including decisions regarding antiviral therapy for influenza as well as to cohort patients as part of infection control in institution settings including outpatient clinics, emergency rooms, and intensive care units.

TABLE 3 Characteristics of respiratory samples with more than one pathogen

Age (y/m+)	Sex	1. Pathogen	2. Pathogen	3./4. Pathogen
4	F	Influenza-A	Metapneumovirus	
1	M	Influenza-A	Metapneumovirus	
1	F	Influenza-A	Metapneumovirus	Coronavirus HKU1 rhinovirus/enterovirus
1+	M	Influenza-A	Metapneumovirus	
1	F	RSV-A	Coronavirus HKU1	Rhinovirus/enterovirus
1+	M	RSV-A	Coronavirus HKU1	Metapneumovirus
1+	F	RSV-A	Rhinovirus/enterovirus	
1+	F	RSV-A	Rhinovirus/enterovirus	
1+	M	RSV-A	Rhinovirus/enterovirus	
0.5+	M	RSV-A	Coronavirus NL63	Metapneumovirus
2	M	RSV-B	Metapneumovirus	
2	M	RSV-B	Rhinovirus/enterovirus	
1	F	RSV-B	Bocavirus	
1	F	RSV-B	Bocavirus	
1	F	RSV-B	Coronavirus HKU1	
7+	F	RSV-B	Adenovirus	
5+	F	RSV-B	Rhinovirus/enterovirus	
5	F	Adenovirus	Metapneumovirus	
40	M	Adenovirus	Rhinovirus/enterovirus	
1	F	Bocavirus	Metapneumovirus	
0.5+	F	Coronavirus OC43	Rhinovirus/enterovirus	
1	M	Metapneumovirus	Rhinovirus/enterovirus	
1+	M	Metapneumovirus	Rhinovirus/enterovirus	

Abbreviation: RSV, respiratory syncytial virus.

The following limitations should be noted. First, batch testing of patient samples is not possible and at the peak season of influenza and RSV, the sequential testing may result in the loss of the TAT advantage (3 samples per hour, 24 per 8 hours, 72 per 24 hours). However, it can be partly compensated for by direct and parallel testing on more than one LIAT instrument. Second, LIAT lacks the identification of influenza virus-A subtypes. Detection of influenza virus-A subtypes may influence isolation procedures in hospital settings. In addition, in immunocompromised patients may be at risk for dual infections, which is rare and usually one pathogen is dominant. In such cases, subsequent multiplexNAT or QNAT provide semiquantitative results that are helpful to identify the main driver of the infection. Because the LIAT is easy to handle, the testing system may be attractive for being used by personnel not trained as professional laboratory analysts. However, in our practice, a qualification program with corresponding documentation and requalification every 1 or 2 years need to be performed in accordance with laboratory regulations, and not only when failing internal and external quality assurance programs.

In conclusion, the LIAT can reduce the TAT compared to conventional multiplexNAT or QNAT. In this study, the sensitivity of the LIAT seemed to be equivalent or slightly increased over current multiplexNAT and comparable to specific QNAT. The specificity was similar to the multiplexNAT. Thus, LIAT seems useful for rapid testing and management decisions regarding infection control and therapy, and could be followed by QNAT to document viral replication and clearance if needed, and/or by multiplexNAT to detect other respiratory pathogens.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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