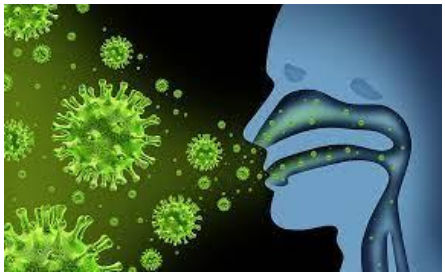

Sent on behalf of William Isenberg, M.D., Ph.D, Chief Medical & Quality Officer, Sutter Health, and Jeffrey Silvers, M.D., Medical Director of Pharmacy and Infection Control, Sutter Health

Emerging Infections Newsletter for Clinicians

July 28, 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.

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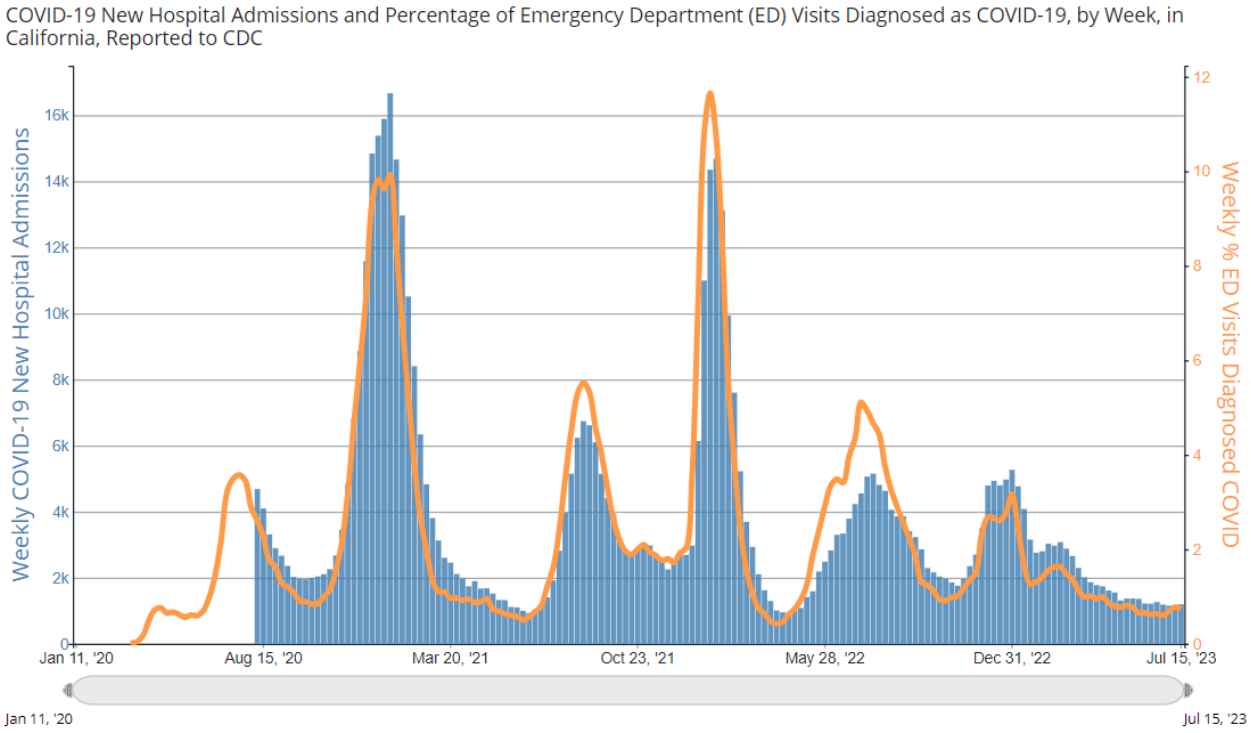
Another Tripledemic Risk

- The 2022-23 respiratory season was our first tripledemic of influenza, RSV and SARS-CoV-2.

- A tripledemic is an informal term that refers to a simultaneous increase in cases of SARS-Cov-2, Influenza, and RSV.
- Although the term is not based on the severity of the outbreaks, simultaneous or sequential infections can lead to increased morbidity and mortality compared to any one infection alone.
- People need to understand all three of these respiratory viruses and know what they can do to protect themselves.

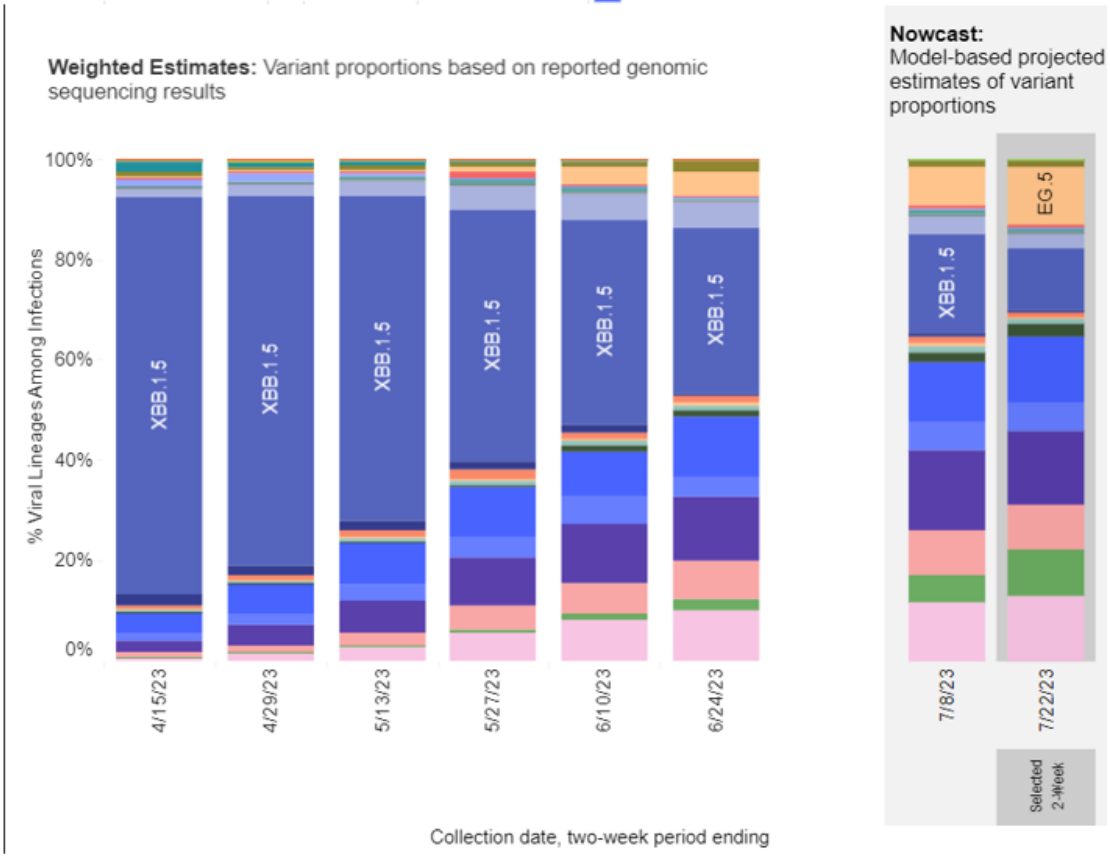
COVID-19

- U.S. Hospitalization Data
  - Hospitalizations in patients with a diagnosis of COVID have been gradually increasing nationally and in California over the last 4 weeks. Emergency department diagnosed COVID has a similar pattern.
  - The graph below shows weekly trends of COVID-19 hospital admissions and percentage of ED visits diagnosed with COVID-19 in California since data collection started August 2020. Hospitalization numbers are still 93% lower than the high measured Jan. 9, 2021. Note the slight uptick for the last four weeks.



- National genomic surveillance data for April 2 through July 22 is below.
  - Essentially all cases are due to a recombinant strain that originated with omicron.

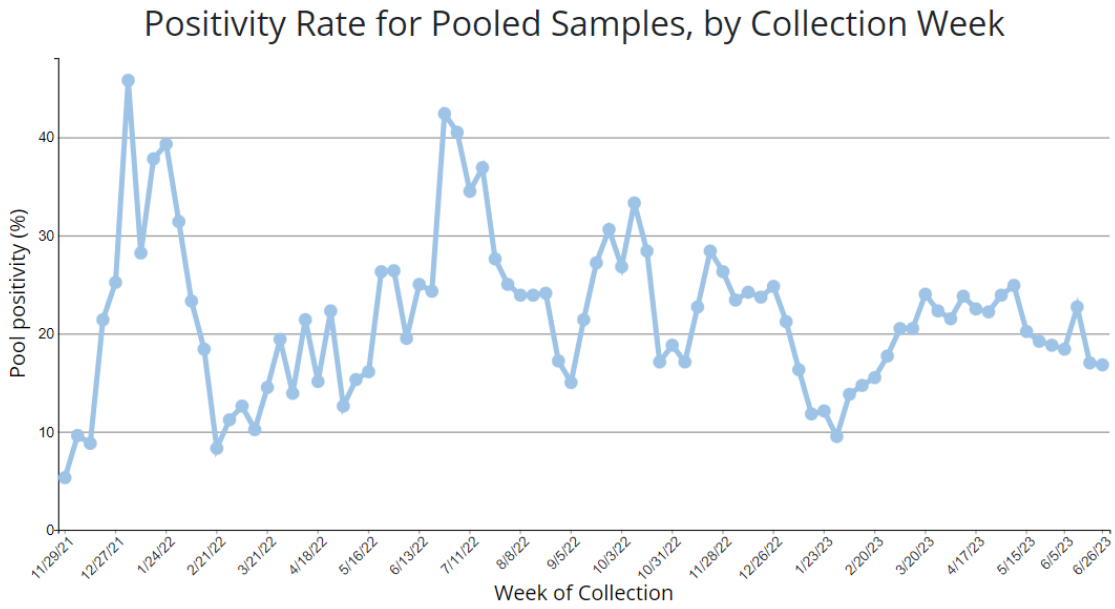
WHO label	Lineage #	%Total	95%PI
Omicron	XBB.1.16	14.8%	12.2-17.8%
	XBB.1.9.1	13.2%	8.3-20.3%
	XBB.2.3	13.0%	10.4-16.1%
	XBB.1.5	12.3%	10.2-14.7%
	EG.5	11.4%	8.3-15.3%
	XBB.1.16.6	9.3%	5.4-15.4%
	XBB.1.16.1	8.8%	7.4-10.4%
	XBB.1.9.2	5.6%	4.0-7.8%



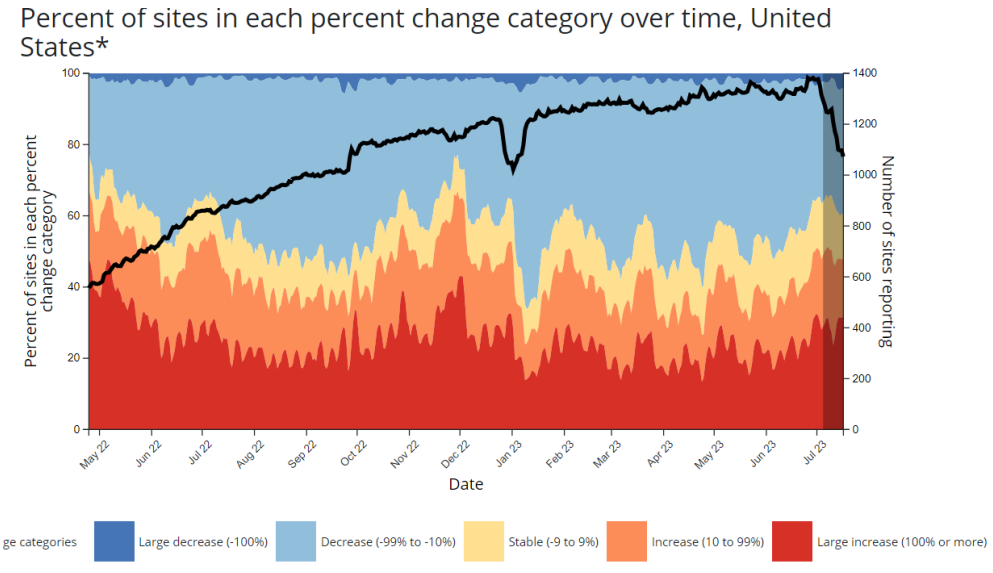
- EG.5 continues to increase in frequency of identification, now representing 11.4% of cases nationally.
  - The WHO added EG.5 to the list of Omicron variants under monitoring on July 19. EG.5 descended from XBB.1.9.2 and has one extra spike mutation.
  - Nothing suggests that the number of cases, morbidity or mortality are affected by this subvariant.
- The new monovalent vaccine is based on XBB.1.5, which now only comprises 12.3% of sequenced isolates in the United States.
  - The belief is that this vaccine will still decrease the risk of severe disease, hospitalization and death.

- International genomic surveillance is performed by sampling international air travelers from more than 25 countries at several major U.S. airports.
  - All positive isolates are sequenced.
  - XBB comprised 17% of the most recent week's international isolates.
  - The graph below shows the positivity rate of pooled samples by collection week. The week of June 26, the positivity rate was 16.8%. This is well below the peak of 42.4%

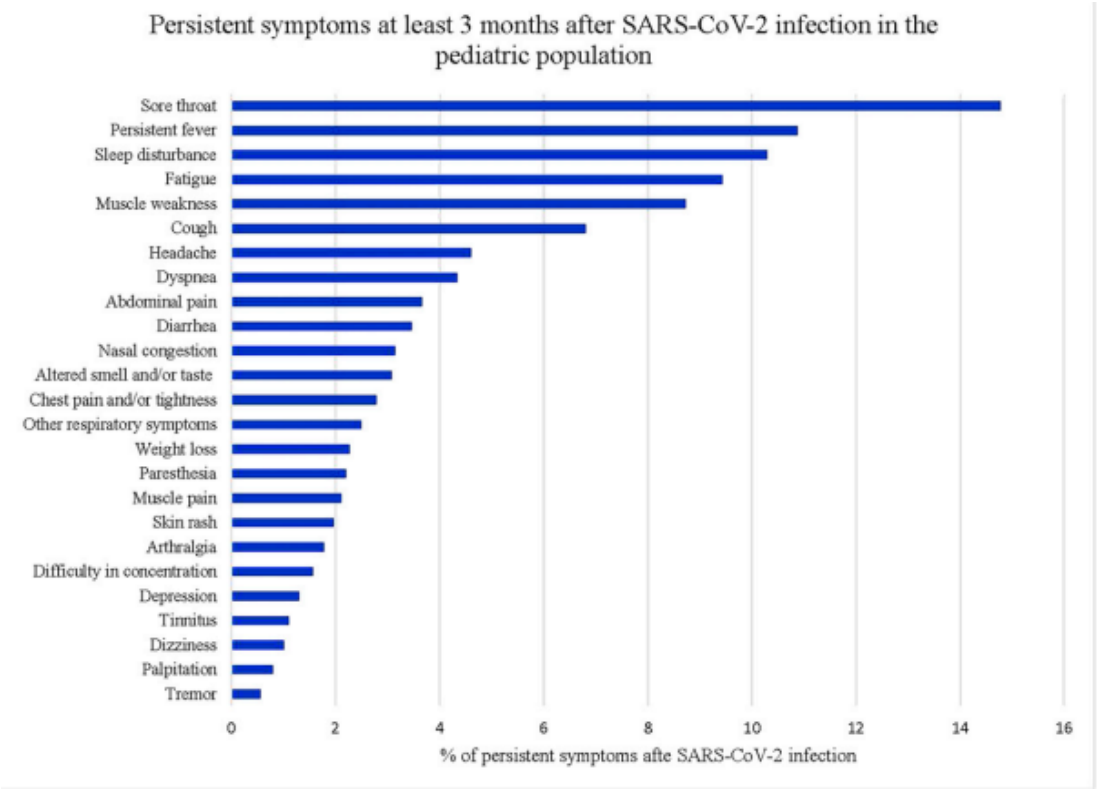
the week of June 27, 2022, but still 7.3% higher than the nadir that was measured this last Jan 30 at 9.5%.



- Wastewater surveillance data shows changes in virus levels over time.
  - Each point in time represents the calculated percentage change over the prior 15 days.
  - The graph below can provide rough insight by looking at the color changes in the last 15 months. Shades of blue represent decreasing amounts of virus, yellow is unchanged and orange/red signify increasing amounts of SARS-CoV-2 virus.
  - On July 16, the light-blue shade represented 35%, orange/red 48% and yellow 13%. This is a modest increase in red/orange from 43% on June 18.
  - A major limitation to interpretation of this data is that this graph does not measure levels of virus. When levels of virus in wastewater are low, a modest increase in virus level can appear much larger when looking at the percent change. Interpretation of this data must be combined with other information such as the weekly trends in hospitalizations discussed above.



- **Long COVID**
  - Pediatrics August 2023 published a systematic review of "Long COVID" features in pediatric patients.
    - Looked at signs/symptoms
      - ✓ 3 or more months from test-positive case of COVID
      - ✓ 19 years old or younger
      - ✓ no alternative diagnosis
    - Published literature, including pre-print literature, from December 2019, through December 2022.
    - Studies on MIS-C (Multisystem Inflammatory Syndrome in Children) and children with immunodeficiency were excluded.
    - Included 27 cohort (19 retrospective, eight prospective) and four cross-sectional studies.
    - More than 15,000 patients
    - More than one out of every six children continued to present with at least one persistent symptom at least three months post-infection.
    - The figure below shows the 20 symptoms by percent having persistent symptoms. Sore throat, persistent fever, sleep disturbances and fatigue were the most common.



    - Systematic reviews and meta-analyses are very difficult looking at present literature. Case definitions, patient locations, recruitment versus population-based studies, socio-economic and/or ethnicity differences, lack of a control group and duration of follow-up led to high heterogeneity.
    - Not a conclusive study but suggests that "Long COVID" is not limited to adults and studies need to include pediatric patients.
  - Lancet eClinical Medicine July 21 published a two-year, prospective, community-based, smartphone-app-recruited, cohort study measuring "Long COVID" cognitive performance (accuracy and reaction times).
    - This large study included over 4,000 participants divided into five cohorts.
      - ✓ Documented asymptomatic COVID

        - ✓ Symptomatic COVID lasting less than 14 days (Short COVID)
        - ✓ COVID with symptoms lasting at least 28 days (Long COVID)
        - ✓ Test negative for SARS-CoV-2 with at least 28 days symptoms (Long non-COVID)
        - ✓ Test negative for SARS-CoV-2 with maximum of three days of mild symptoms consistent with COVID (Healthy non-COVID)
    - Questions asked about perception of cognitive function and utilized 12 cognitive tasks that assessed cognitive domains including working memory, attention, reasoning, and motor control.
    - Two rounds were conducted one year apart to assess changes over time.
    - Factors that were associated with lower cognitive function in all groups were accounted for:
        - ✓ Older age, lower-level education, socio-economic indicators, co-morbidities
    - Findings:
        - ✓ After stratification, persons who reported themselves as "I am back to normal" did not have increased cognitive deficits.
            - This included persons who initially had symptoms lasting more than 12 weeks.
    - Persons who responded "No, I still have some or all of my symptoms" had increased measured cognitive deficits.
    - For those with detectable deficits at initial testing, findings persisted if still symptomatic and resolved if no longer symptomatic.
- **COVID Vaccine**
    - Beginning August 3, 2023, routine ordering for the bivalent vaccine will no longer be allowed and we expect that authorization for use of this vaccine will be discontinued shortly afterwards.
    - **As authorization of the bivalent vaccine is anticipated to stop soon, Sutter will be pausing all new COVID-19 vaccinations as of July 28, 2023.** If immunocompromised or pediatric patients are in the middle of a vaccine series, we will complete the series.
        - **A new Smartphrase--COVID19VACCINEXBBPTINFO-is available** to assist with patient communications and questions.
    - **The new monovalent vaccine is anticipated to be available in late September,** pending FDA/CDC actions.
    - Maximizing vaccination of a large percentage of the population is essential to reduce the risk of another major outbreak. The vaccine must be promoted and made easily accessible for all, including higher-risk populations that frequently have less access to medical care.
    - Multiple articles have been written about COVID-19 vaccination decreasing the risk of long COVID.
    - The value of the vaccine:
        - Preventing disease in older adults and the higher-risk population for progressing to severe COVID-19.
        - Preventing disease in others who may spread it to someone in the higher risk group e.g. healthcare workers.
        - Mitigating the risk of a significant tripledemic.
        - Decreasing the risk of developing "Long COVID".

COVID Take-Home Message:

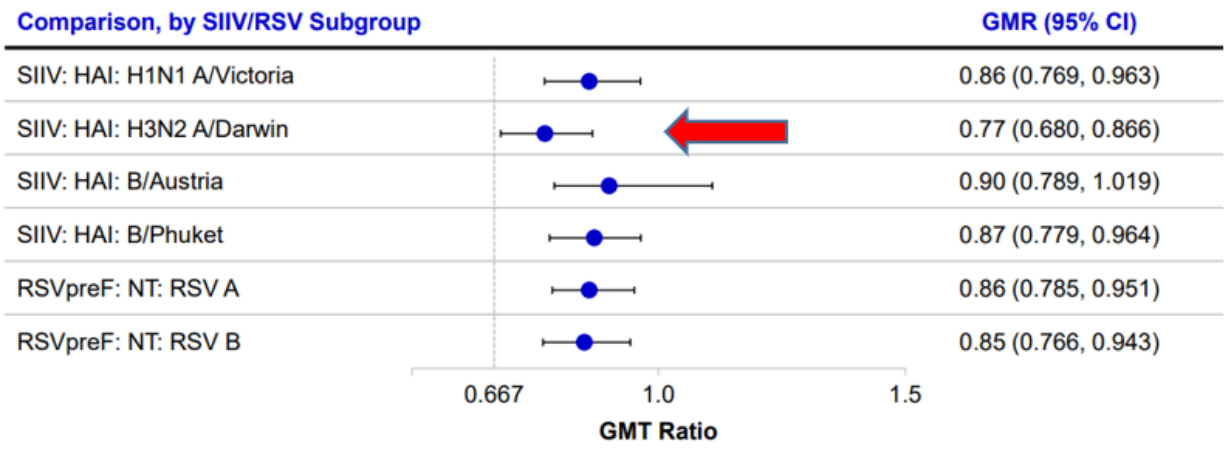
- Cases of COVID appear to be increasing a little. This is supported by hospitalization and emergency department positivity rates and wastewater surveillance.
    - This is not noted in international surveillance data performed in the United States.

    - It may have some relationship to summer activities and relaxation of social protection requirements.
- EG.5 is increasing in frequency of identification but is not showing any evidence of affecting rates or severity of disease.
- "Long COVID" is a complication of COVID that unfortunately continues to negatively impact the quality of life for many people, including children and adolescents. No effective treatments have been identified. Prevention is an important area to address.
- The new COVID monovalent vaccine should be available starting the second part of September. Maximizing vaccine uptake is essential to try to prevent another major outbreak as well as a severe tripledemic during the upcoming respiratory season.
- The value of the vaccine
    - Preventing disease in older adults and the higher-risk population for progressing to severe COVID-19.
    - Preventing disease in others who may spread it to someone in the higher risk group e.g. healthcare workers.
    - Mitigating the risk of a significant tripledemic.
    - Decreasing the risk of developing "Long COVID".

- **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

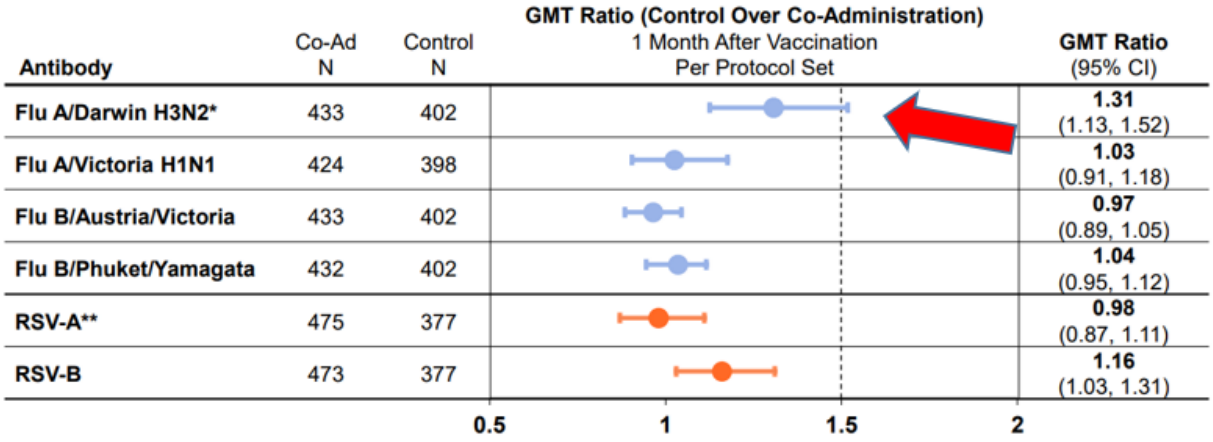
RSV Vaccine

- MMWR July 21 discusses the data leading to the vaccine approval and recommendations for use, including guidance for shared decision making.
    - The CDC recommends that the RSV vaccine should be offered for the 2023-24 season as soon as vaccine supply becomes available.
    - Coadministration with other adult vaccines is considered acceptable by the CDC.
        - The Pfizer and GSK vaccines showed different results when evaluated.
        - Coadministration with the Pfizer RSV vaccine and the flu vaccine met noninferiority criteria for immunogenicity. See graph below.
            - ✓ The immune response of A H3N2 was barely above the threshold (0.667) for inferiority. See Red Arrow.
            - ✓ Titers in general were somewhat lower with co-administration, compared to sequential administration titers (where the GMT would be 1.0). Lower ratios denote worse results.



- Below is the graph of coadministration with the GSK RSV vaccine and the flu vaccine.
  - ✓ A H3N2 titer was inferior when given together. See red arrow.
  - ✓ Titers in general were somewhat lower with co-administration.
    - Note that this table is control over co-administration, so higher ratios denote worse results.

Co-Administration of AREXVY and Licensed Flu-Adjuvanted QIV



Success Criteria: Upper limit ≤ 1.5 of 2-sided 95% CI for Group GMT Ratio (Control Group divided by Co-Ad Group) for RSV vaccine and for each of FLU vaccine strains

- Nirsevimab FDA Approval
  - On July 17, the FDA approved Beyfortus® (nirsevimab-alip) as the first monoclonal antibody for use in infants to protect from RSV through their first season.
    - Use for children up to 24 months of age who remain vulnerable to severe RSV disease, such as those with history of preterm birth or specific heart and lung conditions, through their second RSV season.
    - Unanimous approval from the FDA's Antimicrobial Drugs Advisory Committee (AMDAC).
    - A single dose of nirsevimab demonstrated high and consistent efficacy against RSV lower respiratory tract disease (LRTD) through the entire RSV season.
      - ✓ Followed for 150 days after nirsevimab administration.

Trial	Criteria	Measure	# Enrolled	Nirsevimab	Placebo

03	Preterm 29 to 34.6 weeks	Developed RSV LRTI	1453	25/969 (2.6%)	46/484 (9.5%)
04	35 weeks or greater	Developed RSV LRTI	1490	12/994 (1.2%)	25/496 (5.0%)
05	High risk up to 24 months	Measured Safety			

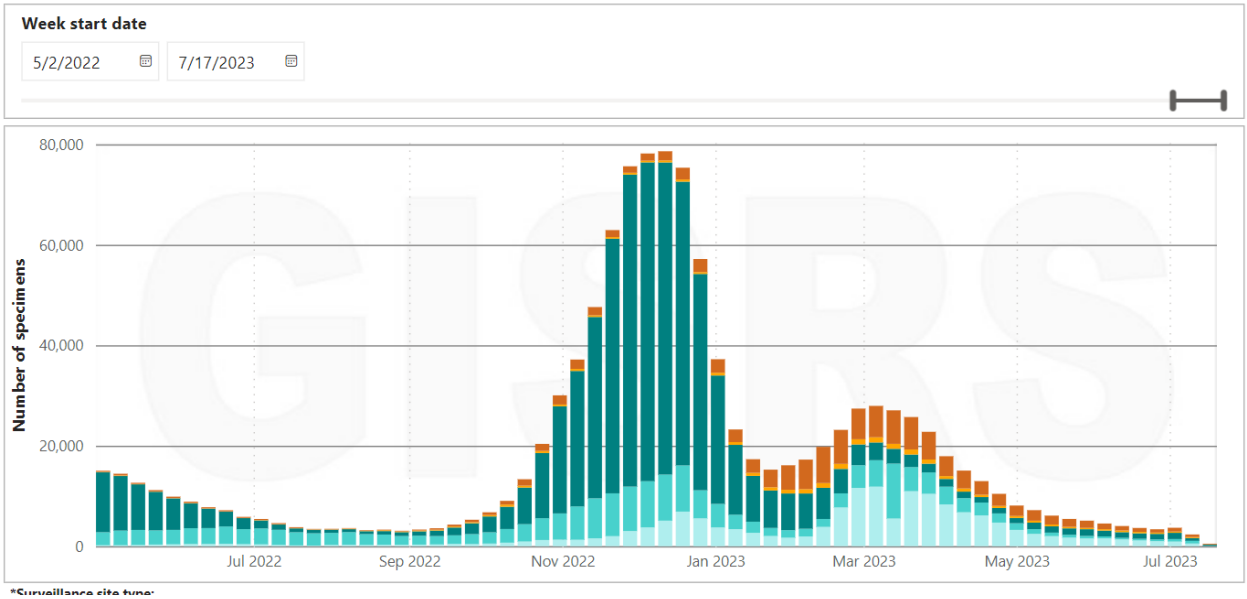
        - Well-tolerated safety profile based on results from the MELODY Phase III Trial.
    - The CDC's Advisory Committee of Immunization Practices is anticipated to discuss recommendations for use of nirsevimab in term and pre-term infants during their quarterly meeting in October.
        - Product release after this meeting.
- RSV vaccine during pregnancy
    - July 21, the European Medicines Agency approved the Pfizer RSV vaccine for administration during pregnancy to enable the pregnant person to develop protective antibodies for the developing baby.
        - Administered between 24-36 weeks gestation.
    - ACIP and FDA will evaluate at a future meeting.

RSV Take-Home Message:

- CDC provided updated guidance on use of the RSV vaccine in adults 60 years and older.
    - They recommend offering as soon as available.
        - Anticipate the second part of August
    - Coadministration with other vaccines is permitted.
        - No data other than with influenza vaccine.
        - Influenza vaccine coadministration resulted in a concerning decrease in geometric mean titers, especially A H3N2. Even when the flu vaccine is administered alone, vaccine effectiveness against influenza A H3N2 is typically lower than any of the other strains.
- Consider not co-administering RSV vaccine with any other vaccines unless there is an anticipated problem in being able to complete both vaccines.
    - Do not defer vaccination if this will result in a "missed opportunity" to vaccinate a person.
- FDA has approved the monoclonal antibody vaccination (Nirsevimab) for infants at high risk for complications from RSV.
- RSV vaccine for administration during pregnancy has been approved in Europe. Waiting for upcoming FDA/ACIP review and decision.

Influenza

- Globally, influenza rates remain low. Graph below shows data from May 2, 2022, through July 17, 2023. The legend is just below the graph.
- Seasonal influenza immunizations should not begin until September.



Herpes Simplex Virus (HSV) Diagnostic Testing

- The gold standard for diagnosis of HSV infections is nucleic acid amplification test (NAAT) of cutaneous/mucocutaneous lesions or cerebrospinal fluid (CSF), as clinically indicated.
- Serologic testing for IgM antibody to HSV is not recommended because IgM tests are less specific than IgG and more prone to false negative results.
- In instances where NAAT is not possible, type-specific IgG testing can be used.
- CDC does not recommend IgM testing for HSV.
- Quest is no longer making the IgM test available, and it will no longer be available for order in Sutter Epic.
- See Sutter Know-Do-Share for more information.

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.