

# Communication Points For Public Health Laboratories Regarding CLIA-Waived Influenza Diagnostic Tests

**This document is intended for internal public health laboratory (PHL) use; PHLs should modify these points as appropriate for specific partners and concerns within their jurisdiction.**

Rapid influenza diagnostic tests (RIDTs) that are categorized as CLIA-waived are widely used in the clinical sector. Laboratories performing CLIA-waived tests are not subject to stringent CLIA quality standards including routine inspections, quality control beyond measures outlined in the package insert, proficiency testing and personnel requirements.<sup>1</sup> The limitations and necessary considerations for appropriate use and interpretation of RIDTs, have been well documented; however, concerns remain regarding their use in the field. (Note: A subset of RIDTs intended for the qualitative detection of influenza viral antigens have recently been re-named as “influenza virus antigen detection (IVAD) test systems” by the US Food and Drug Administration (FDA)). Furthermore, increasing availability of molecular CLIA-waived tests (also included among RIDTs) requires additional considerations that waived or moderate complexity laboratories may not be accustomed to.

To assist public health laboratories (PHLs) in communicating with clinical partners that may utilize these tests, the APHL Influenza Subcommittee has developed the following discussion points. Please note that new assays continue to be approved, so it is important to keep apprised of the methods being used, particularly in laboratories submitting data or specimens to their respective public health departments.

## What tests are we talking about?

- Traditional or first generation visual-read IVAD test systems (e.g., Binax NOW, QuickVue, XPECT)
- Newer generation waived instrument-read IVAD test systems (e.g., Quidel Sofia and BD Veritor)
- Waived molecular tests (e.g., Alere i and Cobas LIAT)

An updated list of these tests can be found at [http://www.cdc.gov/flu/professionals/diagnosis/clinician\\_guidance\\_ridt.htm](http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm).

Please note that assays mentioned above are strictly examples and the discussion points included in this document are not directed towards any particular manufacturer.

## Why should PHLs care about these tests and how clinical partners are using them?

- Variability in performance across tests and impact on patient care

Both false negative and false positive test results occur with any of these assays which can negatively impact patient care. In particular, past performance assessments with IVADs often indicated unacceptably low sensitivity with the older visual-read assays as was apparent during the 2009 pdmH1N1 pandemic. These performance issues have been exhaustively documented in the literature.<sup>2,3</sup> While in general the performance of the instrument-read IVADs and waived molecular tests seems improved, laboratories using these assays must be aware that simplified procedures and instruments do not necessarily guarantee high level performance.

Note: An updated list of publications describing performance characteristics of the various visual- and instrument-read IVADs and waived molecular tests can easily be accessed using PubMed or similar database.

- Potential for biosafety and contamination issues

Since both IVADs and waived molecular tests are likely to be performed outside of the traditional laboratory setting and without use of biosafety cabinets, users need to be cognizant of potential biosafety risks posed to themselves, other nearby personnel and/or others (e.g., patients, family) during the entire testing process (both pre-analytic and analytic). Furthermore, while the risk of amplicon contamination with the “closed system” waived molecular test is likely less than that encountered in complex molecular laboratories, the risk exists nonetheless and creates the potential for false positive results. It is important that the manufacturer’s guidance is followed carefully to minimize amplicon contamination risk.

- Impact on public health surveillance

Tests results and data generated using IVADs are of potential value for virologic surveillance. However, results may not be reported to public health or, if reported, validated. The limitations (briefly described above) of these tests must be kept in mind when assessing the accuracy of the data and when basing public health action on these data. Performance of specific tests against novel or drifted viruses also needs to be considered so these cases are not missed—public health laboratories may want to test a subset of negative specimens from submitters using these assays.

## What are some of the specific concerns or considerations to be aware of?

It is important to fully understand the performance characteristics, performance monitoring and results interpretation for these assays. Also, keep in mind that they can vary across manufacturers, between visual- and instrument-read IVADs and between IVADs and waived molecular tests. Broad potential issues include lack of understanding of basic quality assurance (QA) measures needed to assure test result accuracy, lack of proficiency testing and potential lack of technical or scientific expertise in the event of obviously altered performance.

Users of any of these tests should consider and have a plan to address the following questions:

- How will the assay’s performance characteristics (as they pertain to specific laboratory operation) be assessed? What are the plans and mechanisms for ongoing performance verification and quality control (QC) measure monitoring? Do the plans address requirements outlined in the manufacturer’s instructions?
- What patient groups will be serviced and are the performance characteristics of the chosen assay appropriate for these groups (e.g., outpatient vs inpatient)? What is the impact of a false negative or false positive result on this patient group? Has staff been trained on results interpretation and the impact of different specimen types, stage of illness, patient age and disease prevalence? Have hospital laboratories considered providing a written disclaimer on these reports to alert providers on the limitations of these assays?
- Does staff have access to a technical adviser and know when to reach out to them if needed? Does staff have access to a diagnostic molecular biologist when using a waived molecular test?
- What is the staff’s education background and experience with diagnostic testing? Have they been trained on the proper use and maintenance of any instrumentation?

- When using a waived molecular test, has staff been trained on the differences between molecular assays and IVADs, including the risk for environmental contamination if cartridges are not handled properly and amplified genetic material is released? Do they know how to monitor the performance characteristics and track positivity rates for an artificial spike due to possible contamination?
- For laboratories using a waived molecular test, are appropriate disposal procedures documented and displayed for used cartridges to minimize the risk of environmental contamination with amplified material?
  - ◆ Is there a written plan for environmental monitoring for amplicon contamination in the event of a major increase in positivity rate?
  - ◆ Are there written procedures and are staff trained for routine decontamination of testing area and major decontamination in the event of environmental contamination with amplicon?
- Where is the testing located in the laboratory or testing site? Are biological safety cabinets or other protective devices (shields, etc.) available to safely perform testing, limit cross-contamination and minimize exposure to other personnel including patients?
- Are there written procedures for staff to monitor storage temperatures of reagents?

## Other issues PHLs should consider:

- **What is the state of FDA regulations concerning these tests?**
  - ◆ The FDA recently published a final order that reclassifies IVADs from low risk Class I medical devices to Class II devices. As Class I devices, manufacturers only have to adhere to general controls and do not have to submit 510(k) applications. The reclassification requires a 510(k) submission as well as special controls such as evaluating the performance of the assay on an annual basis against currently circulating strains of influenza and rapid evaluation of assays against newly emerging variant or novel viruses. View the [Federal Register posting](#) for more information including effective dates.
  - ◆ We are currently not aware of any pending FDA actions that specifically deal with waived molecular influenza tests.
  - ◆ The APHL Influenza Subcommittee will continue to monitor this and provide updates when available.
- **How do we identify the users in our state and what are the advantages in doing so?**
  - ◆ It may be advantageous for PHLs to identify the users of RIDTs in their states for a number of reasons, including but not limited to: (i) identifying alternative sources of testing data and specimens to enhance or supplement virologic surveillance; (ii) helping users improve their test performance and results interpretation; and/or (iii) providing to the users updated performance information or notice of FDA actions related to these tests.
  - ◆ Users of these tests can be identified by some combination of communication with clinical laboratories and recognized clinicians within existing surveillance and response networks. Additionally, many test manufacturers may be willing to share information about their clients if they understand the public health reason for doing so.
  - ◆ Members of the APHL Influenza Subcommittee have been engaged with staff from CDC's Division of Laboratory Systems to pilot a process for identifying rapid influenza testing sites based on

CPT codes and CMS Reimbursement and CMS CLIA databases. More information on this can be provided by contacting [fluquestions@aphl.org](mailto:fluquestions@aphl.org).

- **As a PHL, how can I help our clinical sector partners in relation to these assays?**

- ◆ Consider offering validation testing for users in their jurisdiction. PHLs will want to consider testing volume and set appropriate criteria for confirmatory testing, such as the start of season when influenza prevalence is low or if a lab sees a spike in positivity rates that might be due to contamination, before publicizing this service.
- ◆ Offer performance evaluation panels to users on a yearly or twice-yearly basis using stocks of currently circulating influenza viruses residing in their repositories. Providing feedback on the results of these “non-punitive” panels can help in relationship-building and identify other ways the PHL can be an educational and troubleshooting resource to these partners.
- ◆ Share state-specific virologic surveillance data by various means (e.g., electronic, website link). This will provide a picture of influenza prevalence within their jurisdiction and a context for rapid test result interpretation.
- ◆ Serve as a resource by sharing the information and resource links contained within this document after tailoring it to specific partners.

- **Where can I find additional resources on these tests, their performance and education resources for proper use?**

Comprehensive information on all RIDTs including characteristics, pre-analytical considerations and optimizing usage and interpretation can be found at the following websites:

- ◆ <http://www.cdc.gov/flu/professionals/diagnosis/index.htm>
- ◆ <http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm>
- ◆ [http://www.cdc.gov/flu/professionals/diagnosis/clinician\\_guidance\\_ridt.htm](http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm)
- ◆ <https://www.jointcommission.org/siras.aspx>
- ◆ [http://apps.who.int/iris/bitstream/10665/44304/1/9789241599283\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/44304/1/9789241599283_eng.pdf)

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