Sent on behalf of William Isenberg, M.D., Ph.D, Chief Medical & Quality Officer, Sutter Health, and Jeffrey Silvers, M.D., Medical Director of Pharmacy and Infection Control, Sutter Health

Emerging Infections Newsletter for Clinicians

Oct. 5, 2023

Written by Dr. Silvers with contributions from Dr. Joan Etzell (Lab), Lisa Rieg (Pharmacy), and Gordon Sproul (Pharmacy). Please use Google Chrome for the best experience.

Topics

1. Guidance for testing symptomatic patients during the respiratory season
    a. Cepheid 4 plex becoming default in Sutter Health Oct.12.
    b. Cepheid first before the BioFire multiplex respiratory panel.
    c. Delayed peak in SARS-CoV-2 viral concentration with newer strains affects testing.
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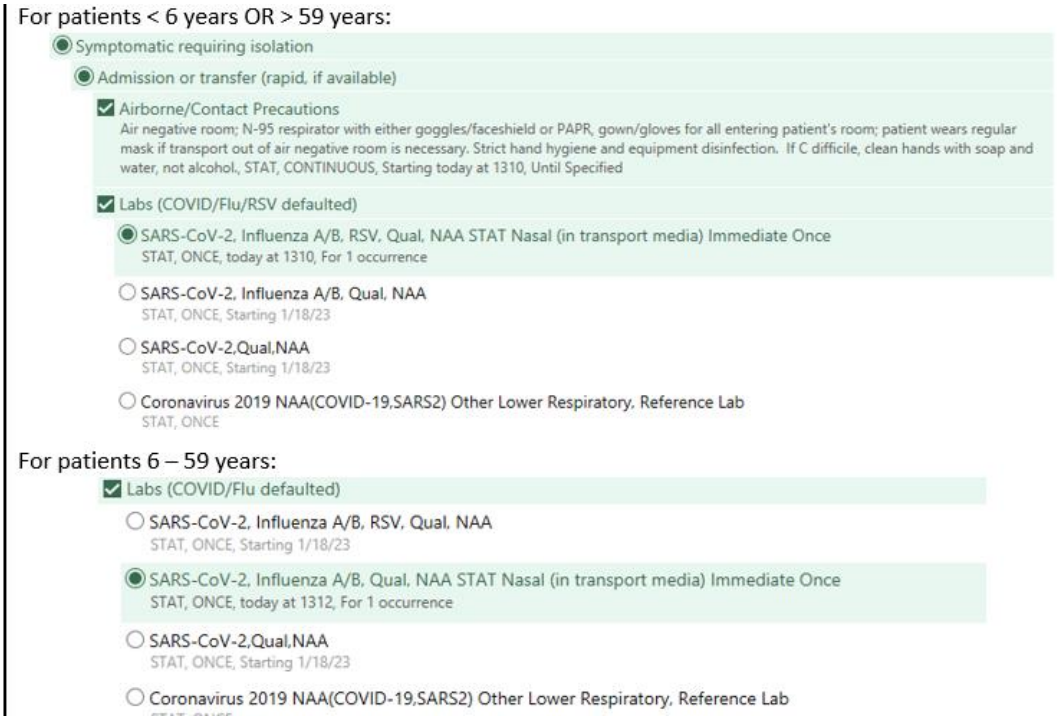
Testing for Respiratory Viruses

- On Oct. 12, Sutter Health EPIC COVID-19 order sets will be updated to default the appropriate COVID/Flu/RSV orders in the acute hospital setting and support the expansion of Cepheid and COVID-19 antigen testing in the ambulatory foundation. Bay and Valley urgent care locations with Cepheid testing will transition at the same time.
  - When testing is indicated, co-testing for COVID-19 and Influenza A/B is recommended.
  - For patients < 6 or >59 years old, RSV should also be considered.
  - COVID/Flu/RSV testing is recommended as initial testing before ordering any other multiplex panel (such as BioFire).
  - Full respiratory panel testing should only be used if COVD/Flu/RSV is negative and additional testing is necessary for clinical decision making.



- A study performed during Omicron was just published in *Clinical Infectious Diseases*. It measured viral load of SARS-CoV-2 and Influenza relative to symptom onset in persons 16 years and older.
  - 348 patients with newly diagnosed, symptomatic, PCR positive COVID
    - 91% had a history of vaccination, natural infection, or both.
    - Female to male 2:1, median age 39.2 years
  - Antigen sensitivity was estimated by percentage of participants with PCR Ct $\leq$ 30 or Ct $\leq$ 25.
  - By both CT (cycle threshold) and antigen concentration measurements, median viral loads increased from the onset of symptoms until a peak on the fourth/fifth day.
  - Antigen sensitivity

	Day 1	Day 3	Day 4
Antigen Sensitivity	30-60%	59-75%	80-93%

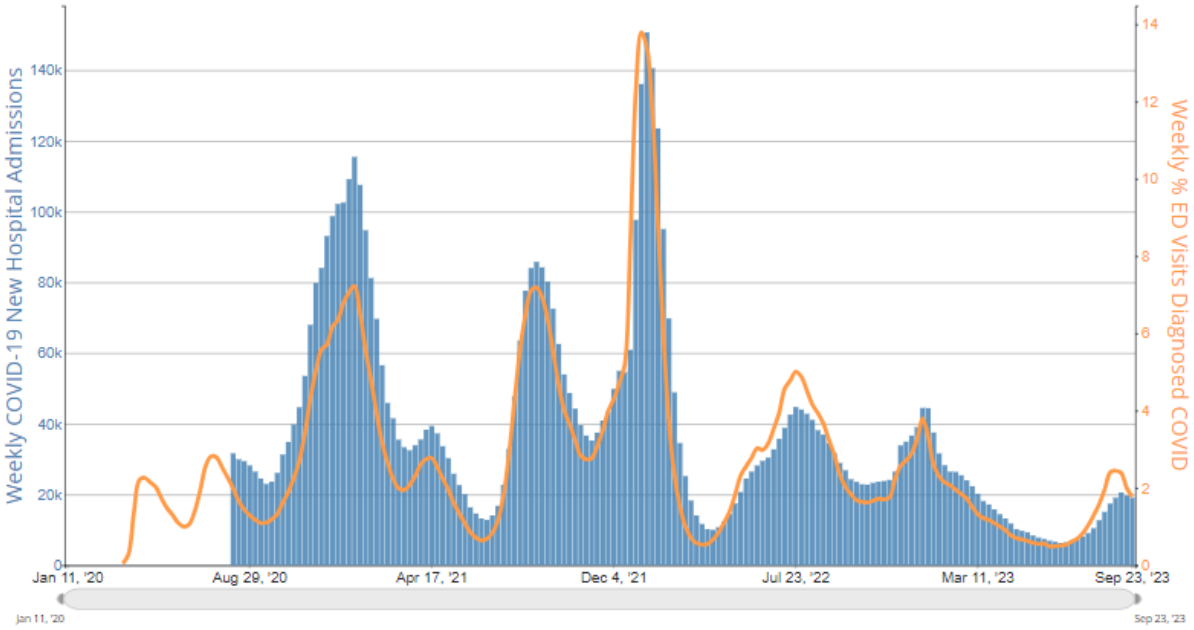
- In contrast, 74 PCR positive patients with influenza had peak viral loads on the second day of symptoms
- Early in the pandemic, SARS-CoV-2 viral loads peaked at the onset of symptoms, similar to influenza. A negative antigen test was considered reliable. With the finding of delayed times from onset to peak viral load, a single negative antigen test in the first few days of illness may not be adequate to rule out COVID.
- In addition, these results increase the likelihood that a person will not have a negative antigen test on day number 5, which CDPH requires before a healthcare worker can return to work.

- **Respiratory Season Testing Take-Home:**
  - Starting Oct. 12, Sutter Health default testing will change from COVID-19 alone to the Cepheid 4- plex including SARS-CoV-2, Influenza A/B and RSV.
    - RSV is recommended for persons less than 6 or greater than 59 years old
  - Larger respiratory panels are not recommended to be ordered unless the Cepheid 4-plex is negative and larger panel results might alter care.
  - SARS-CoV-2 viral loads peak later now than they did with earlier strains and pre-vaccinations. This can result in false negative antigen tests when only a single test is performed.
    - The CDC already recommends a repeat test 48 hours after an initial negative antigen test in a symptomatic person still suspected of having COVID.
    - 48 hours may not be adequate if performed on day number 3 of symptoms.
  - The molecular test performance is not affected by the circulating variants.
  - The delayed peak in SARS-CoV-2 viral load can impact the ability of HCW to test negative and return to work after 5 days of isolation.
  - Masking for source control and vaccinations become more important.

COVID-19

- Hospitalizations in the United States are surrogates for the virulence of the circulating strain. The graph below and the subsequent table now show stable hospitalizations (blue vertical bars) with a concomitant continued decrease in the percentage of patients being diagnosed with COVID in emergency departments (orange run line).

COVID-19 New Hospital Admissions and Percentage of Emergency Department (ED) Visits Diagnosed as COVID-19, by Week, in The United States, Reported to CDC



- The CDC tracks hospital admissions per 100,000 county population. Less than 10/100,000 is considered a low number of new hospital admissions. Two tables are shown below. The first one posted Aug. 28 was when hospitalizations were on the increase. The rate increase was 21.6% in one week. The second shows that nationally we are on the decline. The admissions percent change is now negative at -3.1%.

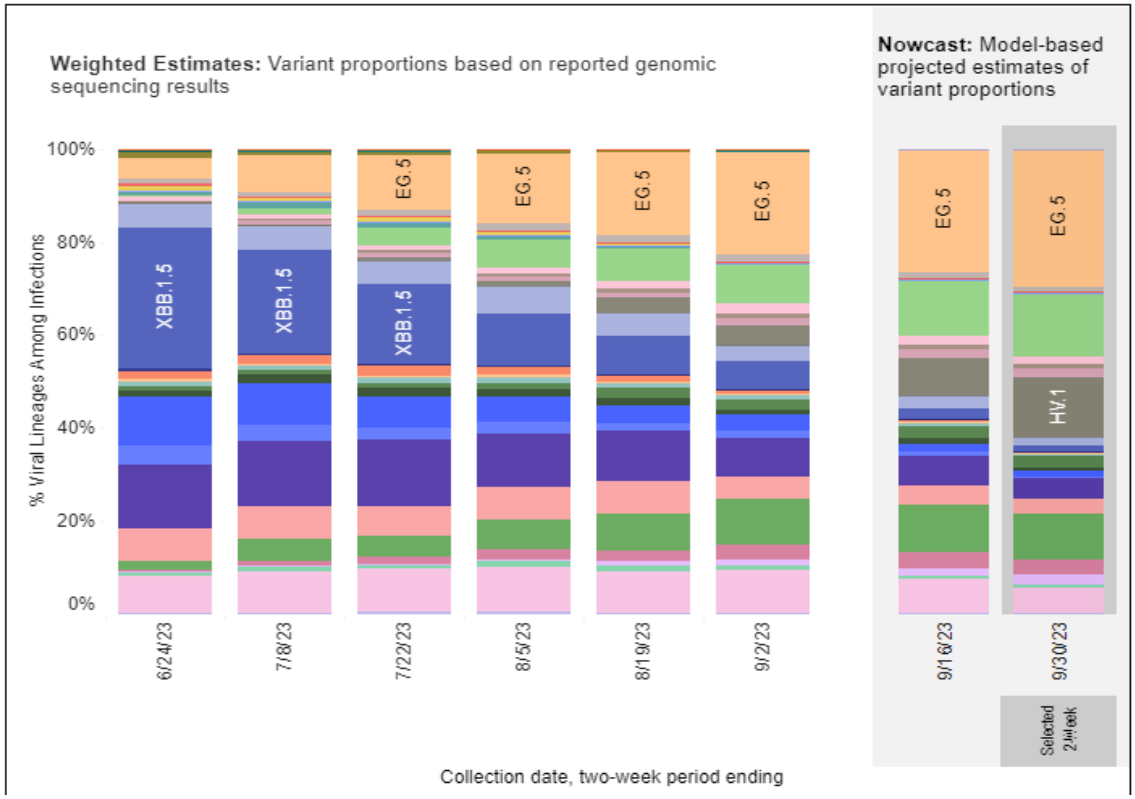
COVID-19 HOSPITAL ADMISSIONS (PAST WEEK)	% CHANGE IN COVID-19 HOSPITAL ADMISSIONS	COVID-19 HOSPITAL ADMISSIONS PER 100,000 (PAST WEEK)
12,613	21.6%	3.8

CDC | Data through: August 12, 2023. Posted: August 24, 2023

COVID-19 HOSPITAL ADMISSIONS (PAST WEEK)	% CHANGE IN COVID-19 HOSPITAL ADMISSIONS	COVID-19 HOSPITAL ADMISSIONS PER 100,000 (PAST WEEK)
19,079	-3.1%	5.75

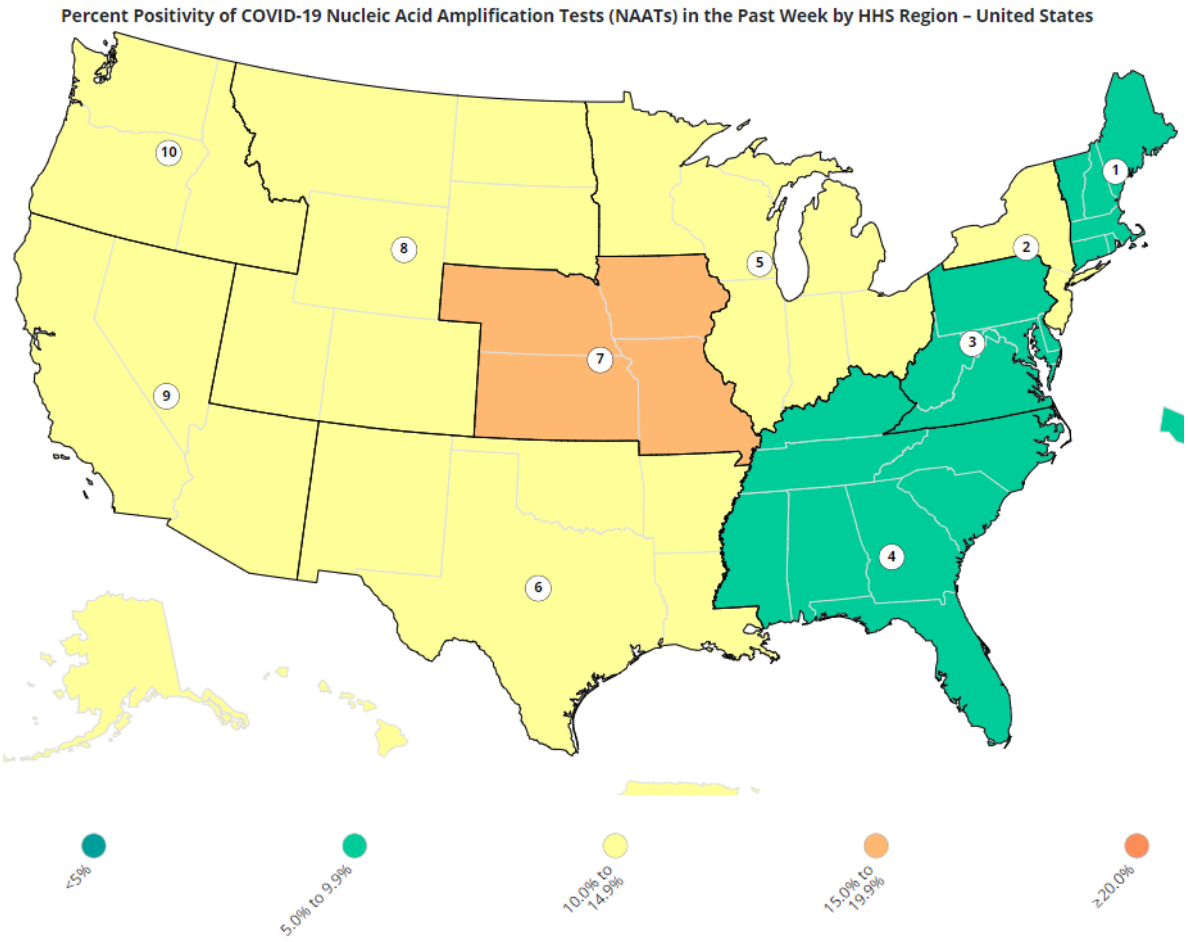
CDC | Data through: September 23, 2023. Posted: October 2, 2023

- National genomic sequencing was updated on Oct. 1 (graph below). EG.5 rates are slowly increasing. FL.1.5.1 and now HV.1 are second and third respectively. HV.1 is an offshoot of XBB.1.9.2. Combined they constitute 56% of isolates.

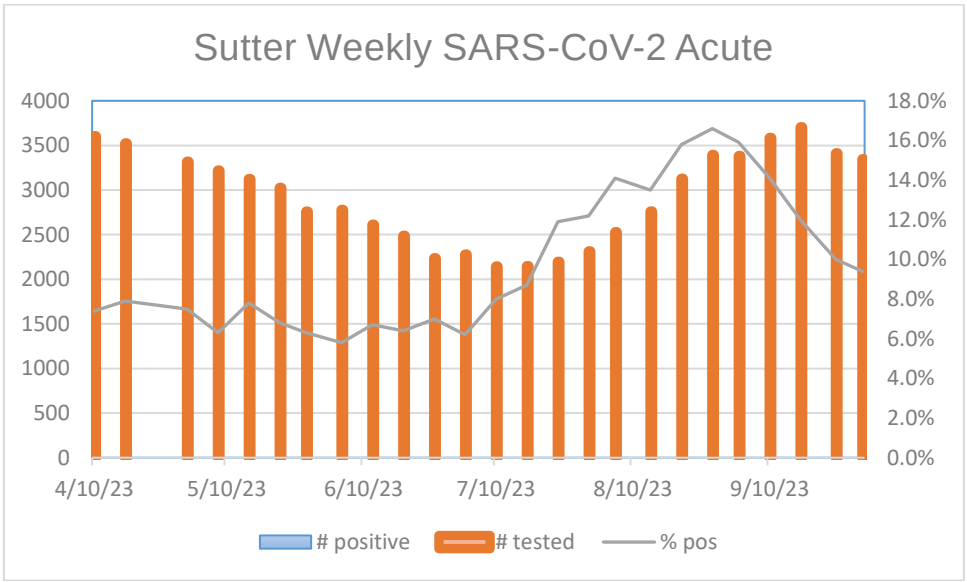


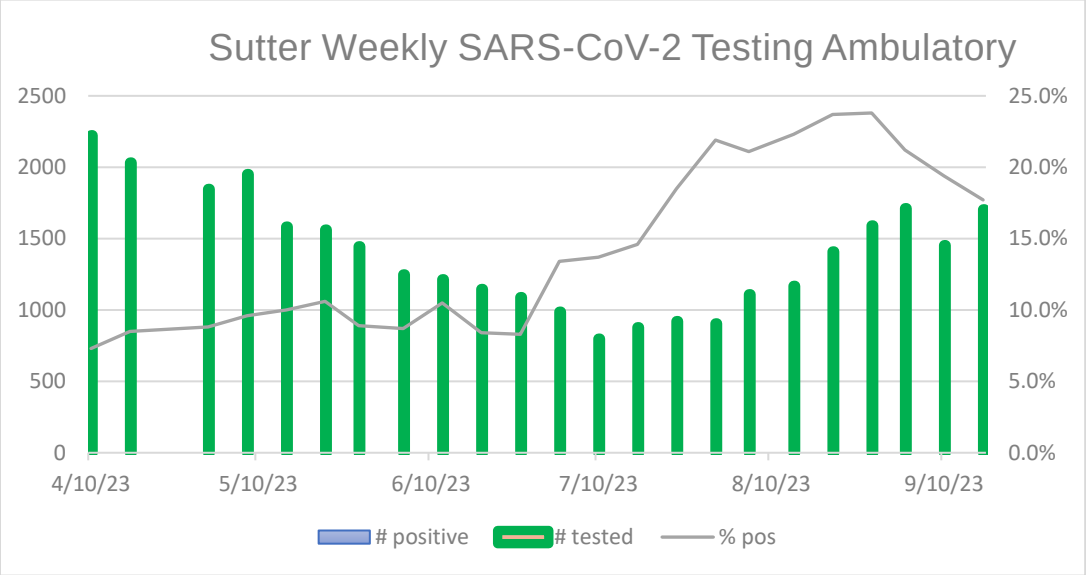
WHO label	Lineage #	%Total	95%PI	
Omicron	EG.5	29.4%	26.4-32.6%	
	FL.1.5.1	13.7%	10.8-17.1%	
	HV.1	12.9%	10.5-15.6%	
	XBB.1.16.6	10.1%	8.6-11.7%	
	XBB.2.3	5.6%	4.7-6.5%	
	XBB.1.16	4.3%	3.8-4.9%	
	XBB.1.16.11	3.2%	2.6-3.9%	
	XBB.1.16.1	3.0%	2.4-3.8%	
	XBB.1.5.70	2.5%	1.9-3.4%	
	XBB.1.16.15	2.0%	1.4-3.0%	

- National molecular test positivity rates by region show a definite downward trend. See the map below. More regions are turning green, and some yellow regions are on the cusp of turning green. Only region 7 is orange and it is on the threshold of turning yellow.



- Updated Sutter testing data below shows decreasing positivity rates with significant levels of testing both in emergency departments and ambulatory environments.





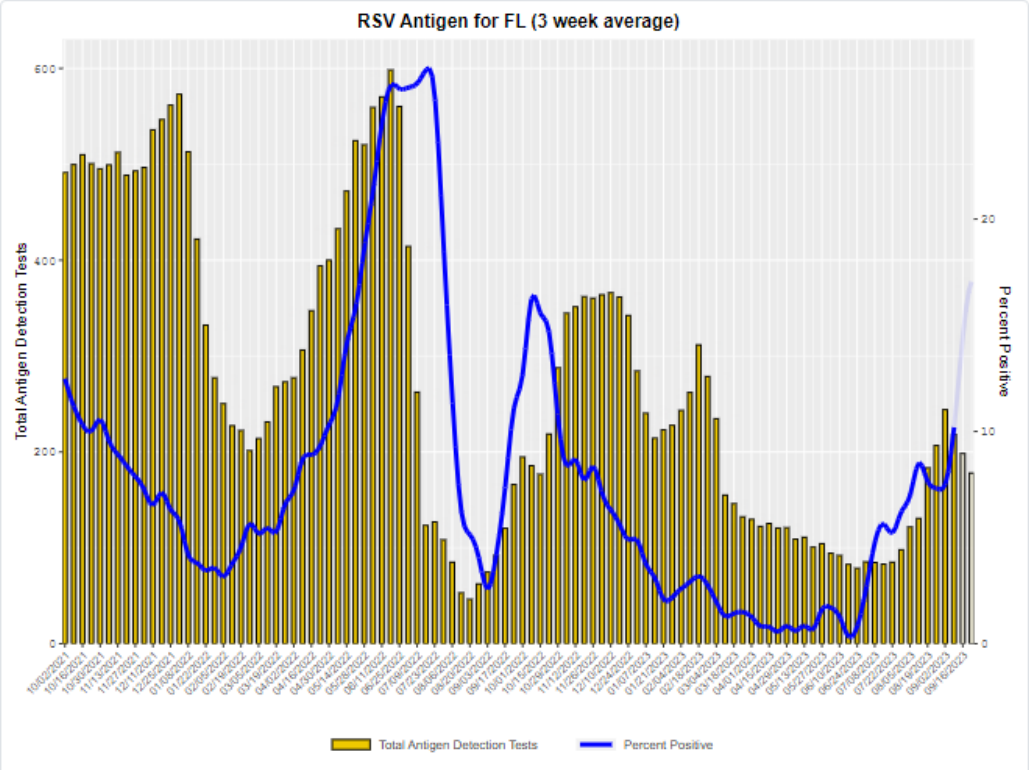
- **COVID-19 Take-Home:**
  - Co-circulation of multiple strains of SARS-CoV-2 continues.
  - Hospitalizations, emergency department visits and Sutter Health testing positivity rates are all trending down. COVID appears to have peaked for now.
  - Although still not low, Sutter ambulatory and emergency department positivity rates are down to 12.9% and 9.4% respectively.
  - Masking for source control is important.
  - The XBB vaccine has significant potential to mitigate a winter outbreak. Don't miss an opportunity to provide this important protection.
  - Sutter is now booking COVID-19 XBB vaccine appointments for individuals 12 years and older online and by phone. Initial appointment availability may be limited in some areas and for certain age groups. Please check our vaccine resources page for updates.

- **Related Links**
  - CDC Caring for Patients
  - CDC Data Tracker
  - CDC Latest Updates
  - CDC Vaccine Information
  - CDPH Tracking and Vaccination Updates
  - Sutter Health for Clinicians
  - Sutter Health for Patients
  - WHO Table of Contents

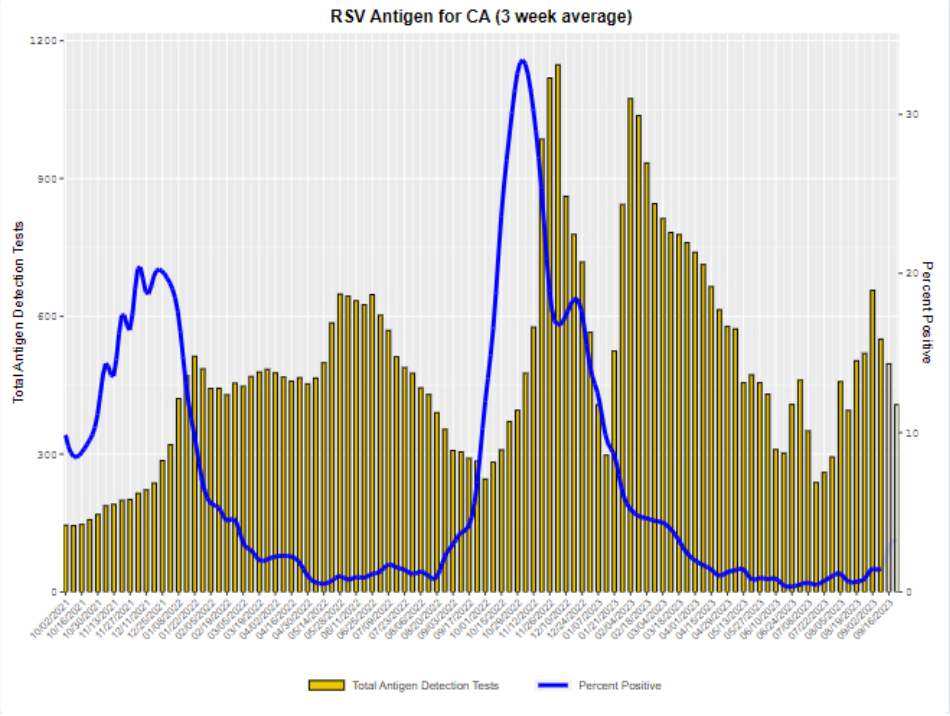
RSV

- Increased cases of RSV are being recognized in parts of the United States. Below is a CDC map showing Florida followed by California. The blue run line in Florida shows that the rate has been greater than the 3% outbreak threshold since July 8. On the other hand, California just crossed that breakpoint for the first time on Sept. 23.

Total Antigen Tests

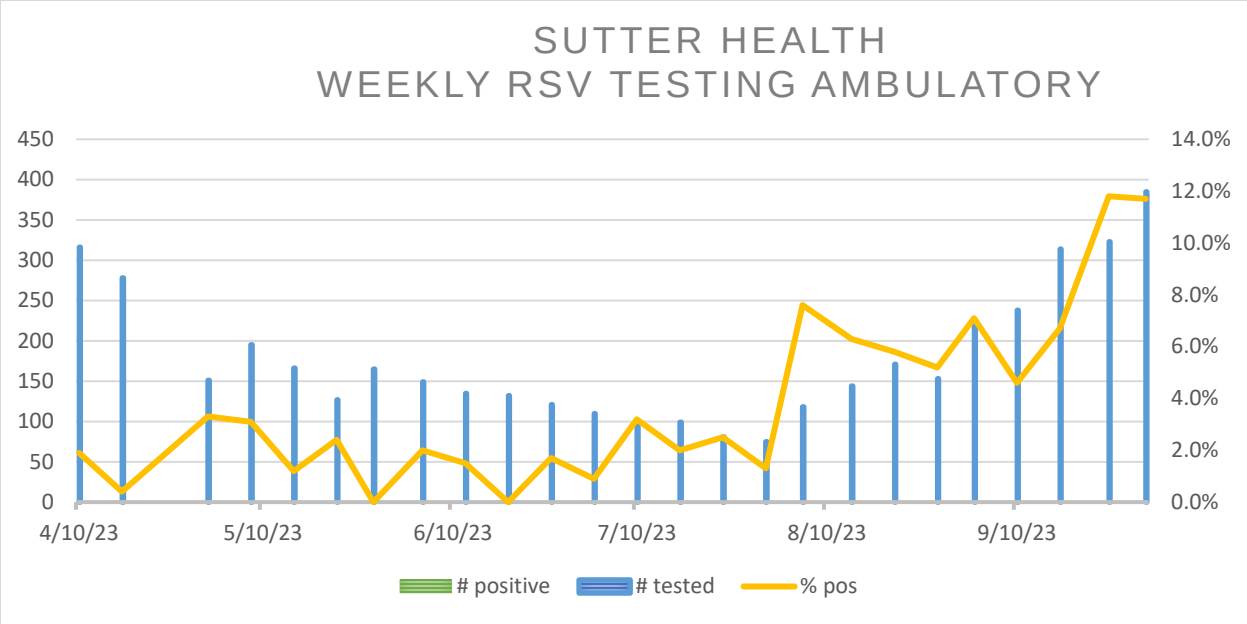


Total Antigen Tests

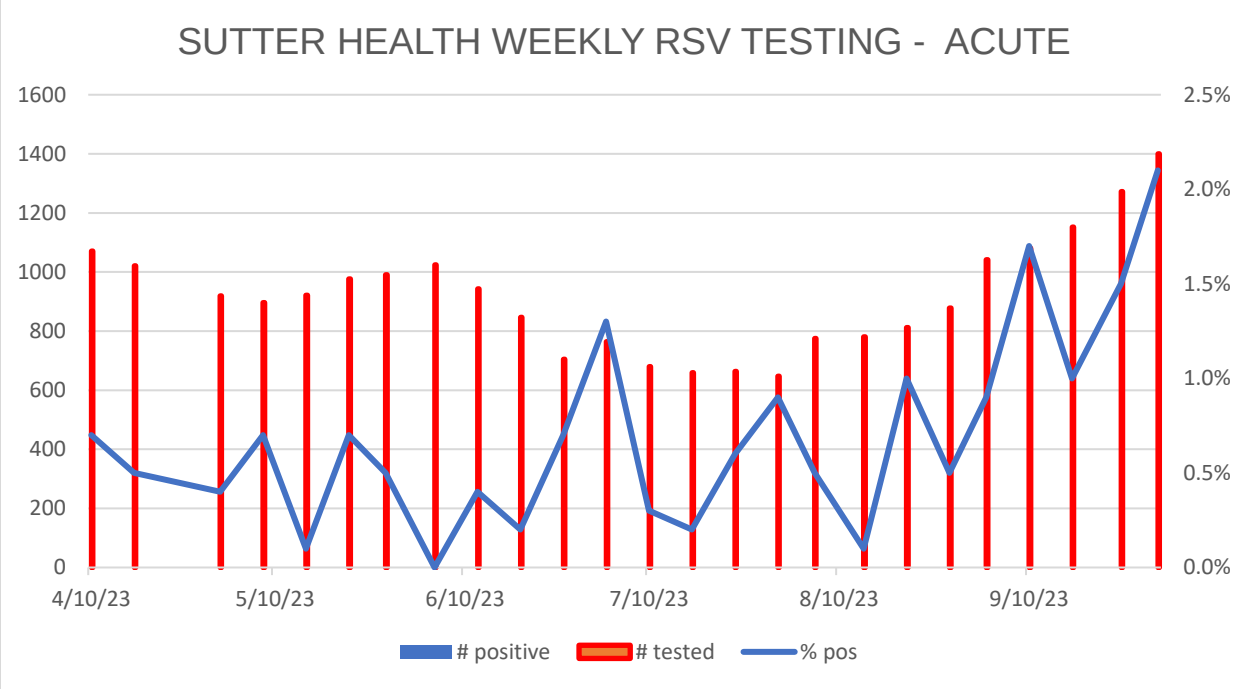


- RSV is still being identified in the ambulatory setting. The amount of testing in ambulatory is gradually increasing and positivity rates are well above the 3% threshold for 9 weeks now. The week ending Oct. 1 had 385 tests ordered. This reflects a 19%

increase in testing compared to the prior week with a sustained increased positivity rate. See graph below.



- Although ED positivity rates remain below 3%, they are increasing in a stepwise fashion since the middle of August. The number of tests being performed has also continued to increase.



- RSV results by age are in the following table for the week ending Oct. 1. Positivity rates in children less than 6 years old are now over 18% in the ambulatory environment and over 5% in the emergency departments.

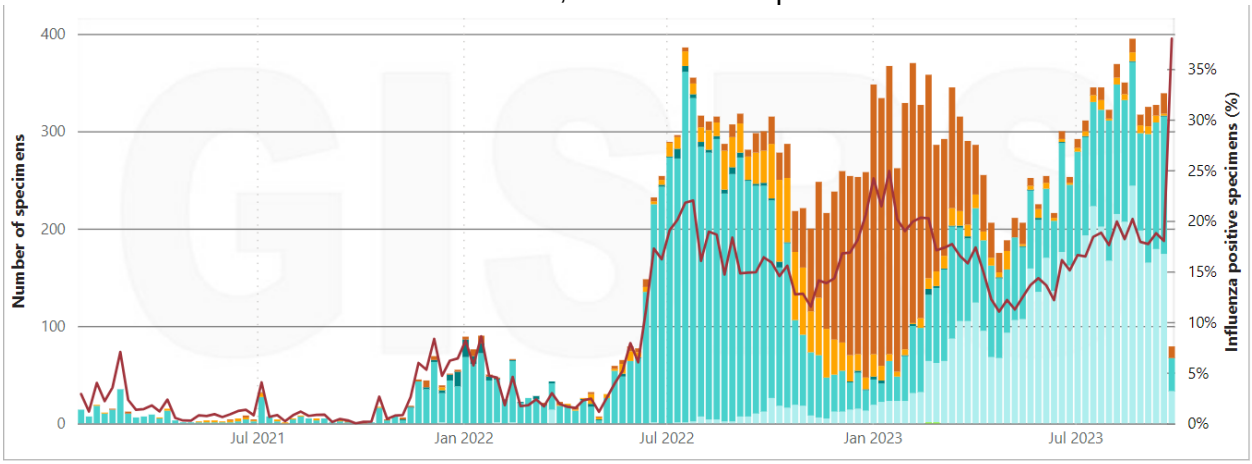
Location	<6 years old		Less than 18 years old		60 years old and older	
	Number Tested	% Positive	Number Tested	% Positive	Number Tested	% Positive
Ambulatory	188	18.6%	239	15.1%	43	0.0%
Acute (ED)	394	5.3%	549	4.6%	461	0.4%

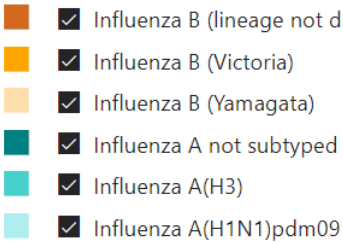
- Most of the increased RSV activity continues to be identified in children less than 6 years old, in the ambulatory environment and probably reflects mild disease. More cases of children less than 6 years old are being seen in emergency departments.
- **Maternal RSV Vaccine:** On Sept. 29, the CDC published guidance on seasonal administration of Abrysvo™ maternal RSV vaccine at 32-36 weeks' gestation to prevent RSV lower respiratory tract infection in infants.
  - The CDC defines "seasonal" as usually September through March.
  - Protection from maternal vaccination may begin to wane after 3 or more months based on MATISSE trial data, making intra-seasonal administration a more effective approach.
- Either maternal vaccination or use of nirsevimab in the infant is recommended to prevent RSV lower respiratory tract infection, but administration of both products is not needed for most infants.
- Coadministration of Tdap and RSV vaccine saw decreased immune response to pertussis components in the Tdap vaccine (non-inferiority criteria was not met).
  - Tdap is recommended to be given every pregnancy between 27-36 weeks' gestation. If it is anticipated the mother will also receive Abrysvo, Tdap should preferably be given during the early part of gestational age (27-32 weeks), followed by administration of Abrysvo™ between weeks 32-36.
- Sutter is already offering Abrsyvo™ RSV vaccine to adults 60 years of age and older in primary and urgent care settings based on Shared Clinical Decision Making. Additional information regarding offering Abrysvo in the OB clinic setting will be available in the coming weeks.

- **RSV Take-Home:**
  - RSV is being identified in Northern California in increasing numbers, mostly in outpatient children less than 6 years old.
  - More children less than 6 years old are being seen in emergency departments secondary to RSV.
  - Outpatient positivity rates in children less than six years old are over 18%. Emergency department positivity rate in that same age group is now 5%.
  - Although positivity rates in persons 60 years and older remain very low, that is the age group with the highest risk of mortality.
  - In appropriate symptomatic patients, testing should still be performed.
  - High-risk patients 60 years and older should be offered the RSV vaccine.
  - Maternal RSV vaccine is now approved with specific guidance about timing and seasonal administration. This is another great option to protect infants against RSV disease.

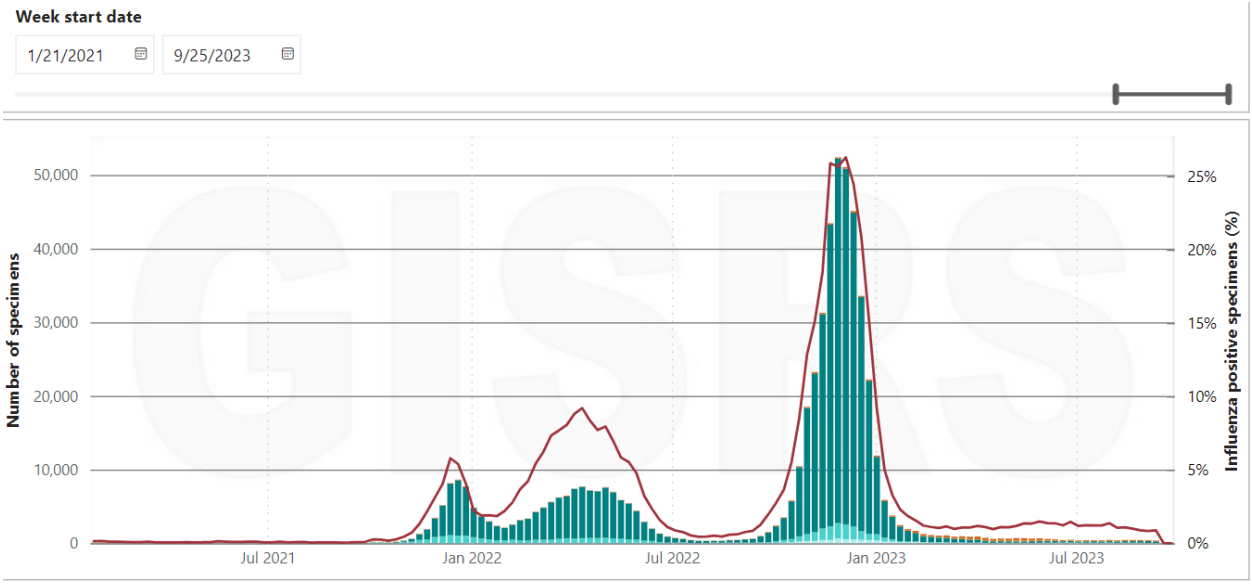
Influenza

- The WHO tracks influenza activity in the world. Overall levels remain low or at inter-seasonal rates.
- South-East Asia appears to have the highest reported activity, which is predominantly influenza A H1N1 and A H3N2. The graph below shows that SE Asia positivity rates are about 20% and appear stable. Reported rates have been above 10% since June of 2022. Note that Influenza was predominantly B from the end of October until early March and then transitioned to influenza A, which now comprises 96% of all isolates.





- Contrast this with the United States where influenza activity remains very low, illustrated by the map below. It is important to note that the first Y axis (number of specimens) is dramatically different between SE Asia and the United States.



- Flu positivity rates in the United States remain very low. No significant evidence of the start of the winter season anywhere at this time.

- **Future flu vaccine trials**
  - Current influenza vaccines have multiple, well-known limitations including short-lived serum antibodies, lack of immunity at the site of infection and lack of robust protection against drifted strains.
  - There are 18 known Influenza A hemagglutinin (HA) subtypes and 2 Influenza B.
  - Providing a true universal flu vaccine that protects against future pandemics would need to protect against all these types.
  - Two approaches to a true universal vaccine include a preparation with all 20 subtypes or a vaccine that provides effective antibodies against the conserved HA stalk. Trials testing a potential universal influenza vaccine have been ongoing for many years.
  - Additional goals in vaccine development are to develop a more effective and a longer- lasting vaccine.
  - Nanoparticle mRNA vaccines hold the most promise for dramatically improving the flu vaccine.
  - The NIH recently announced the start of another phase 1 clinical trial of a universal flu candidate, FluMos-v2. This vaccine contains nanoparticles from six different influenza hemagglutinins (4 influenza A and 2 influenza B). These particles form the framework for production of multiple protective antibodies. This trial will only include 24 individuals.
    - Phase 1 trials are small trials with small numbers of volunteers. The primary objective is to confirm safety already strongly expected from animal studies.
  - Duke Health started a phase 1 trial on their universal mRNA flu vaccine last May.
  - Pandemic preparedness includes areas of the world that typically depend on outside suppliers of the vaccine.
  - A major concern of mRNA technology for producing vaccines is the high likelihood of inequity in vaccine access. As we have seen with the COVID pandemic, only limited parts of the world have been able to obtain, store, and administer the mRNA vaccines.

- **The vaccine will be trivalent again for the 2024-2025 flu season**
  - Influenza B has different epidemiology compared to influenza A.
    - Influenza B viruses widely circulate only in humans.
    - Mutations are much less frequent in Influenza B compared to Influenza A.
    - There are only two identified B lineages, one of which became extinct with the onset of COVID-19.
  - Influenza B/Yamagata lineage has not been identified since March 2020.
    - A few isolates are found representing the live attenuated vaccine strains.
  - The WHO recommendation for the 2024 southern hemisphere influenza season vaccine was recently released. "*It is the opinion of the WHO influenza vaccine composition advisory committee that inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted*."

- **Influenza Take-Home:**
  - Influenza activity remains very low in the United States and much of the world. SE Asia has the highest rates.
  - Universal flu vaccine trials are now studying newer candidates developed with technology that has the potential of improved efficacy in preventing or attenuating disease, and possibly decreasing the frequency of vaccine administration.
  - The 2024-25 flu vaccine should be trivalent again.

- October remains an excellent time to vaccinate against influenza.

Share the Newsletter

Anyone who would like to be added to the Emerging Infections newsletter should send a request to bryan.gardner@sutterhealth.org

This communication is intended for clinicians caring for Sutter patients. If you have questions, please reach out to us at clinicians@sutterhealth.org.