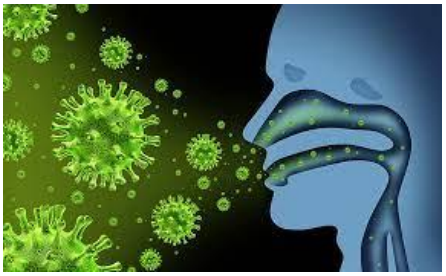

Sent on behalf of William Isenberg, M.D., Ph.D, Chief Medical & Quality Officer, Sutter Health, and Jeffrey Silvers, M.D., Medical Director of Pharmacy and Infection Control, Sutter Health

Emerging Infections Newsletter for Clinicians

August 11, 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. COVID-19
    a. Defining variants
    b. EG.5 – Elevated August 9 to Variant of Interest
    c. United States hospitalizations and ED visits
    d. National genomic sequencing surveillance
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2. RSV
    a. Nirsevimab (Beyfortus®) approved
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COVID-19

The WHO and European CDC use the same three-level classification of COVID variants. These include variant under monitoring (VUM), variant of interest (VOI), and variant of concern (VOC). CDC classification system has an additional top-level "variant of high consequence", which fortunately we have never seen.

As of August 9, EG.5 has been elevated from a VUM to a VOI by the WHO. Previously XBB.1.5 was the most recently labelled VOI. XBB.1.5 is the basis for the upcoming monovalent vaccine. It had been the most frequently isolated subvariant in the United States until this week. The graph below shows that EG.5 has now become the most frequently sequenced isolate in the United States.

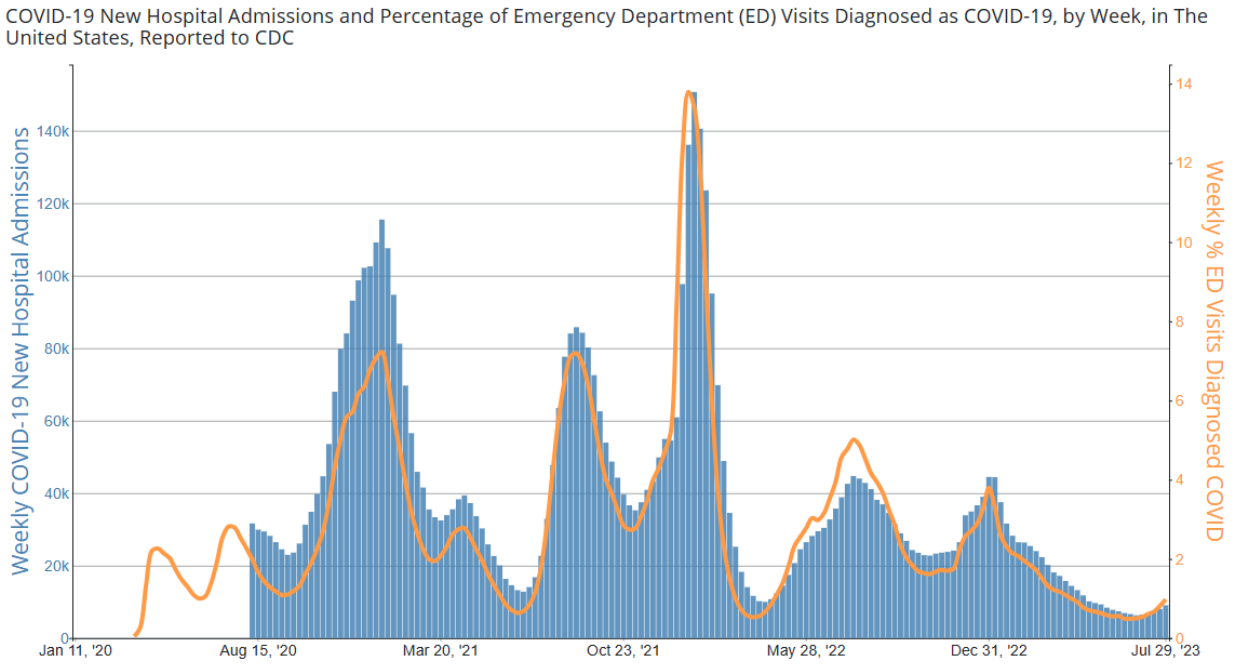
WHO label	Lineage #	%Total	95%PI	
Omicron	EG.5	17.3%	14.1-21.0%	
	XBB.1.16	15.6%	12.5-19.2%	
	XBB.2.3	11.2%	9.5-13.1%	
	XBB.1.5	10.3%	8.6-12.3%	
	FL.1.5.1	8.6%	4.2-16.1%	
	XBB.1.16.6	7.7%	5.6-10.6%	
	XBB.1.16.1	7.2%	6.0-8.7%	
	XBB.1.9.1	5.4%	4.5-6.5%	
	XBB.1.9.2	4.8%	3.5-6.6%	
	XBB	4.4%	3.1-6.1%	

EG.5 has one additional mutation compared to its predecessor XBB.1.9.2. This mutation is S:F456L. This is in the receptor binding domain. The number 456 refers to the amino acid location in the spike protein. Each of the 20 amino acids is assigned an alphabet letter. The S:F denote that two different amino acids regularly were found at this location. The EG.5 has replaced them with leucine (L). EG.5.1 represents almost 90% of EG.5 isolates. This has a second mutation, S:Q52H. This is not in the receptor binding domain.
SARS-CoV-2 frequently mutates. Most mutations don't appear to have any clinical significance. Mutations can affect transmissibility, virulence, and/or resistance to the host immune system. A VUM has identified mutation(s) that can increase those risks. To be escalated to a variant of interest, the CDC requires the following:

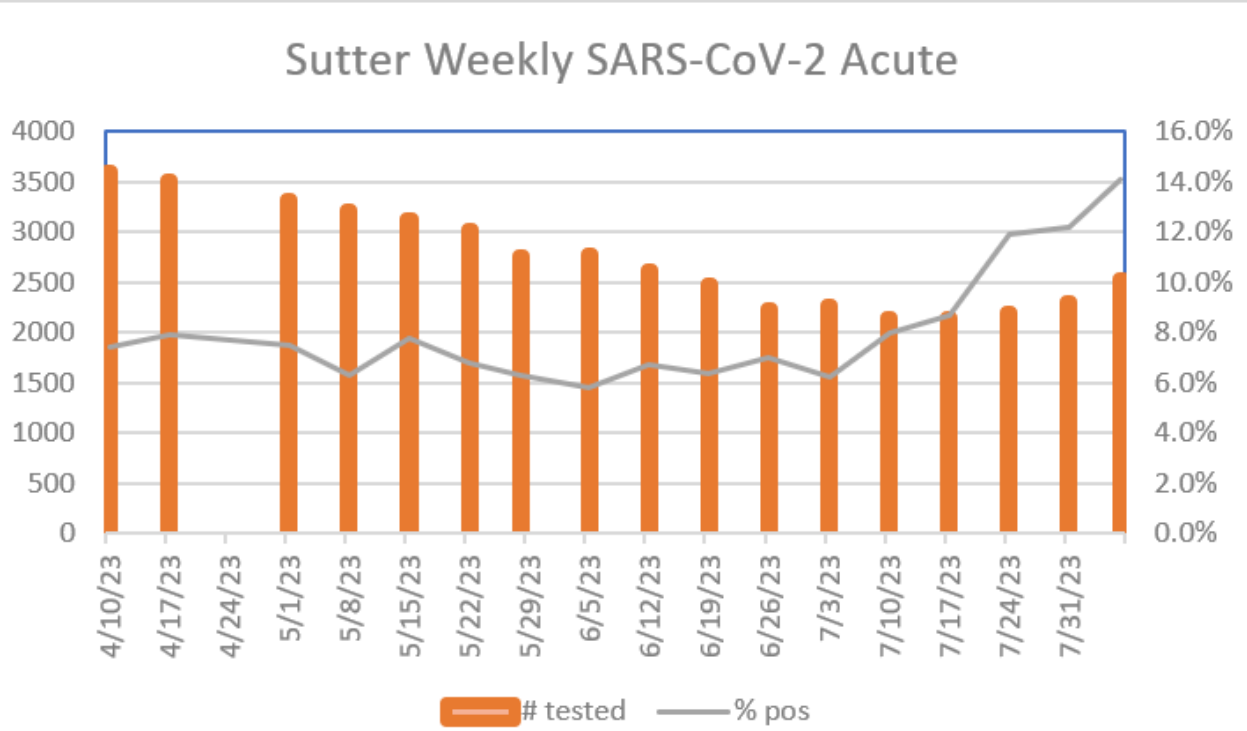
- changes to receptor binding domain (RBD).
- reduced neutralization by antibodies generated against previous infection or vaccination.
- reduced efficacy of treatments, or tests.
- predicted increase in transmissibility or disease severity.

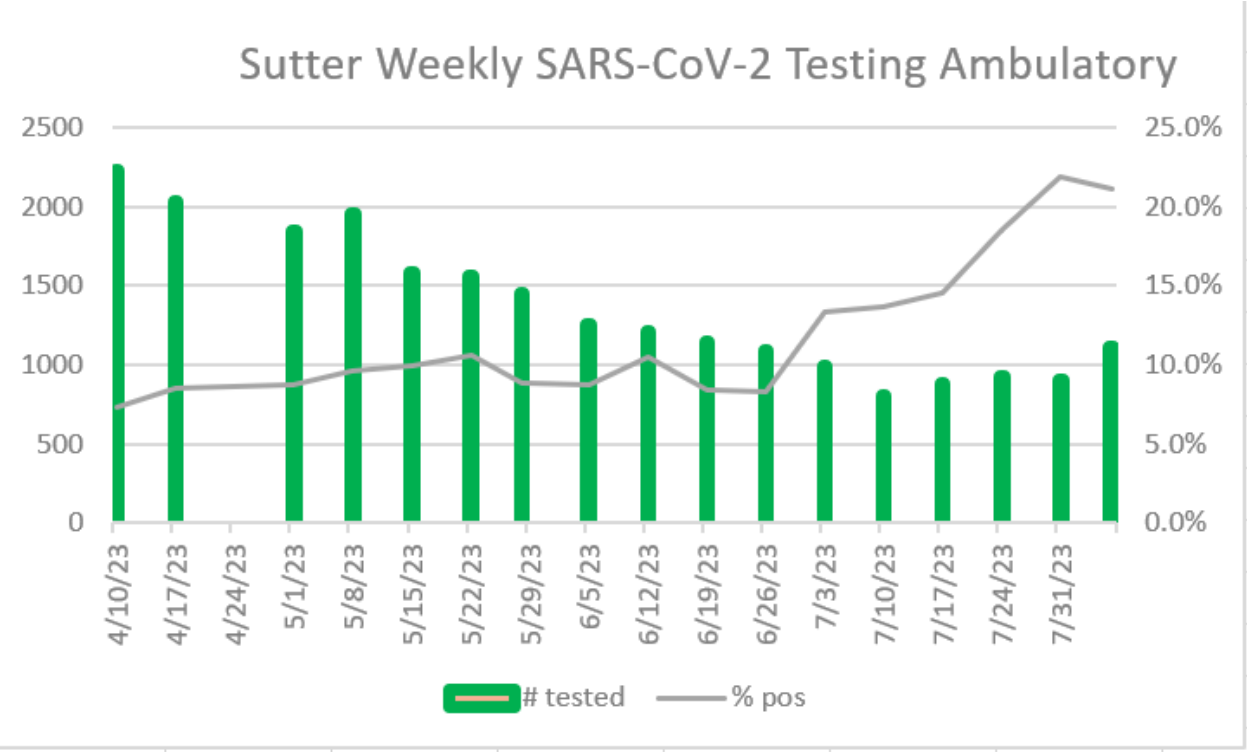
The WHO has identified that EG.5 has a moderate growth advantage compared to other circulating isolates and is currently the fastest growing variant being identified in the world. In addition, the S:F456L mutation has been shown to escape or decrease the neutralization of most XBB.1.5 neutralizing antibodies. This was based on testing performed with a pseudovirus and not the actual SARS-CoV-2 virus. Results using a pseudovirus are not always the same as those testing against the actual SARS-CoV-2 virus. In addition, the testing was only performed in one lab. Fortunately, still no evidence of increased virulence noted.

Hospitalizations and Emergency Department visits in the United States secondary to COVID continue to increase, as shown in the following graph. Importantly, rates remain low and do not suggest a rapid surge.



- Sutter data below show that test positivity rates continue to rise. This supports that patients are becoming more symptomatic with this newer strain and seeking medical care.





- Cough, fever, malaise, and headache are common but shortness of breath and progression to requiring supplemental oxygen are not.
- False negative antigen tests continue to be seen on day 1 of symptoms but are anticipated to be positive by day 2 of symptoms. Molecular tests continue to perform as expected, with minimal risk of false negative tests in symptomatic patients.
- Treatments, such as Paxlovid™, continue to perform as with other strains.

- Variants of interest are anticipated to potentially infect large numbers of people.
- Hand hygiene, masking, testing, and not working when sick are the best measures that we have for now.
- The monovalent vaccine appears to still be a month away from release and it will take 2 weeks after receipt of a dose for maximum protection.
- On July 28 CDPH issued an updated guidance on utilizing facemasks for source control in health care facilities. Multiple variables that should be considered when making a facility decision are discussed in broad terms. These include:
    - Vulnerability of the patient population
    - Risk of staffing shortages
    - COVID-19 hospital admission levels
    - Community levels of SARS-CoV-2
    - Impact of new strains on existing immune protection

COVID Take-Home Message:

- EG.5 has now been elevated from a variant under monitoring to a variant of interest by the WHO.
    - This is based on the new strain growth advantage and laboratory evidence of the virus being able to escape or decrease the efficacy of XBB antibodies.
- Hospitalizations may rise due to the increased numbers of patients becoming infected again
    - Fortunately, this is not due to a significant increase in virulence in this variant.
- It is reasonable to anticipate more ambulatory clinic, urgent care, and emergency department patients.
    - Home testing and the availability of nirmatrelvir/ritonavir (Paxlovid®) will diminish that stress on the health care system
- The best way to protect the workforce is for health care workers to mask for source control.
    - COVID remains an airborne transmissible disease and guidance for management remains unchanged.

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

So much new in RSV prevention for babies and young children

Nirsevimab (Beyfortus®) Monoclonal Antibody

- FDA approved July 17, 2023
    - Aug 3rd – CDC Advisory Committee recommended nirsevimab monoclonal antibody for infants under 8 months of age in their first RSV season and in high-risk babies 8-19 months old including American Indian and Alaska Native (AIAN) children in their second RSV season.
    - Availability is expected for the upcoming 2023-2024 RSV season.
- Long serum half-life allows for a single dose to cover the RSV season
    - No evidence of waning efficacy observed in pivotal trial over 150 days

- Melody phase III Trial was key to FDA approval in the US
- Assessed efficacy of nirsevimab in infants born at a gestational age of at least 35 weeks.
- The number needed to treat to prevent one hospitalization for lower respiratory tract infection (LRTI) of any cause was 53.1 (95% CI, 29.4 to 250.0), a number that was consistent with that in the primary cohort in the MELODY trial.
- An estimated 57 days of hospitalization for LRTI of any cause were averted for every 1000 infants who received nirsevimab.
- In term and late-preterm infants, a single dose of nirsevimab provided a consistent level of protection against in season hospitalization for RSV-associated LRTI, including severe RSV-associated LRTI requiring supplemental oxygen or intravenous fluids.

Palivizumab (Synagis®)

- Palivizumab is approved for prevention of RSV in high-risk infants.
- Monoclonal Antibody (MAB) Meta-analysis (Sun M et al.)
    - The meta-analysis concluded with moderate- to high-certainty that 3 MAB (nirsevimab, palivizumab, and motavizumab) when compared to placebo were associated with significantly reduced RSV-related infections.
    - With moderate-certainty evidence, both motavizumab and palivizumab were associated with significant reductions in intensive care unit admissions per 1000 participants.
    - Nirsevimab was associated with significantly reduced supplemental oxygen use per 1,000 participants.

	Palivizumab (Synagis®)	Nirsevimab (Beyfortus®)
Indication	For the prevention of serious LRTI caused by RSV in the following pediatric patients: • premature birth (less than or equal to 35 weeks gestational age) and 6 months of age or younger at the beginning of RSV season • bronchopulmonary dysplasia or hemodynamically significant congenital heart disease with additional caveats	• All neonates and infants born during or entering their first RSV season • Children 8 to 19 months of age with increased risk of severe RSV through their second RSV season
Action	a recombinant neutralizing human immunoglobulin G1 kappa monoclonal antibody directed against the RSV fusion (F) protein. Differing from nirsevimab, it targets antigenic site II on the RSV F protein which is exposed in both prefusion and post-fusion conformations.	a recombinant neutralizing human immunoglobulin G1 kappa monoclonal antibody directed against the prefusion conformation of the RSV fusion (F) protein. Nirsevimab has a three amino acid substitution to extend its half-life and reduce recruitment of Fc effector functions.
Regimen	Requires a course of 5 monthly doses throughout the RSV season	**Infants <8 months age:** A single IM dose, prior to or during the RSV season (usually October through March). **High-risk 8-19 months:** Two 100 mg injections administered IM simultaneously prior to second RSV season Per FDA, children who have received nirsevimab should not receive palivizumab for the same RSV season
Cost	$ 1,800 - $3,500 per dose (based on weight). Up to $17,500 per child who receives the usual 5 monthly RSV season doses.	Estimated $500 per 100mg dose

Nirsevimab and maternal vaccination with Abrysvo®

- Currently, Abrysvo® is only FDA approved for RSV prevention in adults ≥60 years of age. An expanded indication for use in pregnant individuals to help protect against the complications of RSV disease in infants from birth through six months is pending FDA approval in the fall.
- Assuming Abrysvo® will be recommended as a maternal vaccine, the CDC is exploring considerations for use of nirsevimab in infants whose birthparent received third trimester RSV vaccination.

RSV Take Home Message:

- Nirsevimab (Beyfortus®) provides single dose protection for neonates and infants during their first RSV season and for high-risk children 8 to 19 months of age during their second RSV season.
- This is a very significant breakthrough in protecting children against what can be a devastating disease.
- Both products are monoclonal antibodies that provide passive immunity compared to the active immunity stimulated by other vaccines.
- Palivizumab has much more limited indications, requires multiple monthly injections, and is dramatically more expensive than nirsevimab. Nirsevimab does have more data on use in very young premature babies.

- Nirsevimab and palivizumab should not be administered during the same season.
- An RSV vaccine to administer during pregnancy may be approved this fall. The CDC will develop guidance on the use of nirsevimab in infants whose birthparent received the RSV vaccine.

Candida auris (C. auris)

- C. auris is a highly transmissible, multidrug resistant, nosocomial pathogen. It is notable for persistence in the environment in health care facilities where it can spread through contact with contaminated surfaces or equipment. Facilities with endemic C. auris or that care for patients with C. auris need to ensure that cleaning and disinfection of surfaces and shared equipment is performed with agents effective against C. auris.

- Infection Control and Hospital Epidemiology just published a study evaluating effectiveness of commonly used disinfectants including quaternary-ammonium-alcohol (Quat), hydrogen-peroxide-based disinfectants, and sodium hypochlorite (bleach).
  - In 2017, the Environmental Protection Agency (EPA) published recommendations for testing using a clade II strain which was sensitive to echinocandins (caspofungin, micafungin, and others)
  - In 2021, the test strain was changed to a drug resistant clade IV strain which was felt to possibly be less susceptible to UV-C light and low concentrations of bleach.
  - The results are in the table below

Disinfectant Group	Number of Products Tested	Number that showed killing of >5 logs against all 4 clades	Percentage effective against all strains of C. auris
Chlorine-based (bleach)	5	5	100
Peracetic acid-based (Oxycide™)	1	1	100
Hydrogen Peroxide	4	3	75
Quat.	8	0	0
Quat. plus alcohol	4	2	50
Phenolic Acid	1	0	0

  - Sporicidal agents such as bleach and OxyCide™ are effective against C. auris whereas quaternary-ammonium disinfectants and the tested phenolic acid product have limited activity.
  - The addition of alcohol to the Quat increased activity of some, but not all products.
  - Limitations in this study included
    - Only 1 test organism from each of the 4 C. auris clades
    - Did not allow physical cleaning from wipes, which could improve efficacy.
    - Bleach concentration was at least 4% (≥ 4306 parts per million of free chlorine).
      - Lower concentrations might not be as effective.
    - This was a lab-based study.

***Candida auris* Take-Home Message:**

- Not all products are effective at killing C. auris on surfaces. When activity against C. auris is needed, choose agents labelled with sporicidal activity or activity against C. auris.

- If the circulating C. auris is also resistant to echinocandins, the disinfectant should also list activity against “drug-resistant C. auris”.
- Failure to adequately clean a hard surface or shared equipment can lead to nosocomial transmission of an extremely dangerous healthcare pathogen.

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.