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 16, 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

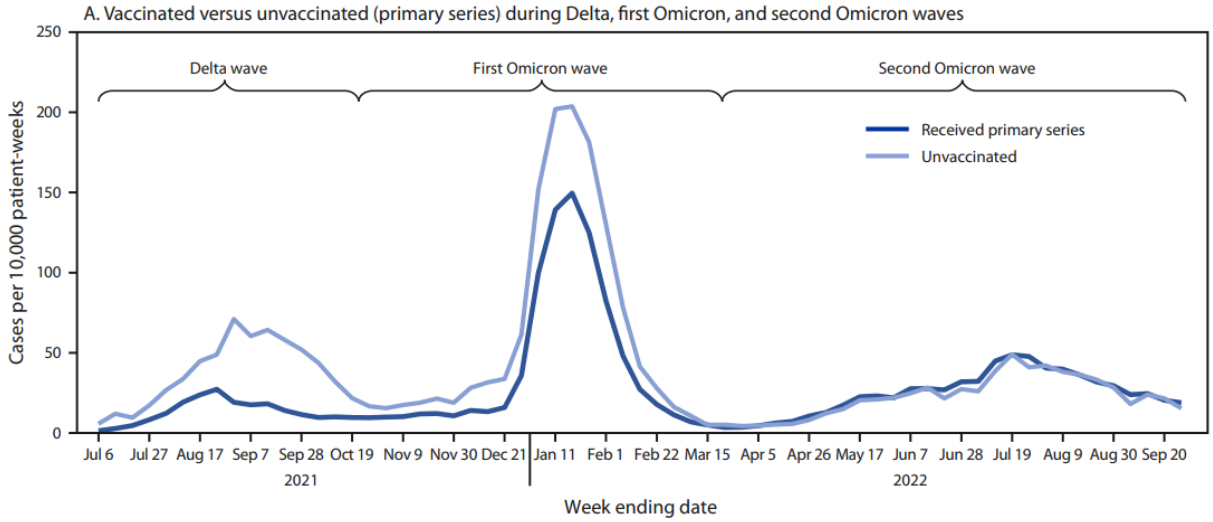
1. COVID-19
    a. COVID vaccines and outpatient treatment in understudied populations
        i. Patients with chronic kidney disease (CKD), including dialysis.
            1. The vaccine lowered the risk of acquiring disease in two out of three waves
            2. Paxlovid dose-adjusted for dialysis patients, safe and effective
            3. Remdesivir use in patients with advanced chronic kidney disease including dialysis
        ii. Pregnancy® and lactation
            1. Paxlovid® evidence
    b. United States hospitalizations and ED visits
    c. Sutter data
    d. Take-home COVID
2. Why were the Adenovirus-vector vaccines associated with thrombosis and thrombocytopenia?
3. West Nile Virus update in California
4. False positive Influenza B rapid test
5. Share the newsletter

COVID-19

Pregnant persons and patients requiring chronic maintenance dialysis are two groups of patients frequently excluded from studies related to COVID treatment and prevention. These patients are high risk for complications, and providers have needed to extrapolate data to make decisions.

- The MMWR August 11 reported outpatient dialysis-unit data on patients diagnosed with COVID-19 or COVID-related death.
    - Data from June 30, 2021, to September 27, 2022, broken into the three waves.

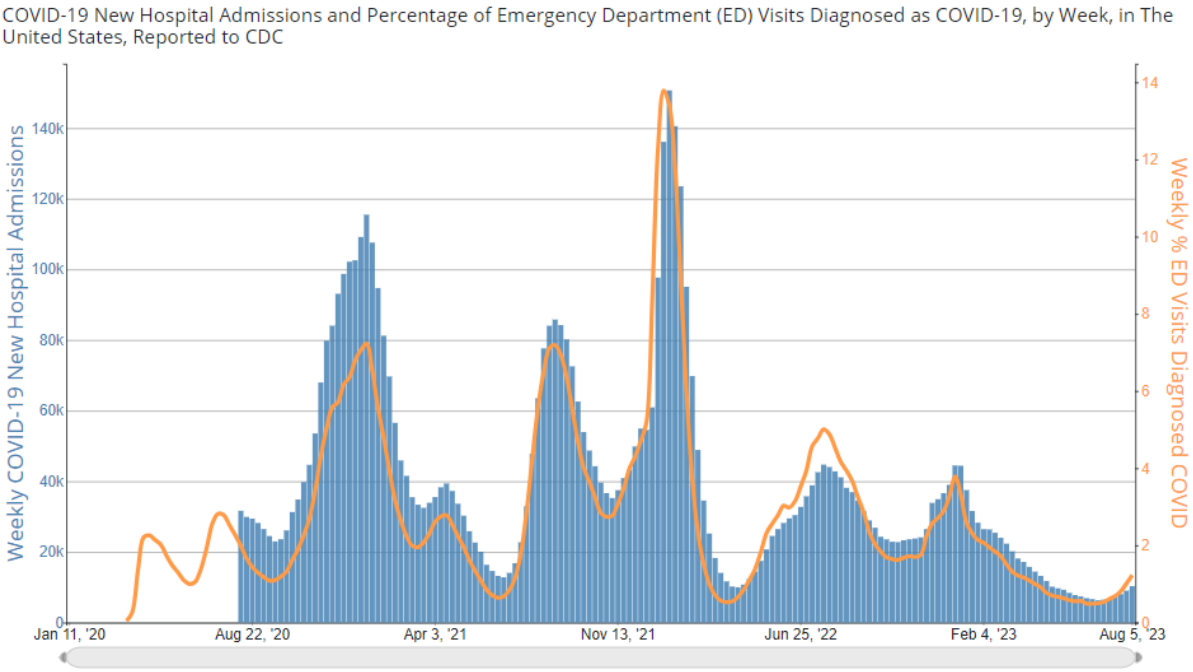
        - Delta from June 30 to October 25, 2021
        - Omicron (1) from Oct. 27, 2021, to March 22, 2022
        - Omicron (2) from March 23 to Sept. 27, 2022
    - Infection rates between vaccinated and unvaccinated dialysis patients were compared. The graph below shows that dialysis patients who received a primary vaccine series were less likely to develop infection during Delta and the first Omicron wave. The vaccine didn't provide any benefit during the second Omicron wave. This may have been due to virus mutations or waning immunity.
    - Infection rates among dialysis patients were similar to the general population.



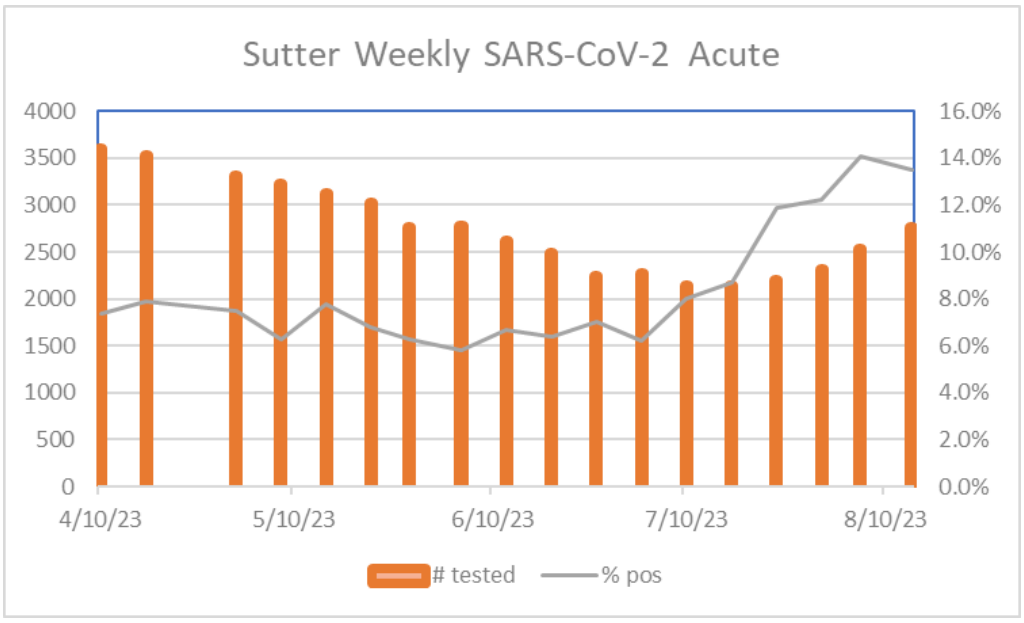
    - No data on vaccination status and COVID-related death.
    - Death rates secondary to COVID increase by age, and the average age of dialysis patients is 68 years old. Although not shown in this report, it is believed that the death rate of dialysis patients who develop COVID is higher than the national death rate.
    - Limitations of this report:
        - This is only outpatient facility data. Home dialysis patients might have lower rates of infection and/or COVID-related death.
        - This is self-reported data and COVID-related death was broadly defined. Data may be inaccurate and is likely incomplete.
        - Death rates based on vaccine status were not obtainable.
- Paxlovid® treatment in patients with dialysis-dependent renal failure.
    - Clinical Infectious Diseases August 2023 published a study showing safety and viral response to a dose adjusted regimen. FDA approval has not yet been issued.
- Remdesivir in CKD including dialysis
    - On July 14, 2023, the FDA updated the approval of remdesivir to include treatment of patients with COVID-19 who have advanced CKD including dialysis.
    - These patients are at high risk for severe COVID-19. The approval was based upon positive results from phase 1 study data, as well phase 3 REDPINE trial, which evaluated the pharmacokinetics and safety of remdesivir for COVID-19 patients with severe renal impairment.
        - Demonstrated no significant difference in all-cause death or invasive mechanical ventilation by Day 29 between the remdesivir and placebo groups.

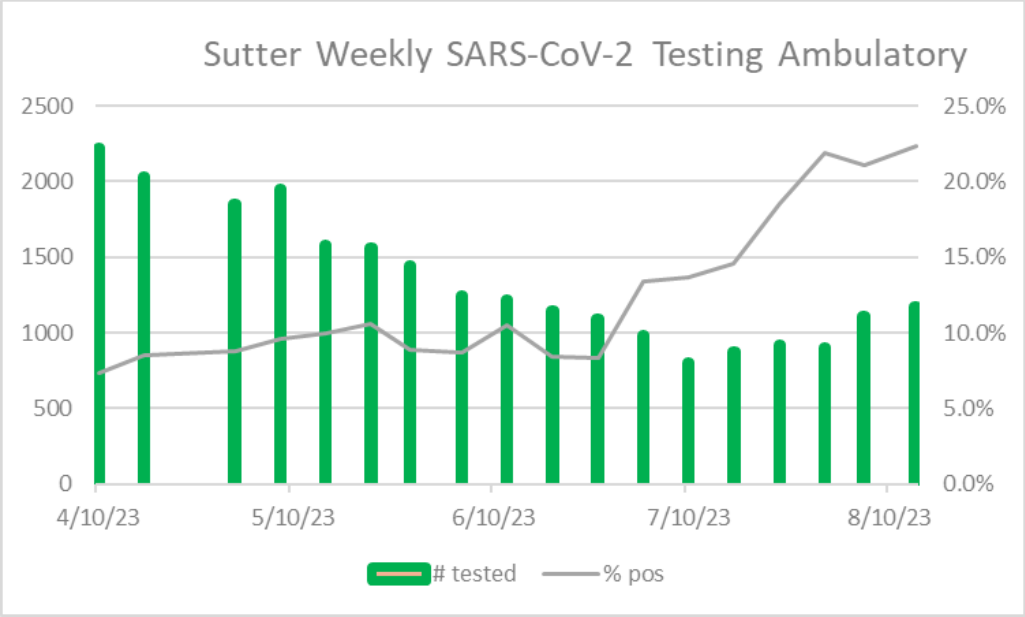
        - The study was underpowered due to low participant enrollment.
    - Remdesivir Prescribing information has been updated to reflect that no dosage adjustment is recommended in patients with any degree of renal impairment, including those on dialysis.
- Pregnancy and lactation are frequent exclusions from studies, yet pregnant persons are at increased risk of complications from SARS-CoV-2. Vaccines published an evidence-based review in 2023.
    - Ritonavir is an inactive addition to nirmatrelvir whose sole purpose is to boost the bioavailability of nirmatrelvir and maintain nirmatrelvir levels in the target range. Multiple years of experience have accumulated using ritonavir as part of the treatment regimen in pregnant women living with HIV.
        - Pre-term birth (PTB) has been reported in several studies when comparing ritonavir boosted protease-inhibitor (PI) regimens versus non-boosted PI regimens. Some of the data have been conflicting but the CDC HIV treatment guidelines say "*Regimens that include PIs boosted with ritonavir may be associated with an increased risk of PTB compared with non-boosted PI regimens".*
        - It is difficult to know whether five days of ritonavir in Paxlovid® will have the same effect because patients living with HIV typically take the ritonavir for months to years.
    - Nirmatrelvir during pregnancy has even less information available. It is a cysteine PI. Cysteine proteases are found in many organisms but nirmatrelvir is a virus-specific inhibitor with minimal crossover effects in human cells. One animal model study published March 2022 did not identify any adverse effects on fertility, reproduction, or teratogenicity in rats or rabbits.
    - Society for Maternal-Fetal Medicine COVID treatment guidelines recommend the use of Paxlovid® during pregnancy, using shared decision-making, stating the following: "*No human pregnancy data are available on nirmatrelvir. Ritonavir is used extensively in pregnancy with documented safety."*
    - NIH recommends use of Paxlovid® during pregnancy, if indicated. Breastfeeding can continue while a patient receives Paxlovid®.

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.



- Updated Sutter data below again show that more tests are being performed and test positivity rates remain elevated. This supports that patients are becoming more symptomatic with this newer strain and seeking medical care.





- 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.

COVID Take-Home Message:

- COVID in Dialysis Patients
  - The MMWR just published data that vaccination against COVID in dialysis patients lowered the risk of becoming infected with the virulent Delta variant and during the first Omicron wave. Efficacy was not seen during the second Omicron wave, but that may have been due to mutations in the virus and/or waning immunity.
    - It is anticipated that the new monovalent vaccine will provide that needed additional protection.
  - Paxlovid® is safe and effective when given with appropriate dosage adjustments.
  - Remdesivir can be safely given without any dosage adjustments for renal disease.
- COVID during pregnancy and lactation
  - Paxlovid® consists of two different medications. Ritonavir has been associated with preterm delivery when administered long term for HIV. The risk associated with five days of treatment with Paxlovid® is unclear. There is no human data on nirmatrelvir but it appears safe in animal models. NIH and Maternal-Fetal-Medicine Society both recommend use of Paxlovid® during pregnancy, if indicated.
  - Breastfeeding can continue when Paxlovid® is being taken.
- Hospitalizations and emergency department visits continue to slowly increase secondary to the new COVID EG.5 variant.
- Sutter is testing more patients for COVID in the emergency departments and ambulatory settings. Positivity rates remain high, despite increased testing.

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

Adenovirus-vector vaccines thrombocytopenia and thrombosis explained

- Two adenovirus-vector SARS-CoV-2 vaccines were introduced in 2019 (Oxford ChAdOx1 and J&J Ad26.COV2.S). They were developed as an alternative approach for mass vaccinations of the public.
- June 3, 2021 the NEJM reported five patients with post vaccine thrombocytopenia and venous thrombosis, termed vaccine-induced, immune, thrombotic thrombocytopenia (VITT). These patients were not taking any heparin-based products.
- NEJM on August 10 published a report of 2 patients who developed thrombosis, thrombocytopenia, and VITT-like antibodies after adenovirus infection. They were both heparin naïve. The VITT-like antibodies bind directly to PF4 (Platelet factor 4). Heparin induced antibodies are against heparin complexed with PF4.
    - This article described the first two cases of symptomatic adenovirus infection with binding to PF4. Both patients had a life-threatening syndrome, identical to what was seen after the adenovirus-vector vaccine. One presented with a gastrointestinal infection and the other with respiratory tract symptoms.
    - This helps explain why VITT was seen after the adenovirus-vector vaccines. Even though a rare complication, additional studies are needed to ensure that future adenovirus-vector vaccines will not have the same risk.

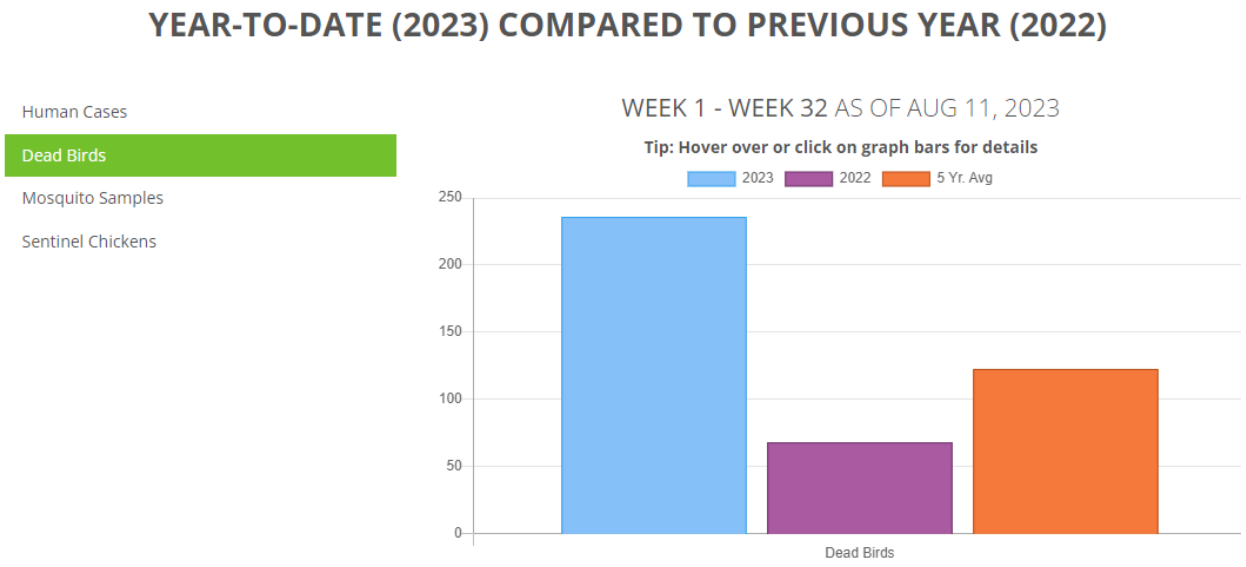
Adenovirus Take-Home Message

- The adenovirus-vector COVID vaccines were identified to be associated with the. development of VITT. Although this syndrome has similarities to the HIT syndrome (heparin induced thrombocytopenia), the initiation binding mechanism to PF4 is different.
- Adenovirus has now been associated with the development of an identical syndrome to VITT.
- VITT after an adenovirus-vector vaccine or after an acute adenovirus infection remains rare.
- This should be in the differential of idiopathic thrombosis and thrombocytopenia.

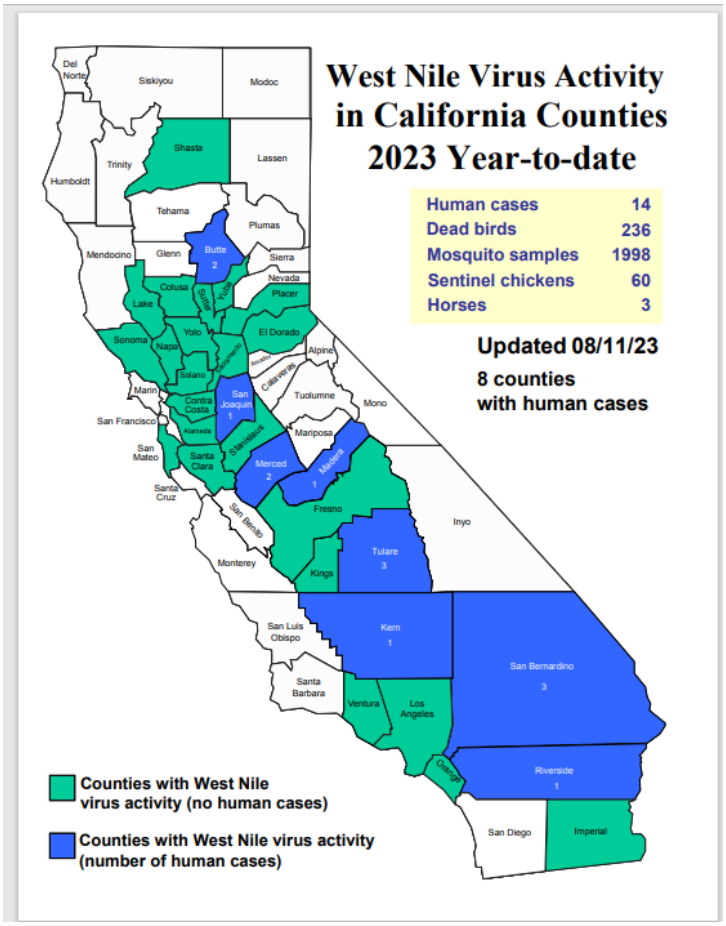
West Nile Virus (WNV)

- WNV is a mosquito transmitted infection that predominantly results in asymptomatic infections. About 1 in 150 people with WNV will develop severe illness, with meningitis, encephalitis, or flaccid paralysis being the most severe. Post-infection residual fatigue and depression are common.

- After the heavy winter rains, cases of WNV were predicted to rise this summer. The graph below illustrates that the number of cases identified in dead birds is more than twice the average over the last five years and four times higher than the same frame in 2022.



- Cases diagnosed in humans remains about the same as the last five years average. Notably, of the 14 cases in humans, 6 were diagnosed in the last week. They are from Butte, Madera, Merced, Riverside, and San Bernardino counties. Yolo county just reported their first patient with WNV disease this week.
- The map below shows WNV activity in 2023, year-to-date.



- Neurodegenerative disease such as Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease are associated with neuroinflammation. Nature Reviews Neurology, March 2023 presents data that supports that the neuroinflammation may be secondary to a viral pathogen in the genetically correct host. There isn't data on WNV, but this is a budding field of research.

West Nile Virus Take-Home Message

- Multiple counties in California have increased WNV activity in birds. This is much higher than the average seen over the prior 5 years, presumably because of the heavy winter rains.
- The 14 cases reported in humans this calendar year is average.
- Yolo county just reported their first infection in a human in 2023. (Not yet shown on CDPH map).
- WNV infection is usually asymptomatic. Only about 1 in 150 infected people develop neurologic complaints.
- Neurotropic viral pathogens may be associated with the development of neurodegenerative diseases. Research is still in a nascent phase.

False positive Influenza B rapid test.

- Rapid influenza diagnostic tests (RIDT) are known to have major limitations in sensitivity and specificity.
- False positive results for Influenza B have been seen in our ambulatory locations when using the Sofia Influenza Antigen Test. This is similar to what was seen during the 2022-23 influenza season, when almost no Influenza B was circulating.
- Over the past month, the positivity rate for influenza B by Sofia method is ~5-10%, a number significantly higher than PCR which showed a positivity rate for influenza B of <0.2% over the same time period.
- If the Sofia antigen test is positive for influenza B and result confirmation is clinically required, a sample should be sent for PCR testing.

Influenza Testing Take-Home Message

- RIDTs are quick and simple to perform but problems with sensitivity and specificity can lead to false positives and false negatives.
- False positives can also occur during times when influenza activity is low.

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.