



Emerging Infections Newsletter for Clinicians

Nov. 16, 2023

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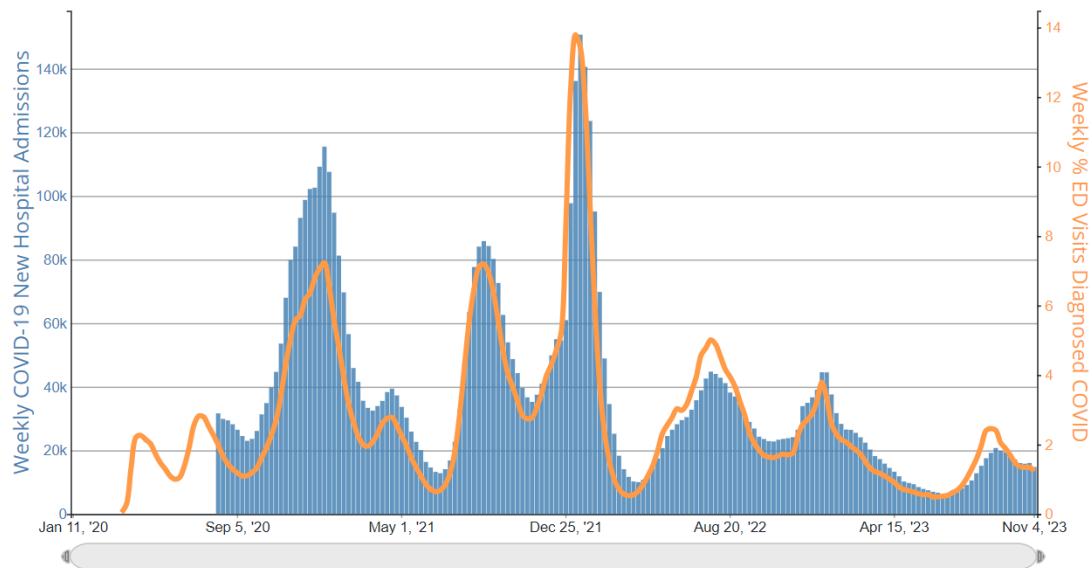
Tripledemic

- A tripledemic is a term that refers to the simultaneous circulation of three respiratory viruses, specifically SARS-CoV-2, RSV and influenza. It does not refer to multiple simultaneous infections in an individual, although they do occasionally occur.
- The term tripledemic does not reflect the severity of the outbreaks. Hospitalizations increase during outbreaks of any of these three viruses. The concern is that simultaneous outbreaks could potentially infect a lot more people, increase morbidity and mortality and create stress on our healthcare systems.

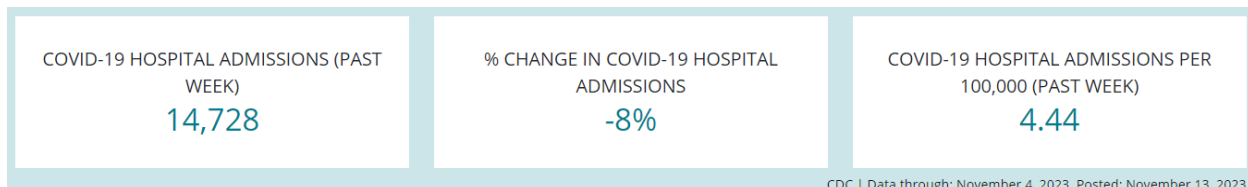
COVID-19

- [Hospitalizations](#) in the United States are a surrogate for the virulence of the circulating strain. The graph below and the subsequent table show:
 - One month of stable to slowly decreasing rates of hospitalizations (blue vertical bars) and 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. Nationally, rates remain below 5/100,000 and hospitalization rates are continuing to drop. The admissions percent change in the last week was down another 8%.

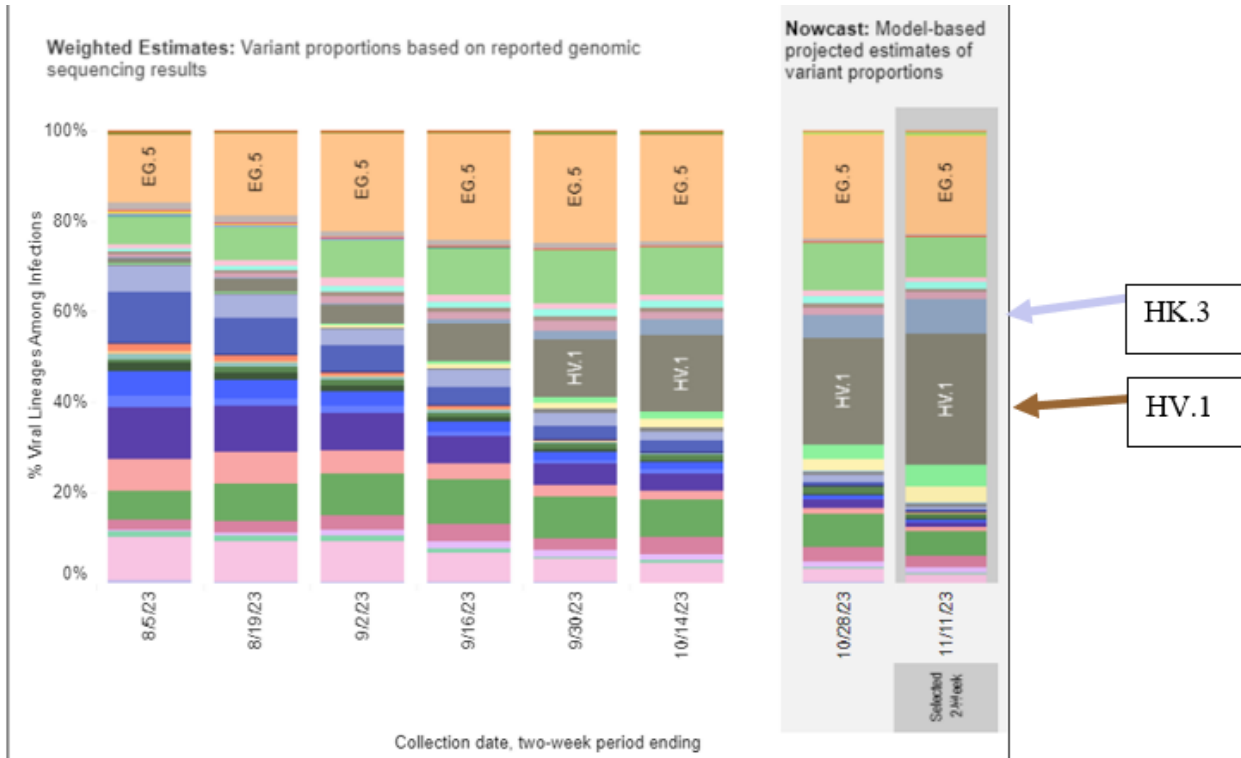


CDC | Data through: November 4, 2023. Posted: November 13, 2023

- [National genomic sequencing](#) is updated every 2 weeks by the CDC. The most recent information goes through Nov. 11 (graph below). HV.1 is still the most frequently sequenced

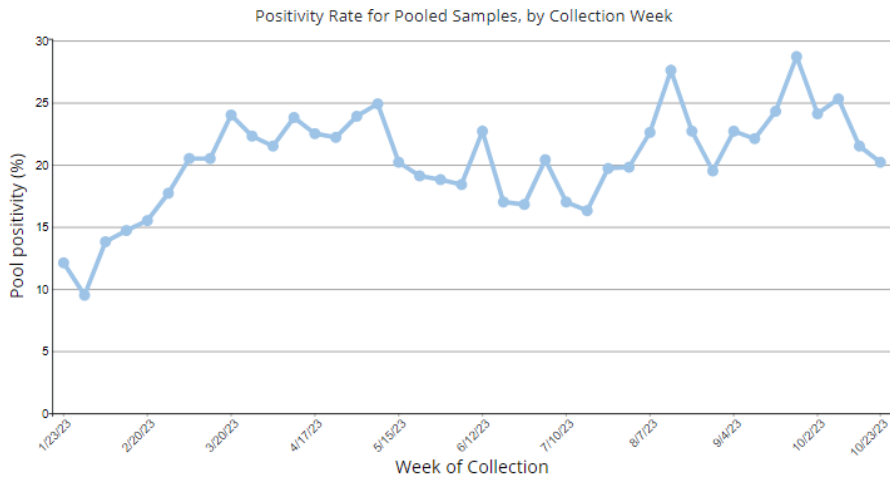
isolate (Brown arrow). The top four isolates still constitute almost 70% of all sequenced strains. They are all derived from XBB.

- HK.3 (light purple arrow) is highlighted because of the frequency of isolation in international travelers (discussed below).

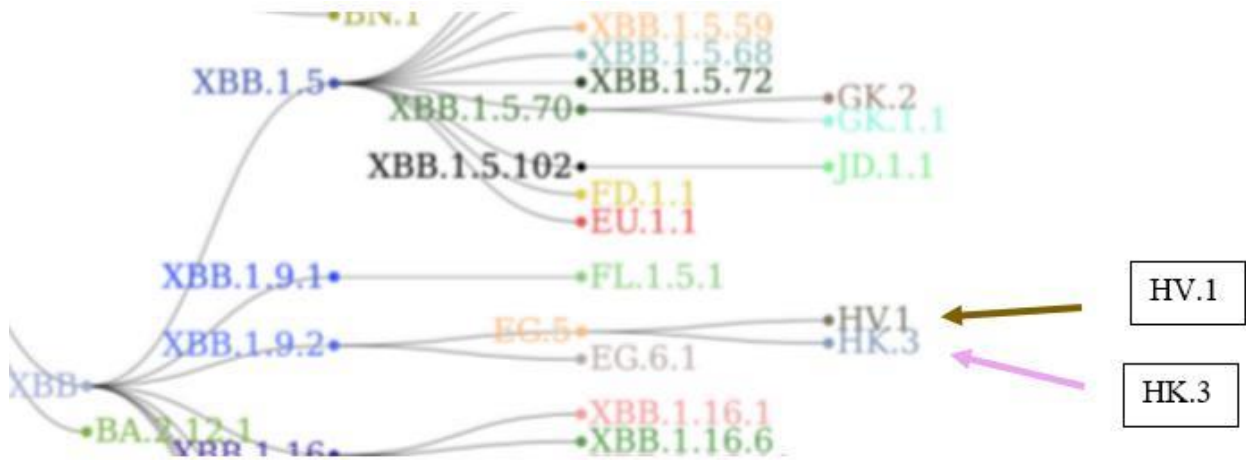


Omicron	Lineage	Current %	Range %	Color
	HV.1	29.0%	26.0-32.1%	Dark Grey
	EG.5	21.7%	19.3-24.2%	Orange
	FL.1.5.1	9.3%	8.0-10.8%	Light Green
	HK.3	7.8%	6.2-9.9%	Light Purple
	XBB.1.16.6	5.6%	4.7-6.6%	Dark Blue
	JD.1.1	4.6%	3.4-6.1%	Green
	JF.1	3.5%	2.7-4.5%	Yellow
	XBB.1.16.11	2.5%	2.0-3.2%	Pink

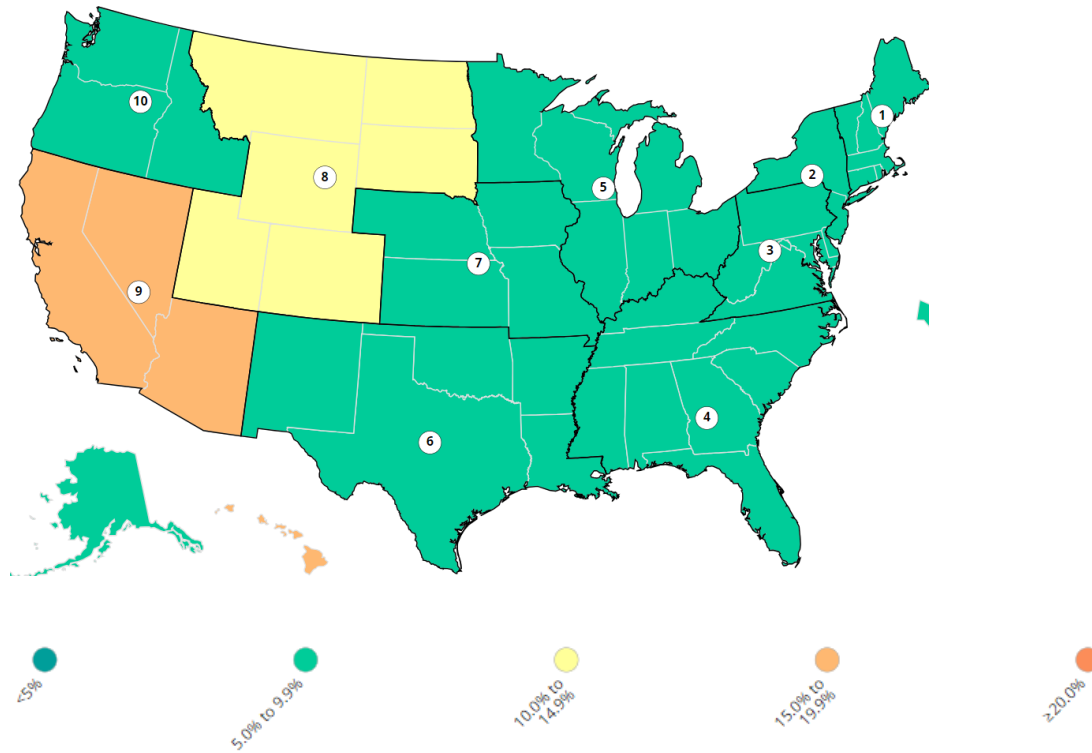
- Surveillance of international air travelers is conducted at several major U.S. airports as an early warning system and to fill gaps in worldwide genomic surveillance. It covers flights from more than 135 countries.
- The graph below shows a continued high positivity rate of at least 20%. [Fifteen different variants](#) (data not shown) were identified the week of Oct. 23.
- Although none are dominant, HK.3 has now been on the list since Aug. 21. It has moved to the most frequently sequenced international isolate in two months. Note that it is number 4 in the United States (light purple arrow in genomic sequencing graph above).



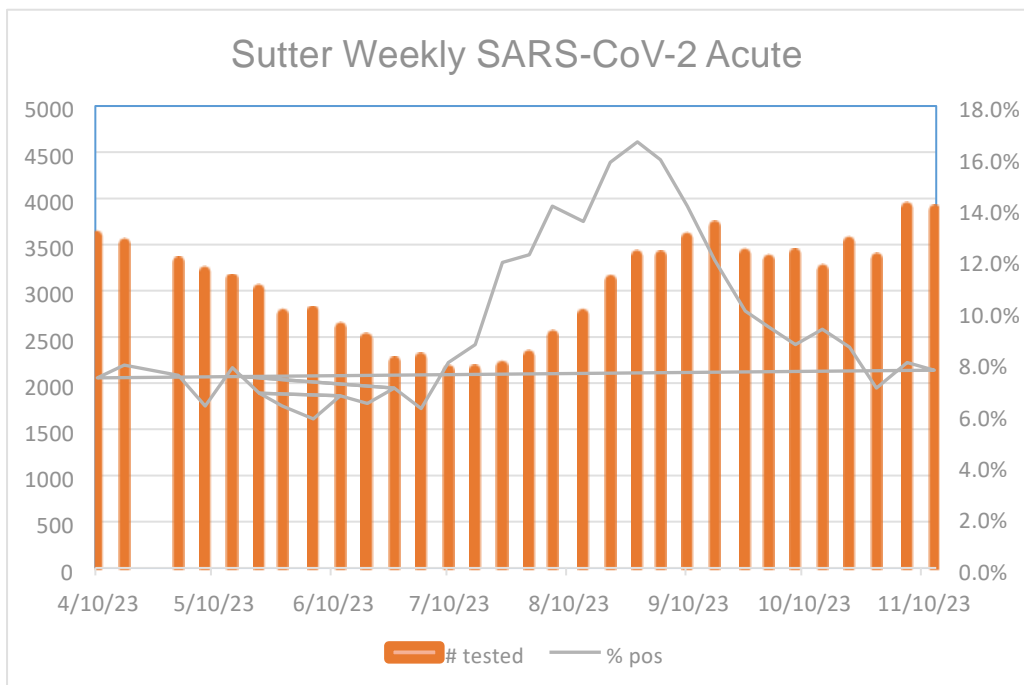
- Part of the [Pango Lineage](#) is shown below. HV.1 (brown arrow) and HK.3 (light purple arrow) are both from EG.5. They are all derived from XBB, which is the basis for the new COVID vaccine. Vaccine protection against these variants is expected to be good.

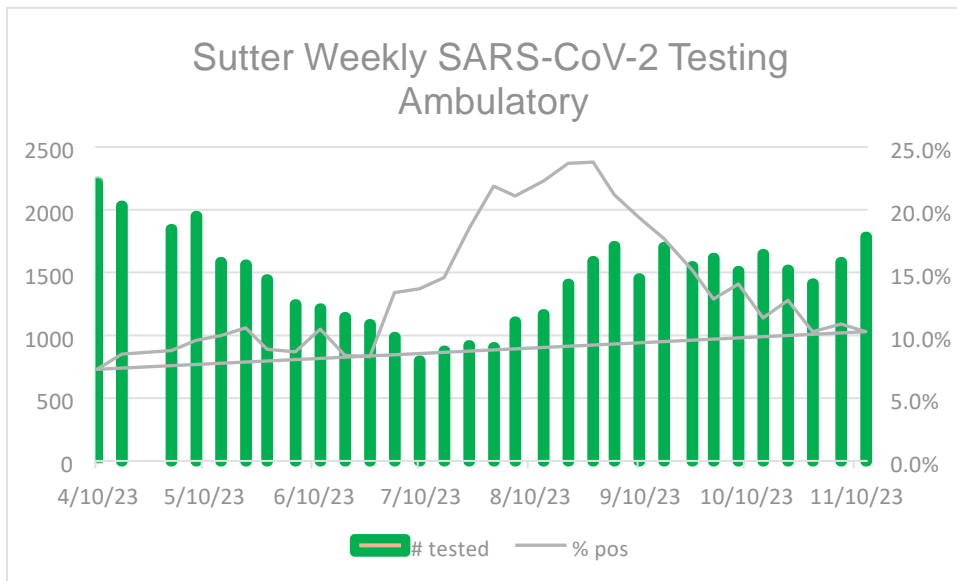


- [National](#) molecular test positivity rates by region were updated on Nov. 13 and are demonstrated on the map below. Most of the country is now green, representing a positivity rate of less than 10%.
- Region 9, including California moved from yellow to orange. The region 9 reported positivity rate went from 11% to 16.7%. Region 9 includes Arizona, Hawaii, Nevada and California.
- Drilling down on the CDC data, it is not clear what states in region 9 are actually seeing this high positivity rate. [California](#) reports a test positivity rate of only 6.9% in the last 7 days through Nov. 4.



- Updated Sutter testing data below shows slowly decreasing positivity rates, well off of the peak reached over 2 months ago. Significant levels of testing are being performed in emergency departments and ambulatory environments.





- Intravenous vitamin C had been recommended by various groups as a treatment for patients hospitalized with COVID-19.
 - [JAMA Network](#) reported results of two multi-center, international, 24-month, prospective trials (LOVIT-COVID and the REMAP-CAP). A total of 2,590 patients were enrolled, including critically ill patients receiving organ support and non-critically ill (40 sites). Of these, 1,493 received vitamin C and 1,097 served as control.
 - IV Vitamin C administered to hospitalized patients with COVID-19 *did not* improve organ support-free days or hospital survival.
 - The trial was terminated early when statistical triggers for harm and futility were met.
 - Intravenous vitamin C was not helpful and was possibly harmful.
- Paxlovid® remains the first choice in the [NIH](#) recommendations for treatment for mild-to-moderate COVID in persons at high risk for progressing to severe disease. The risk of rebound (virologic relapse) after a course of Paxlovid® is [commonplace knowledge](#) although there is debate about the actual frequency of rebound.
- [Annals of Internal Medicine](#) published a small, very robust, observational study from Boston on Nov. 14. Virologic relapse (VR) was defined as either a positive SARS-CoV-2 culture, after a prior negative result, or two consecutive, defined, elevated viral loads within 20 days of the initial positive test. The table below demonstrates the results

Category	# Participants	Number w/ Rebound	% with Rebound
Paxlovid	72	15	20.8%
Untreated	55	1	1.8%

- 50% of patients with VR were symptomatic and all 16 had a positive culture. No statistically significant differences between the composition of the groups, but the small size limited the testing.
- **COVID-19 Take-Home:**
 - Hospitalizations, emergency department visits and Sutter testing positivity rates are all trending down.

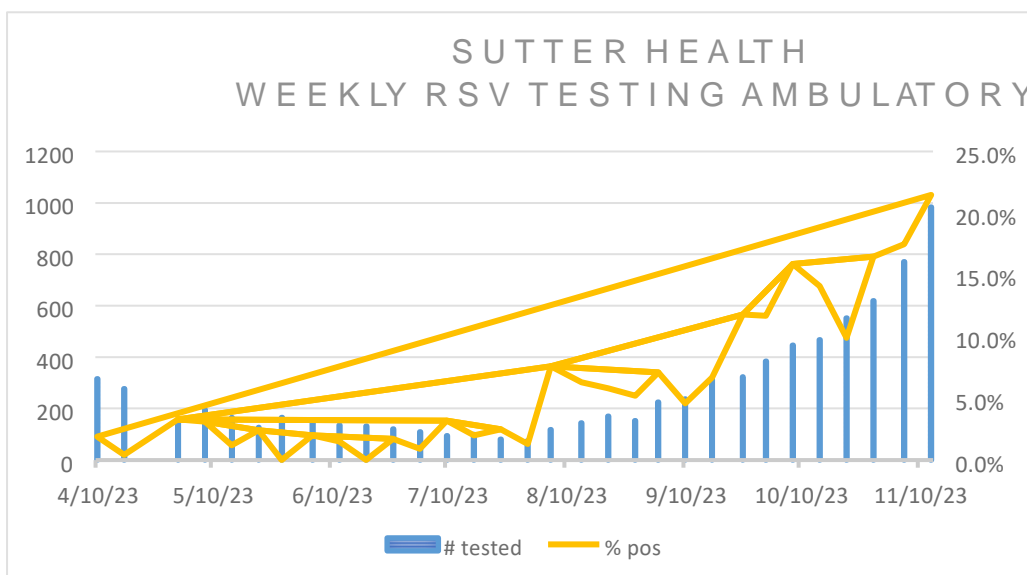
- CDC genomic sequencing shows that HV.1 remains the most commonly identified variant in the United States. Multiple variants are circulating. None show increased virulence at this time.
- Random testing of international passengers still shows a SARS-CoV-2 positivity rate of at least 20%. HK.3 is the most common isolate, but this is related to HV.1
- The map of national testing data for region 9 is a little difficult to validate. It does not seem congruent with other available information. For now, evidence supports that cases of COVID are trending down at least in California.
- Sutter ambulatory and emergency department positivity rates are 10.3% and 7.7% respectively.
- Evidence does not support the use of IV vitamin C in the treatment of hospitalized patients with COVID-19.
- Paxlovid®-rebound may be much more common than previously suggested. Although rebound occurs without taking Paxlovid® (1.8% in this most recent study), this is well below the 20.8% seen in patients who took Paxlovid®. In spite of this being a very small study, it used very objective measurements of viral rebound and is congruent with anecdotal opinions.

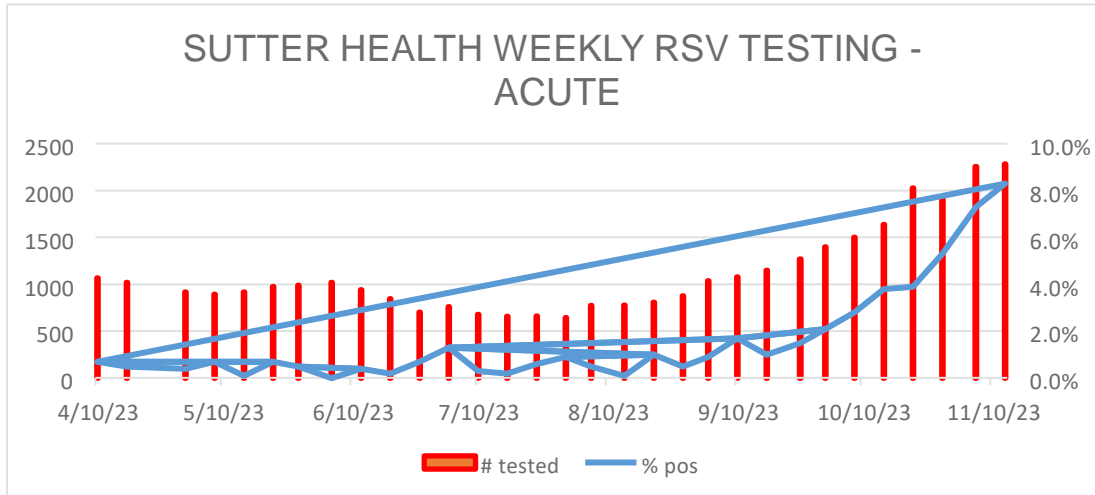
- **Related Links**

- [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

- RSV identification rates are escalating in both the ambulatory and emergency departments in Sutter. The amount of testing is simultaneously increasing and positivity rates in ambulatory are now over 20% and 8.3% in the emergency departments. The RSV season in Northern California seems widespread.
- See two graphs below.





- RSV results by age are in the following table for the week ending Nov. 12. Positivity rates continue to increase. All ages are now increasing.
 - More people 60 years and older are being diagnosed with RSV in the emergency department.
 - Since patients who go to the emergency department tend to be sicker than those seen in other environments, this suggests that RSV-associated hospitalizations may start to increase.
- See table below.

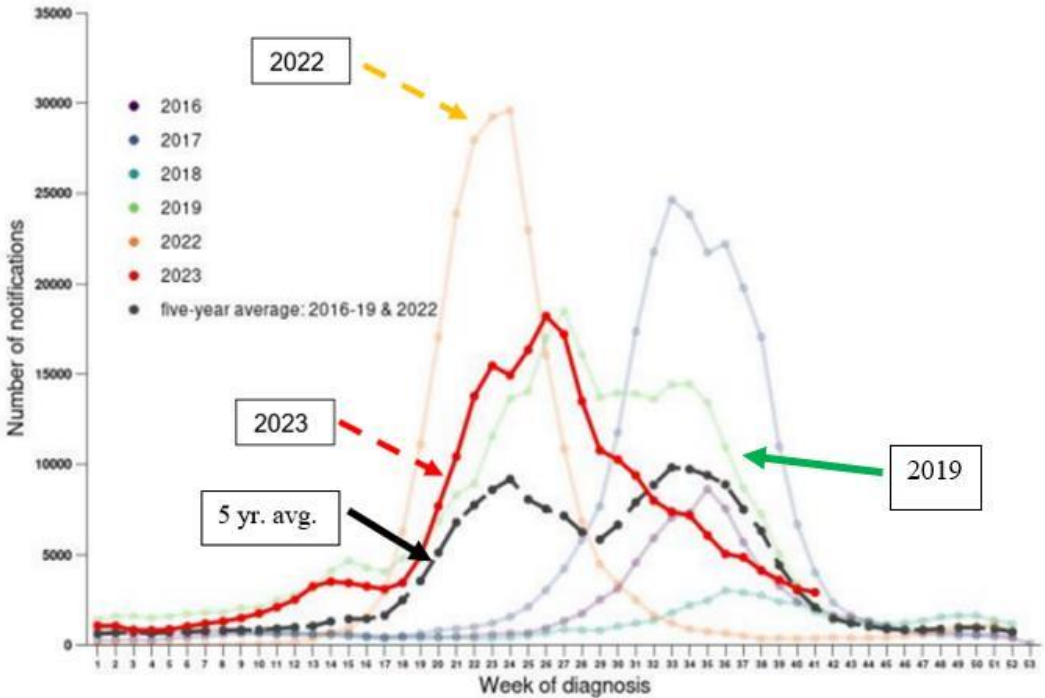
Location	<6 years old		6 to < 12 years old		≥ 60 years old	
	Number Tested	% Positive (number)	Number Tested	% Positive (number)	Number Tested	% Positive (number)
Ambulatory	396	37.6% (149)	130	13.1% (17)	140	11.4% (16)
Acute (ED)	605	19.8% (120)	129	8.5% (11)	1052	3.4% (36)

- Extremely limited availability of nirsevimab (Beyfortus®) continues.
- **RSV Take-Home:**
 - The RSV season is here in California. In Northern California, more than one out of every three children ≤ 6 years old tested for RSV in the outpatient environment is positive and 20% are positive in the ED in that age group.
 - Equally notable is that RSV is starting to be identified in higher numbers in persons 60 years and older. Increased RSV associated hospitalizations may start to increase.
 - Nirsevimab supply remains limited.

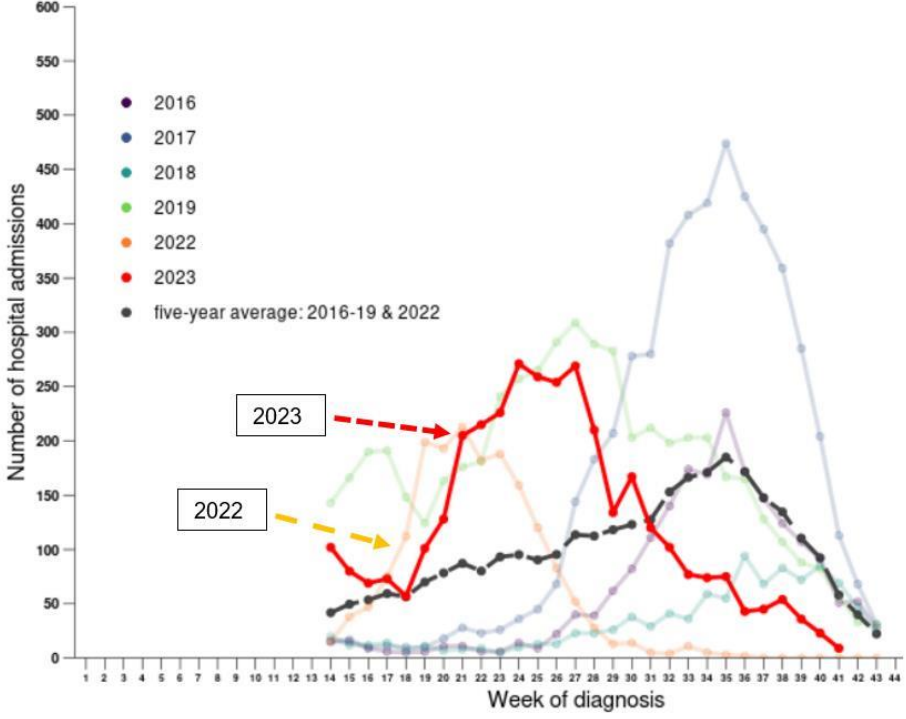
Influenza

- Using [Australia](#) as a surrogate for the prior Southern Hemisphere respiratory season provides some useful surveillance data on influenza.

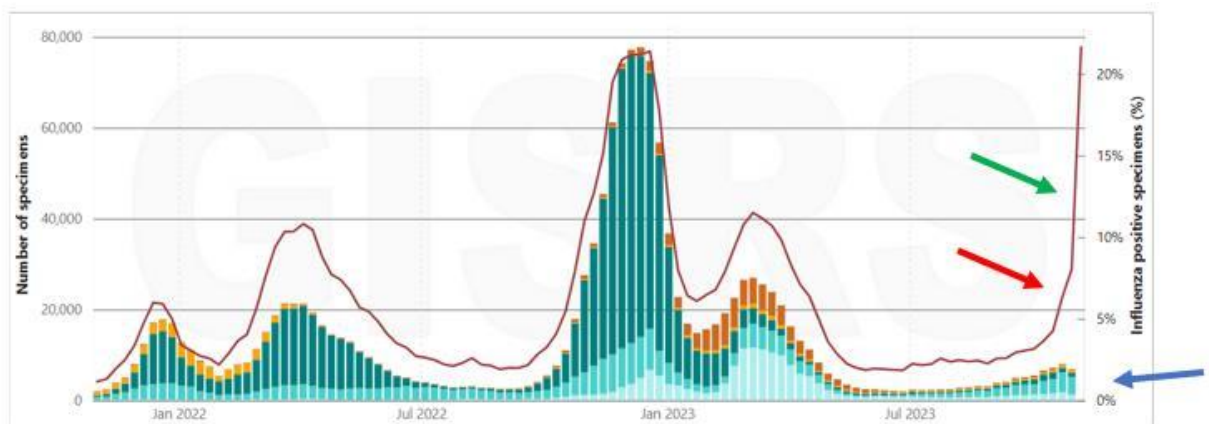
- The graph below shows 8 years of weekly new cases of laboratory-confirmed influenza. The red run line reflects the 2023 season. Onset was fairly typical compared to the 5-year average (black arrow).
- The peak of new cases was similar to 2019 (Green arrow, pre-COVID), but notably significantly lower than the 2022 season (orange line).



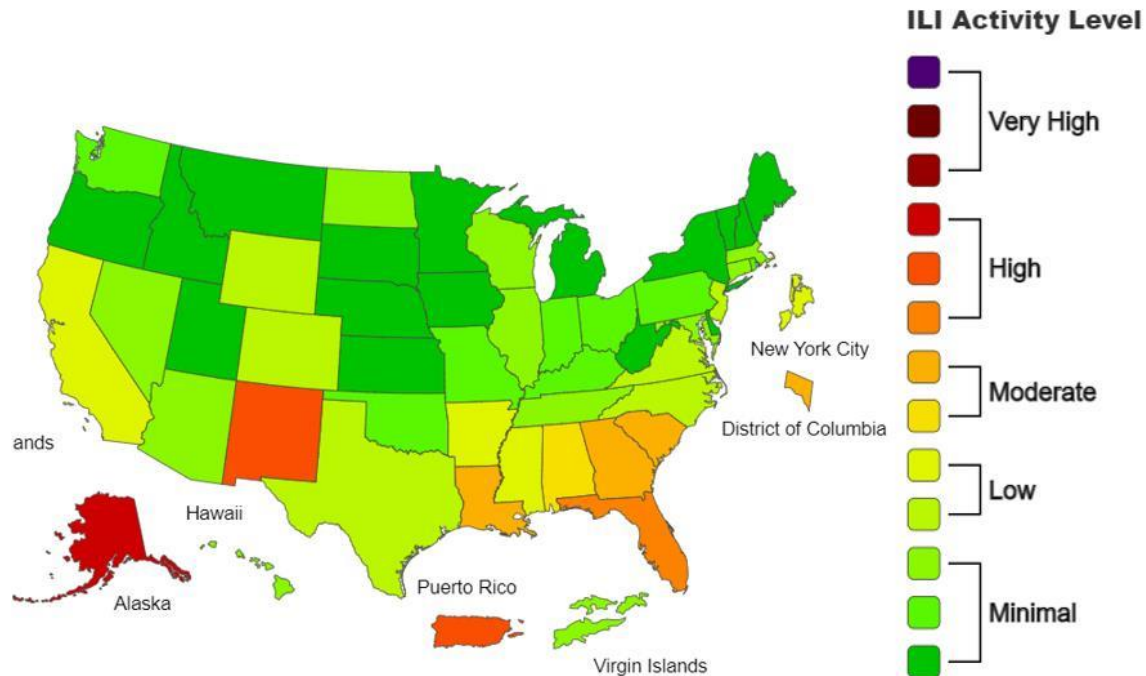
- Severity is a separate measurement that reflects outcomes or complications. The graph below shows that influenza in Australia in 2023 (red run line) resulted in more hospitalizations than was seen in 2022 (orange line), even though more people developed influenza in 2022.



- The final point to consider before drawing any conclusions is a comparison of circulating strains and vaccine match in Australia versus the United States. In 2022, the A H3N2 that predominated in Australia was very similar to what we experienced last season.
- In 2023, Australia identified predominantly A H1N1, which is what we are currently seeing in the United States. The vaccine composition used in Australia had an older strain, whereas all of the influenza vaccines in the [United States](#) are using an updated strain.
- The 2023 season in Australia, although not as widespread in 2023 compared to 2022, was more severe. Compared to the 5-year average, both identification of cases and hospitalizations were higher in 2023.
- The updated A H1N1 in the United States vaccine is likely a closer match to what is circulating, but the impact is determined by uptake of the vaccine and each person's risk of severe disease.
- The [WHO](#) released their biweekly global influenza update on Nov. 14. This includes the most recent two weeks of data up to Oct. 29.
 - Increased activity in the Northern Hemisphere continues in Western and Eastern Asia.
 - Influenza A predominates with both A H3N2 and A H1N1 being detected.
 - The Southern Hemisphere has inter-seasonal, low levels of detection.
 - From Oct. 16 to 29, 262,187 specimens were tested.
 - ✦ 14,448 were positive (5.5%).
 - ✦ 86% were influenza A, with H3N2 twice as common as H1N1.
- The graph below shows influenza activity in the Northern Hemisphere for the last 2 years. Cases are starting to rise (shown by the blue arrow). Shades of teal represent influenza A and brown represents influenza B. The red arrow points out that the positivity rate has spiked up. The sharp increase at the end is an artifact of incomplete data (green arrow).

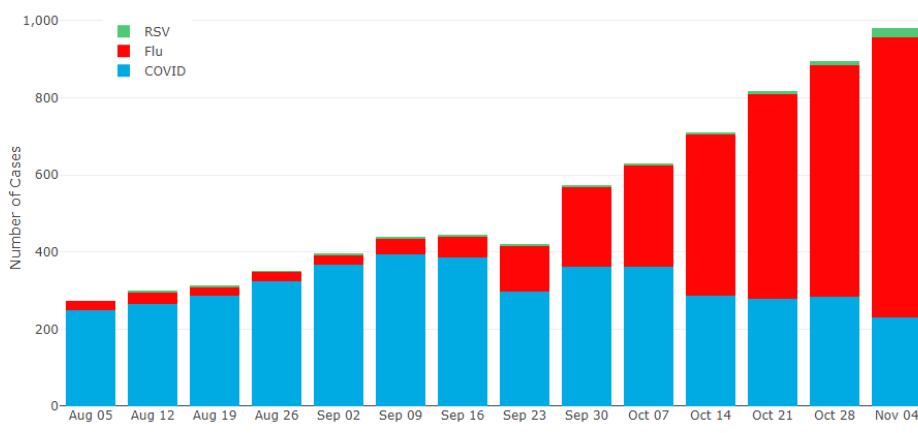


- Influenza-like activity (ILI), the surrogate for influenza used by the [CDC](#), is on the map below showing data in the week ending Nov. 13. Disease in the United States is increasing.
- California has now moved up to moderate. Since influenza is not a reportable disease in many states, except for hospitalizations and deaths, it is difficult to get accurate numbers. As identifications continue to increase, this map is likely a good surrogate for true influenza.

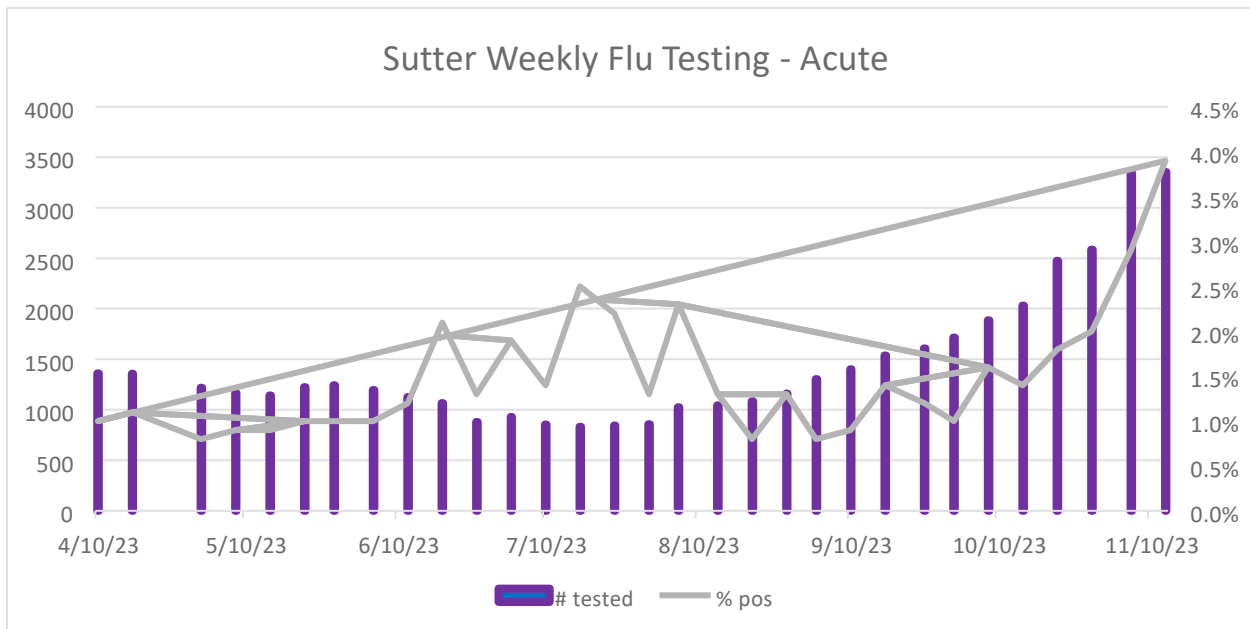


- The [CDC](#) reports that out of 56,471 specimens tested by clinical labs during week 44 (ending Nov. 4), 1,687 were positive (3.0%). Influenza A H1N1 continues to dominate, representing 90% of the influenza A isolates.
- [Anticipated vaccine match](#) is determined by measuring the activity of ferret-derived vaccine antibodies against samples from circulating strains. Since May 2023, all the circulating strains were recognized by the vaccine antibodies.
- [Alaska](#) does track lab-confirmed cases of influenza and COVID. RSV just became reportable September 2023. Thus, RSV data (green) is not interpretable at this time. The graph below confirms that Alaska has a twindemic with flu and COVID-19, but COVID identification rates (blue) are decreasing while influenza (red) is increasing.

Lab-Confirmed COVID-19, Flu and RSV Cases by Week



- The graph below shows Sutter emergency department influenza positivity rates. Testing rates have increased as all symptomatic persons being seen in emergency departments are being tested for influenza and SARS-CoV-2. RSV testing? has age-preferred criteria. Positivity rates are now almost 4% consistent with increasing circulation of influenza.



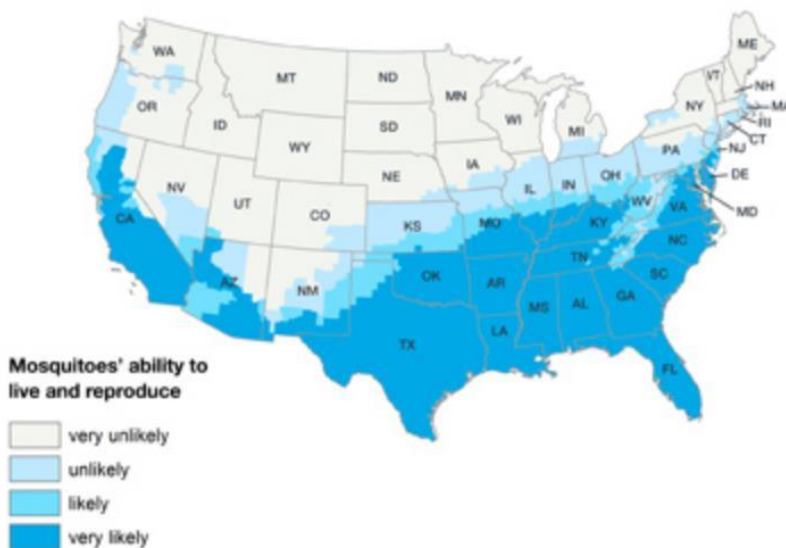
- **Influenza Take-Home:**

- The 2023 season in Australia, although not as widespread in 2023 compared to 2022, was more severe. Compared to the 5-year average, both identification of cases and hospitalizations were higher in 2023.
- If Australia results provide any useful information about our potential influenza season, one could postulate that the severity of disease in the United States will be worse in 2023-24 than the 2022-23 season.
 - ✦ Key points that support this is that A H1N1 predominated in Australia as it is so far in the United States.
 - ✦ Vaccine match and uptake can significantly affect this. Although the vaccine match looks good, influenza [vaccinations rates](#) appear to be lower this year compared to last year.
 - ✦ Many countries in Asia are experiencing predominantly A H3N2. If that were to become the dominant strain in the United States, all of the potential value of the Australia data would be made moot.
- Although the WHO reports that worldwide influenza activity remains low, the positivity rate has increased from 3.2% up to 5.5% in the last 2 weeks.
- Influenza activity is increasing in most parts of the United States. Alaska has a twindemic of influenza and SARS-CoV-2.
- Vaccinate.

Dengue

- Mosquitoes do not all present the same risk of disease transmission. This newsletter has been tracking WNV in California through the 2023 season. That is transmitted by the Culex mosquito. There are seven Culex species in the United States, all that are believed to be capable of transmitting WNV. Some also can transmit Western and Eastern Equine Encephalitis.
- Two weeks ago, the newsletter discussed the *Anopheles* mosquito that can carry malaria. Of the 400-plus species of *Anopheles* mosquitoes identified in the world, only about 40 can serve as vectors for malaria.

- The *Aedes* mosquito genus is comprised of more than 950 species, but only two species (*Aedes aegypti* and *Aedes albopictus*) pose the highest risk of disease transmission in the United States.
 - *A. albopictus* feed on animals and people and are therefore less likely to spread viruses. *A. aegypti* prefers humans as their host and are more likely to transmit diseases. The *Aedes* mosquito can carry yellow fever, Zika, dengue and chikungunya.
- The map below, although from 2017, shows the [CDC estimated](#) potential range of *A. aegypti*.



- Dengue is a systemic viral illness that can range from asymptomatic to rapidly progressive life-threatening distributive shock. It is also colloquially called “break-bone fever.”
- The incubation period is usually four to 10 days. Symptomatic persons usually present with high fever, headaches, retro-orbital pain, severe myalgias (classically including the lower back and legs) and large joint arthralgias.
- Nausea, vomiting and rash are also common. Laboratory testing clues include leukopenia and thrombocytopenia. [Medscape](#) provides an excellent overview.
- Most cases of Dengue identified in California are travel related and not locally acquired. In the last 8 years, only two cases of locally acquired Dengue have been reported in California, both of those in October 2023 ([Pasadena](#) and Long Beach). Within the continental United States, locally transmitted disease is uncommon, other than [Florida](#).

• **Dengue Take-Home:**

- Mosquito bites may all feel the same, but the risk of mosquitoes carrying a disease varies by genus.
- Locally transmitted dengue has now been identified in two epidemiologically unrelated persons in Southern California.
- The risk of local transmission of Dengue in California remains extremely low. Most cases will be related to travel acquisition. Diagnosis requires vigilance and consideration of the diagnosis.
- Remember that it is frequently referred to as “break-bone fever” because of the symptoms that a patient reports.

Increasingly Antibiotic Resistant *N. gonorrhoea*

- *N. gonorrhoea* has gradually developed resistance to many classes of antibiotics used to treat these infections. Ceftriaxone IM, has become the last available recommended treatment for gonorrhoea globally.
- The Global Antibiotic Research and Development Partnership (GARDP) co-sponsored a phase 3 trial of investigational oral zoliflodacin in the treatment of uncomplicated urogenital gonorrhoea.
- In a GARDP [press release](#), zoliflodacin demonstrated statistical non-inferiority in curing patients compared with the global standard treatment of ceftriaxone IM (500 mg) plus oral azithromycin. No serious adverse events were noted.
- If FDA approves, zoliflodacin will be the first new antibiotic for treating gonorrhoea in decades.