Influenza testing and the FDA reclassification- Where do we go from here?

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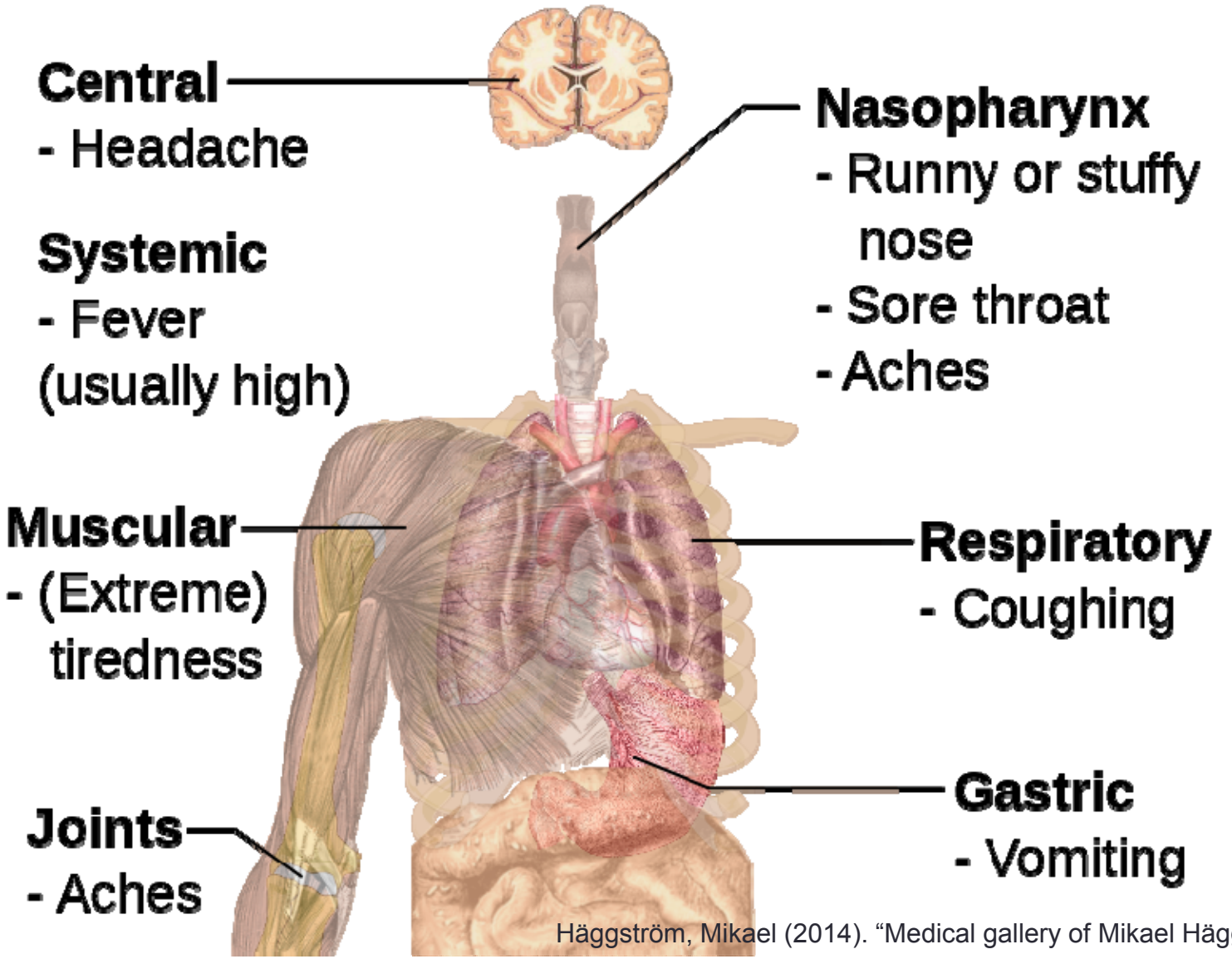
Objectives

- Review FDA Influenza reclassification requirements to provide understanding of changes following the January 2018 enforcement date
- Introduce the different types of influenza tests available, following FDA RIDT reclassification
- Explain the pros and cons of each type of influenza testing
- Discuss the 2017/2018 influenza season and lessons learned to prepare for future season

Influenza virus

- RNA viruses
- 5-20% of US population is affected each year
- Approximately 36,000 deaths each year in US with more than 200,000 hospitalizations
  - Ranges from 4,000-50,000 deaths per year
- Most deaths are in elderly
  - But can also occur in healthy individuals (2009 H1N1)

Symptoms of influenza



Häggström, Mikael (2014). “Medical gallery of Mikael Häggström 2014”.

Influenza A vs. B

Influenza A

- Can cause disease in a wide variety of animals
- More severe disease than B
- Divided into subtypes based on two surface proteins:
  - Hemagglutinin (H)- ~13 types
    - Allows virus to bind to cells for infection
  - Neuraminidase (N)~ 9 types
    - Allows new viruses to escape from cells

Influenza B

- Causes a milder flu, usually in the spring months
- Broken down into lineages
  - e.g. B/Yamagata, B/ Victoria

Spread of influenza

- Spread person-to-person
- Droplets spread when coughing, sneezing, talking
  - Can spread about 6 feet away
- Touching contaminated surfaces and then touching nose, mouth
- Avoiding spread- Wash hands, surgical mask, vaccination!

Remember: You can spread flu one day before you are symptomatic!

HEALTH

This Flu Season Is the Worst in Nearly a Decade

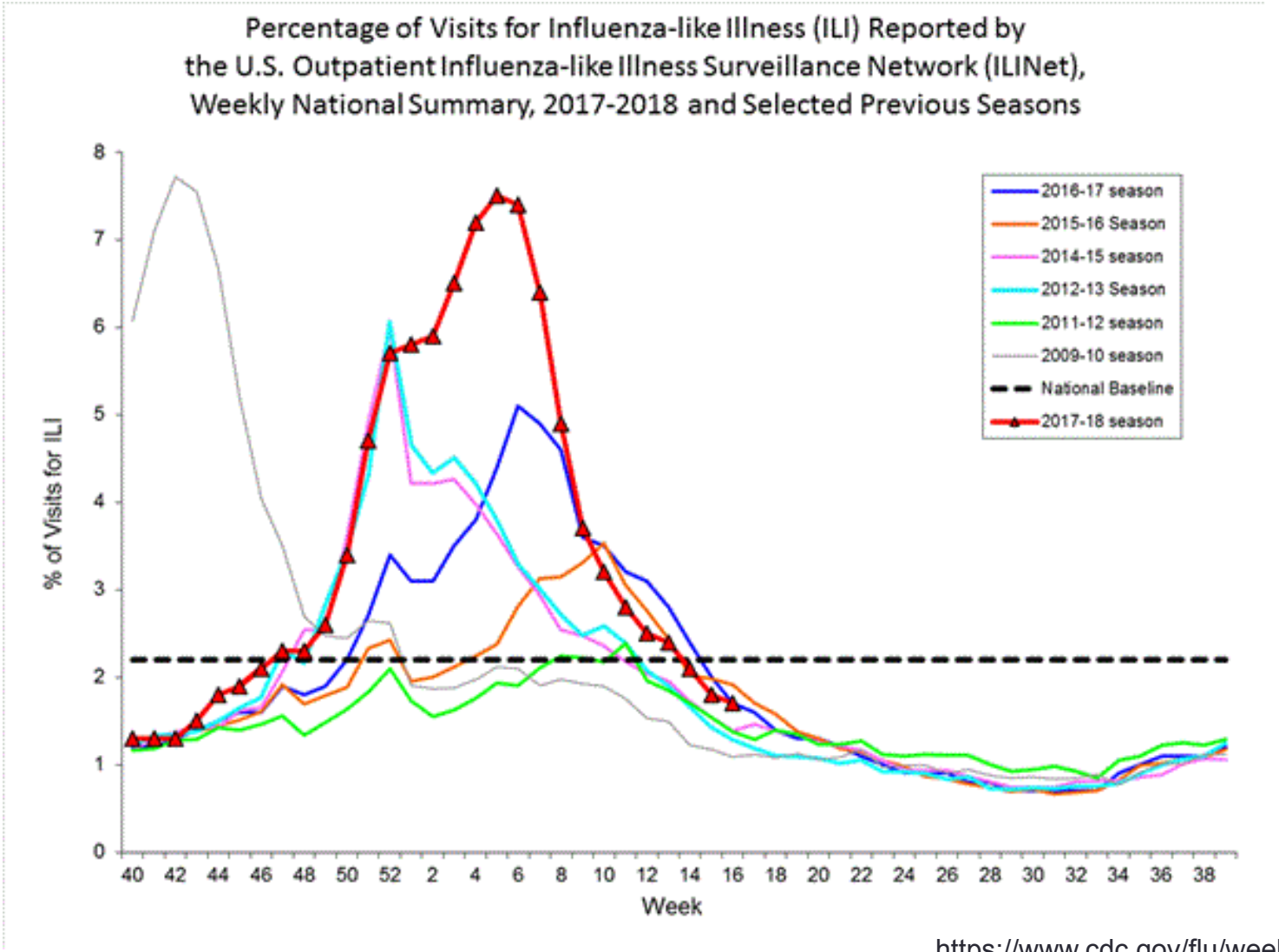
By DONALD G. McNEIL Jr. JAN. 26, 2018

An emergency room nurse treating a flu patient in Vista, Calif., this month. Mike Blake/Reuters

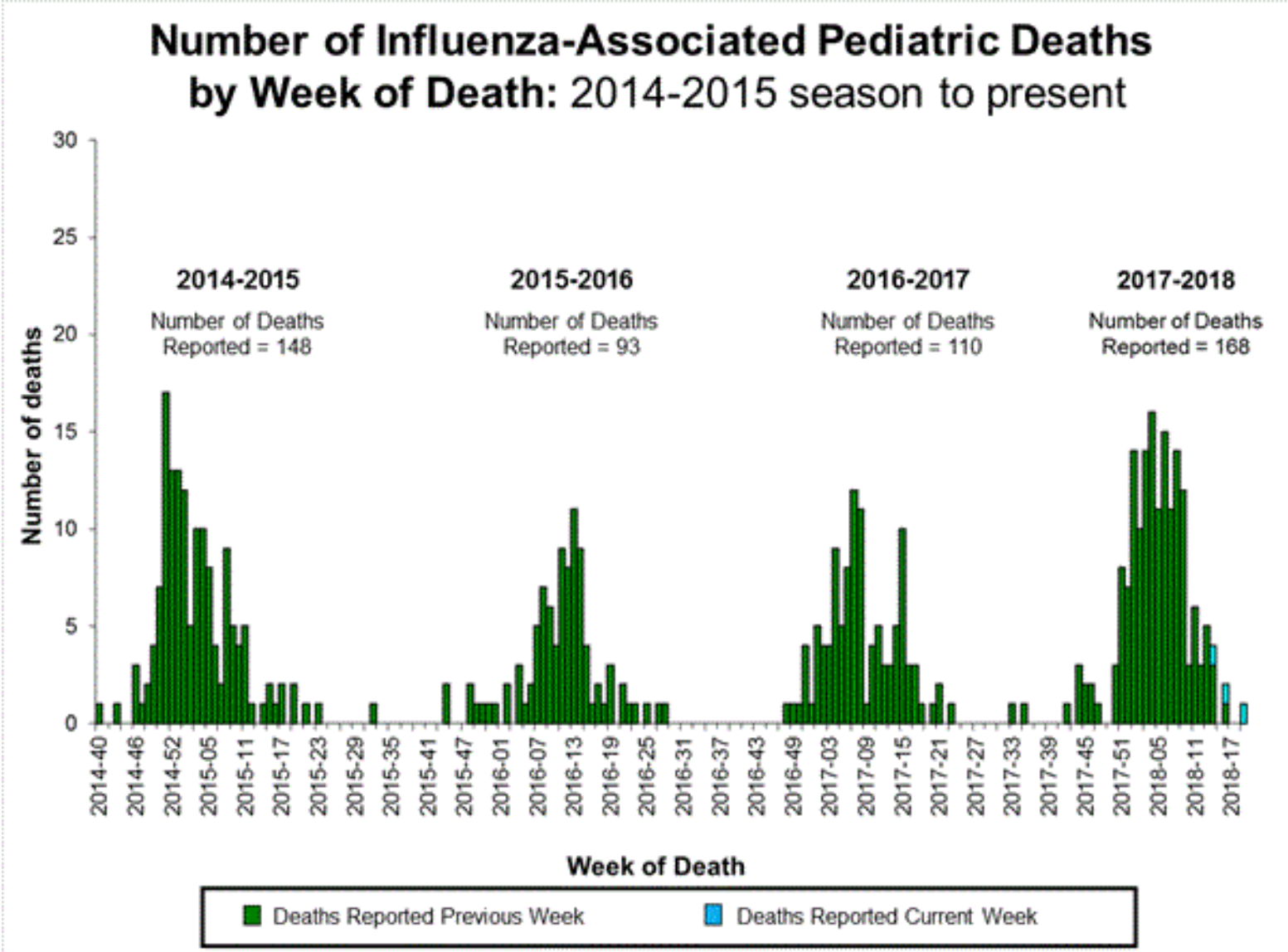
RELATED COVERAGE

The Flu Outbreak Has Peaked but Still Has Weeks to Go JAN. 18, 2018

How did this flu season compare to others?

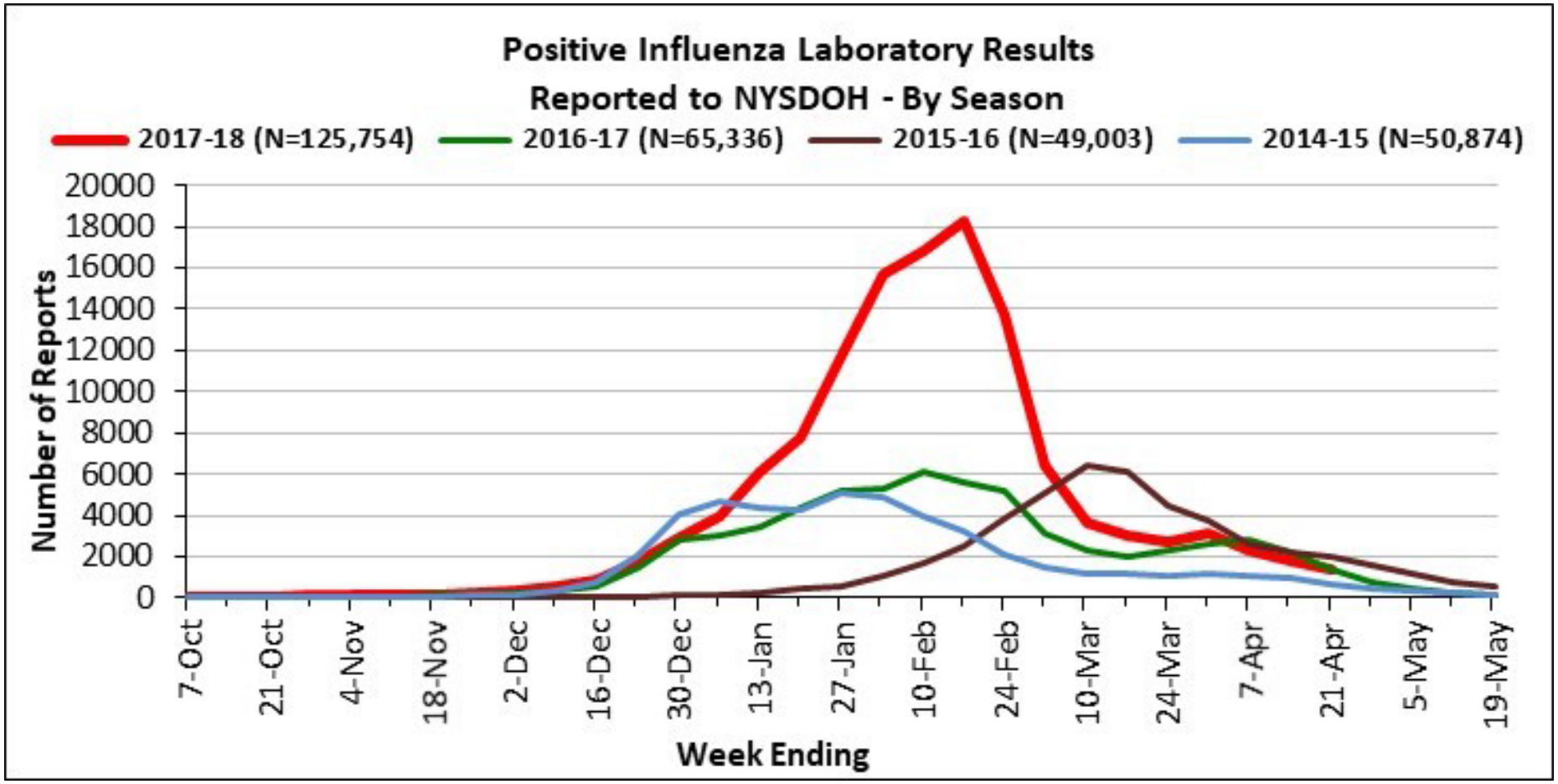


https://www.cdc.gov/flu/weekly/index.htm



https://www.cdc.gov/flu/weekly/index.htm

Lab-confirmed influenza cases- NY



https://www.health.ny.gov/diseases/communicable/influenza/surveillance/2017-2018/flu_report_current_week.pdf

How does the flu virus change?

ANTIGENIC "DRIFT" VS. "SHIFT"

Drift – small genetic changes over time

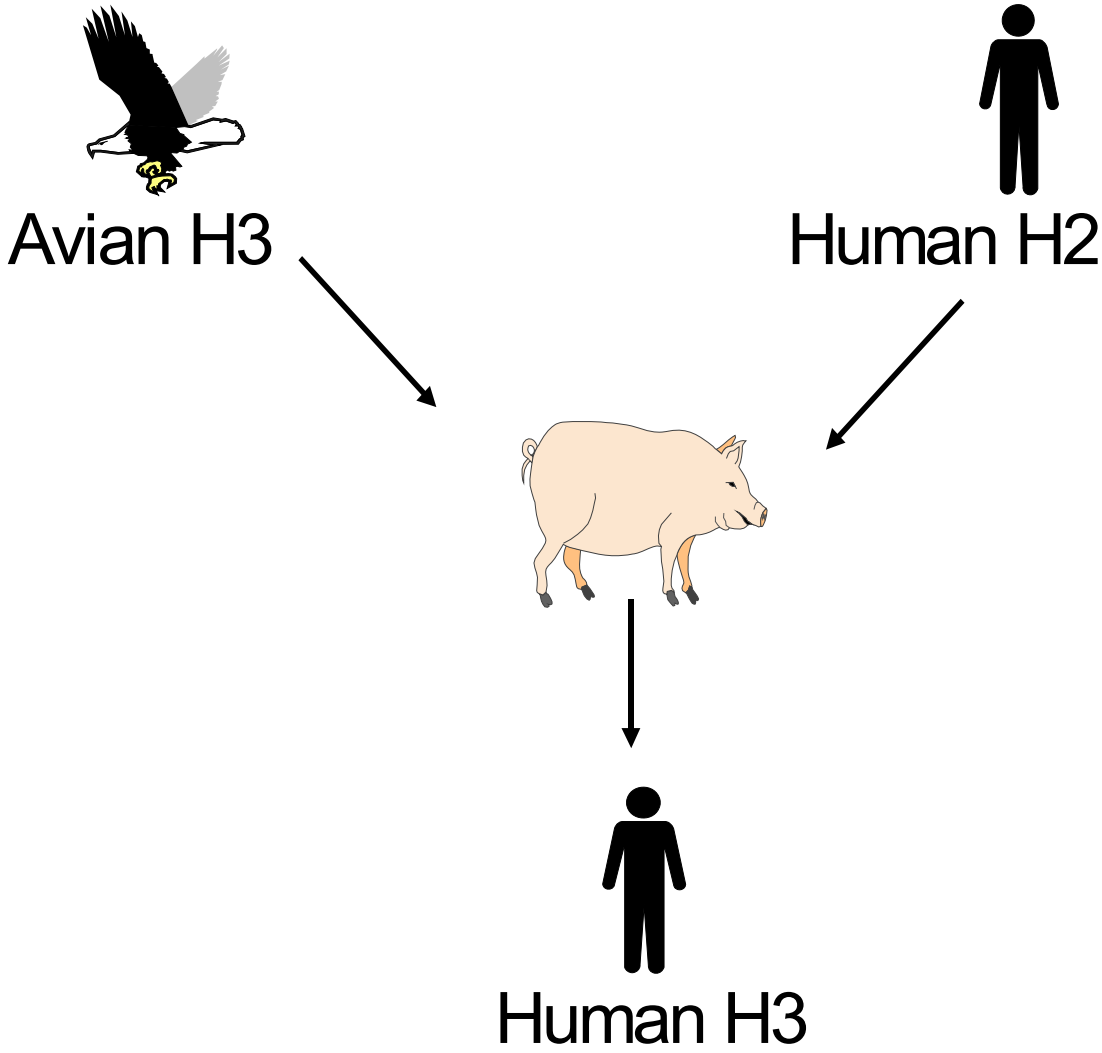
- More typical, yearly change in influenza virus
- Reason why a new vaccine formulation is needed every year, even for the "same" virus

Shift – major change resulting in a new hemagglutinin and/or neuraminidase

- Leads to a new virus to which people's immune system is naïve
  - Can lead to influenza pandemics
- Occurred in 2009 – Novel H1N1

Changes can and will affect
the performance of influenza tests

How does antigenic shift happen?



Influenza testing methodologies

Method[1]	Types Detected	Acceptable Specimens[2]	Test Time	CLIA Waived[3]
Rapid Influenza Diagnostic Tests[4] (antigen detection)	A and B	NP[5] swab, aspirate or wash, nasal swab, aspirate or wash, throat swab	<15 min.	Yes/No
Rapid Molecular Assay [influenza viral RNA or nucleic acid detection]	A and B	NP[5] swab, nasal swab	<20 minutes[6]	Yes/No[6]
Immunofluorescence, Direct (DFA) or Indirect (IFA) Florescent Antibody Staining [antigen detection]	A and B	NP[4] swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours	No
RT-PCR[7] (singleplex and multiplex; real-time and other RNA-based) and other molecular assays [influenza viral RNA or nucleic acid detection]	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum	Varies (1 to 8 hours, varies by the assay)	No
Rapid cell culture (shell vials; cell mixtures; yields live virus)	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum; (specimens placed in VTM[8])	1-3 days	No
Viral tissue cell culture (conventional; yields live virus)	A and B	NP[5] swab, throat swab, NP[5] or bronchial wash, nasal or endotracheal aspirate, sputum (specimens placed in VTM)		

CDC. Rapid Diagnostic Testing for Influenza: Information for Clinical Laboratory Directors
https://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm#table2

Point-of-care testing (POCT)

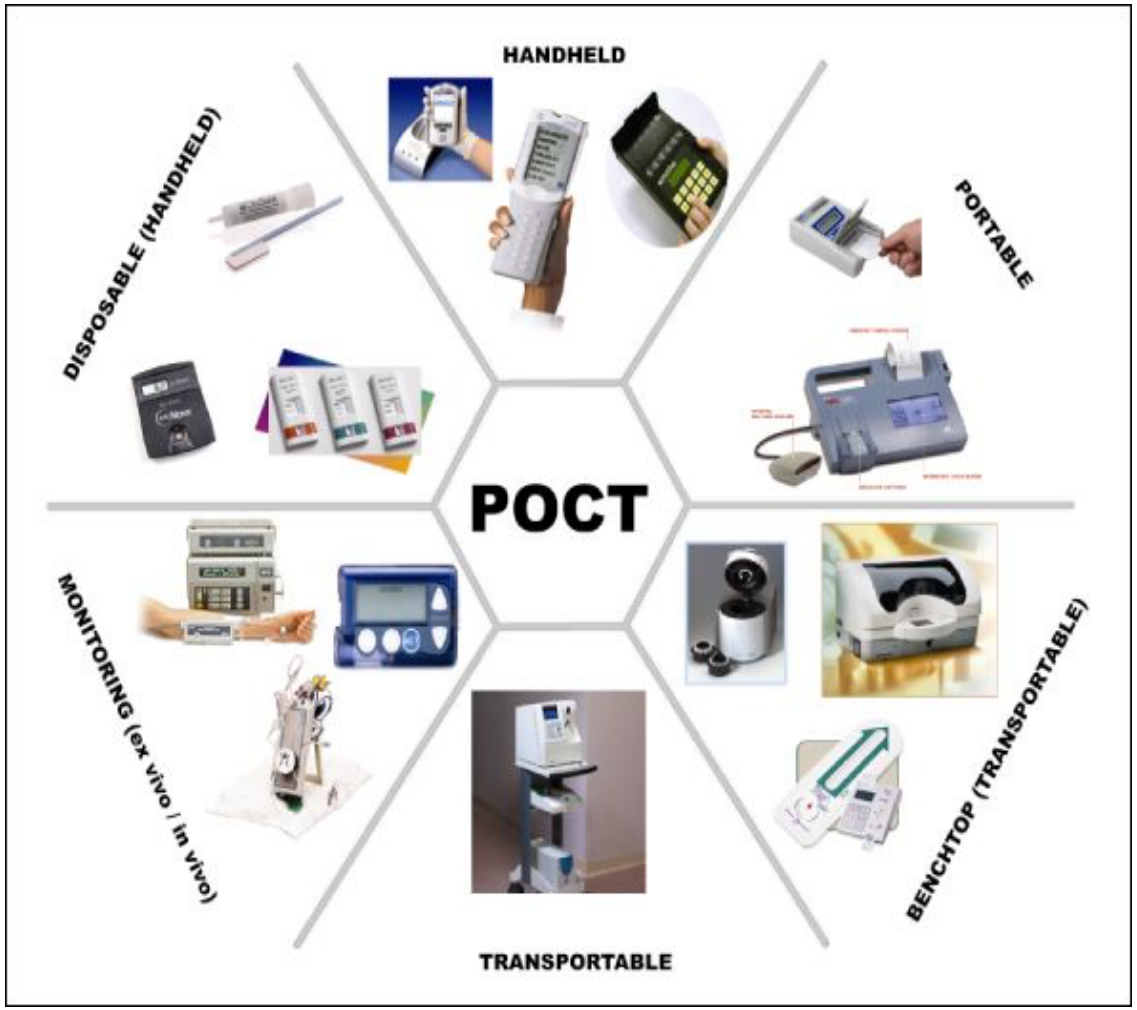
Testing performed <u>while</u> patient care is occurring

Main advantage is time gained

Therapeutic choices in real time

- Identify treatment to administer
- Avoid unnecessary drugs/treatments

Requires simple platforms with accurate results

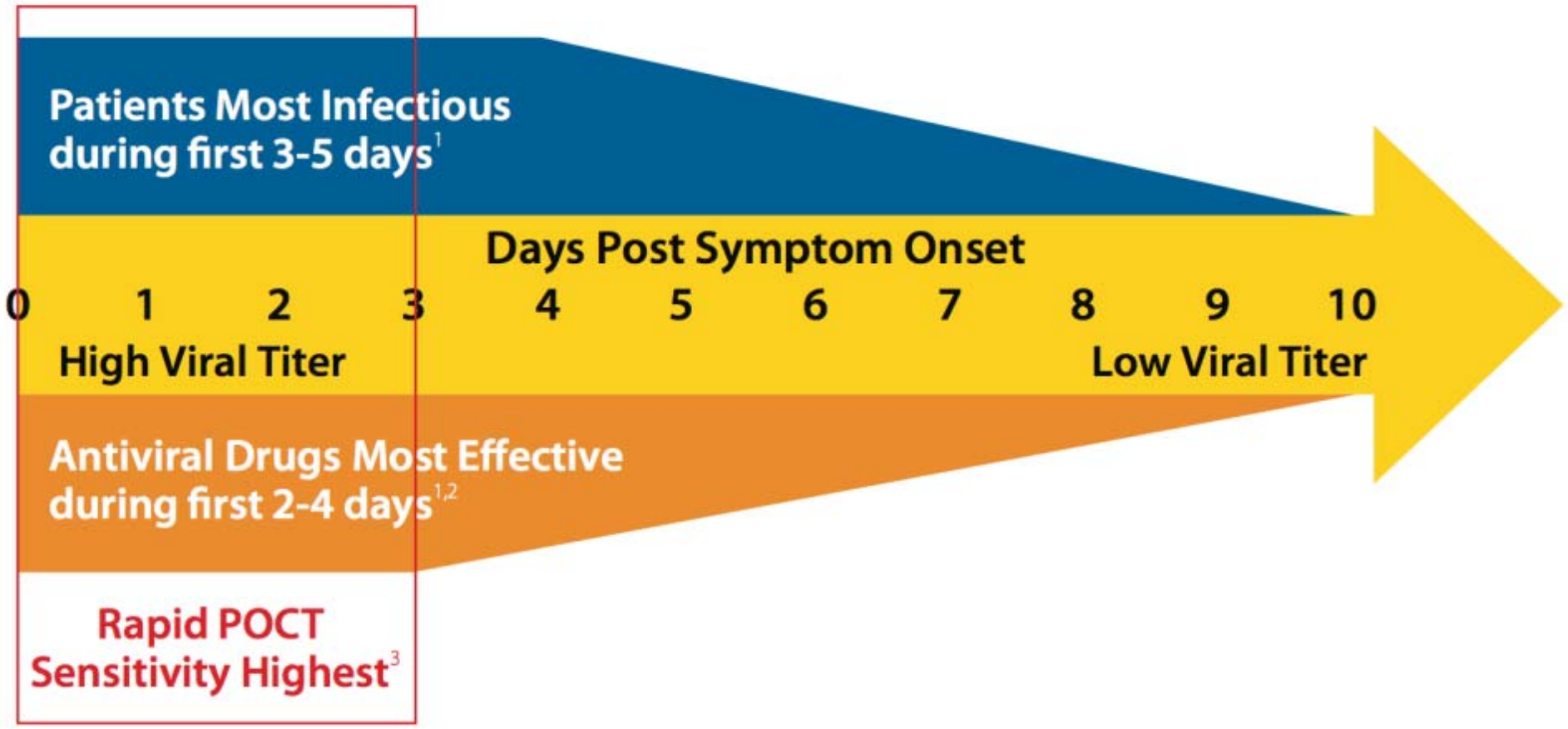


https://i.pinimg.com/736x/0c/26/a9/0c26a969cd5be705139c9a71f39e3665--point-of-care-testing-lab-tech.jpg

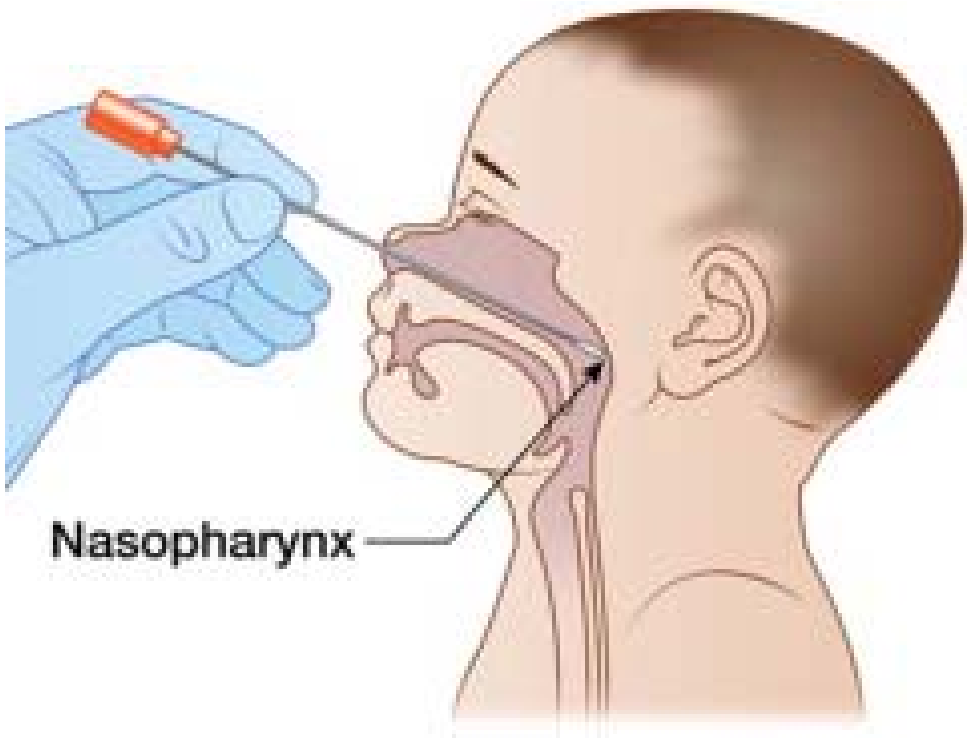
POCT for influenza

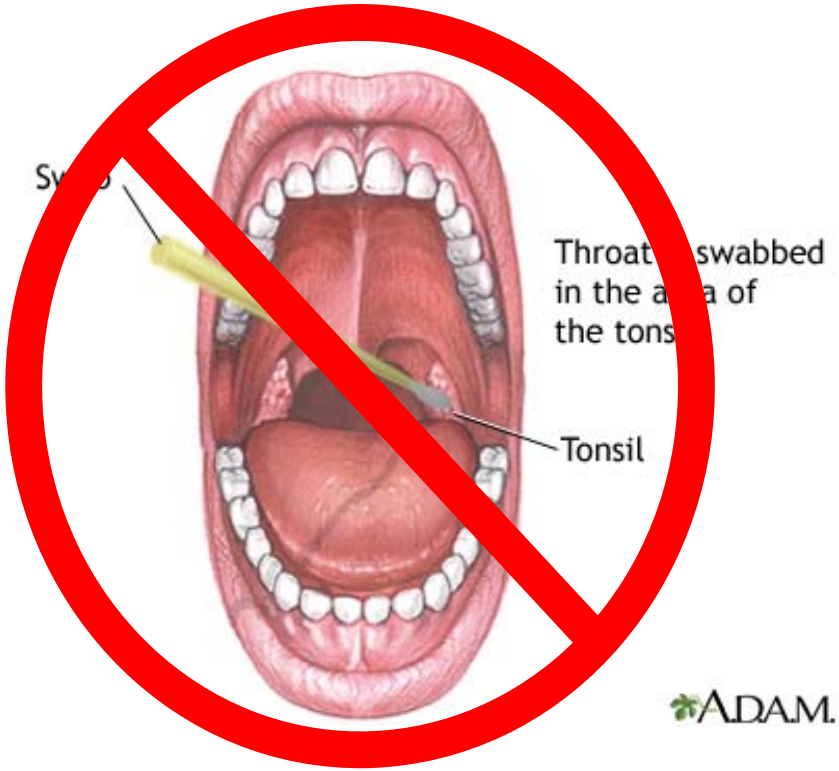
- These are CLIA waived tests that can be performed by facilities with a Certificate of Waiver
- Increasingly larger portion of infectious disease testing
- Huge advantage of rapid answer for treatment decisions
- QUALITY is key- results must approach the same sensitivity and specificity of laboratory tests

Timing is everything!



So is proper specimen collection!

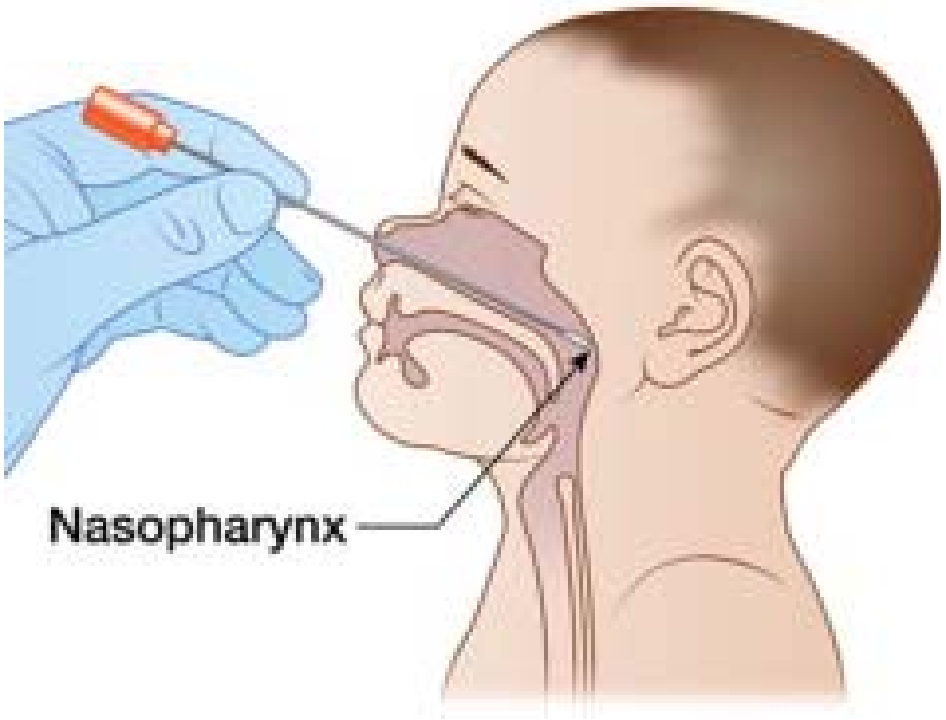




C. Satzke et al. / Vaccine 32 (2014) 165–179

Specimen collection

- Ideally, collected within 3 days of symptom onset
- Use sterile Dacron/nylon swab, Insert into the posterior pharynx and tonsillar areas, remove swab and place into viral transport medium
- Test ASAP or keep specimen at 4°C



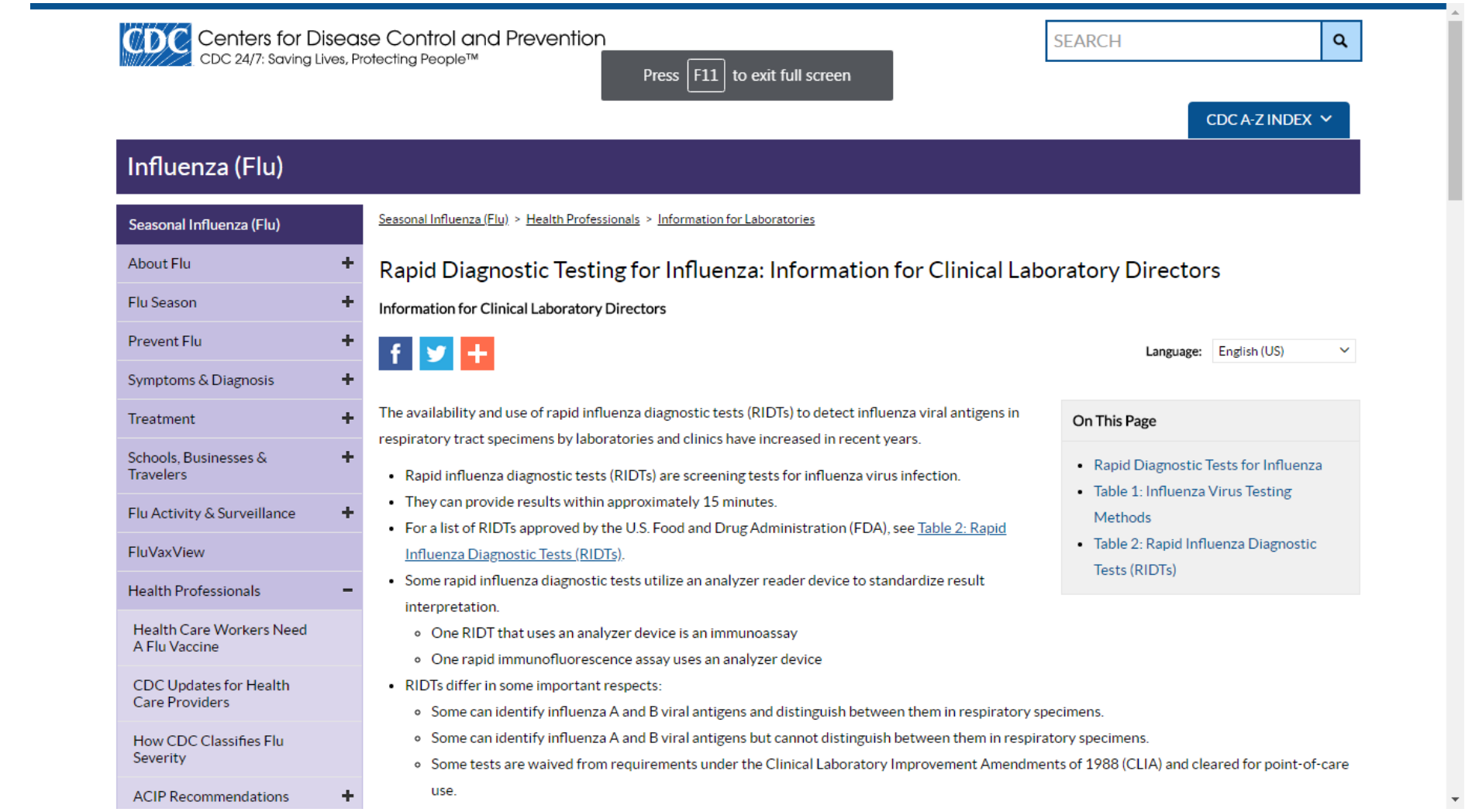
C. Satzke et al. / Vaccine 32 (2014) 165–179

Types of Point-of-Care tests for influenza

- Rapid Influenza Diagnostic Tests (RIDTs)
  - Directly detect viral influenza antigens
- Molecular assays (NAATs)
  - Amplify and detect the viral nucleic acids

Rapid antigen detection tests

- Immunoassays—viral nucleoprotein antigens
- Qualitative resulting
- Vary greatly in their sensitivity
  - Negative RIDT results are unreliable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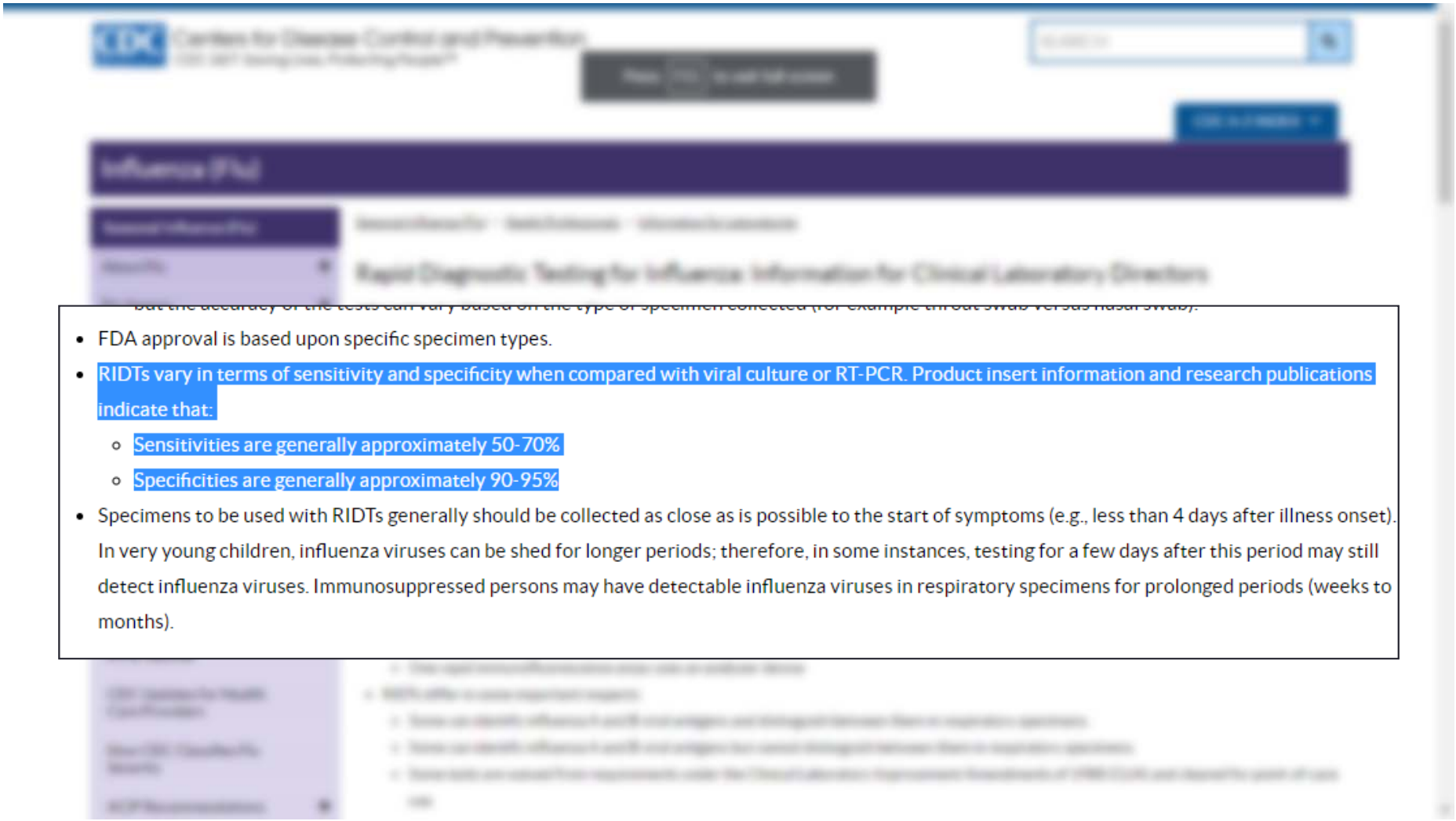
FluVaxView
Health Professionals
Health Care Workers Need A Flu Vaccine
CDC Updates for Health Care Providers
How CDC Classifies Flu Severity
ACIP Recommendations
Seasonal Influenza (Flu) > Health Professionals > Information for Laboratories
Rapid Diagnostic Testing for Influenza: Information for Clinical Laboratory Directors
Information for Clinical Laboratory Directors
Language: English (US)
The availability and use of rapid influenza diagnostic tests (RIDTs) to detect influenza viral antigens in respiratory tract specimens by laboratories and clinics have increased in recent years.
Rapid influenza diagnostic tests (RIDTs) are screening tests for influenza virus infection.
They can provide results within approximately 15 minutes.
For a list of RIDTs approved by the U.S. Food and Drug Administration (FDA), see Table 2: Rapid Influenza Diagnostic Tests (RIDTs).
Some rapid influenza diagnostic tests utilize an analyzer reader device to standardize result interpretation.
One RIDT that uses an analyzer device is an immunoassay
One rapid immunofluorescence assay uses an analyzer device
RIDTs differ in some important respects:
Some can identify influenza A and B viral antigens and distinguish between them in respiratory specimens.
Some can identify influenza A and B viral antigens but cannot distinguish between them in respiratory specimens.
Some tests are waived from requirements under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and cleared for point-of-care use.
On This Page
Rapid Diagnostic Tests for Influenza
Table 1: Influenza Virus Testing Methods
Table 2: Rapid Influenza Diagnostic Tests (RIDTs)



- FDA approval is based upon specific specimen types.
- RIDTs vary in terms of sensitivity and specificity when compared with viral culture or RT-PCR. Product insert information and research publications indicate that:
  - Sensitivities are generally approximately 50-70%
  - Specificities are generally approximately 90-95%
- Specimens to be used with RIDTs generally should be collected as close as is possible to the start of symptoms (e.g., less than 4 days after illness onset). In very young children, influenza viruses can be shed for longer periods; therefore, in some instances, testing for a few days after this period may still detect influenza viruses. Immunosuppressed persons may have detectable influenza viruses in respiratory specimens for prolonged periods (weeks to months).

Literature showing poor sensitivity of RIDTs

J Clin Virol. 2007 Jun;39(2):132-5. Epub 2007 Apr 23.

Performance of six influenza rapid tests in detecting human influenza in clinical specimens.

Hurt AC[1], Alexander R, Hibbert J, Deed N, Barr IG.

N Engl J Med. 2009 Dec 17;361(25):2493. doi: 10.1056/NEJMc0909049. Epub 2009 Nov 18.

Rapid-test sensitivity for novel swine-origin influenza A (H1N1) virus in humans.

Blyth CC, Iredell JR, Dwyer DE.

J Clin Virol. 2009 Jul;45(3):191-5. doi: 10.1016/j.jcv.2009.06.005. Epub 2009 Jun 16.

Evaluation of multiple test methods for the detection of the novel 2009 influenza A (H1N1) during the New York City outbreak.

Ginocchio CC[1], Zhang F, Manji R, Arora S, Bornfreund M, Falk L, Lotlikar M, Kowerska M, Becker G, Korologos D, de Geronimo M, Crawford JM.

What changed THIS YEAR with rapid influenza virus antigen detection tests (RIDTs)?

- **These tests were classified as Class I devices**
  - General controls were considered sufficient
- **FDA has re-classified them to Class II**
  - Both general and special controls must now be followed
    - Enforcement began **January 12th, 2018**

What does this mean?

What is a medical device (as per FDA)?

"an instrument, apparatus…intended for use in the diagnosis of disease or other conditions…"

Can range from dental floss to prosthetic heart valve

https://commons.wikimedia.org/wiki/File:Aortic_Karboniks-1_bileafter_prosthetic_heart_valve.jpg
http://www.mwdental.com/media/catalog/product/cache/1/thumbnail/1000x1000/9df78eab33525d08d6e5fb8d27136e95/4/4/440-0500_6.jpg

FDA classification of a medical device:

- **Based on the risks associated with the device**
- **One of three categories—Class I, Class II, and Class III**

Class I devices

are deemed to be low risk and are therefore subject to the least regulatory controls (general controls).

e.g., dental floss

Class II devices

are higher risk devices than Class I and require greater regulatory controls to provide reasonable assurance of the device's safety and effectiveness (general and special controls).

e.g., condoms

Class III devices

are generally the highest risk devices and are therefore subject to the highest level of regulatory control. Class III devices must typically be approved by FDA before they are marketed (pre-market approval.)

e.g., replacement heart valves

https://www.fda.gov/aboutfda/transparency/basics/ucm194438.htm

General vs. special controls

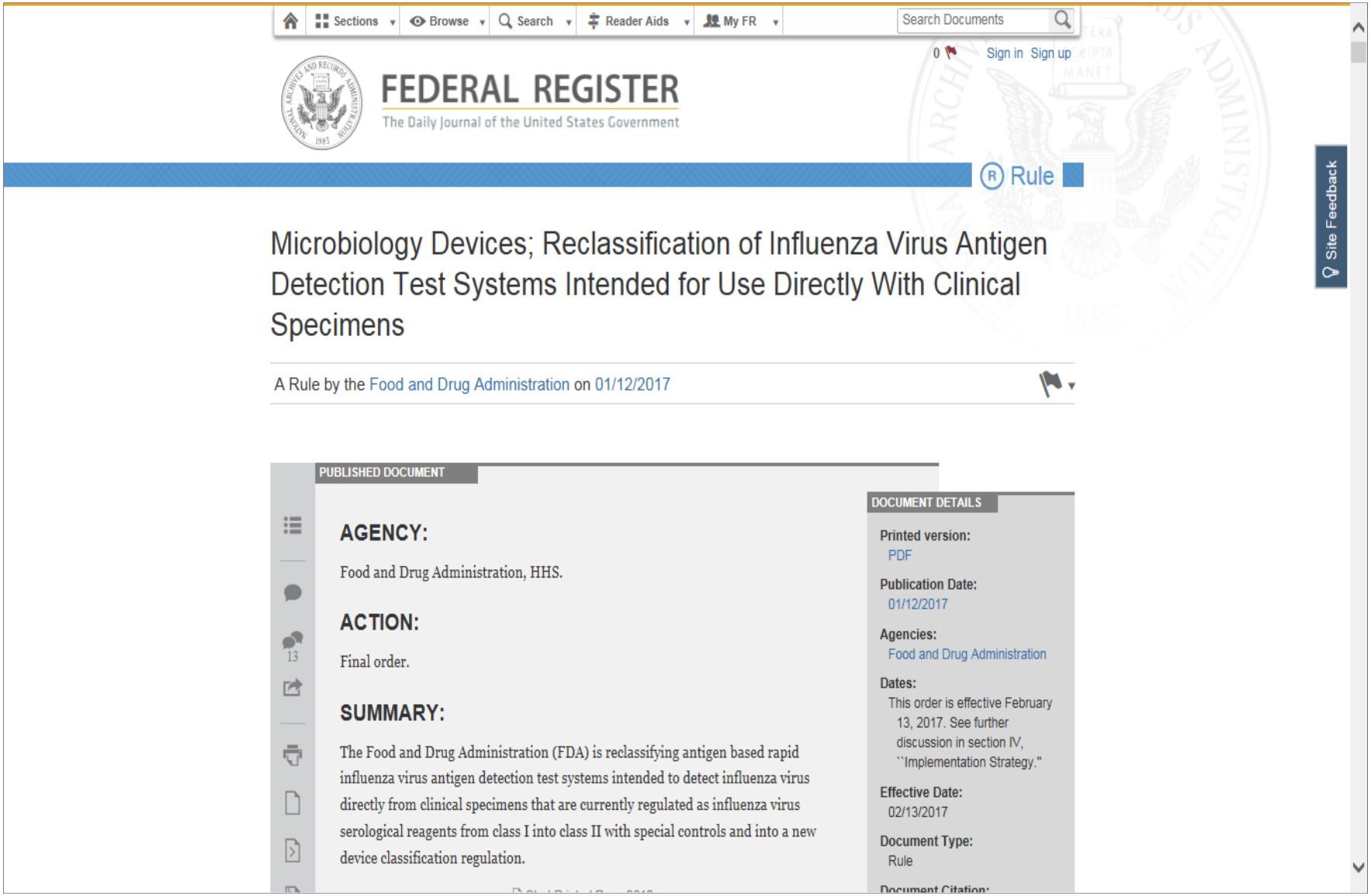
General controls apply to all medical devices (unless exempt)

- Sufficient for low risk (Class I) devices
- Include protections regulating adulteration/misbranding, registration, listing with FDA, Good Manufacturing Practices, proper labeling, and reporting adverse reactions, etc.

Special Controls are required when general controls alone are not sufficient (Class II)

- Include guidelines, performance standards, special labeling, etc.

FDA decision



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FEDERAL REGISTER

The Daily Journal of the United States Government

Rule

Site Feedback

Microbiology Devices; Reclassification of Influenza Virus Antigen Detection Test Systems Intended for Use Directly With Clinical Specimens

A Rule by the Food and Drug Administration on 01/12/2017

PUBLISHED DOCUMENT

AGENCY:

Food and Drug Administration, HHS.

ACTION:

Final order.

SUMMARY:

The Food and Drug Administration (FDA) is reclassifying antigen based rapid influenza virus antigen detection test systems intended to detect influenza virus directly from clinical specimens that are currently regulated as influenza virus serological reagents from class I into class II with special controls and into a new device classification regulation.

DOCUMENT DETAILS

Printed version:
PDF

Publication Date:
01/12/2017

Agencies:
Food and Drug Administration

Dates:
This order is effective February 13, 2017. See further discussion in section IV, ``Implementation Strategy.''

Effective Date:
02/13/2017

Document Type:
Rule

Document Citation:

Enforcing compliance

"For antigen based RIDTs that have been legally marketed prior to February 13, 2017, FDA does not intend to enforce compliance with the special controls until January 12, 2018. If a manufacturer markets such a device after January 12, 2018, and that device does not comply with the special controls, then FDA would consider taking action against such a manufacturer under its usual enforcement policies."

https://www.federalregister.gov/d/2017-00199/p-94

Why the change with flu RIDTs?

- During the H1N1 influenza pandemic of 2009, questions were raised about the sensitivity of RIDTs
  - Lower sensitivity than package insert
- Concerns raised about the overall quality of influenza testing
- **Overall goal:** lower the number of misdiagnosed influenza infections by increasing the number of devices that can reliably detect the influenza virus

https://www.federalregister.gov/d/2017-00199/p-19

Why have rapid antigen tests been re-classified?

"A false negative result may lead to failure to provide a correct diagnosis and the appropriate treatment of infection caused by influenza virus and may contribute to unnecessary treatment for another suspected condition. A false negative result will also provide incorrect epidemiological information leading to failure to initiate appropriate corrective measures to control and prevent additional infections."

"A false positive result on the other hand may lead to delayed treatment of a respiratory infection caused by another etiologic agent, which could potentially result in a more serious patient outcome. A false positive result will also provide incorrect epidemiological information on the presence of influenza in a community, which may result in unnecessary patient isolation or contact limitations and in unnecessary close contact investigations."

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/UCM356185.pdf

Minimum performance criteria

Sensitivity

Flu A Point estimate of 90% with 80% lower bound of the 95% confidence interval
Flu B Point estimate of 80% with 70% lower bound of the 95% confidence interval

Specificity

All influenza detection devices should demonstrate specificity with a lower bound of the 95% confidence interval exceeding 90% for both, Flu A and Flu B.

b. When compared to a molecular comparator method:

Sensitivity

Flu A Point estimate of 80% with 70% lower bound of the 95% confidence interval
Flu B Point estimate of 80% with 70% lower bound of the 95% confidence interval

Specificity

All influenza detection devices should demonstrate a specificity estimate with a lower bound of the 95% confidence interval exceeding 90% for both, influenza A and influenza B.

Addition requirements for RIDTs…

- Required use of a currently appropriate and FDA accepted comparator method for establishing performance of new antigen based RIDTs.
- Required annual analytical reactivity testing of contemporary influenza strains.
- Required analytical reactivity testing of newly emerging strains under certain situations involving an emergency or potential for an emergency.

What was the timeline for this change?

Rule was published 01/12/2017

- Effective Date:02/13/2017

For antigen-based RIDTs legally marketed prior to 2/13/2017:

- Manufacturers needed to obtain a new 510(k) clearance and demonstrate compliance with the special controls included in the new clinical performance standards before marketing their changed or new devices

FDA allowed a one-year transition before enforcement of new rule (January 12, 2018)

What does this change mean for you?

Sales of non-compliant tests halted January 12th, 2018

Purchased tests could be used by customers until their expiration date

- Was NOT a violation to use past 1/12/18

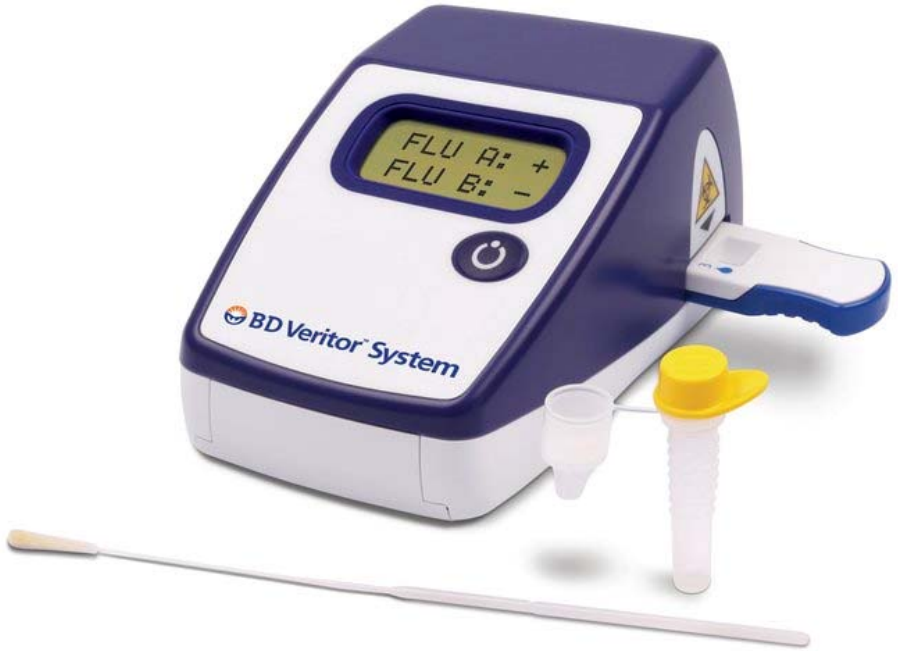
These tests are no longer available, so clinics and hospitals will need to pick one of the compliant options

SOME CLIA-WAIVED RIDT OPTIONS

BD Veritor™ System for Rapid Detection of Flu A+B (BD)

Chromatographic immunoassay with automated reader design

- **Run time:** 10 minutes
- **Specimen types:** Nasopharyngeal swabs in transport media and nasopharyngeal wash aspirates



BinaxNOW® Influenza A&B Card 2 (Abbott)

Chromatographic immunoassay with automated reader design

- **Run time:** ~15 minutes
- **Specimen types:**
  Nasopharyngeal (NP) swab and nasal swab specimens

OSOM® Ultra Influenza A & B (Sekisui)

Immunochromatographic assay with visual read

- **Run time:** 10 – 15 minutes
- **Specimen types:** Nasal and nasopharyngeal swab
  **Moderately complex nasal aspirate/wash specimens*

Sofia® Analyzer and Influenza A+B FIA (Quidel)

Lateral flow immunoassay+ fluorescence with automated reader

- **Run time:** 15 minutes
- **Specimen types:**
  Nasal swab, nasopharyngeal swab and nasopharyngeal aspirate/wash specimens

RIDT pros and cons

Pros	Cons
▸ Rapid results ▸ Simple to use ▸ Several designated as CLIA waived (POCT eligible)	▸ Poor sensitivity ◦ False negatives common ▸ Bad at detecting novel viral strains

CLIA WAIVED MOLECULAR OPTIONS

Molecular POCT tests for influenza

- Traditionally designated by CLIA as moderate/high complexity and have been performed in the clinical laboratories
  - Only rapid antigen testing was available as CLIA waived
- CLIA waived tests have recently become available

CLIA waived molecular tests for infectious diseases

- **January 8th, 2015:** First CLIA waived test for influenza A and B (Alere i Influenza A&B)
- Followed by the Roche cobas Influenza A/B
- Recent additions: Cepheid, Sekisui, BioFire, etc.

Molecular solutions to POCT barriers

Problems

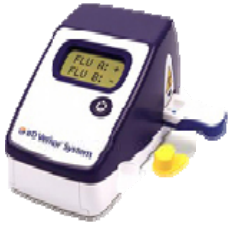
- Not accurate enough for definitive diagnosis
  - E.g. RIDTs
- Too difficult to perform at point-of-care
  - E.g. traditional molecular
- Too Expensive

Solutions

- Increasing sensitivity and specificity
  - Molecular flu/strep testing
- POCT designed to be user-friendly and more error-proof
- Costs decreasing over time and reimbursement that matches test costs

DE2

The power of sample amplification



Amplified
Sample

Not Amplified
Sample

Slide 46

DE2 BinaxNOW card wrong, this version no longer available.
Deane, Emily, 6/1/2018

Alere™ i (Alere)

- 8-13 minutes to result for Flu/RSV
- Isothermal Amplification
- Interpreted by instrument

Flu: CLIA-waived for use with nasal swabs (direct) only

LIAT - Lab In a Tube (Roche)

20 minutes to results Flu/RSV

RT-PCR

Interpreted by instrument

Flu: CLIA-waived for use with nasopharyngeal swabs

Xpert Xpress Flu (Cepheid)

20-30 minutes to result Flu A/B

RT-PCR

Interpreted by instrument

Flu: CLIA-waived for use with nasal/nasopharyngeal swabs

Silaris™ Influenza A&B Test (Sekisui)

30 minutes or less for flu A & B

RT-PCR amplification followed by hybridization and colorimetric visualization of amplified products on a test strip flu A & B

Results are interpreted visually by the operator

Flu: CLIA-waived for use with nasal swabs

Molecular testing pros and cons

Pros	Cons
Can amplify genome	Typically costs more
Highly sensitive and specific	Takes longer

Strong Flu Season Boosts Rapid Molecular Flu and Lab-Based Testing

Feb 16, 2018

NEW YORK (360Dx) – Rapid molecular flu tests are gaining ground, buoyed by a strong flu season and increasing dissatisfaction with rapid antigen flu tests, labs and manufacturers said.

This year's flu season is on track to beat some recent records, US Centers for Disease Control Acting Director Anne Schuchat said during a conference call earlier this month, and makers of rapid molecular flu tests, as well as labs that offer them say the powerful flu season is helping to further boost usage of the tests which had already been steadily gaining acceptance in recent years.

"These rapid molecular tests have taken hold right now across the country," said Holly Batterman, Quest Diagnostics laboratory medical director and medical director for infectious disease in San Juan Capistrano, California.

Quest first began offering rapid molecular influenza tests in 2014 and then rolled the tests out to 18 regional labs across the country in 2015 and 2016, Batterman said. The tests were rolled out to regional labs to put them closer to patients, as clinicians have turned to rapid molecular flu tests due to their high sensitivity and specificity, she said.

Rapid antigen tests, which have low sensitivity, can have false negative rates of 50 percent or higher, an issue that can be concerning to clinicians, especially in a flu season with many reported hospitalizations or complications, Batterman said

Breaking News

- Sweet Wormwood Genome Provides Clues for Boosting Production of Antimalarial Compound
- VC Aspire Universal Forms Personalized Medicine Investment Fund
- Freenome, Biognosys Partner on Early Cancer Detection
- Loss-of-Function, Truncating Variants in UK Biobank Data Point to New Drug Targets
- MDxHealth Q1 Revenues Up 50 Percent
- Waters Q1 Revenues Up 7 Percent

Comparison of Methods

	RIDT	Laboratory Molecular	POCT Molecular
Fast	X		X
Convenient	X		X
Actionable results	X	X	X
POCT- friendly	X		X
Little/No subjectivity		X	X
LIS/EMR interfaced		X	X
High sensitivity/specificity		X	X
Low Cost	X		

Summary

- If you already switched to molecular, or a Class II RIDT
  - You're good!
- If you stocked up on RIDTs at the beginning of last flu season
  - Verify that the tests you have are Class II compliant
    - If they are…you're good!
    - If they are NOT…start considering other tests for the upcoming season

Avoid switching to a "new" flu test mid-season

Thank you!

Questions?