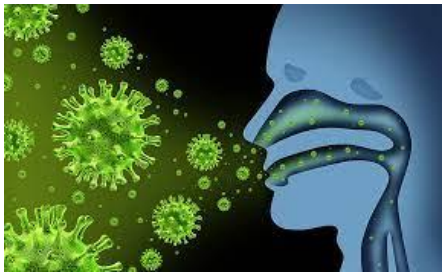


Sent on behalf of William Isenberg, M.D., Ph.D, Chief Medical & Quality Officer, Sutter Health, and Jeffrey Silvers, M.D., Medical Director of Pharmacy and Infection Control, Sutter Health

Emerging Infections Newsletter for Clinicians

June 15, 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.

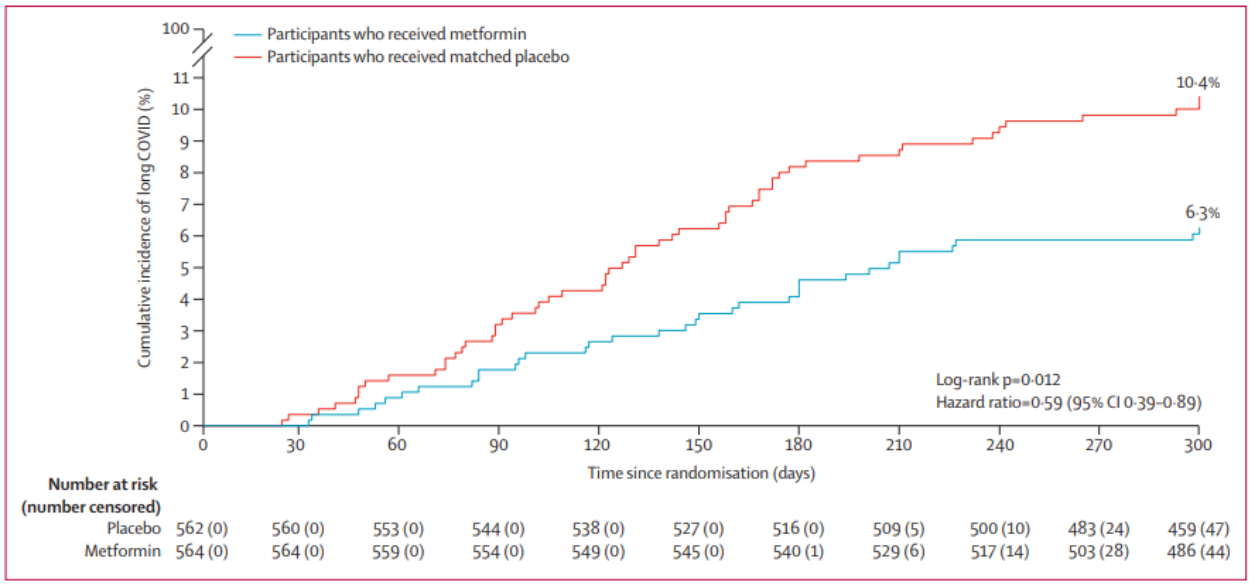
Topics

1. COVID-19
    a. Prevention of Post-acute Sequelae of SARS-CoV-2 Infections (PASC or Long COVID)
        i. Metformin
    b. United States sequence data
        i. XBB.2.3 increasing
    c. Vaccine
        i. FDA recommendations anticipated this week
        ii. China approved first trivalent vaccine which now includes XBB
2. Influenza increasing in Australia
    a. What are they seeing
    b. What can we learn
    c. What might we anticipate for our season
3. Mpox
    a. Mpox vaccine and equity
4. Dengue, chikungunya and Zika Update
    a. Three diseases with one vector
    b. Situation in the Americas
    c. Encouraging results in chikungunya vaccine
5. Marburg virus
    a. Outbreaks are declared over
6. RSV monoclonal antibody nirsevimab
    a. FDA recommends approval of monooclonal antibody to protect newborns and young children against RSV
7. Share the newsletter

COVID-19

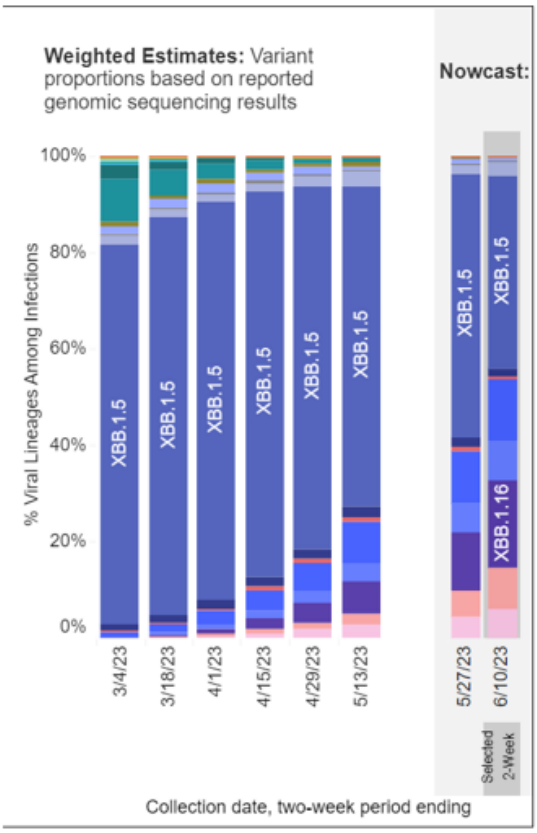
- Prevention of PASC
    - Although we do not have any proven effective treatments for PASC, there is new data on metformin reducing the risk of developing PASC.

    - Lancet, dated June 10, published a 30-day post-infection study of the effect of metformin on the development of PASC.
  - COVID-OUT, a multi-site, RCT evaluated the effect of a 2-week course of metformin in potentially reducing development of PASC. Enrollment included 1,323 SARS-CoV-2 test-positive adults with an elevated BMI (> 25 kg/m^2).
  - 85% of participants completed 300 days of follow-up. Metformin versus placebo were evenly divided.
  - The data show a significant, dose-dependent effect in lowering SARS-CoV-2 viral load within days of administration.
    - About 50% of subjects were vaccinated with the primary COVID vaccine series.
  - Results demonstrated a 41% reduction in PASC compared with placebo. See graph below.
  - The difference was even greater (63% lower) among those who had started taking metformin within three days of first experiencing COVID-19 symptoms.



- NIH guidelines do not recommend initiating metformin but continue it in patients who are already taking it.
- *The Medical Letter*, on May 29, stated "Off-label use of metformin to prevent long COVID in high-risk patients with normal renal function is reasonable, but confirmatory data from a trial more specifically focused on long COVID would be welcome."
- Metformin is associated with several GI-related adverse events and, rarely, lactic acidosis.
- Metformin did not decrease the risk of severe COVID.

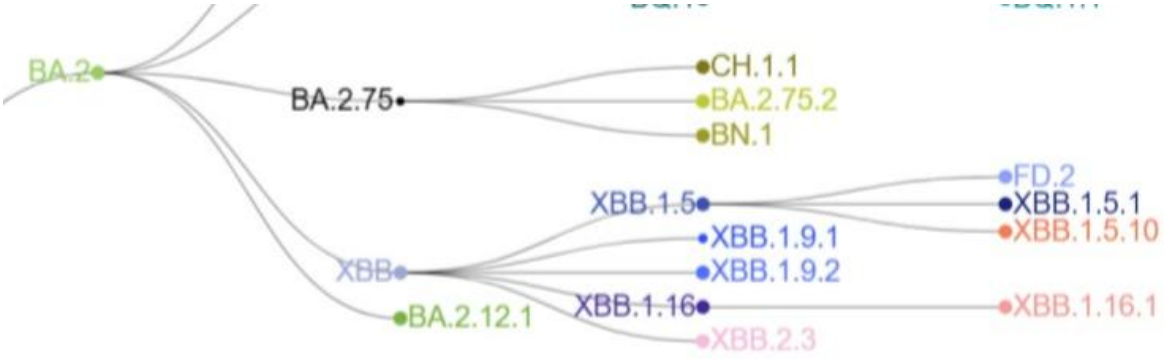
- **U.S. Sequence Data**
  - A gradual shift in dominant strains continues. Although some new isolates are increasing, a significant escalation in cases in the near-term is not anticipated.
  - Genomic sequencing data below shows the percentage of isolates due to a particular sequence. This does not correspond with virulence or activity levels in any community.



VHO label	Lineage #	US Class	%Total	95%PI
Omicron	XBB.1.5	VOC	39.9%	36.7-43.2%
	XBB.1.16	VOC	18.2%	15.5-21.2%
	XBB.1.9.1	VOC	12.5%	11.0-14.3%
	XBB.1.16.1	VOC	8.4%	6.1-11.5%
	XBB.1.9.2	VOC	8.4%	6.3-11.1%
	XBB.2.3	VOC	6.0%	4.4-8.1%
	XBB	VOC	3.0%	2.0-4.7%

XBB.2.3

- XBB.2.3 is increasing and now comprises 6.0% of sequenced isolates. It does not appear to have increased virulence. A snapshot of the relevant part of the Pango lineages below shows that XBB.2.3 has developed from the original recombinant XBB and is not an offshoot of the other circulating XBB strains.



- Vaccine update
  - This week, the FDA is anticipated to recommend the updated mRNA vaccine for distribution in September.
  - China has approved the first vaccine that provides additional coverage against XBB (Coviccine® Trivalent).
    - This is a recombinant, insect-derived, adjuvanted, subunit vaccine targeting the receptor binding domain (RBD) and HR protein (responsible for viral fusion and entry).

- This vaccine has specific antigens against delta (most virulent strain to date), BA.5 (from omicron) and XBB.1.5 (major circulating variant in large parts of the world in 2023)
- This contrasts with the WHO recommendation to move to a monovalent XBB vaccine
  - ✓ Wuhan-related strains (e.g. Delta) and omicron are not currently circulating to any significant degree in the world.
  - ✓ Concerns have been raised about blunted immune response when antigens are repeated in vaccines.

Take-Home on COVID

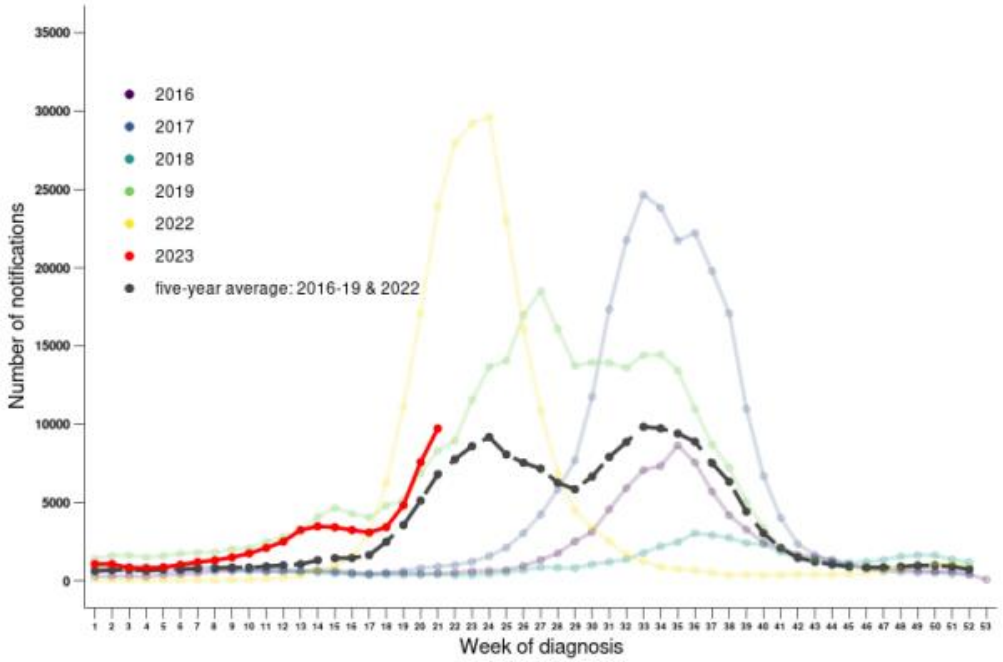
- The COVID-OUT study showed that metformin started within 7 days of symptom onset and a positive test within 3 days of enrollment reduced the risk of PASC by 40% in overweight adults (BMI>25kg/m^2).
- The best effect was seen when treatment was initiated within 3 days of symptom onset.
  - None of these patients received nirmatrelvir/ritonavir (Paxlovid®), which has also been shown to reduce the risk of PASC.
  - The NIH guidelines on metformin use have not been updated since Dec. 1, 2022
  - *The Medical Letter* considers off-label use reasonable but recommends further studies.
  - Providers can consider whether use is appropriate. Dosing should be the same as described in the COVID-OUT study.
- Circulating strains of COVID seem relatively stable now.
- China has released the first trivalent SARS-CoV-2 vaccine. The United States is more likely to follow the WHO recommendations of an XBB-based monovalent vaccine for this autumn.

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

Influenza

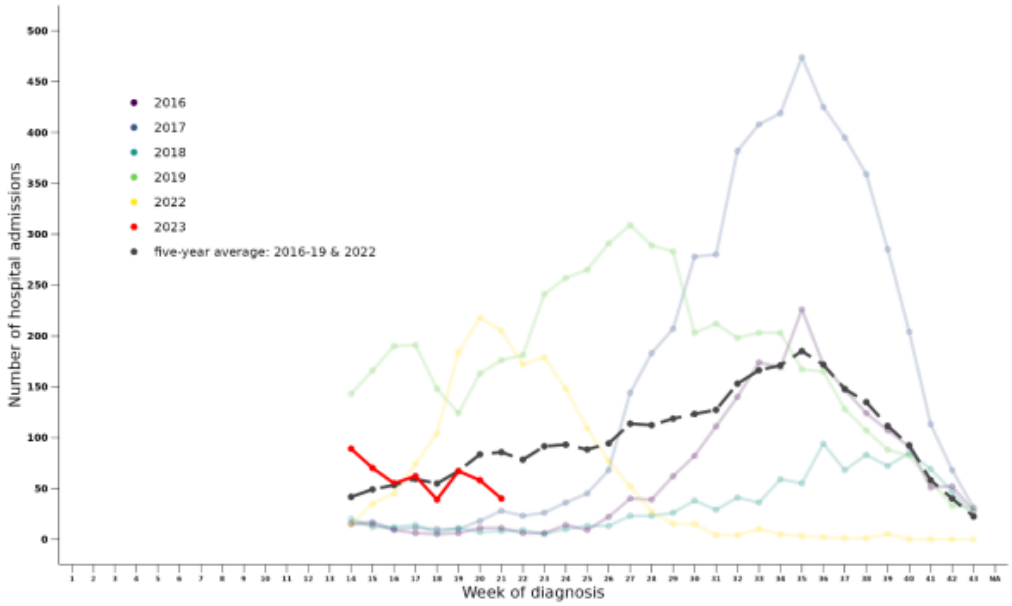
- Australia is starting to see a pick-up in cases of influenza. The most recent Australian Influenza Surveillance Report includes data from May 15 to May 28.
- Data is inadequate to assess the season's potential severity.
- 75% are influenza A, mostly untyped.
  - H1N1 is 80% and H3N2 is 20% of the typed strains.
- The highest reported rates have been in children through 14 years old.
- The graph below shows lab-confirmed notifications by week of diagnosis.
- Although rates are on a rapid incline, they are well below the large season that was experienced in in 2022 and are more similar to 2016 and 2018.

Figure 3: Notifications of laboratory-confirmed influenza, Australia, 1 January 2016 to 28 May 2023, by year and week of diagnosis*



- Hospitalizations due to influenza are not increasing (Shown in the graph below). This may be because the largest reported rates of disease are in children thus far.

Figure 6: Number of influenza hospitalisations at sentinel hospitals, from April to October, 2016 to 2023 by year and week of diagnosis*



- Early data on the vaccine match shows:

Strain	Number Tested	Vaccine Match
A H1N1	439	96.4%
A H3N2	124	74.2%

B	389	98.5.%

- Comparison of Australia vaccine strains versus United States is in the table below.
  - A H1N1 will be a different strain in the United States vaccine compared to Australia. This is a new strain for the 2023-2024 season
  - Everything else matches between the Southern Hemisphere and Northern Hemisphere selected vaccine strains.
  - A H3N2 strains are identical to last year's vaccines.
  - B Victoria was updated for the 2022-23 vaccine.

Influenza Strain	Egg Based		Cell Based	
	United States	Australia	United States	Australia
A H1N1	A/Victoria/ 4897/2022	A/Sydney/ 5/2021	A/Wisconsin/ 67/2022	A/Sydney/ 5/2021
A H3N2	A/Darwin/9/2021		A/Darwin/6/2021	
B Victoria	B/Austria/1359417/2021			
B Yamagata	B/Phuket/3073/2013 Probably Irrelevant as B Yamagata likely extinct			

Take-Home on Influenza

- We frequently look at Australia's influenza season to try to anticipate what we might see in our subsequent winter.
- It is too early to draw any conclusions.
- Early data shows increased cases, predominantly in children without a dramatic increase in hospitalizations.
- Influenza A H1N1 appears to be dominating.
- Australia is reporting an excellent match with H1N1 at 96.4% and B Victoria at 98.5%.
- Influenza A H3N2 is always the most difficult strain to match to vaccine because of mutations and frequent circulation of more than one clade. Last season, in the Northern Hemisphere A H3N2 vaccine match was excellent at over 90%. We have had some years where the match is below 15%.
- The Northern Hemisphere H1N1 vaccine strain is a newer one than being used in Australia. It is reasonable to remain optimistic that it will also be an excellent match for the upcoming Northern Hemisphere season.
- H3N2 vaccine strains are identical in both hemispheres. We will watch to see as the situation evolves. This is still considered a good match at 74.2%. More than one clade circulating can potentially impact effectiveness.

MPOX

- The CDC, on June 9 published an update on vaccination of the at-risk population.
  - They utilized a different approach by evaluating the shortfall.
  - Shortfall analysis measures the percentage of persons who have not achieved a certain health outcome—first dose of the Jynneos Mpox vaccination in this study.

- Shortfall analysis does not require a comparison group because the goal is 100% vaccination rates for each ethnic or racial group.
- The measurement used was 100% minus the percentage of people vaccinated in an at-risk group.
- Although efforts were successfully implemented to increase vaccination rates in racial and ethnic minority groups last year, the end result did not reach the goal.
- The shortfall analysis revealed that in appropriate vaccine candidates, 78% of black persons and 75% of non-Hispanic American Indian or Alaska Native have not received their first dose of vaccine. Numerically this compares to 67% White, 63% Hispanic/Latino and 39% Asian candidates were unvaccinated.
- Efforts to address health disparity in this population should focus vaccine efforts on those with the highest shortfall.

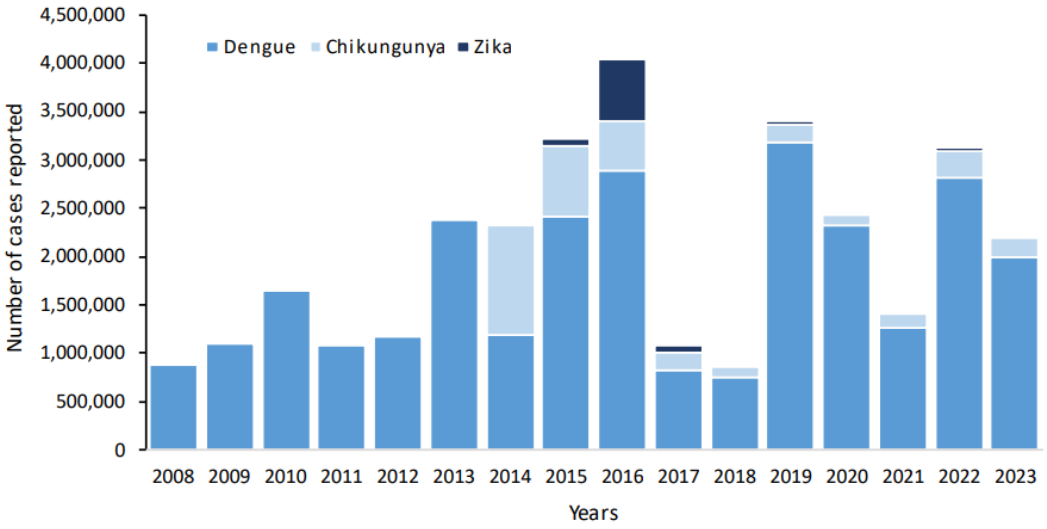
Mpox Take Home

- Looking at shortfall with a goal of 100% vaccination rates for high-risk persons in each ethnic or racial group, black persons, non-Hispanic American Indians and Alaska Natives have the largest unmet need for vaccination against Mpox.

Dengue, Chikungunya and Zika in the Americas

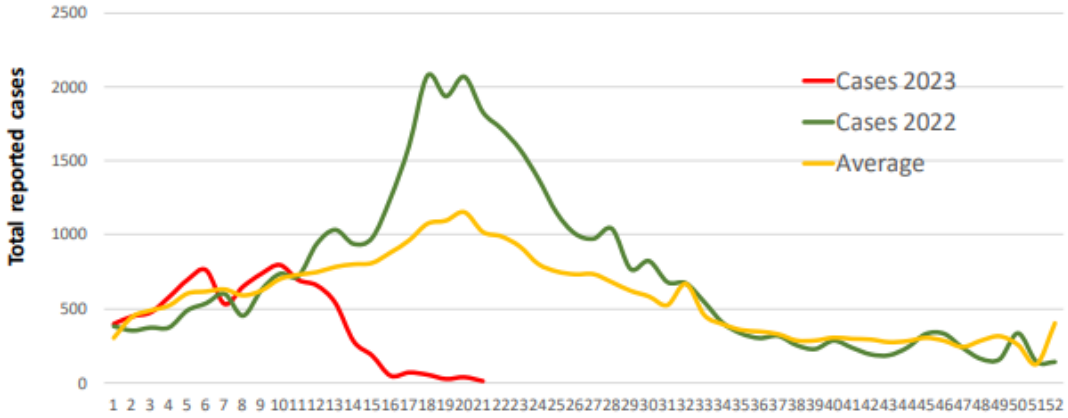
- Three different arbovirus diseases are endemic in the Caribbean, Central and South America.
- They are all transmitted by Aedes mosquitoes (A. aegypti, and A. albopictus).
  - These mosquitoes are found in California
  - A. aegypti is the biggest risk of causing transmission because it prefers to feed on humans. A. albopictus also feeds on other animals.
- Dengue typically comprises 90% of the reported cases of these arboviruses, with chikungunya about 9% and 1% Zika.
- Dengue outbreaks typically peak about every 3 to 5 years. The highest reported number of cases in the last 15 years was in 2019. Dengue cases in 2022 were more than double the number reported in 2021. See graph below
- Cases in the first five months of 2023 are 12% higher than the comparable period in 2022.
- Brazil has the highest number of cases of Dengue, but it has been reported this year in Costa Rica, Guatemala, Honduras, Mexico, Puerto Rico and multiple countries in South America.

Figure 1. Distribution of dengue, chikungunya and Zika cases by year of notification. Region of the Americas, 2008-2023 (until EW 21 of 2023).



- MMWR dated June 9 reported a very large ongoing outbreak of chikungunya virus (CHIKV) disease in Paraguay.
  - The name is derived from the Makonde African word for "bending up."
  - The first autochthonous case was reported in Paraguay in 2015. The 2015-16 season had 5,221 reported cases.
  - Between Oct.1, 2022 and March 11, 2023, 81,037 cases have been reported. This represents a 15-fold increase.
  - Most cases of CHIKV are believed to be symptomatic (72-97%), presenting with fever and severe polyarthralgia (hence the name). This polyarthralgia can persist for months to years in about 50% of all infected people. Intra-partum transmission is well described.
  - This is the opposite of Dengue where about 80% of infected persons are asymptomatic.
- A single-dose, live-attenuated chikungunya vaccine performed well.
  - Lancet June 12 published a phase 3, double-blind, multicenter, randomized, placebo-controlled trial in the United States.
  - Adults without any history of immune-mediated or chronic arthritis or arthralgia.
  - The vaccine safety protocol included 3,082 vaccine and 1,033 placebo recipients.
    - Adverse safety events were similar to other licensed vaccines, unrelated to age. One patient developed mild myalgia and another patient developed SIADH, both believed to be secondary to the vaccine.
  - The per-protocol population looking at immunogenicity included 362 vaccine and 96 placebo recipients.
  - Seroprotective neutralizing antibody titers were identified in 99% of the vaccine recipients at 28 days post vaccination. Titers dropped at day 180 but remained well above the seroprotective levels.
  - In the last 55 years, multiple vaccine trials against chikungunya have been conducted and terminated for distinct reasons. This is the first phase three trial thus far that is anticipated to lead to a potential vaccine.
- Zika cases have a different trend. The large outbreak in 2016 led to 651,470 reported cases, which was followed by a drop in annual cases until last year when 406,249 cases were reported. The graph below shows the dramatic decrease in cases this year compared to the 5-year average and 2022 information.

Figure 14. Zika cases in 2022, 2023 (up to EW 21) and the last 5-year average – Region of the Americas.



Dengue, Chikungunya and Zika Take Home

- Dengue represents about 90% of all reported cases of the top three Aedes-transmitted infections. Case numbers might exceed the 2016 outbreak, which was the largest in the last 15 years.
- Chikungunya has a very distinctive presentation with severe polyarthralgias. Paraguay has had an exceptionally large outbreak. This is 15-fold higher than the previous record in that country.
- After over 50 years of studies, a live-attenuated, single-dose vaccine against chikungunya has shown sustained immunogenicity at 180 days and a very good safety profile.
    - Patients with prior history of significant arthritis or arthralgias were excluded.
- Zika is not being identified frequently in the Americas at this time.
- Although cases in California are uncommon and almost always travel-related, the fact that the correct mosquito vector is in California raises the risk of local transmission occurring.
- Always consider travel history when evaluating patients with fever and an uncertain diagnosis.

Marburg Virus Disease (MVD) Outbreak

- Marburg Virus is in the same family as Ebola Virus.
- The Marburg Virus Disease outbreak that started in Equatorial Guinea on Feb.13, has now been controlled, passed through two incubation periods (42 days) without any additional cases and is declared over. Forty patients were identified, 35 who died (87.5% mortality). Five cases were in healthcare workers.
- The outbreak in Tanzania was declared March 21, 2023 and considered ended on June 2. A total of nine cases with five deaths (56%) were reported
- Although overlapping in onset, and both being their first outbreak of MVD in their countries, they were over 3,000 miles apart and unrelated.
- Because of the work through the CDC and WHO, no cases were identified in other countries from those outbreaks.

MVD Take Home

- Two simultaneous, unrelated, MVD outbreaks in parts of Africa that had not previously experienced this were declared over.
- Combined mortality was 82%

RSV Monoclonal Antibody

- On June 8, the FDA's Antimicrobial Drugs Advisory Committee unanimously recommended use of nirsevimab for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease (LRTD) in newborns and infants born during or entering their first RSV season.
- The committee also voted to support use for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season based on a favorable benefit risk profile.
- Recommendations were primarily based on results of the Melody Phase III trial (NEJM).
- Approximately 3,000 infants born at gestational age (≥35 weeks) were randomized 2:1 to receive a single weight-based dose of nirsevimab versus placebo between July 2019 to March 2021.
- Through day 150 following injection (Table S5-S6):
  - Incidence of medically attended RSV lower respiratory tract infection (LRTI) was 12/994 (1.2%) in the nirsevimab arm and 25/496 (5.0%) in the placebo arm for a relative risk reduction of 74.9% (p <0.0001).
  - The incidence of hospitalization due to RSV was 6/994 (0.6%) in the nirsevimab arm and 8/496 subjects (1.6%) in the placebo arm for a relative risk reduction of 60.2% (p=0.09).
  - Most common adverse reactions in the nirsevimab group were rash (0.5%) and irritability (0.2%), which were comparable to placebo during a 360-day follow up.
- Nirsevimab is anticipated to receive FDA approval ahead of the 2023-2024 RSV season.

RSV Take Home

- The phase 3 MELODY trial showed that a single dose of nirsevimab provided high and consistent efficacy against RSV LRTD. This was sustained through the entire RSV season.
- Nirsevimab is intended to be administered either before or during RSV season, in those born healthy at term, preterm, or with specific health conditions that make them vulnerable to RSV disease.
- Nirsevimab was well tolerated with a favorable safety profile that was consistent across all clinical trials.
- The FDA is currently reviewing nirsevimab for potential approval by Q3 2023.

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.

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