Diagnosis and Management of Respiratory Viruses

Francesca Lee, M.D.
Associate Professor, Pathology and Internal Medicine
Technical Director, UTSW Microbiology Laboratory and Preanalytical Services

Everything you need to know in one slide

Test patients if they are symptomatic, if they are at high risk for complications, if the test result will impact management of patient and/or infection prevention/public health decisions

The virus(es) of interest depend on the host and the environment

How well a test performs depends on many factors, but an NPS for a PCR-based test gives you the greatest flexibility.

Only a few viruses have targeted treatment options.

Dr. Cutrell will teach you about SARS CoV-2

Should the patient be tested?

- Will testing affect clinical management?
  - Antiviral/antimicrobial initiation or de-escalation
  - Additional testing

- Will testing affect others?
  - Prophylaxis of contacts
  - Infection control/public health interventions

- Is the patient at high risk for complications?
  - Adults 65 or older
    - Kids <2
  - Pregnant → 2 weeks postpartum
  - Nursing home/long-term care facilities
  - Non-Hispanic Black, Hispanic or Latino, American Indian or Alaska Native persons
  - Asthma
  - Neurologic/neurodevelopment conditions
  - Blood disorders (sickle cell disease)
  - Chronic lung disease
  - Endocrine disease (diabetes mellitus)
  - Heart disease
  - Kidney disease
  - Liver disorder
  - Metabolic disorders (inherited, mitochondrial)
  - BMI 40 or greater
  - Age <19 on long term ASA or salicylate-containing medications

Impact of testing on management

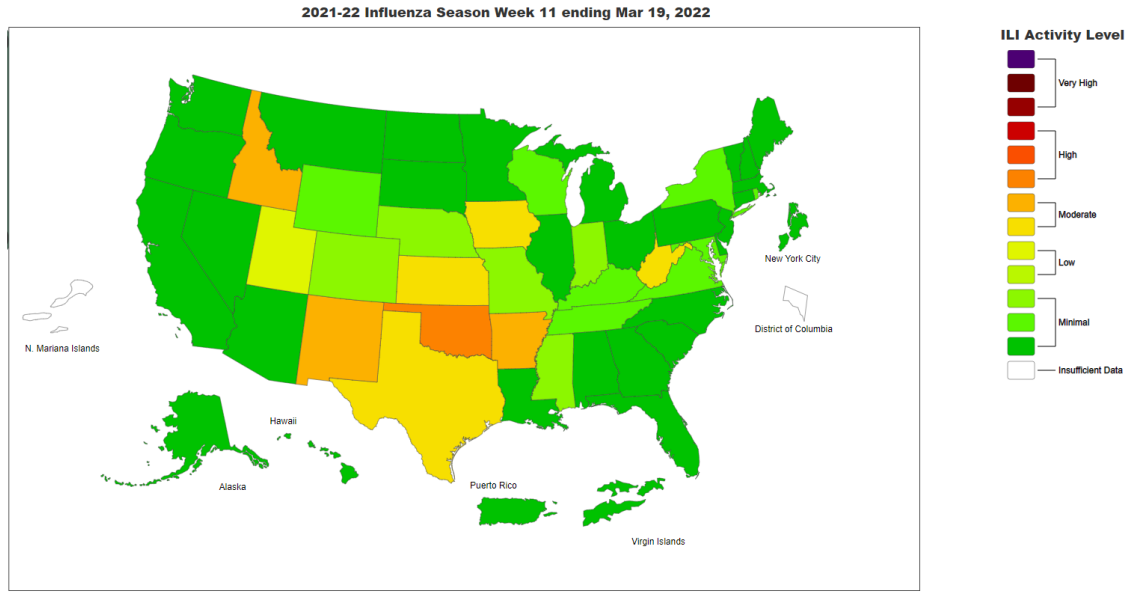
- Mixed results
  - 720 patients between 2015/2016- half rapid multiplex molecular (POCT), half not tested[1]
    - No difference in mean duration of antibiotics, adverse outcomes
    - POCT group positive outcomes: 1)had single dose or brief courses; 2)received timely/appropriate influenza therapy; 3)reduced length of stay (LOS)
  - Reduction of antibiotic duration noted comparing rapid multiplex molecular assay vs standard PCR with 2 day TAT[2]
    - Also used procalcitonin
    - Many high risk populations excluded
  - If influenza detected using rapid molecular testing, fewer antibiotics were started, and more high risk patients were treated with oseltamivir[3]
    - No difference in LOS
  - Rapid molecular testing did not decrease Emergency Department time to disposition or antibiotic management[4]
  - Patients with molecular confirmation of SARS CoV-2 receive systemic antibacterial prescriptions, despite no evidence of bacterial infection[5]
- Virus confirmation does impact decisions on patient isolation protocols

[1]Lancet ID 2017 28392237. [2]Clin Microbiol Infect 2019 31229593 [3]BMC Infec Dis 2021 33827458
[4]Am J Emer Med Vol 37(5) [5]CID 2020 32358954

Which virus(es) should be considered?

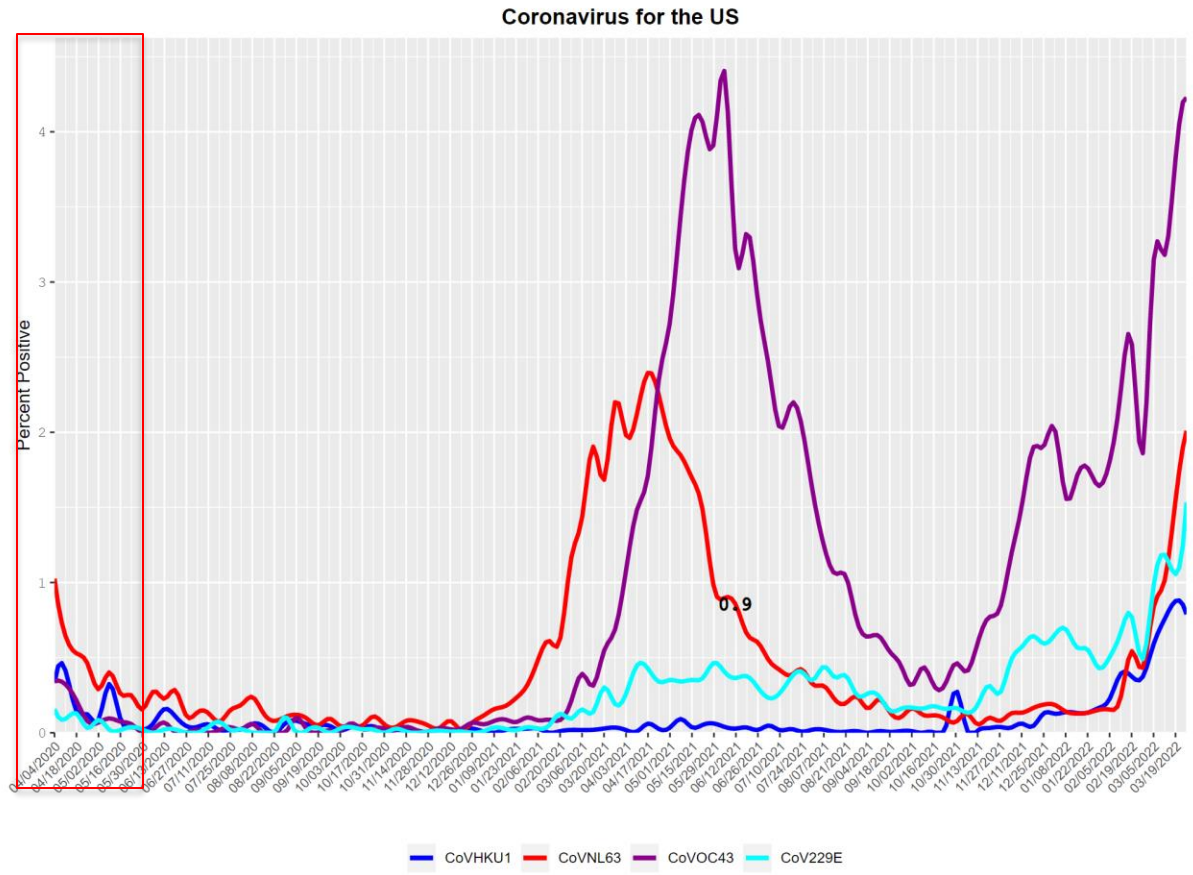
- What virus(es) currently circulate?
  - SARS CoV-2 affects every discussion
  - CDC and state/local health departments can provide information on other respiratory viruses

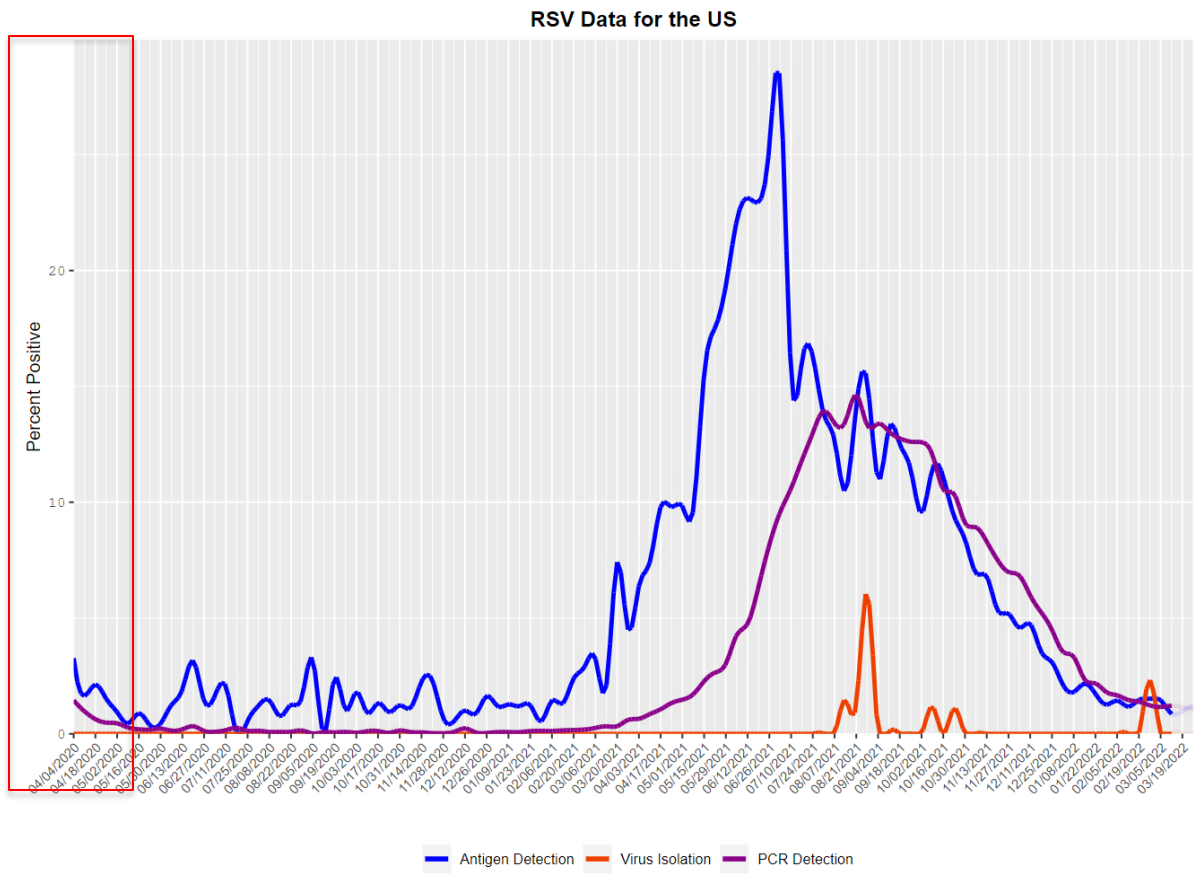
- Contacts/ travel/ exposures that may impact differential diagnosis?
  - Flu is less seasonal, more year-round in tropics
  - Exposure to children or persons with other known infections can guide testing approaches



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

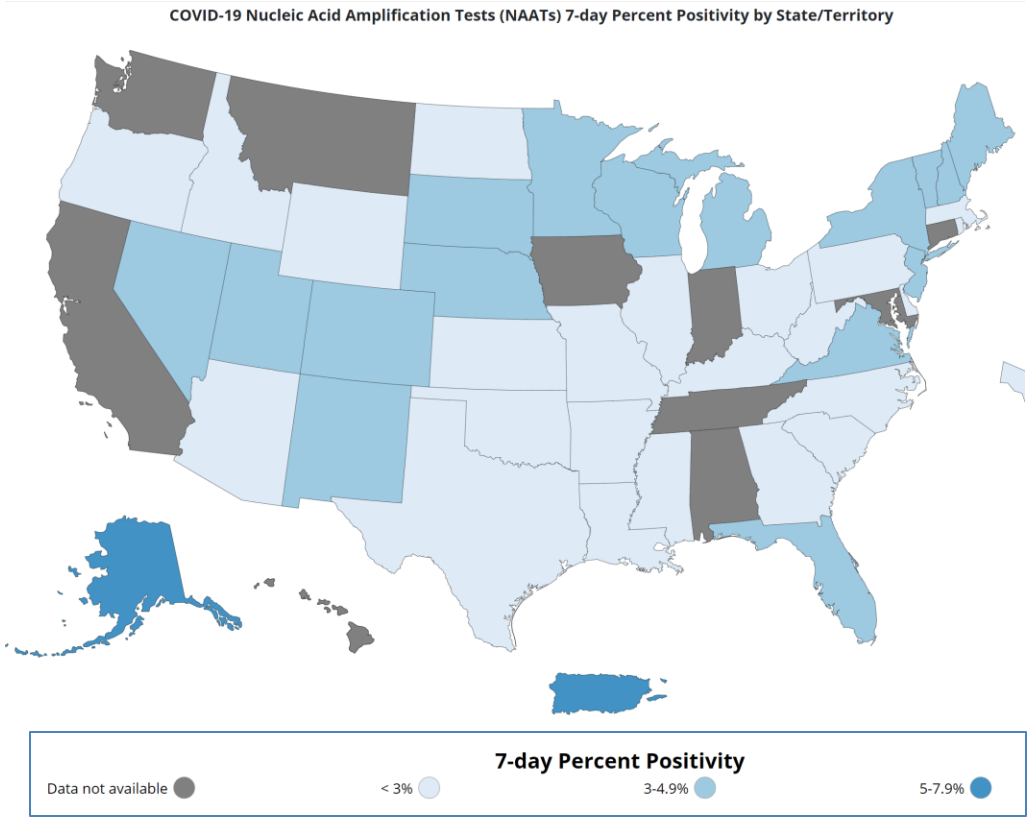
Which virus(es) should be considered?





https://www.cdc.gov/surveillance/nrevss/index.html

SARS CoV-2



COVID-19 Community Levels – Use the Highest Level that Applies to Your Community

New COVID-19 Cases Per 100,000 people in the past 7 days	Indicators	Low	Medium	High
Fewer than 200	New COVID-19 admissions per 100,000 population (7-day total)	<10.0	10.0-19.9	≥20.0
	Percent of staffed inpatient beds occupied by COVID-19 patients (7-day average)	<10.0%	10.0-14.9%	≥15.0%
200 or more	New COVID-19 admissions per 100,000 population (7-day total)	NA	<10.0	≥10.0
	Percent of staffed inpatient beds occupied by COVID-19 patients (7-day average)	NA	<10.0%	≥10.0%

The COVID-19 community level is determined by the higher of the new admissions and inpatient beds metrics, based on the current level of new cases per 100,000 population in the past 7 days

COVID-19 County Check

Find community levels and prevention steps by county.

Select a Location (all fields required)

Texas | Dallas County

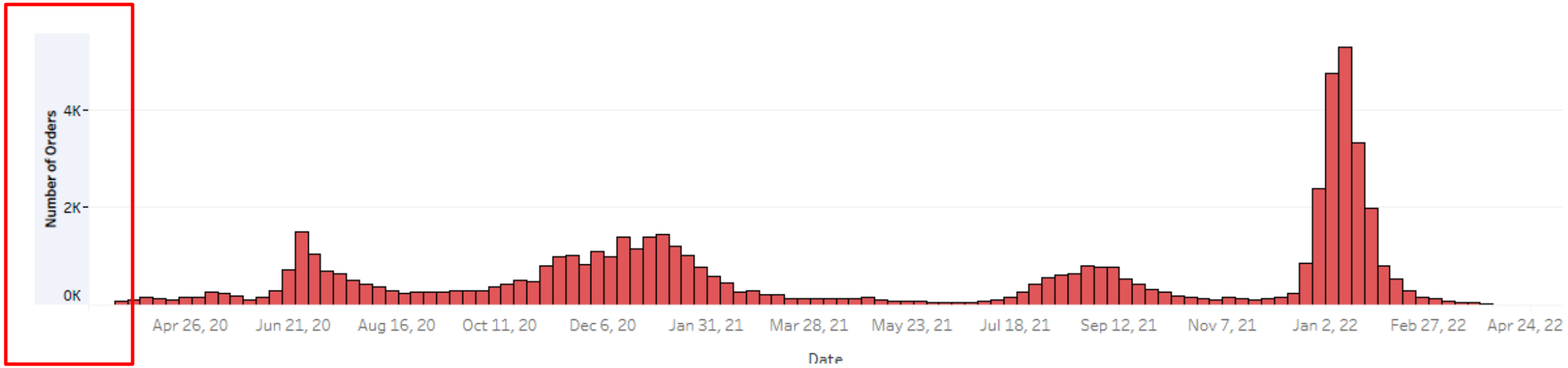
< Start Over

Low

In **Dallas County, Texas**, community level is **Low**.

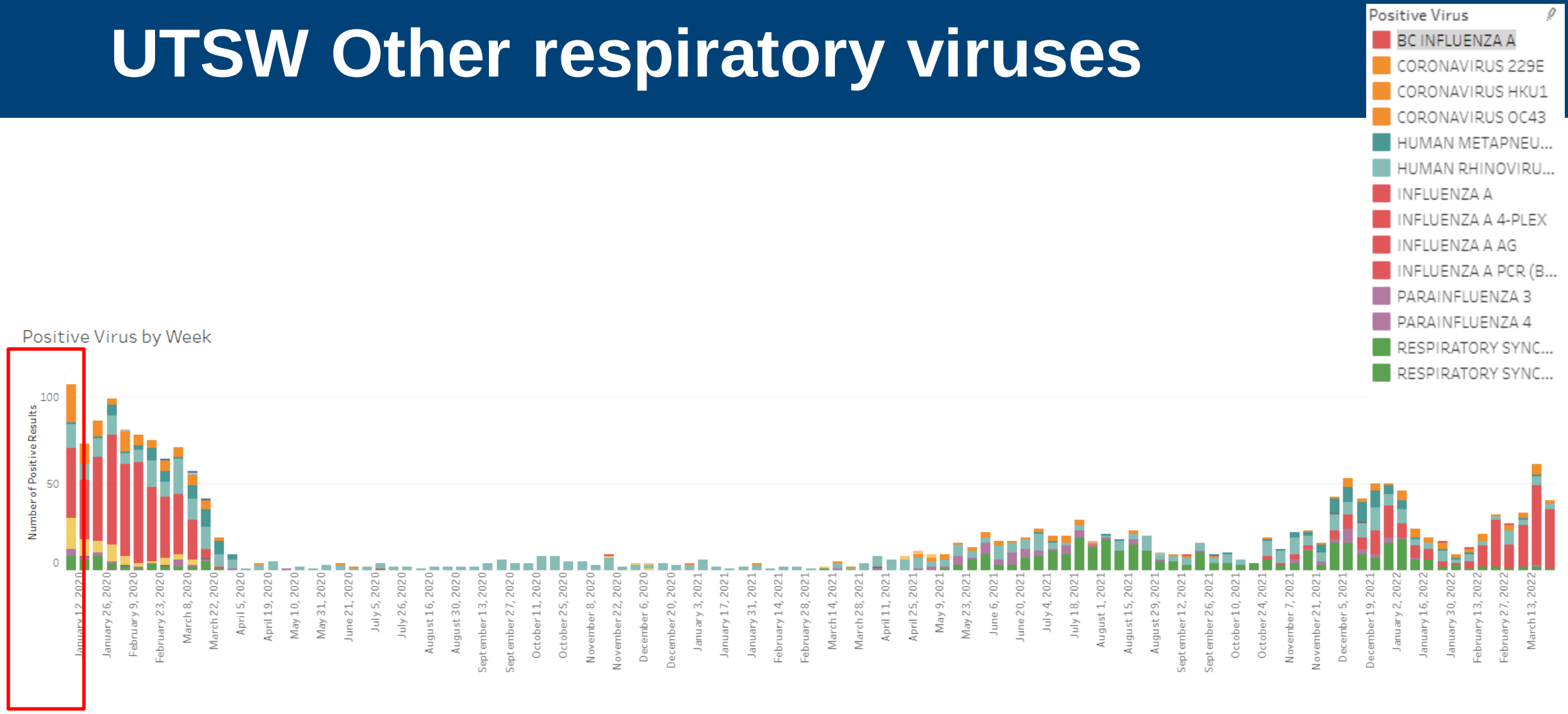
https://covid.cdc.gov/covid-data-tracker/#datatracker-home

UTSW SARS CoV-2 positive results



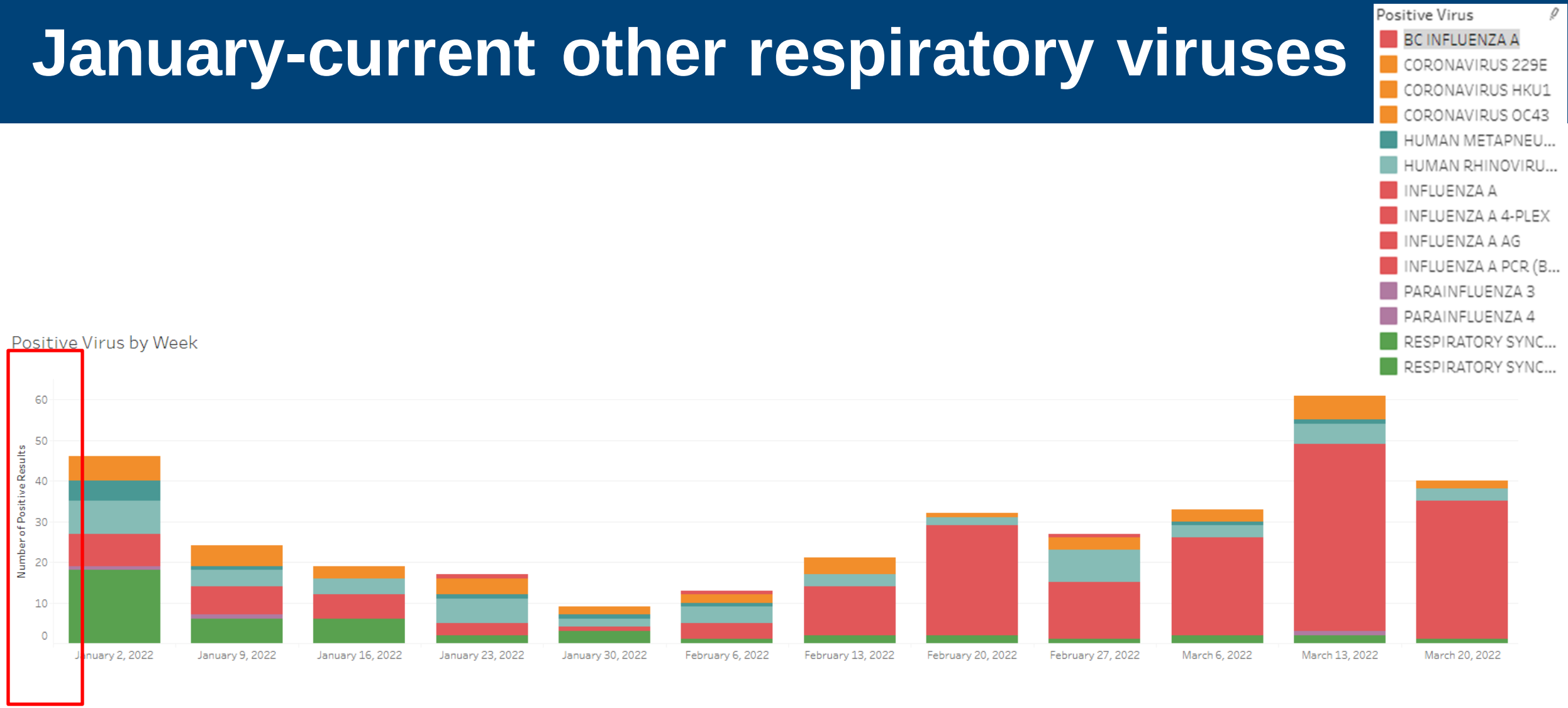
Courtesy of Dr. Ellen Araj

UTSW Other respiratory viruses



Courtesy of Dr. Ellen Araj

January-current other respiratory viruses



Courtesy of Dr. Ellen Araj

How to choose a test

Supply chain and allocation challenges affect test availability

Turn-around-time (TAT) for test

- What is acceptable based on the clinical presentation? – outpatient vs ED vs inpatient
- Is there a speed/sensitivity trade-off?

How many viruses do you want to look for?

- Will you "screen" with a narrow panel, and expand if this is negative? Can this be done easily?

Method of collection

- NPS lets you look for the greatest number of viruses
- SARS CoV-2 only testing lets you use the greatest variety of collection devices/specimens

Sensitivity and specificity of the test

- Depends on the test design and specimen collection factors

Positive/negative predictive value of the test

- Depends on prevalence of disease

	PCR	Antigen	Serology

SARS CoV-2
Influenza A/B
Respiratory syncytial virus A/B
Adenovirus
Coronavirus NL63, HKU1, 229E, OC43
Parainfluenza 1-4
Human metapneumovirus
Rhinovirus/enterovirus
	• Preferred modality for respiratory virus detection
	• Available as single target tests, e.g.:
	  • SARS CoV-2
	  • FluA/B
	• Available as complexed, or highly complexed assays, e.g.:
	  • SARS CoV-2 + FluA/B + RSV
	  • Multiple targets including all listed
		• Not available for all viruses
		• Generally reduced analytical sensitivity compared to PCR.
		  • Rapid TAT may acceptable "cost"
		  • Less likely to find residual DNA in previously infected patients
		• Depending on FDA approval, may be performed on NPS, NS, or NPA/NPW.
			• **Not for acute diagnosis**
			• Possibly for SARS CoV-2 in complex cases (e.g. MIS-C) without confirmed diagnosis
			• Otherwise mainly for research or epidemiological purposes

NP-nasal swab; NPS-nasopharyngeal swab; NPA- nasopharyngeal aspirate; NPW- nasopharyngeal wash. TAT- Turn-around-time.

Complexity	Product	Method	Platform/ Instrument	Influenza Viruses Detected	Influenza A Virus Subtypes Differentiated	Other Respiratory Viruses Differentiated	Approved Specimens	Test Time
High, Moderate	BioFire Respiratory Panel 2.1 (RP2.1)	Nucleic Acid Detection	FILMARRAY® 2.0 and FILMARRAY® TORCH systems	Influenza A, Influenza B	A(H1), A(H1)pdm09, A(H3)	SARS-CoV-2,ADV, Coronavirus 229E, HKU1, NL63, OC43, hMPV, RV/EV, PIV 1-4, RSV	**NPS**	1 hour
High, Moderate, Waived	BioFire Respiratory Panel 2.1-EZ (RP2.1-EZ)	Nucleic Acid Detection	FILMARRAY® 2.0 EZ Configuration System	Influenza A, Influenza B	A(H1), A(H1)pdm09, A(H3)	SARS-CoV-2,ADV, Coronavirus 229E, HKU1, NL63, OC43, hMPV, RV/EV, PIV 1-4, RSV	**NPS**	Approximately 45 minutes
High, Moderate	ePlex Respiratory Pathogen Panel 2	Nucleic Acid Detection	ePlex System	Influenza A, Influenza B	A(H1), A(H1)pdm09, A(H3)	SARS-CoV-2,ADV, Coronavirus 229E, HKU1, NL63, OC43, hMPV, RV/EV, PIV 1-4, RSV	**NPS**	<2 hours
High, Moderate	QIAstat-Dx Respiratory SARS-CoV-2 Panel	Nucleic Acid Detection	QIAstat Dx Analyzer System 1.0	Influenza A, Influenza B	A(H1), A(H1)pdm09, A(H3)	SARS-CoV-2,ADV, Coronavirus 229E, HKU1, NL63, OC43, hMPV, RV/EV, PIV 1-4, RSV	**NPS**	1 hour
High, Moderate	cobas SARS-CoV-2 & Influenza A/B	Nucleic Acid Detection	Cobas 6800/8800 Systems	Influenza A, Influenza B	Not Differentiated	SARS-CoV-2	Healthcare provider-collected NPS and NS, and self-collected NS (collected in a healthcare setting with instruction by a healthcare provider)	3-8 hours
High, Moderate, Waived	cobas SARS-CoV-2 & Influenza A/B Nucleic Acid Test	Nucleic Acid Detection	Cobas Liat Systems	Influenza A, Influenza B	Not Differentiated	SARS-CoV-2	Healthcare provider-collected NPS and NS, and self-collected NS (collected in a healthcare setting with instruction by a healthcare provider)	20 minutes
High, Moderate	Xpert Xpress SARS-CoV-2/ Flu/RSV	Nucleic Acid Detection	GeneXpert Dx and GeneXpert Infinity systems	Influenza A, Influenza B	Not Differentiated	SARS-CoV-2, RSV	NPS, NS, NW/NA	<40 minutes
Waived	Xpert Xpress SARS-CoV-2/ Flu/RSV	Nucleic Acid Detection	GeneXpert Xpress System (Tablet and Hub Configurations)	Influenza A, Influenza B	Not Differentiated	SARS-CoV-2, RSV	**NPS**	<40 minutes
High, Moderate, Waived	Sofia 2 Flu + SARS Antigen FIA	Antigen Detection	Sofia FIA Analyzer	Influenza A, Influenza B	Not Differentiated	SARS-CoV-2	NPS, NS within first 5 days of onset of symptoms	15 minutes
High	Quest Diagnostics RC COVID-19 +Flu RT-PCR	Nucleic acid detection	Roche cobas SARS-CoV-2 & Influenza A/B	Influenza A, Influenza B	Not Differentiated	SARS-CoV-2	When ordered by a healthcare provider: NS specimen is self-collected at home using the Quest Diagnostics Self-Collection Kit for COVID-19 +Flu	Patient ships the self-collected specimen to Quest Diagnostics overnight via FedEx
High	Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay*	Nucleic Acid Detection	Applied Biosystems 7500 Fast Dx Real-Time PCR Instrument	Influenza A, Influenza B	Not Differentiated	SARS-CoV-2	NPS, NPW, NPA, NS, NA, TS, sputum, TA, BAL	4 hours

https://www.cdc.gov/flu/professionals/diagnosis/table-flu-covid19-detection.html ; last updated 2020

How “good” is the test?

A word about Ct values:
- Not standardized across platforms
- Tests are designed to be qualitative (yes/no), not quantitative
- Should NOT be used for clinical decision-making

Analytical variables

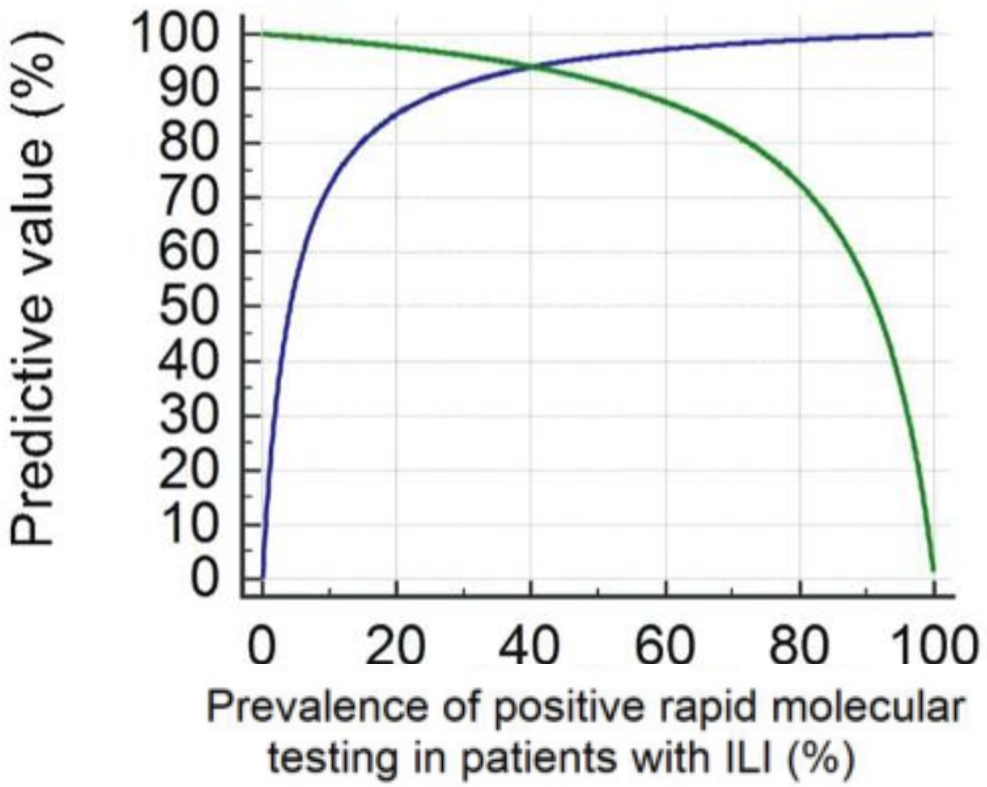
- Efficiency of nucleic acid extraction
- Design of the primer/probe sequences
- Efficiency of the PCR chemistry in the assay
- Method for defining/determining Ct value
- Lower limit of detection (analytical sensitivity)
- Lack of cross-reaction with other targets (analytical specificity)

Pre-analytic Variables

- Efficiency of sample collection
  - Device used
  - Duration of collection
- Timing of collection relative to symptom onset
- Specimen storage and transport conditions
- Age of sample at time of testing
- Specimen type—
  - matrix effect
  - level of viral RNA in different specimen types

https://www.cap.org/member-resources/articles/how-good-are-covid-19-sars-cov-2-diagnostic-pcr-tests
https://www.aphl.org/programs/preparedness/Crisis-Management/Documents/APHL-COVID19-Ct-Values.pdf

Importance of pretest probability



Prevalence of positive rapid molecular respiratory virus testing in ILI (%)	PPV (%)	NPV (%)
2.5	37.4	99.8
5	55.1	99.5
10	72.1	99.0
15	80.4	98.4
20	85.3	97.7
25	88.5	96.9
30	90.9	96.1

Positive Predictive Value
Negative Predictive Value

When disease prevalence is low, positive results have higher likelihood of being false positive.

CID 2020. 32369578

UTSouthwestern Medical Center

Antigen vs PCR (or other molecular test)

- Antigen tests face the same preanalytical challenges
  - Most antigen tests sample the anterior nares, which may have lower viral loads at baseline
  - If CLIA waived (no laboratory oversight) – quality control procedures are less stringent

- For SARS CoV-2
  - Antigen tests are 30-40% less sensitive compared to PCR
  - Specificity is similar
  - In patients with very high viral loads, this gap narrows

- For influenza
  - Antigen tests may be up to 50% less sensitive compared to PCR
  - Many are less sensitive for Flu B
  - There are newer antigen tests using instruments to standardize interpretations, that may improve the clinical performance

https://www.cdc.gov/flu/professionals/diagnosis/index.htm

CID, Volume 68, Issue 6, 15 March 2019, Pages e1–e47

Treatment Options

	Treatment	Patient type
Influenza Virus	Neuraminidase inhibitors; Endonuclease inhibitors	Treatment indicated based on disease severity, risk of progression
Respiratory Syncytial Virus	*Ribavirin ± IVIG/steroids*	No FDA approved regimen for adults. Treatment is off-label for transplant recipients.
	Multiple investigational agents	
Parainfluenza Virus	*Ribavirin ± IVIG/steroids?*	
	DAS 181-investigational	
Human Metapneumovirus	*Ribavirin ± IVIG/steroids?*	
Adenovirus	*Cidofovir, brincidofovir* ,IVIG	
Rhinovirus	None	
Human Coronaviruses (other)		

Adapted from Bitterman & Kumar, Viruses 2021. 34834953

Influenza treatment options

Neuraminidase inhibitors:

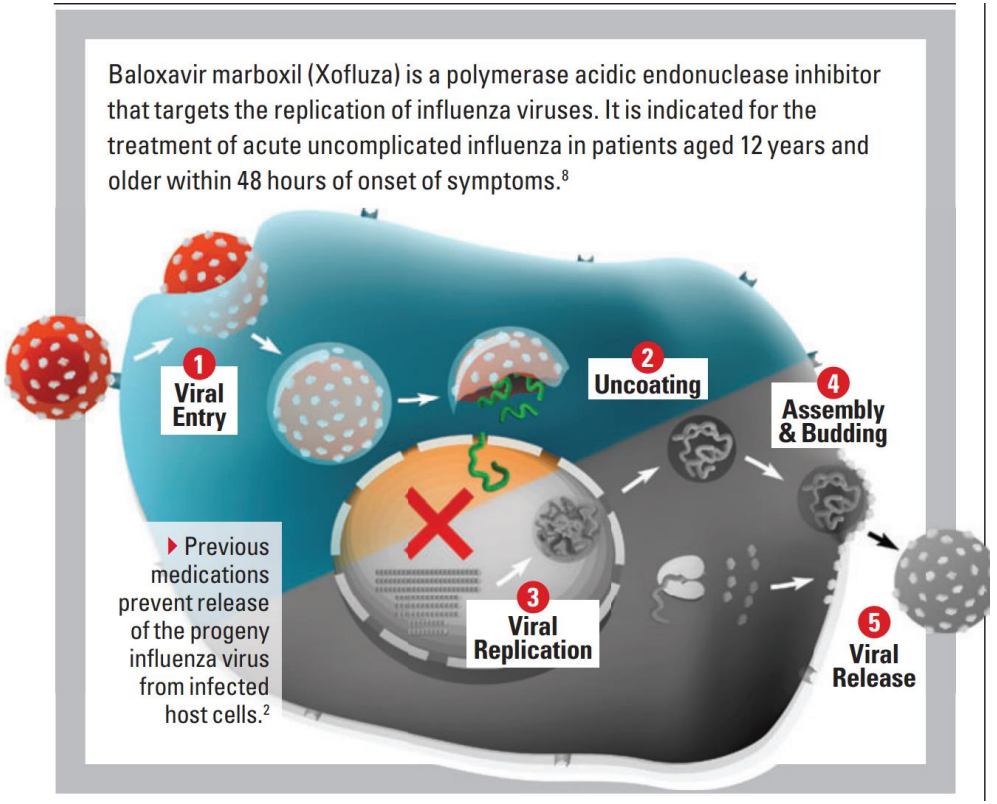
- Blocks the viral neuraminidase enzyme.
- Active against both influenza A and B
  - **Oseltamivir**: preferred agent in most cases, including hospitalized
  - Peramivir
  - Zanamivir

Endonuclease Inhibitor

- Targets PA subunit of viral polymerase complex; Interferes with RNA transcription, blocking virus replication.
- Active against both influenza A and B; may have better activity than oseltamivir against Flu B.
  - **Baloxavir**

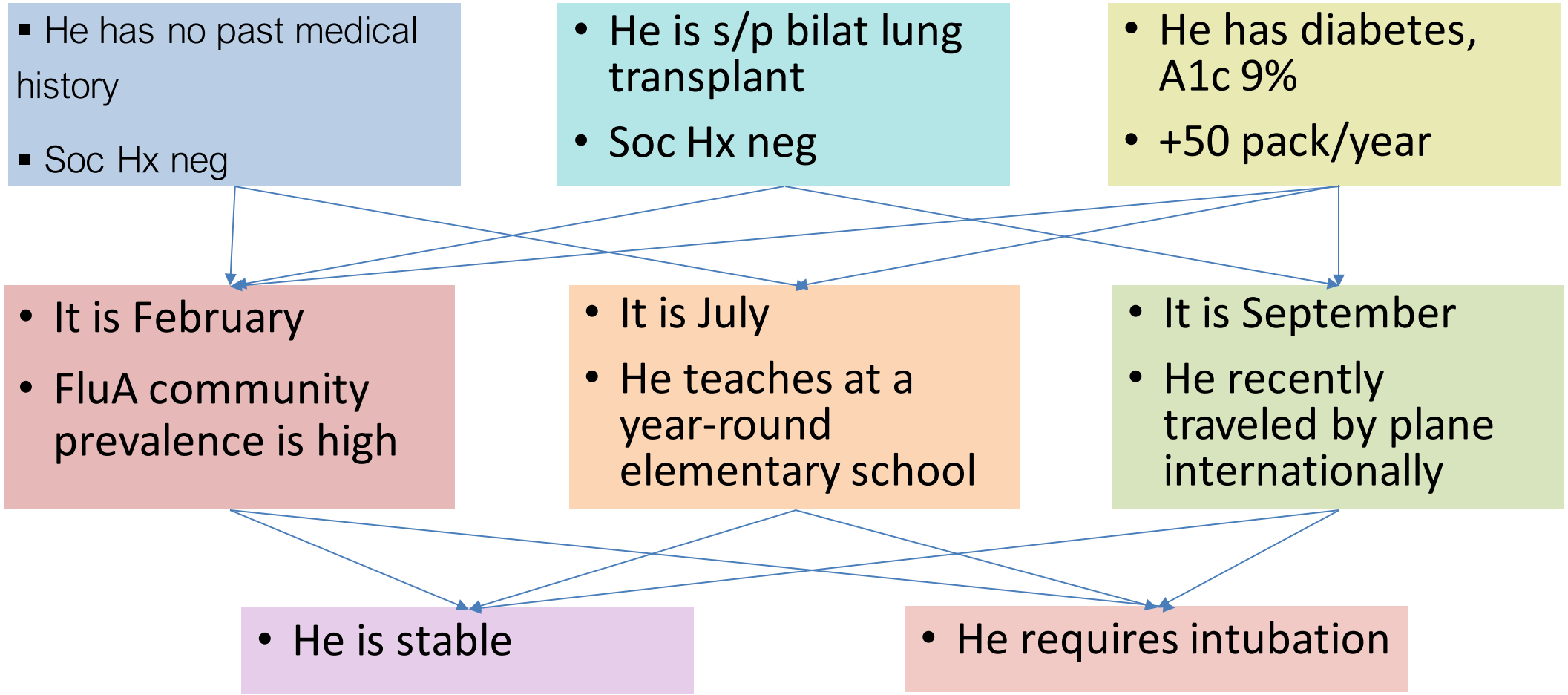
Indications

- Hospitalization
- Severe/complicated/progressive illness
- At high risk for complications from influenza



Contem Ped Feb. 2019; Curr Opin Vir 2019; Lancet ID 2020

45 year old male presenting with T 100.4, HR 110, cough, rhinorrhea, sore throat, fatigue.



Everything you need to know, again

Test patients if they are symptomatic, if they are at high risk for complications, if the test result will impact management of patient and/or infection prevention/public health decisions

The virus(es) of interest depend on the host and the environment

How well a test performs depends on many factors, but an NPS for a PCR-based test gives you the greatest flexibility.

Only a few viruses have targeted treatment options.

Dr. Cutrell will teach you about SARS CoV-2

Questions

- Thank you!