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Review

CLIA-waived molecular influenza testing in the emergency department and outpatient settings

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ABSTRACT

Respiratory tract infections are a common cause of visits to emergency departments and outpatient settings. Infections with influenza viruses A and B in particular, are responsible for significant morbidity and mortality in both pediatric and adult populations worldwide. A significant number of influenza diagnoses occur in the emergency departments with many being performed using rapid influenza diagnostic tests (RIDT) which have sensitivities as low as 30% depending on the specific RIDT and patient population. More recently, rapid molecular tests for the detection of influenza viruses A and B have become commercially available as point-of-care platforms. In the United States, several of these new tests are approved by the Food and Drug Administration as CLIA-waived tests. In this report, we review the data on the analytical and clinical performance of RIDTs and CLIA-waived molecular tests, present and discuss potential key challenges and opportunities for implementation of CLIA-waived molecular tests at or near point of care in the emergency departments and outpatient settings.

1. Introduction

Infections with influenza viruses A and B cause seasonal epidemics of respiratory illness and are responsible for significant morbidity and mortality in both pediatric and adult populations worldwide. Unfortunately, diagnosis of influenza infection can be challenging based solely on clinical signs and symptoms. Point-of-care tests (POCTs) for detection of influenza virus in the outpatient or emergency department settings make it possible to promptly establish the etiology of infection and potentially impact medical decision making. Rapid influenza testing performed in the emergency department for febrile infants and young children has been shown to decrease additional testing (e.g. complete blood count, blood culture, chest x-ray), the total length of time spent in the emergency department, and total medical charges [1–4]. Health care providers in outpatient facilities such as community health centers and physician offices rely heavily on results of rapid influenza testing performed at the point of care for determining whether a patient receives antiviral medications [5,6]. However, clinicians also consider treatment as early as possible for patients with severe, complicated or progressive illness or for those at higher risk of complications due to influenza infection regardless of rapid test results, particularly for tests with suboptimal sensitivity [7]. Studies have noted the effect of rapid influenza testing in reducing the unnecessary use of anti-bacterial among children and adults. Fewer antibiotics were prescribed when the diagnosis of influenza in emergency departments (ED) and physician offices was made with a rapid influenza test [2,5,8,9].

Influenza virus POCTs should afford rapid results and have a high degree of sensitivity and specificity compared to more complex traditional testing performed in a laboratory setting. With reliable POCT results in hand, providers can make patient management decisions that improve outcomes for the patient or hospital. In some instances, the impact may also be a more cost-effective solution compared to laboratory-based testing. Influenza POCTs should be simple to perform and interpret by non-laboratory personnel using uncomplicated instrumentation, contain internal controls to ensure validity of results, have temperature-stable components that allow easy and prolonged storage, reduce the risk of pre-analytical errors such as handling, transporting and labeling of specimens, and be relatively inexpensive.

1.1. Rapid influenza diagnostic tests (RIDTs)

RIDTs, detecting influenza A and/or B antigens, have been used extensively for many years in settings at or near the point of care including physicians' offices, urgent care centers, and small laboratories

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Table 1
Comparison of Class I vs Class II Medical Devices.

Risk to patient	Class I low	Class II moderate
Controls	General Controls Examples: registration and listing, notifications of risks repair, replacement adverse event reporting	General and Special Controls Examples: performance standards, postmarket surveillance, guidelines
Approval Process	generally, exempt from FDA 510(k)	most require 510(k) FDA submission, must demonstrate substantial equivalence
Manufacturing	subject to good manufacturing process (GMP) but generally exempt from design controls	subject to GMP including design controls

where more complex viral diagnostic capabilities may not be available. During periods of higher prevalence, positive results by these rapid methods correlate well with actual influenza virus infection. However, many antigen-based RIDTs have suffered from poor performance in terms of analytical and clinical sensitivity and low negative predictive values compared to molecular detection methods with pooled sensitivity calculated to be 62.3% and pooled specificity of 98.2% [10]. Because of these limitations, several organizations and professional societies have cautioned clinicians about the utility of RIDTs for certain patient populations and how results should be interpreted. The U.S. Centers for Disease Control and Prevention (CDC) has recommended that follow-up testing of negative RIDT results be performed with a more sensitive and specific method such as reverse-transcriptase polymerase chain reaction (RT-PCR) since RIDTs may not reliably exclude influenza infection and misdiagnosis can have potentially serious consequences [11–13]. Because of these ongoing concerns, the U.S. Food and Drug Administration (FDA) has recently up-classified RIDTs from class I (low risk) to class II (moderate risk) devices subject to special controls and performance standards (Table 1). The intent of the reclassification was to assure the reliability and accuracy of the tests, reduce the likelihood of false negative results, aid clinicians in making appropriate treatment decisions, and enable effective infection control and public health response during influenza outbreaks [14]. As of February 2018, six RIDTs have demonstrated acceptable clinical performance and are available for use in primary care (Table 2).

1.2. CLIA-waived molecular testing for influenza virus

In the U.S., with the implementation of the Clinical Improvement Amendments of 1988 (CLIA), performance standards for laboratory testing are regulated by the Centers for Medicare and Medicaid Services. The classification of laboratory tests is determined by complexity (waived, moderate, and high). Those tests that are considered CLIA-waived must use direct, unprocessed specimens and be easy to perform with negligible chance of error. CLIA-waived tests can be performed by individuals without formal laboratory training and outside traditional laboratories at the point-of-care. In 2015, the first CLIA-waived molecular test for detection of influenza virus was cleared by the FDA. Since then, four additional molecular test systems have received a waiver for detection of influenza virus in respiratory specimens (Table 3). The currently available CLIA-waived molecular Flu tests employ several different methodologies and some also allow for simultaneous detection of RSV or other respiratory pathogens from the same sample [15]. The performance characteristics of several of these tests have been assessed at POC sites as well as within central laboratories. The specificities of the assays for detection of influenza A and B viruses are greater than 97%. Among assays with published results using clinical samples, the range of sensitivities from selected publications for detection of influenza A and B viruses are shown in Table 4. At the time of this writing, there were no published studies for the CLIA-waived FilmArray respiratory panel EZ, the Alere version 2 or the Accula FluA/FluB assays.

To date, few studies have examined outcomes using molecular testing at the point of care, but the trends appear to show that diagnosis of influenza infection by POCT results in significantly higher rates of antiviral prescription and significantly shorter length of stay in the ED [16].

2. Challenges and considerations for implementation of CLIA-Waived molecular testing

A recent report from the Agency for Healthcare Research and Quality (AHRQ) shows that the number of ED visits increased by 14.8% between 2006 and 2014 with an increase of greater than 250% for influenza diagnosis in the ED [17]. Other settings besides the EDs where patients present for POCTs for influenza include outpatient and walk-in clinics, physicians' offices and more recently community pharmacies [14,18,19]. Until recently, POCTs for influenza was done almost exclusively using antigen-based RIDTs, which require minimal infrastructure, have workflows like other non-infectious disease POC tests (e.g. pregnancy or glucose tests) and are performed by non-laboratory staff. While implementation of POCTs has its own challenges, implementing CLIA-waived molecular Flu tests testing may bring a new set of challenges. The following section describes some of the known challenges with POC testing and other considerations in deciding to implement CLIA-waived molecular Flu test in the ED or outpatient settings.

2.1. Challenge 1: Clinicians' workflow

In the ED and other outpatient settings, the decision to test implies that the result is necessary to determine the need for admission, further

Table 2
Class II Rapid Influenza Diagnostic Tests.

Test Name	Instrument	Specimen	Turn-around time
Alere Influenza A/B	None	NS	10 min
Binax Now Influenza A/B card 2	Alere Reader	NS	15 min
BD Veritor FluA + B	BD Veritor Reader BD Veritor Reader +	NPS, NS	10 min
Sofia Influenza A + B Sofia Influenza A + B 2	Sofia Analyzer Sofia Analyzer 2	NS, NPS, NPA, NPW (VTM), NPW (D)	15 min
QuickVue Influenza A + B	None	NPS, NS, NA, NW	10 min

NS: Nasal swab; NPS: Nasopharyngeal swab; NPW: Nasopharyngeal washings; NPA: Nasopharyngeal aspirate NW: Nasal washings; NA: Nasal Aspirate; VTM: Viral transport media; D: Direct specimen.
https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm. Accessed December 10th, 2018.

Table 3
CLIA-waived molecular tests.

Test name	Sample type	Turn-around time (minutes)	Date cleared
Alere I Influenza A/B	NPS, NPS in VTM	< 15	1/2015
Alere I Influenza A/B v2	NS, NS or NPS in VTM	< 15	09/2017
Xpert Xpress Flu	NPS, NS	< 30	12/2017
Xpert Xpress Flu + RSV	NPS	< 30	07/2018
Cobas Liat Influenza A/B	NPS	< 20	09/2015
Cobas Liat Influenza A/B, RSV	NPS	< 20	08/2016
FilmArray Respiratory Pane EZ	NPS	< 60	10/2016
Accula Flu A/Flu B	NS	< 30	02/2018

NS: Nasal swab; NPS: Nasopharyngeal swab; VTM: Viral transport media.
https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm. Accessed December 10th, 2018.

Table 4
Sensitivities of CLIA-waived molecular tests for detection of influenza A and B viruses.

Platform	Flu A sensitivity (%)	Flu B sensitivity (%)	References*
Alere i	63.8–99.3	81.5–100	[27,28,29,30,31]
cobas Liat	99.2–100	97.9–100	[31,32,33,34]
Xpert Xpress	98.6–100	96.3–97.9	[29,32,35]

* Not an exhaustive list. Selected to represent the published reported ranges of sensitivity and specificity.

monitoring or release of the patient with specific recommendations for treatment or a follow-up visit. When the results of the rapid POC test affects a critical decision point in the evaluation workflow, the benefits are clear; but if the results of the POC test require additional, non POC tests results for complete evaluation of the patient, then the impact may be reduced [20]. For influenza, test results will primarily inform two decisions: 1) to administer antiviral therapy (e.g. oseltamivir; baloxavir), which currently must be administered within 48 h of symptoms-onset for maximum benefit, and 2) if patient will be admitted, a decision to implement droplet precautions. In considering decision 1, a rapid, accurate CLIA-waived molecular Flu test is ideal given that the outcome of a positive result facilitates initiation of appropriate therapy, while a negative result may reassure the patient and clinician to exclude influenza from the differential diagnosis. For decision 2, while a positive result may guide the decision of implementing droplet precautions on admission, a negative result may require additional testing to rule out other transmissible viral infections and the use of a CLIA-waived molecular Flu test may have limited utility. This is particularly relevant for institutions with a high number of immunocompromised patients where droplet precautions are instituted for all respiratory viruses [21].

2.2. Challenge 2: testing location

In deciding where POC or CLIA-waived testing should be performed, a few issues should be considered including the space or infrastructure needed for testing and the test turn-around time (TAT) to results. Adopting a test with a TAT of 20 min when transport to a laboratory may take twice as long, diminishes the impact on patient care. Many EDs suffer from overcrowding, and dedicating space for testing may be a significant challenge [22]. Other testing location options include testing at the bedside, particularly for small footprint analyzers or testing at a satellite laboratory within reasonable distance to the point of care. While CLIA-waived molecular Flu tests may not require the use of a biosafety cabinet or a dead air box to prevent amplicons contamination, this issue should be considered when selecting a location to implement POC molecular influenza tests.

2.3. Challenge 3: Testing personnel

In the US, POC testing is often CLIA-waived, which means testing may be performed by trained, non-laboratory staff. Molecular testing has traditionally required highly skilled medical technologists and an infrastructure with unidirectional workflow to reduce the risk of false positive results due to contamination by nucleic acid amplicons [23]. In recent years, with the availability of sample-to-result platforms, performance of molecular testing does not always necessitate specialized skills or infrastructure. Rapid, CLIA-waived molecular Flu tests are among the first nucleic acid- based tests available as POCTs. While these tests are simple to perform and closed-systems, the risk of environmental (staff or other samples) or amplicon contamination (e.g. from a broken pouch/cartridge) is minimal but not non-existent. In deciding who performs these tests, the following questions can be considered: 1) Would this task add yet another challenge on the time-constrained ED staff or pharmacists who would need to acquire and maintain additional skills? 2) Will contamination of the environment with amplicons be a risk, and if so how and who will monitor this issue? 3) Who will be responsible for the training, competency and quality management of the testing? 4) Will the test interface with a laboratory information system (LIS) and if so, who and how will it this be implemented and monitored? 5) Will additional testing and correlation with other laboratory tests be necessary, and if so how will discrepancies be resolved?

2.4. Challenge 4: Economic consideration

RIDTs have the distinct advantage of being relatively inexpensive compared to molecular POC Influenza tests, which are on average significantly more expensive. In addition to the cost of the test, following questions should also be considered when implementing a CLIA-waived molecular Flu test: 1) Could testing be performed within the existing infrastructure, lab ED, a satellite lab, centralized lab or within the pharmacy space? 2) How many platforms will be needed to maintain an adequate throughput? In many cases, the throughput of current platforms is low, usually one test at the time. This adds complexity if several platforms need to be implemented and if additional analytes (e.g. Group A *Streptococcus*) will also be tested. 3) Would connectivity with POC middleware be possible and what would the cost of establishing and maintaining this connection be? 4) Is the patient volume of the POC site justify the added cost? 5) Would inadequate or limited reimbursement and coverage from payers make the test not cost-effective? 6) Will implementation of the tests inform meaningful decisions regarding patient management such as appropriate use of antivirals or antibiotics, ancillary testing reduction, shortened time in the ED and implementation of appropriate infection control measures?

While not unsurmountable, a review and discussion of the challenges described here should help in determining the most appropriate set-up for testing.

3. Regulatory considerations

3.1. Regulation of molecular rapid influenza tests in the United States

An increased number of FDA cleared influenza tests are being classified as CLIA-waived. Manufacturers seek this classification as it facilitates access to a broader market, and for patients and providers more access to the tests near their point of care. The result is that influenza tests are performed in settings that may not have the foundational benefit of a clinical-laboratory-focused quality management system. CLIA-waived tests are described in section 353(d)(3) of the Public Health Service Act, as "simple laboratory examinations and procedures which, as determined by the Secretary, have an insignificant risk of an erroneous result, including those which— (A) have been approved by the Food and Drug Administration for home use, (B) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results (C) the Secretary has determined pose no reasonable risk of harm to the patient if, performed incorrectly." [24]. CLIA waived tests are not subject to the CLIA regulations for quality control, verification and validation, proficiency testing and personnel standards [24]. Accrediting agencies, including the College of American Pathologists (CAP) and The Joint Commission (TJC) recognize the waived classification, but may require additional controls for the labs they accredit.

Outpatient locations employing waived molecular flu tests under their institution's clinical laboratory CLIA certificate have the advantage of being part of that laboratory's quality management system. Though not required for a waived test, this will often include the deployment of a test system that has undergone method verification, specific training for operators, competency assessments, monitoring of personnel, controls, proficiency testing, and access to knowledgeable liaisons in the clinical laboratory. The clinical laboratory would most likely direct the multi-departmental coordination necessary for the selection, implementation, monitoring, and maintenance of the most appropriate test for the patient population served. This is valuable in assuring the quality and utility of the test results. However, not all outpatient locations performing CLIA waived testing are part of a health system's clinical laboratory's certification. Stand-alone ED's, independent walk-in and urgent care clinics, physicians' and group practice laboratories, and pharmacies could have their own CLIA certificates. If these sites are only performing waived tests, they will register as CLIA waived laboratories. Under federal law, these laboratories and sites are not subject to the CLIA regulations for quality management, PT, and personnel as stated above, though individual states may impose further requirements or restrictions. Under CLIA, their requirements are to: appoint a person who is responsible for the testing, follow manufactures' instructions for testing and, allow random inspections by the Centers for Medicare & Medicaid Services (CMS). However, individual states may impose additional requirements for oversight of POC or CLIA-waived testing. Of the 261,756 CLIA registered laboratories, approximately 71% hold a certificate of waiver (CoW) [25]. In 2002 CMS inspected 2% of CoW laboratories and had planned to continue this practice as several quality issues were found. The project was cancelled in 2016 [26].

Monitoring the regulatory landscape for POC tests is particularly important for waived and non-waived labs. The US FDA can change the categorization of a waived test if there is evidence that the results or the performance of test pose a new or greater risk to patients than originally determined. Therefore, the individual named responsible for the oversight of the tests, must always know and understand the status of their categorization.

3.2. European and global regulation of molecular rapid influenza tests

Simple, rapid, molecular testing for infectious diseases are commonly employed outside of the United States where FDA test categorizations have no regulatory impact. Several countries (Australia, Brazil, Canada, China, Japan, Russia, Singapore, South Korea, the United States, FDA) and several organizations [World Health Organization (WHO), the Asian Harmonization Working Party (AHWP), Pan American Health Organization (PAHO)] have formed the International Medical Device Regulators Forum to work towards international medical device regulatory harmonization (http://www.imdrf.org/index.asp).

The CE-IVD mark is the standard in Europe and is acceptable to some countries outside of the European Union. The WHO has an IVD pre-qualification process for their priority diseases and their use in resource limited countries (https://www.who.int/diagnostics_laboratory/evaluations/en/). However, most countries have their own regulatory agencies and processes for IVD approval.

Globally, laboratories, hospitals, and health systems are governed by their own national or regional regulations, often - as in the US, by separate entities than those regulating the IVDs. Depending on those regulations, laboratories may have to be accredited/ licensed by their specific national organizations, or if adopted by their country, accredited to ISO 15189:2012 – *Medical laboratories- requirements for quality and competence* and / or ISO 22870:2006 — *Point of care testing (POCT) – Requirements for quality and competence-* which is used in conjunction with ISO 15189. Because of the global recognition of the ISO standards, some laboratories choose ISO accreditation, even when it is not required. Those laboratories certified to ISO15189 or ISO22870 must choose and implement all their tests based on the clinical and technical specifications required for their service. POC tests are not an exception. Laboratories must assure the continued control and validity of the pre-examination, examination and post- examination processes they implement, through a rigorous laboratory quality management system that includes selection, validation, quality control and external assessment, quality assurance, personnel monitoring, and corrective action implementation. Similar to the United States, those outpatient locations that manage their POC testing within their health system's clinical laboratory ISO certification will have the benefit of being under a controlled quality laboratory management system.

4. Models for implementation of POC molecular influenza testing

Taking into consideration the analytical performance of the CLIA-waived molecular Flu test, the challenges described in previous sections, the regulatory landscape and the overall potential impact on patient care, several models can be used to implement POC molecular influenza testing in the ED or other outpatient settings.

4.1. Testing at an onsite point-of-Care (STAT) laboratory

This set-up, which minimizes pre-analytical transport time and shortens the time to results, is one that includes a POC laboratory inside of the ED, the physician office or pharmacy with testing performed by medical technologists and laboratory activity under the supervision of the laboratory director. This set-up is more likely to be found in large academic centers EDs with a high volume of patients.

4.2. Testing at a nearby core laboratory

In a space or staff-constrained environment, performing tests in a core laboratory or satellite laboratory close to the ED or outpatient clinic may still provide adequate time to results to positively impact clinical decisions. Even with a core laboratory further away from the outpatient location, benefits would still be possible, especially if the laboratory is staffed 24 h/7 days per week. This set-up can benefit both large academic centers or community hospitals with a high volume of patients presenting at outpatient locations.

4.3. Testing at a clinical Virology/Microbiology laboratory

While transport time may decrease the benefit of rapid, CLIA-waived molecular tests performed in a hospital laboratory, implementation in this setting would be the simplest and least disruptive approach to ED or outpatient clinics' workflow and would still offer the advantage of a rapid turn-around time to results when compared to more extensive testing that may require hours to perform. Additionally, testing will continue to be performed by skilled laboratorians who would be performing similar testing throughout the year and thus, less emphasis would need to be placed on maintaining competency between the start or end of influenza testing.

5. Conclusions

The diagnosis of influenza has entered a new era with the availability of CLIA-waived molecular Flu test. Rapid molecular tests have the potential to significantly improve the care and experience of patients presenting to the emergency departments or outpatient clinics by providing rapid and accurate results without the need for additional testing. In this report, we provided background information and discussed issues for laboratorians and other healthcare professional to consider when planning implementation of these new tests in their facilities.

Disclosures/Disclaimers

This Report is a product of the PASCV Clinical Practice Committee (CPC) developed to provide guidance and recommendations to healthcare professionals considering implementation of CLIA-waived molecular tests. It is not clinical advice and does not represent all possible approaches to implementation. Members of the 2018–2020 PASCV CPC included N. Esther Babady (Chair), James J. Dunn, and Roberta Madej.

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N. Esther Babady: Conceptualization, Supervision, Writing - original draft, Writing - review & editing. **James J. Dunn:** Writing - original draft, Writing - review & editing. **Roberta Madej:** Writing - original draft, Writing - review & editing.

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