Emerging requirements for infectious disease IVD quality control material

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Objectives

To assess the use of liquid-stable, qualitative External Quality Assessment (EQA) samples containing native, inactivated Influenza A, Influenza B, and Human Respiratory Syncytial Virus (RSV) in respiratory infectious disease diagnostics, for both immunodiagnostic and Nucleic Acid Amplification Test (NAAT) methods, representing widely-used Point-of-Care Tests (POCT) in the market.

Materials and Methods

The Respiratory EQA samples used in the study comprise both preserved nucleic acids and antigenic properties, and have a design stability of at least 75 weeks from the date of manufacturing under storage conditions of 2-8°C. They were manufactured by quantification, stabilization, inactivation, and dilution of native viral preparations in Microbix' proprietary liquid Universal Transport Medium (UTM). The samples were supplied to the American Proficiency Institute (API, collaborating with LGC in Europe) and used as blinded positive samples for immunodiagnostic and NAAT-based tests, as part of the Respiratory EQA evaluation panel of clinical laboratory performance in the USA. The samples were used to monitor the whole process of extraction, separation and detection and were distributed to the participants in three separate EQA events per year.

The following products from the EQA Respiratory panel were included in the analysis:

Product Name	Catalogue	Viral strain	Volume/Format
Influenza A Positive Sample	PT-13-01	Influenza A/New Caledonia/20/99	1 mL Liquid sample in proprietary UTM
Influenza B Positive Sample	PT-14-01	Influenza B/Hong Kong/5/72	
RSV Positive Sample	PT-07-01	Human respiratory syncytial virus, Long strain	

Table 1: Respiratory panel positive samples – product characteristics

All the participants in the EQA program were asked to process the EQA samples (part of the Respiratory panel) as per patient sample handling guidance described in the Original Equipment Manufacturers' (OEMs) Instructions for Use for both NAAT and Immunodiagnostic methods.

Results

The results from the 2-year (2015-2016) EQA sample performance follow-up are shown in Tables 2 and 3 below.

Respiratory panel 2015	Samples tested	Immuno-diagnostic tests	Nucleic Acid tests (NAAT)	Specificity per method	
				Immuno-diagnostic	NAAT
PT-07-01 - RSV Positive	6067	6035	32	98.66%	100.00%
PT-13-01 - Influenza A Positive	3803	3562	241	98.68%	99.55%
PT-14-01 - Influenza B Positive	1957	1840	117	97.28%	100.00%
Totals	**11827**	**11437**	**390**		

Table 2: EQA positive samples – data summary for 2015

Respiratory panel 2016	Samples tested	Immuno-diagnostic tests	Nucleic Acid tests (NAAT)	Specificity per method	
				Immuno-diagnostic	NAAT
PT-07-01 - RSV Positive	5964	5838	126	98.81%	100.00%
PT-13-01 - Influenza A Positive	2027	1799	228	98.94%	99.56%
PT-14-01 - Influenza B Positive	4546	4216	330	97.16%	100.00%
Totals	**12537**	**11853**	**684**		

Table 3: EQA positive samples – data summary for 2016

Since the detection methods used for the EQA Respiratory panel are qualitative, all the testing results were reported as either "Positive", "Negative" or "Invalid". All the "Invalid" results from the study were combined with the "Negative" and used in the samples specificity calculations. "Specificity per method" defined in Tables 2 and 3 was calculated based on the percentage of the samples reported correctly as a proportion of total samples analyzed per sample type.

The temporal assessment of performance data, in this case the comparison of results from 2015 and 2016 (Tables 2 and 3) is critical aspect of EQA sample performance evaluation in an environment where testing methods and platforms are changing over time. The methods in use during the study period are described in Tables 4 and 6. The number and type of methods in use has continued to grow, as shown in Tables 5 and 7, where additional methods for the detection of influenza A and B, and RSV are shown for the period 2017-2018. Both the detection limits and the detection technologies used in the variety of immunodiagnostic and NAAT Point-of-care Test (POCT) methods may vary widely and longitudinally. Over the time of the present study, the increase in the use of NAAT in the field is apparent and is a trend that is expected to continue. The performance of the EQA samples per category (immunodiagnostic or NAAT) was virtually unchanged over time. However, the increasing use of NAAT is expected to result in improvements in the specificity EQA scores over time due to the higher specificity of the NAAT methods.

OEM	Test	Method	Platform	RSV
Cepheid	GeneXpert Flu/RSV XC	NAAT	RT-PCR	++++
Abbott Alere	Binax NOW	ImmunoDx POCT	Immuno LFD	++
	Clearview RSV			++
BD	Directigen EZ RSV			++
	Veritor System RSV			++
meridian BIOSCIENCE	Tru RSV			++
Fisher HealthCare	Sure-Vue			++
QUIDEL	QuickVue			++
	Sofia			++
remel	Xpect RSV			++

Table 4. EQA RSV test methods for 2015-2016

OEM	Test	Method	Platform	RSV
Cepheid	GenXpert Xpress Flu/RSV	NAAT	RT-PCR	++++
Roche	cobas LIAT Flu A&B/RSV	NAAT POCT		
QUIDEL	Solana RSV + hMPV		RT-HDA	++++
Abbott Alere	Alere i		RT-NEAR	++++
				++++

Table 5. Additional EQA RSV test methods for 2017-2018

OEM	Test	Method	Platform	Influenza A&B
Cepheid	GeneXpert Flu/RSV XC	NAAT	RT-PCR	++++
Roche	cobas LIAT Flu A&B/RSV	NAAT POCT		++++
Abbott Alere	Alere i		RT-NEAR	++++
	Binax NOW	ImmunoDx POCT	Immuno LFD	++
BD	Directigen EZ Flu A+B			++
	Veritor System RSV			++
meridian BIOSCIENCE	Tru Flu			++
HENRY SCHEIN	OneStep+ Flu A&B			++
OraSure Technologies	Advantage Flu A & B			++
QUIDEL	QuickVue			++
	Sofia			++
remel	Xpect Flu A&B			++
SEKISUI	OSOM Flu A&B			++

Table 6. EQA Influenza A&B test methods for 2015-2016

OEM	Test	Method	Platform	Influenza A&B
Cepheid	GenXpert Xpress Flu/RSV	NAAT	RT-PCR	++++
QUIDEL	Solana Flu A&B	NAAT POCT	RT-HDA	++++
SEKISUI	OSOM Flu A&B Ultra	ImmunoDx POCT	Immuno LFD	++
McKESSON	Consult Flu A&B			++
CardinalHealth	LifeSign Status Flu A & B			++
	Flu A&B			++

Table 7. Additional EQA Influenza A&B test methods for 2017-2018

LEGEND:
++ = Low to medium positive signal
++++ = Strong positive signal

Conclusions

The IVD market is fragmented across test methodologies therefore it is apparent that there is an emerging need for intact whole organism controls that are broadly compatible - not only across the platforms of multiple IVD manufacturers (OEMs), but also across technologies, including immunoassay and NAAT.

Intact pathogens inactivated by physical methods and stabilized in a proprietary UTM at optimized concentrations were successfully used as EQA samples in cross-platform and cross-method qualitative detection of the Influenza A, Influenza B and RSV. The "specificity per method" varies in the range of 97.1%-98.94% for immunodiagnostic methods and from 99.55% to 100% for NAAT, showing acceptable performance of the product design and formulation.

We feel strongly that the future of controls lies in such broad QC cross-compatibility spanning platforms and technologies.

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