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 22, 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. United States sequence data
        i. Data remains stable.
    b. Vaccine update
        i. FDA Advisory Committee recommendation monovalent XBB variant
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    d. CDC complicates COVID vaccine recommendations again
2. Shigella
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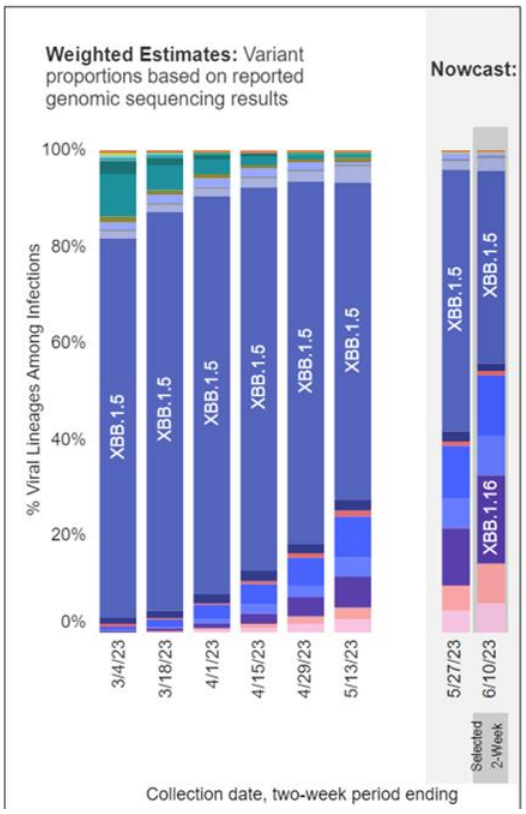
COVID-19

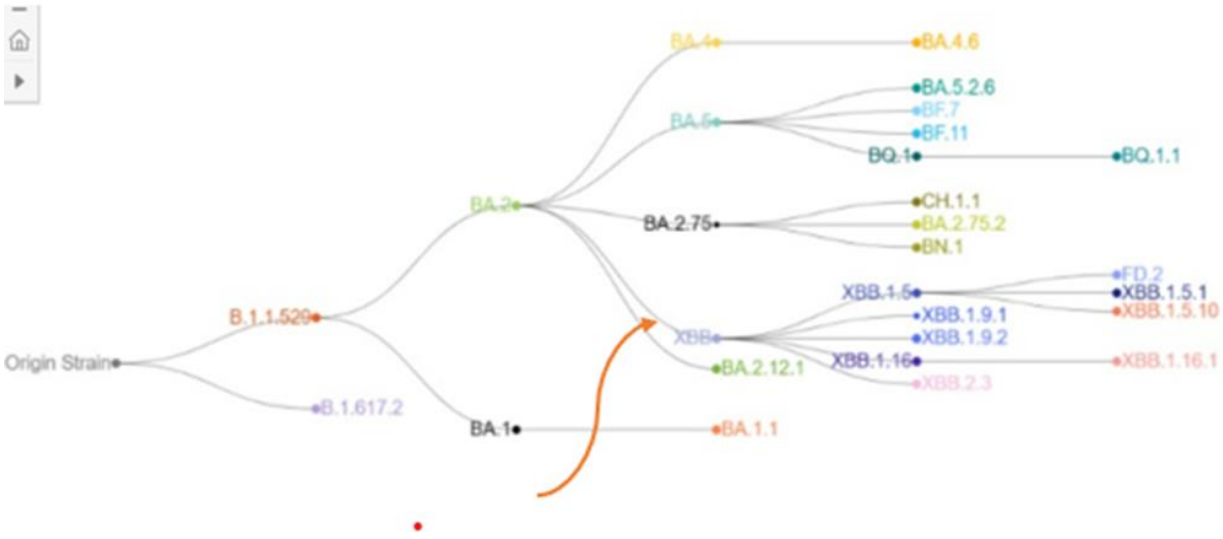
- U.S. Sequence Data
  - The genomic sequencing data below shows the percentage of isolates due to a particular sequence. The number of circulating strains is increasing but a significant escalation in cases in the near-term is not anticipated.
  - The genomic sequencing data does not correspond with virulence or activity levels in any community.



WHO 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.1.5.1	VOC	1.6%	1.2-2.1%

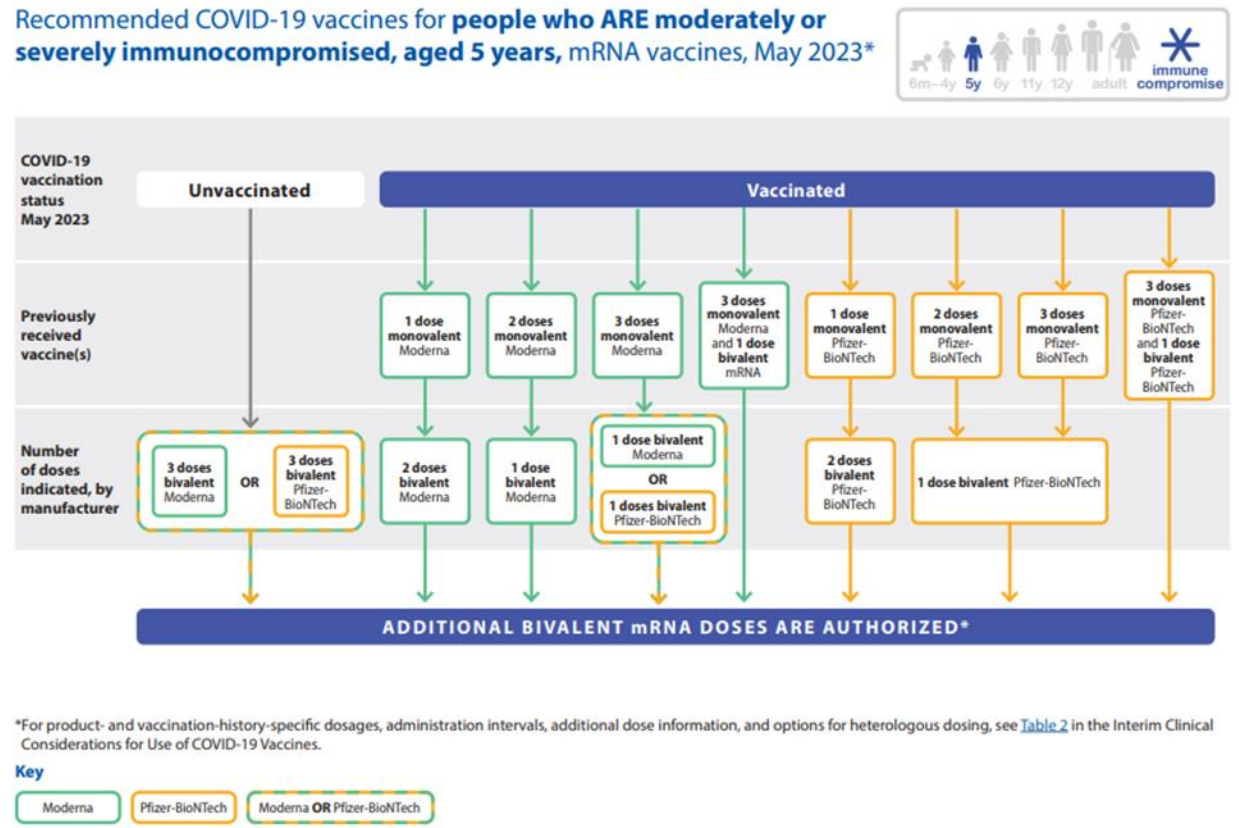
- **FDA Advisory Committee Meeting on COVID-19 Vaccine Strain Composition**
  - On June 15**,** the FDA Vaccine and Related Biologic Products Advisory Committee (VRBPAC) unanimously recommended converting all 2023-2024 COVID-19 vaccines to a monovalent XBB-lineage.
  - Reasons why the Committee changed to a monovalent XBB strain:
    - XBB recombinant variants continue to dominate, representing 98% of circulating variants in the U.S. as of 6/10/2023.
    - The ancestral Wuhan strain (“index”) and antigenically closely related variants such as Alpha, Beta, Gamma and Delta no longer circulate in humans.
    - Omicron (BA.1 and BA.2) and related variants (other than the recombinant XBB variants) circulate in minimal and progressively decreasing amounts.
    - Currently approved COVID-19 vaccines elicit undetectable or very low neutralizing antibody titers against XBB lineages.

        - Due to immune evasion, protection against hospitalization and severe disease is waning following administration of the current bivalent COVID-19 vaccines.
        - Repeated exposure to the index virus through receipt of multiple existing vaccines may reduce response to the new vaccine variant.
    - XBB.1.5 was recommended
        - Although progressively decreasing in frequency, it remains the dominant variant.
        - This aligns with the WHO and European Medicines Agency recommendations.
        - All COVID-19 vaccines manufacturers shared either preclinical (animal studies) or clinical data showing stronger neutralizing antibody response when primed or boosted with a monovalent XBB containing vaccine versus bivalent.
        - The majority of available evidence was for XBB.1.5.
        - Vaccination history did not impact results.
        - No additional safety concerns noted.
    - Expect FDA and CDC recommendations and authorization for the XBB-containing COVID-19 vaccine by late summer or early fall.
    - Until further notice, currently approved omicron bivalent vaccines will be available.
- The PAGO lineage below shows the most recent interpretation of the evolution of the SARS-CoV-2 virus.
    - The original strain (Wuhan) which included Alpha, Beta, Delta and Gamma ultimately mutated into omicron.
    - We previously thought that BA.1 was the original omicron and that it mutated and created BA.2. It is now believed that B.1.1.529 gave rise to both BA.1 and BA.2. BA.2 is the source of essentially all circulating strains at this time.
    - XBB (shown by the orange wavy arrow) is a recombinant of 2 strains of omicron. All of the non-XBB strains are from accumulation of mutations.



- Although the COVID vaccination schedule has been simplified for persons 6 years and older, there is still a lot of complexity to persons 6 months to 6 years old and for persons who are moderately to severely immunocompromised.
    - **All persons 6 months and older who are moderately to severely immunocompromised should still complete a three-dose primary mRNA series.**

- Infographics for the various permutations in the immunocompromised are sorted by age.
- It is separated into 6 months-4 years, aged 5 years, 6-11 years old and 12 years and older.
- An infographic example is below.



- **Take-Home on COVID:**
  - FDA VRBPAC unanimously recommends manufacturing of a monovalent XBB COVID-19 vaccine, with a preference toward XBB.1.5.
  - There is no change to recommendations for currently authorized Omicron Bivalent COVID-19 vaccines to date.
  - Anticipate FDA emergency use authorization and CDC recommendations to occur for updated monovalent COVID-19 vaccines by autumn.
  - Schedules for COVID vaccinations for the moderately to severely immunocompromised and 6 months to 6 years of age remain complicated.

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

Shigella and Antimicrobial Stewardship

- Shigella causes an extremely contagious diarrhea syndrome that is almost always symptomatic.
- It passes easily through the stomach as it is acid resistant. Fewer than 100 organisms can cause disease.
- Most patients have self-limiting disease although antibiotics are recommended for patients with either prolonged or complicated cases.
- Although fecal-oral contact has historically been the standard mode of transmission, sexual transmission among gay, bisexual, and MSM is now more common.
- There are no known substantial animal or environmental reservoirs, other than occasional cases in non-human primates. The expansion of resistance is usually due to the acquisition of plasmids by the Shigella strains.
- Multidrug-resistant organisms (MDR) are resistant to more than three of the treatment classes (fluoroquinolones, β-lactams, tetracyclines, third-generation cephalosporins, trimethoprim, aminoglycosides, macrolides and sulphonamides). Extremely drug resistant (XDR) refers to shigella strains sensitive to no more than two of the treatment classes.
- In September 2021, England began identifying male patients with XDR *Shigella sonnei* infections.
  - Transmission rates were extensive in sexual networks and disease was severe resulting in multiple hospitalizations.
  - A plasmid-encoded, extended-spectrum β-lactamase (ESBL) with resistance to ceftriaxone was identified.
  - Resistance to multiple other antibiotics are carried on that plasmid.
  - Because plasmids can be horizontally spread to other enterobacterales, concern was raised that *S. flexneri* could also acquire this high-risk plasmid.
- Lancet June 23 published data looking at the emergence and epidemiologic spread of XDR *S. flexneri* between 2015 and 2022, using whole genome sequencing and determining the organism serotype.
  - An increase in both MDR and XDR *S. flexneri* was also identified starting September 2021.
  - Because of the temporal development of the *S. flexneri* outbreak after the *S. sonnei* outbreak, the commonality with transmission amongst MSM, and the genomic similarity between the plasmids on both Shigella species, it appears likely that the plasmid was transmitted from the *S. sonnei* to the *S. flexneri* species.
  - Not only are these organisms.resistant to most antibiotics, they also appear to have higher morbidity than previous strains.
  - The blue bars on the graph below show that a few cases of ESBL-plasmid containing *S. flexneri* isolates were identified between 2015 and 2020 (one isolate in 2016, two isolates in 2019, and one isolate in 2020). Numbers increased significantly starting September 2021.

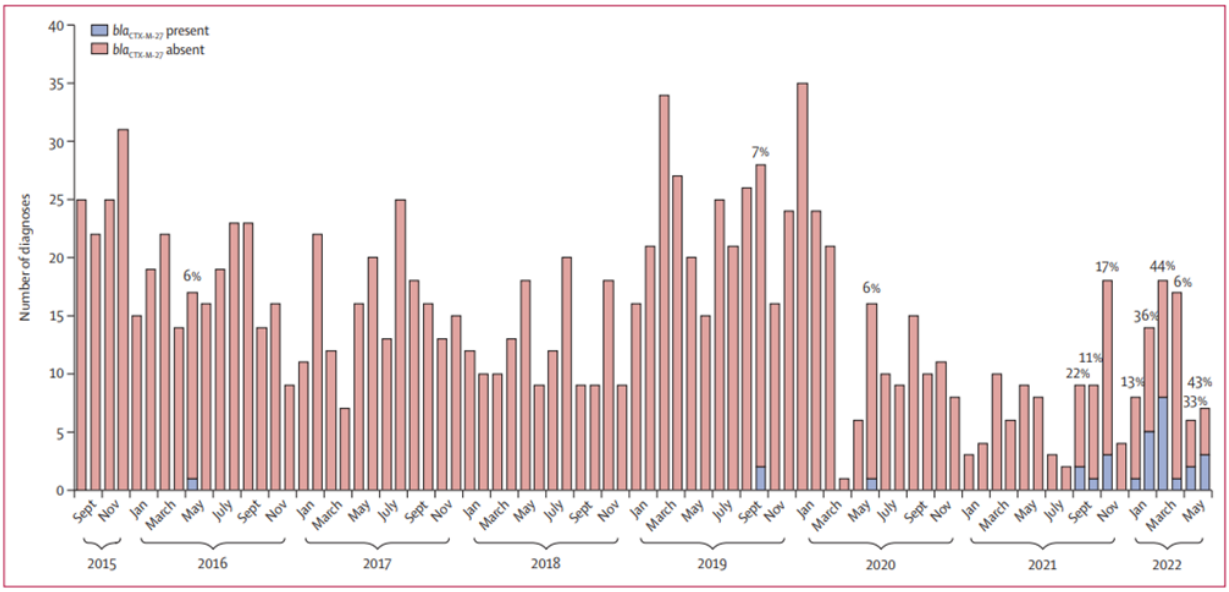


Figure 2: Shigella flexneri serotype 2a diagnoses by presence or absence of $bla_{CTX-M-27}$ and specimen date, with percentage present provided, in England, from September, 2015, to June, 2022*
*June 2022 data were not complete.

- The good news is that plasmids are not always stable. The strain fitness measured by the SOS response to DNA damage, conjugation ability of the organism and antimicrobial resistance genes may be altered by the plasmid.
- Proceedings Biological Science from August 2022 published a study of two different Shigella plasmids and demonstrated the different survival effect attributed to the plasmid.
  - Two different plasmids that resulted in Shigella resistance to azithromycin were identified from 2008 to 2014. One led to global spread while the other had limited distribution. Genomic sequencing revealed 49 genes shared by both plasmids but 122 genes unique to each plasmid.
  - Comparing bacteria growth with or without either of these plasmids, one plasmid did not negatively impact bacterial growth and did not react to sub-inhibitory concentrations of antibiotics compared to the other plasmid. Combined with increased antimicrobial resistance genes, the more fit plasmid was globally disseminated.
  - Although this study only looked at two plasmids versus a control, it demonstrates how antimicrobial resistance genes may be successfully transmitted to and from some strains but not others. Understanding the intricacies will help predict the transmission risk of a multidrug-resistant organism.
- Some plasmids are useful to bacteria to prevent death from antibiotics. Reducing antibiotic pressure through antimicrobial stewardship can decrease the fitness advantage provided by the plasmid.

- **Take-Home on Shigella and Antimicrobial Stewardship**
  - Shigella is more frequently identified as a sexually transmitted infection, especially in MSM. (men who have sex with men).
  - Shigella carries plasmids that result in MDR and XDR organisms. This is especially common in MSM and some of these strains are associated with increased morbidity.
  - Not all plasmids lead to unchanged or improved fitness of the organisms. Understanding the plasmid-related factors that negatively affect organism fitness might ultimately lead to new treatments that reverse antimicrobial resistance.

- These studies show the increased spread of antibiotic-resistant plasmids by Shigella that started in 2021.
- Two different plasmids were identified. One decreased the organism fitness and remained limited in spread. The other did not have a major negative impact and has been transmitted successfully to other parts of the world.
- Maintenance of plasmids by organisms has an energy cost. By limiting antibiotic use, some plasmids will stop providing survival benefit to the organism and could cease to be carried.

Norovirus and Cruise Ships

- Gastrointestinal outbreaks are known to occur on cruise ships. According to CDC data, Norovirus has been the most commonly reported and identified etiology since 1996. In 2004, 32 outbreaks were reported. Seventeen of the 18 outbreaks (94%) with an identified etiology were due to Norovirus.
- The rates of gastroenteritis outbreaks on cruise ships decreased between 2006 and 2019.
- Between 2017- 2019, there were an average of 11 identified outbreaks per year. Very few outbreaks were identified during COVID as the number of cruise tours dramatically decreased.
- In 2023, there have already been 13 reported outbreaks, all due to Norovirus. Although the actual number of cruise tours is not included, this year is projected to have the largest number of passengers in a year, exceeding the pre-pandemic 2019 peak by 12%.
- Simultaneously, the present trend could result in the highest number of reported outbreaks of gastroenteritis since 2004.
- Even with these numbers the CDC states that acute gastroenteritis is "relatively infrequent on cruise ships."
- The Vessel Sanitation Program at the CDC monitors to prevent outbreaks and is involved with outbreak mitigation.
- People who are embarking on a cruise need to be advised to frequently wash their hands with soap and water. Alcohol hand-sanitizers are not effective against norovirus.

- **Take-Home on Norovirus and Cruise Ships**
  - Data supports that gastroenteritis outbreaks on cruise ships are usually caused by Norovirus.
  - This year is on track to have the largest number of outbreaks since 2004.
  - Advise people planning to go on a cruise to practice frequent hand hygiene with soap and water. Alcohol-based sanitizers are not effective.
  - Bleach wipes can disinfect contaminated surfaces. Other products specifically labeled to have efficacy against norovirus are also good alternatives.

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