

Microbiology Devices Panel Medical Devices Advisory Committee Proposal for the reclassification of rapid influenza detection devices



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Perspective



- **Wadsworth Center, NYSDOH**
 - Public health surveillance
 - Research and development
 - Diagnostic testing
 - Regulatory oversight/Clinical Laboratory Evaluation Program
- **Clinical settings**
 - Academic medical centers
 - Primary care sites
- **Clinicians, industry, academia, public health**

Influenza Testing: Clinical Utility



- To determine whether influenza is present in a patient population
 - Influenza commonly diagnosed on clinical symptoms if highly prevalent in the community
- To distinguish from other respiratory agents
- To assess need for further testing
- To confirm influenza infection prior to treatment
 - Antibiotics vs antiviral drugs
- To identify outbreaks and decide prophylactic regimens
- To determine cohorting, other intervention strategies, and help minimize spread

Influenza Surveillance Goals



- **Detect the onset, duration and spread of influenza activity**
- **Measure the severity of influenza during a season**
- **Determine populations affected**
- **Identify special risk groups**
- **Monitor the prevalence of circulating virus types and subtypes**
- **Determine match to annual vaccine strains, monitor genetic and phenotypic changes, determine changes to vaccine composition**
- **Monitor for novel subtypes with pandemic potential**
- **Monitor for circulating drug-resistant variants**
- **Provide information to: policy makers, emergency response officials, clinicians, the public, and media**

Influenza Testing Laboratories for NYS Patients: 1



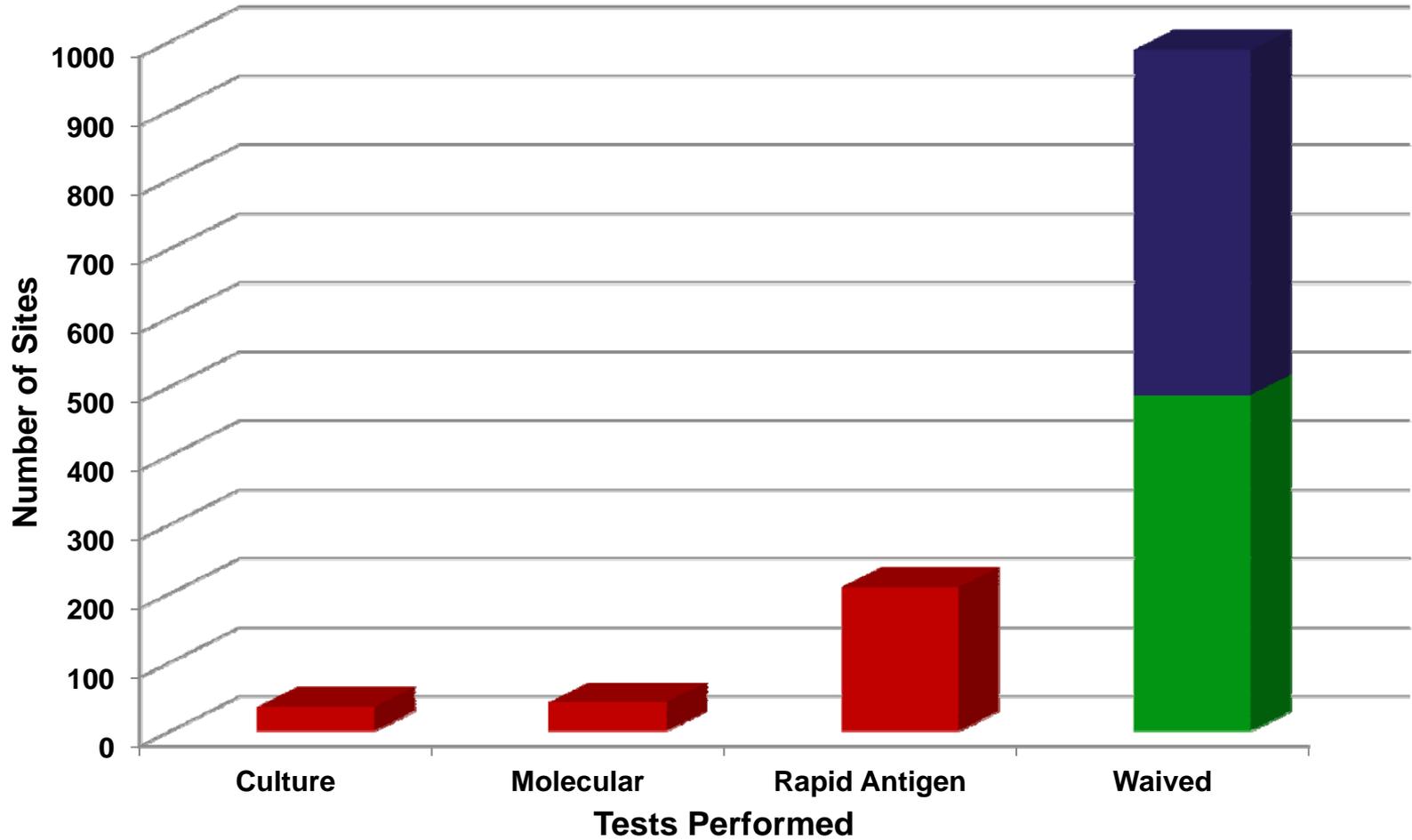
- **Laboratories performing moderate or high complexity testing, holding NYS permits for Virology testing and performing the following influenza testing:**
 - **Virus culture: 35**
 - **Molecular testing: 42**
 - **Rapid antigen detection: 209**
- **Extensive QMS**
 - **Must meet very extensive operating standards and regulations**
 - **undergo biennial CLEP inspections**
 - **Proficiency testing, competency assessments**
 - **May also have CAP/Joint Commission inspections**

Influenza Testing Laboratories for NYS Patients: 2



- **Limited Service Laboratories in NYS**
 - 5,000 laboratories in NYS – can only perform waived testing
 - 488 approved to perform rapid influenza antigen testing
 - Much less QMS and QA oversight:
 - ✦ Reduced operating standards and regulations
 - ✦ No PT required, ~2% of labs are inspected
 - ✦ “Must follow manufacturers’ instructions”
- **From the federal CMS database in NYS**
 - 1,432 physician office laboratories (POLs) perform moderate or high complexity testing (e.g. chemistry, drug testing, coagulation, microscopy)
 - ✦ Inspected every 2 years, similar regulations to CLIA
 - 1,085 perform microscopy (PPMP)
 - ✦ Also eligible to perform waived testing
 - ✦ Not inspected at all
 - 5,065 perform waived testing
 - ✦ Reduced operating standards and regulations
 - ✦ No PT required, ~2% of labs are inspected
 - ✦ “Must follow manufacturers’ instructions”

Influenza Test Sites for NYS Patients

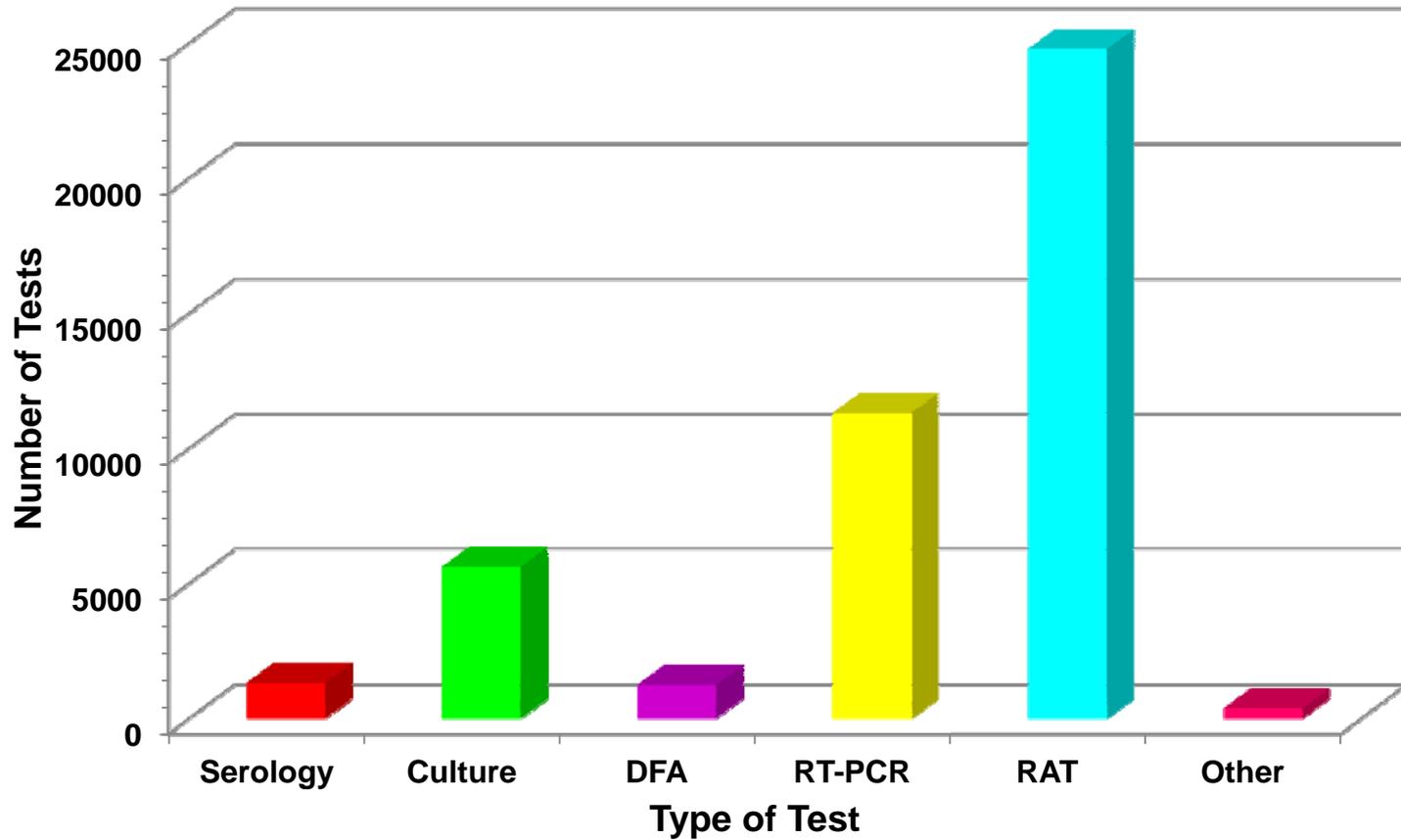


The ongoing need for availability of influenza rapid antigen tests



- **Results obtained within 15 min**
 - Only rapid liquid DFA as fast – requires experienced microscopist, centrifuge...
 - Results available in time to inform treatment decisions, additional testing needs, patient cohorting, timely prophylaxis
- **Simple to perform**
 - Do not require highly technically skilled staff to perform
 - Do not require high maintenance equipment

Positive Influenza Lab Tests Reported to NYS ECLRS for 2012-2013 Season (N=44703)



Approximately 14.5% of reports either missing test type or test type not easily determined by Stat Unit. Those reports

Issues with Influenza Detection and Diagnosis : 1



- Changes in influenza viruses over time can adversely affect test sensitivity
- Rapid influenza antigen detection tests are prone to false positive results during times of low influenza prevalence (all but peak season)
 - ✦ Impacts influenza surveillance
 - ✦ May result in unnecessary or inappropriate antiviral treatment and patient management
 - ✦ Necessitates excessive confirmatory testing in the public health setting
 - Jeopardizing resources for other activities

Concerns regarding rapid influenza antigen tests



- **Variable sensitivity and specificity reported:**
 - **Chartrand et al. 2012, Annals of Internal Medicine 156:500-511**
 - ✦ **Meta-analysis of 159 studies (multiple decades) on the evaluation of rapid influenza tests**
 - **Sensitivity 62.3 (95% CI: 57.9 – 66.6)**
 - **Specificity 98.2 (95% CI: 97.5 – 98.7)**
 - ✦ **Less sensitive in adults (53.9%) than children (66.6%)**
 - ✦ **More sensitive for influenza A (64.6%) than influenza B (52.2%)**
 - **Chu et al. 2012, Influenza Other Resp Viruses 6:80-86**
 - ✦ **Meta-analysis of 17 studies on the evaluation of rapid influenza tests for influenza A/H1pdm09**
 - **Sensitivity 51% (95% CI: 41 – 60)**
 - **Specificity 98% (95% CI: 94 – 99)**

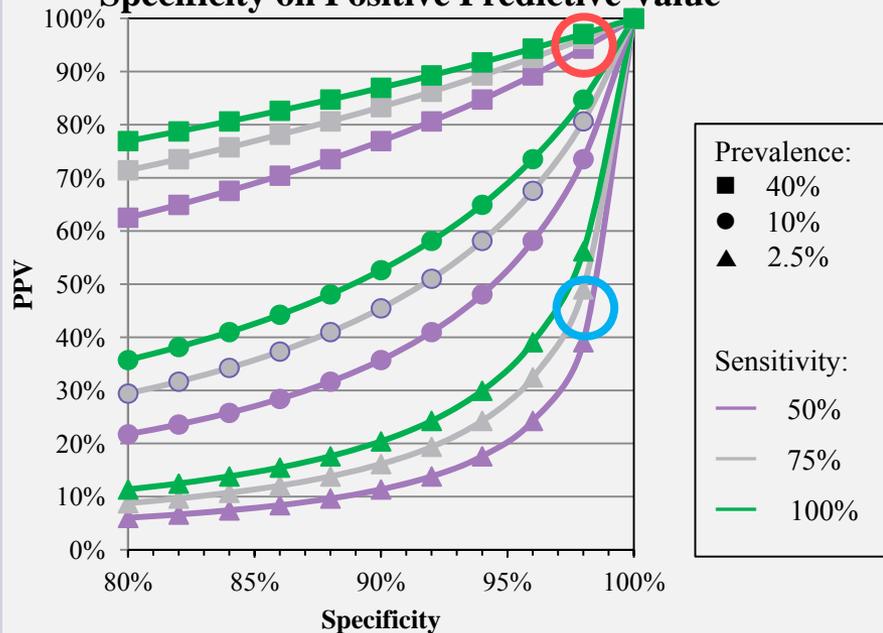
PPV and NPV: at Sens 65%, Spec 98%

When prevalence is high: PPV is high and NPV is low

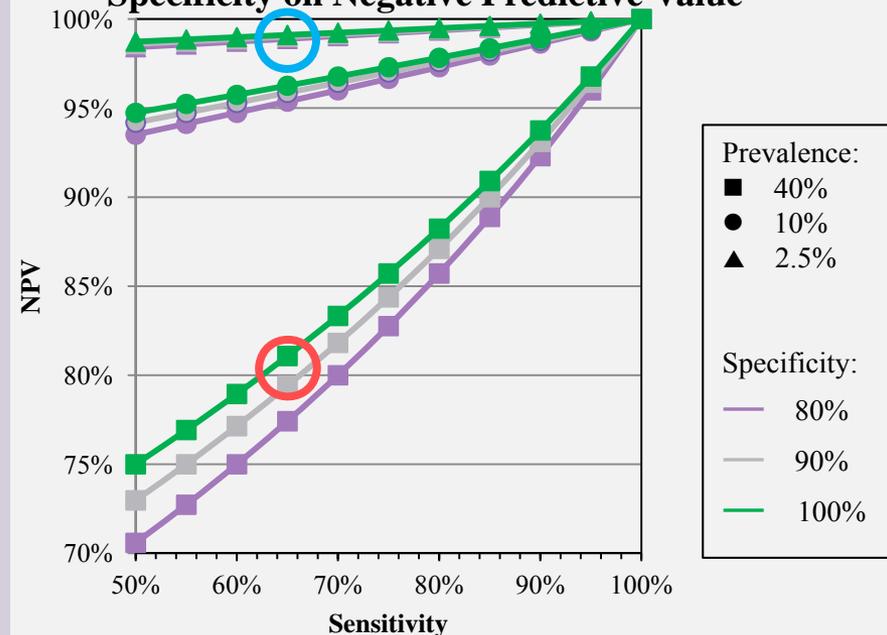
When prevalence is low: NPV is high and PPV is low

In any location, influenza prevalence is usually very high only briefly

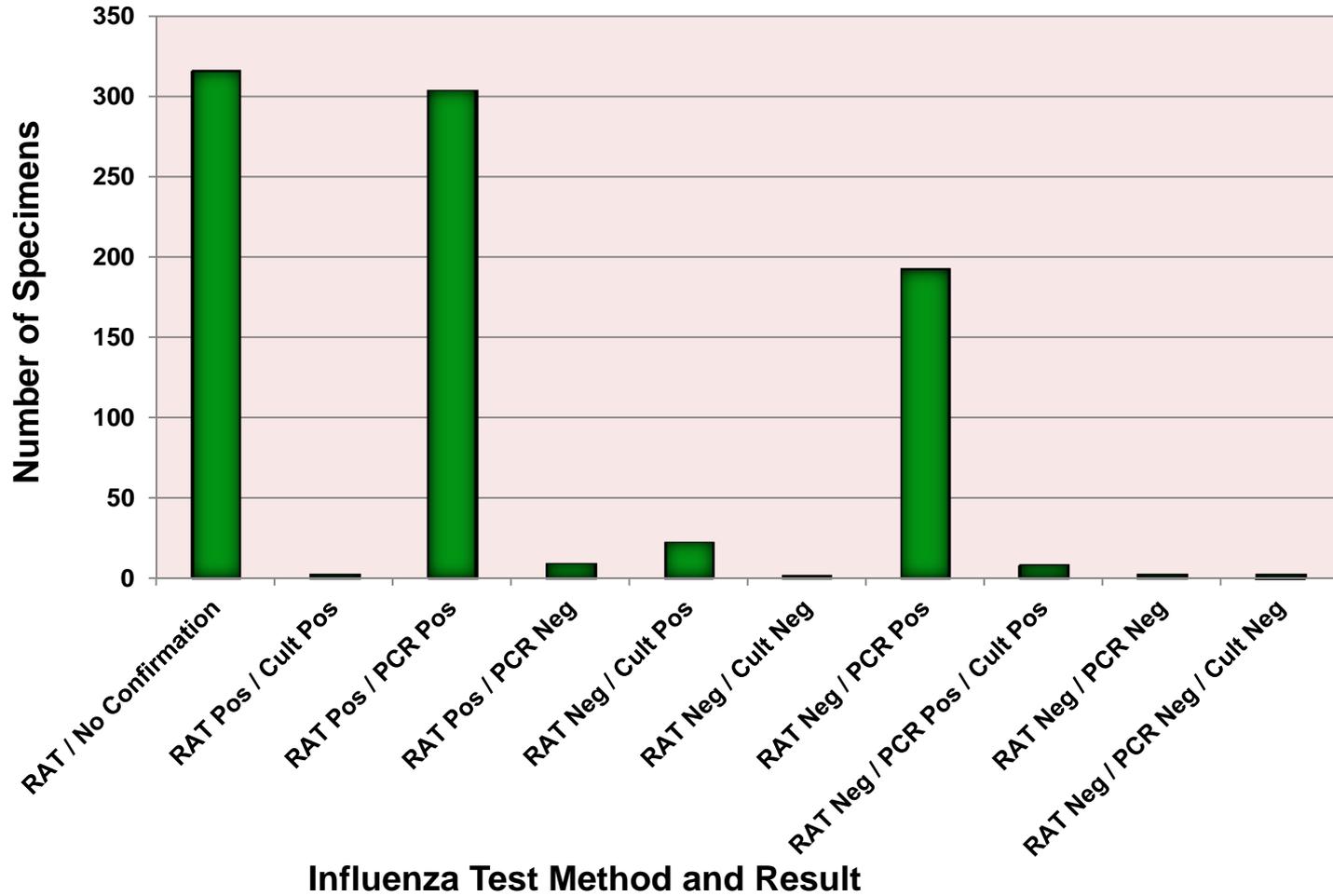
Impact of Prevalence, Sensitivity, and Specificity on Positive Predictive Value



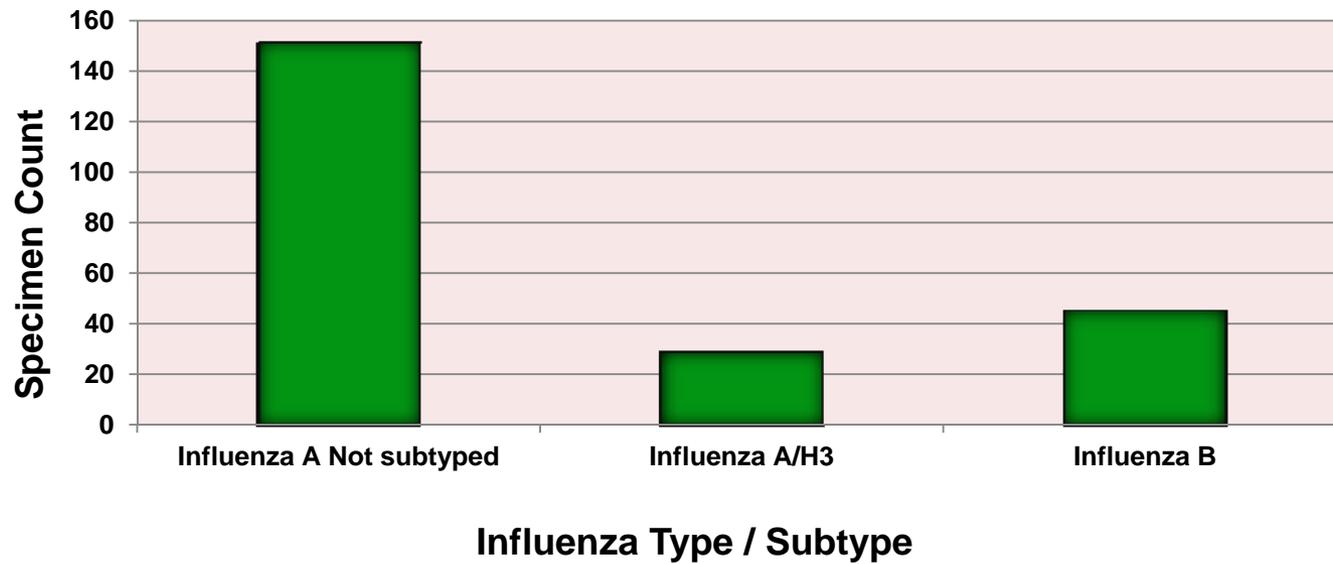
Impact of Prevalence, Sensitivity, and Specificity on Negative Predictive Value



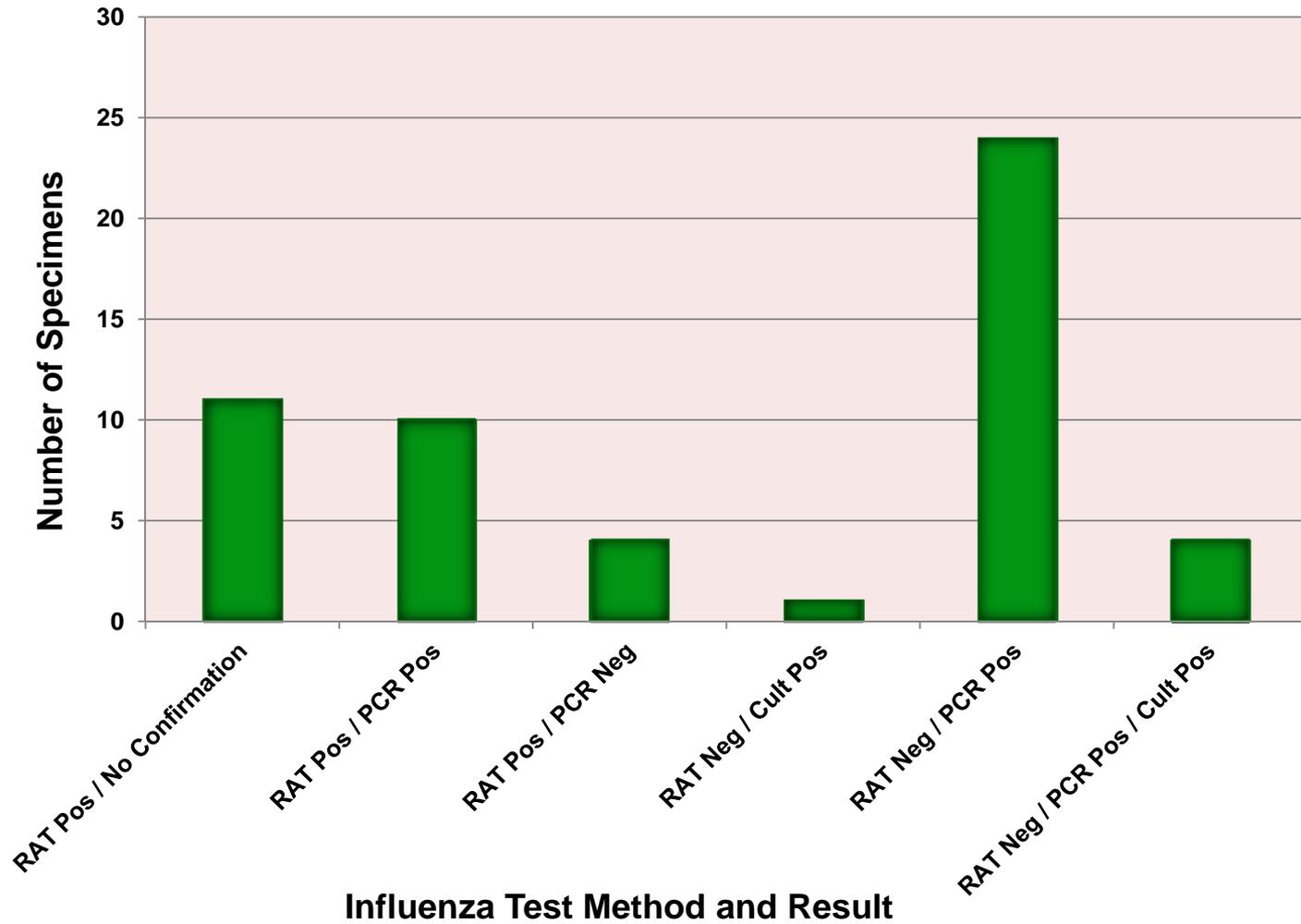
NYS EIP Surveillance Data 2012 - 2013



Influenza Type / Subtype, False Negative Rapid Tests EIP 2012-13



NYS EIP Surveillance Data 2011 - 2012



Challenges and concerns for rapid tests continue

RAPID COMMUNICATIONS

A comparison of rapid point-of-care tests for the detection of avian influenza A(H7N9) virus, 2013

C Baas^{1,2}, I G Barr^{1,2}, R A Fouchier³, A Kelso¹, A C Hurt (aeron.hurt@influenzacentre.org)^{1,2}

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Citation style for this article:

Baas C, Barr IG, Fouchier RA, Kelso A, Hurt AC. A comparison of rapid point-of-care tests for the detection of avian influenza A(H7N9) virus, 2013. Euro Surveill. 2013;18(21):pii=20487. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20487>

Article submitted on 21 May 2013 / published on 23 May 2013

Six antigen detection-based rapid influenza point-of-care tests were compared for their ability to detect avian influenza A(H7N9) virus. The sensitivity of at least four tests, standardised by viral infectivity (TCID₅₀) or RNA copy number, was lower for the influenza A(H7N9) virus than for seasonal A(H3N2), A(H1N1)pdm09 or other recent avian A(H7) viruses. Comparing detection limits of A(H7N9) virus with Ct values of A(H7N9) clinical specimens suggests the tests would not have detected most clinical specimens.

[7,8] and may also enable the quarantining of infected cases to prevent further spread of the virus. Real-time PCR is now considered the gold standard laboratory-based assay for the detection of influenza virus infections due to its high sensitivity and specificity [6] and, although such assays have already been developed for the detection of influenza A(H7N9) virus [6], they require a high level of laboratory expertise and may not be available in all places where cases occur.

From: Baas C et al. A comparison of rapid point-of-care tests for the detection of avian influenza A(H7N9) virus 2013. Eurosurveillance 18(21) May 2013



- **LOD in TCID₅₀/mL for the 6 POC test kits investigated**
 - **H7N9 detection**
 - ✖ 10E5 to 10E5.5 for 5 test kits
 - ✖ One test kit unable to detect any of the dilutions tested
 - **H1N1 detection**
 - ✖ 10E2 to 10E5
 - **H3N2 detection**
 - ✖ 10E2.5 10E5
- **LOD in RNA copies/mL for the 6 POC test kits investigated**
 - **H7N9 detection**
 - ✖ 1.6x10E5 to 5.0x10E5
 - ✖ One test kit unable to detect any of the dilutions tested
 - **H1N1 detection**
 - ✖ 4.6x10E3 to 4.5x10E6
 - **H3N2 detection**
 - ✖ 6.3x10E3 to 2.6x10E6
- **Empirical testing and comparisons between POC and molecular tests in clinical samples is essential.**

*Virus not detected at any concentration tested

Issues with Influenza Detection and Diagnosis : 2



- **Influenza assays being considered for FDA clearance have been compared to culture as the “gold standard”**
 - **Variable reference point**
 - ✦ **Non-standard conditions, variable cell sensitivity, variable strain growth**
- **The “gold standard” in diagnostic testing has moved increasingly to rRT-PCR**
 - **Standardized methodology**
 - **Detection limits**
- **Post-market surveillance critical to ensure ongoing acceptable performance of influenza detection devices**
 - **Influenza viruses are constantly evolving, changes can alter the ability of an assay to detect the virus.**

Reclassification Support



- **Initial requirements for standardization and improvement of reference method**
 - Culture sensitivity is variable across strains and subtypes from year to year and across different cell lines
- **Initial requirements for proven high performance**
 - Establish performance across samples from multiple patient groups
 - ✦ Or place clearly marked limitations for users on packaging
 - Transition to evaluation by comparison with molecular methods
- **Post-market performance evaluation**
 - Changes with virus evolution may alter assay sensitivity
 - Require post-market monitoring of sensitivity and specificity for contemporary circulating strains
 - Prompt response to the detection of adverse performance changes
 - Clear instructions, utility and limitations, on packaging for users