Infectious Diseases Watch

Labor Day Edition

September 5, 2022

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General Infectious Diseases

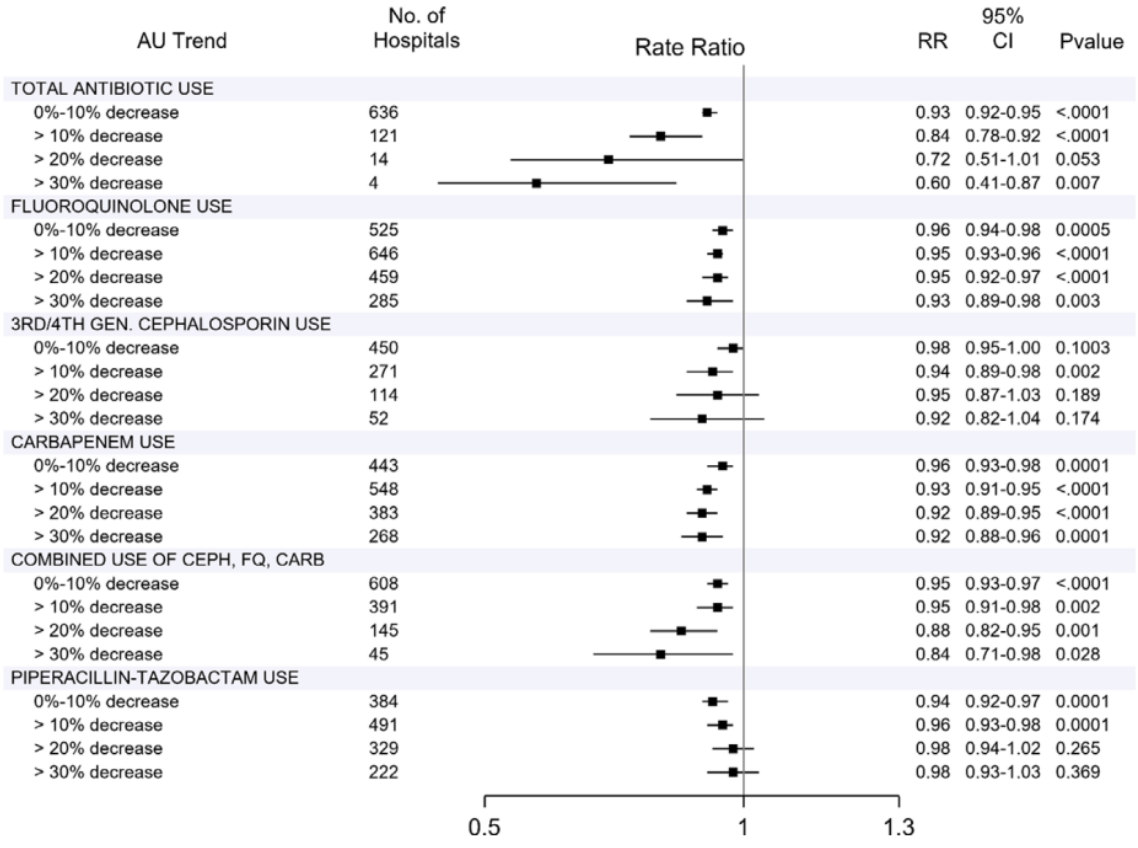
Associations of facility-level antibiotic use and hospital-onset Clostridioides difficile infection in US acute-care hospitals, 2012–2018 ICHE 2022; 43: 1067-1069

doi.org/10.1017/ice.2021.151

They used adult hospital discharge and inpatient charge records for antibiotic use, CDI tests and treatment from ACHs(acute care hospitals) contributing to the Premier Healthcare Database from January 1, 2012, to December 31, 2018. A case of HO-CDI was defined as a hospital discharge with an ICD code specifying enterocolitis due to Clostridioides difficile (ICD-9 008.45 or ICD-10 A04.7, A04.71, or A04.72) in any secondary diagnostic position and inpatient treatment with metronidazole (parenteral or oral), fidaxomicin, or vancomycin (oral) initiated on hospital day 3 or later after admission. Facility-level monthly rates of HO-CDI were calculated per 10,000 patient days (PD). Hospital antibiotic use was measured by days of therapy (DOT) per 1,000 PD and examined through monthly rates of total antibiotic use and use of 7 antibiotic classes: fluoroquinolones, third- and fourth generation cephalosporins (cephalosporins), piperacillin-tazobactam, carbapenems, β-lactam/β-lactamase inhibitor combination (excluding piperacillin-tazobactam), clindamycin, and penicillins. In addition, they evaluated combined use of 3 high-risk antibiotic classes: fluoroquinolones, cephalosporins, and carbapenems. All models adjusted for hospital confounders: urban or rural location, bed size, teaching status, census division, primary nucleic acid amplification test (NAAT) utilization, proportion of patients aged ≥65 years, average Gagne comorbidity score, patient case-mix index, proportion of discharges with a surgical diagnosis-related group (DRG), and community-onset CDI (CO-CDI) cases per 100 discharges.

In a cross-sectional multivariable analysis, overall antibiotic use was significantly associated with the facility-level HO-CDI rate. For every 50 DOT per 1,000 PD increase in antibiotic use, there was a 2.8% increase in the HO-CDI rate (rate ratio [RR], 1.028; P < .001). In a class-specific model, 10 DOT per 1,000 PD increases in the use of carbapenems, cephalosporins, and piperacillin-tazobactam were each independently associated with 1.3%, 0.6%, and 1.1% increases in the HO-CDI rate, respectively. In all models, primary NAAT utilization was associated with a 16% higher HO-CDI rate compared with hospitals without primary NAAT

utilization. Decreases in fluoroquinolone and carbapenem use corresponded with annual decreases in HO-CDI rates of 4%–7% and 4%–8%, respectively. Decreases in the combined use of cephalosporins, fluoroquinolones, and carbapenems corresponded with annual decreases in the HO-CDI rate of 4%–16%.

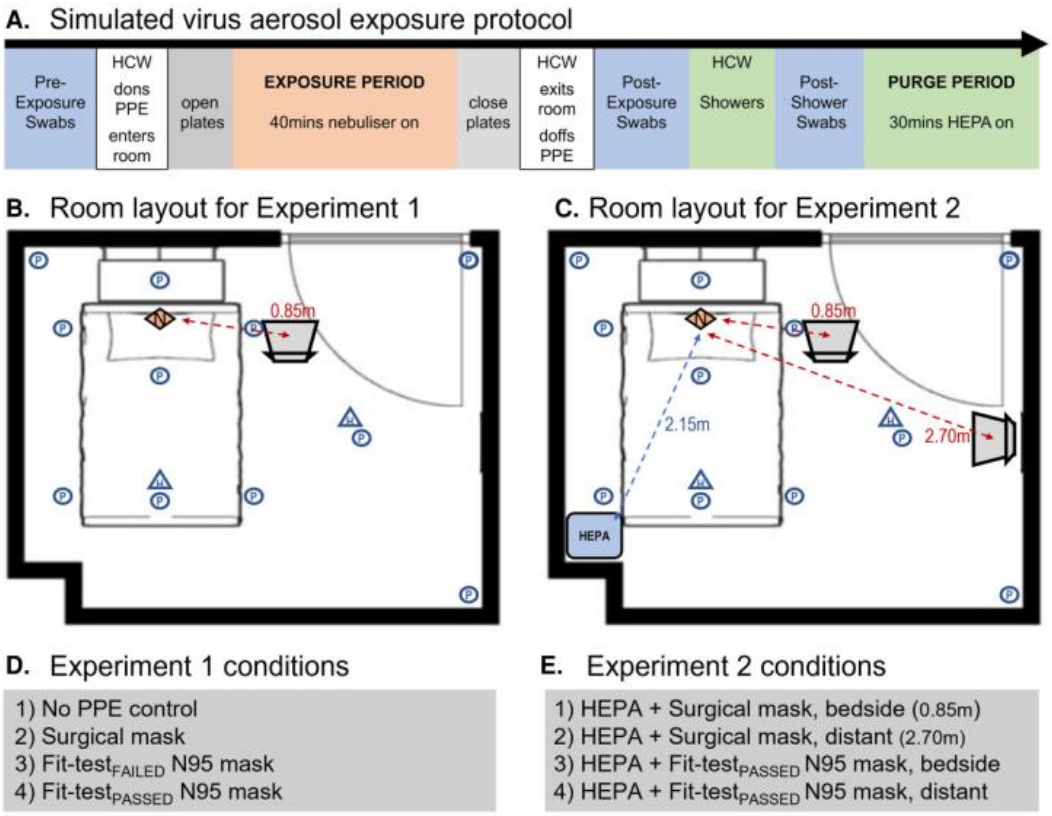


Comment: Like other studies**,** higher levels of total antimicrobial use as well as use of third- and fourth generation cephalosporins, carbapenems, and piperacillin-tazobactam were associated with higher rates of HO-CDI and decreases in total antibiotic use, especially fluoroquinolones, carbapenems, and combined use of fluoroquinolones, third- and fourth generation cephalosporins, and carbapenems corresponded with decreases in HO-CDI. Recent reports still demonstrate widespread inappropriate use; therefore, reductions in total antibiotic use are increasingly important, particularly among hospitals with high antibiotic use. In addition, this report suggests that significant reductions in HO-CDI rates can be achieved with a more targeted approach that focuses on combined use of cephalosporins, fluoroquinolones, and carbapenems. Several papers have focused on reduction of fluoroquinolones with some success. Reducing third and fourth generation cephalosporins and carbapenems may be more challenging, but achievable. These findings should encourage ACHs to invest efforts into monitoring antibiotic use targeting unnecessary and inappropriate use across all classes of antibiotics. The new Joint Commission R^3 Report (Requirement, Rationale, Reference) has added a new standard [EP10] which states the hospital allocates financial resources for staffing and information technology to support the antibiotics stewardship program.

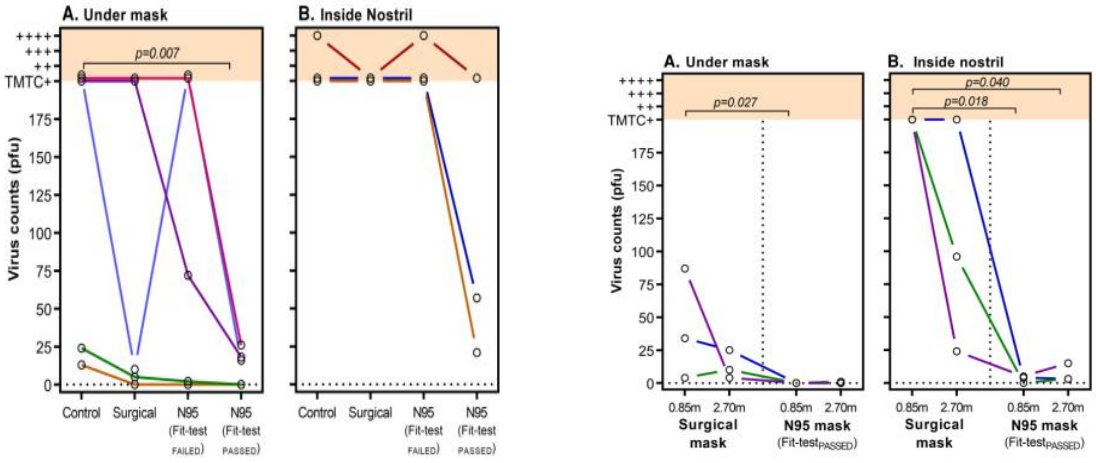
Fit-Tested N95 Masks Combined With Portable High-Efficiency Particulate Air Filtration Can Protect Against High Aerosolized Viral Loads Over Prolonged Periods at Close Range J Infect Dis 2022; 226:199–207

doi.org/10.1093/infdis/jiac195

The investigators nebulized a benign bacteriophage PhiX174[nonhazardous model virus] within a sealed room with no ventilation, and then HCW wearing PPE (mask, gloves, gown, face shield) was exposed to nebulized viruses (10^8 copies/mL) for 40 minutes in a sealed clinical room. Virus exposure was quantified via skin swabs applied to the face, nostrils, forearms, neck, and forehead. Experiments were repeated with a HEPA filter (13.4 volume-filtrations/hour) Each condition was repeated up to 5 times with and without a portable high-efficiency particulate air (HEPA) filtration unit in the room (providing 13 air changes per hour) and with the volunteer next to the aerosol generator vs distanced from the generator (0.85 m vs 2.7 m from the aerosol source).



The investigators found that in the absence of HEPA filtration, virus counts within the nostrils were high with both a surgical mask and a poorly fitted N95 respirator but trended lower with a fitted N95 (P = .06). When the HEPA filter was activated, nasal viral recovery remained high with surgical masks but was significantly lower and very low with a fitted N95 respirator both near and far from the aerosol generator. Gloves and gowns were associated with significantly lower viral recovery from hands and forearms but not from the uncovered neck.



HEPA Filter+PPE

Comment: This study is the first to conduct live virus aerosol experiments to systematically examine HCW virus contamination and the interaction between virus aerosol, PPE, distance, and air filtration using a portable HEPA filter. The investigators found that the combination of a properly fitted N95 mask and portable HEPA filter provided near complete protection against high viral aerosol loads at close range for prolonged periods of time. More importantly, surgical masks provided inadequate protection even when combined with HEPA filtration and at distances of up to 2.70 m (~ 9 feet). Previous reports of surgical and N95 mask penetration properties show that peripheral leak is more important than the filtering properties of the mask material. [Cochrane Database Syst Rev 2020; 4:CD013582] These findings reinforce the necessity of proper fit testing of N95 respirators for all forward-facing HCWs, a process that is not universal practiced. Patients with airborne infectious diseases are typically cared for in negative-pressure rooms if available. These rooms are designed with 12 air exchanges/hour. An alternative method is to filter the air within a patient room with portable HEPA filters. The CDC has recommended that HEPA filters can be used in lieu of negative-pressure rooms while hospital facilities are being renovated/repaired or if a negative pressure room is not available. Putting this study into perspective, this was an experimental study using high quantities of a marker virus rather than a clinical observational trial. Therefore, caution should be used in against making direct quantitative comparisons (based on absolute PFU values in each mask condition) against published minimum infective doses for respiratory viruses. They aerosolized a higher viral load (10^8/mL) compared to aerosols generated by patients infected with coronaviruses. However, in light of the emergence of more transmissible variants of SARS-CoV-2 this study highlighted the gaps in protecting HCWs who are exposed. Healthcare providers must deploy mitigation strategies to optimize HCW safety. N95 masks that pass a quantitative fit-test combined with adequate ventilation should be the standard.

In an excellent editorial Kompas and Rhee make several salient points.

1. Initial CDC's guidelines discounted aerosol-based transmission because of the protective effect of distance. Investigators assumed that because aerosols do not travel well beyond 6 feet, the rarity of transmission beyond 6 feet ruled out aerosol-based transmission.

2. Klompas and Rhee point out that distance is protective against both aerosol-borne and droplet-borne pathogens. This is because infection risk is a function of infectious dose; the more virus one is exposed to by virtue of concentration or duration, the greater the likelihood of infection. Distance diminishes infection risk with aerosol-borne pathogens because aerosols diffuse with distance from the source and get diluted by the surrounding air, leading to lower viral concentrations, especially in well ventilated areas.

3. Aerosol inhalation is the dominate way respiratory viruses are transmitted. Therefore, respiratory protection for HCWs seeing patients with respiratory viral infections is critical.

4. They conclude it is high time to modify infection control guidelines for respiratory viruses to recognize that most transmission is attributable to aerosol inhalation. They recommend "switching from the current confusing and non-evidence-based mosaic of different precautions for different viruses to one universal set of respiratory viral precautions that includes wearing gowns, gloves, eye protection, and fitted respirators in well-ventilated spaces."

Impact of Pneumococcal Conjugate Vaccines on Antibiotic-Nonsusceptible Invasive Pneumococcal Disease in the United States J Infect Dis 2022; 226:342–351

doi.org/10.1093/infdis/jiac154

Antibiotic-nonsusceptible invasive pneumococcal disease (NS-IPD) incidence declined dramatically in the US after introduction of pneumococcal conjugate vaccines (PCVs) into the immunization schedule (7-valent PCV7 in 2000, replaced by the 13-valent PCV13 in 2010). Investigators identified IPD cases through the CDC Active Bacterial Core surveillance during 1998– 2018. Isolates intermediate or resistant to ≥1 antibiotic class were classified as nonsusceptible. They calculated annual rates of IPD (cases per 100 000 persons).

From 1998 through 2018, NS-IPD incidence decreased from 43.9 to 3.2 among children ,5 years and from 19.8 to 9.4 among adults ≥65 years. Incidence of vaccine-type NS-IPD decreased in all age groups, whereas incidence of nonvaccine type (NVT) NS-IPD increased in all age groups; the greatest absolute increase in NVT NS-IPD occurred among adults ≥65 years (2.3 to 7.2). During 2014–2018, NVTs 35B, 33F, 22F, and 15A were the most common NS-IPD serotypes.

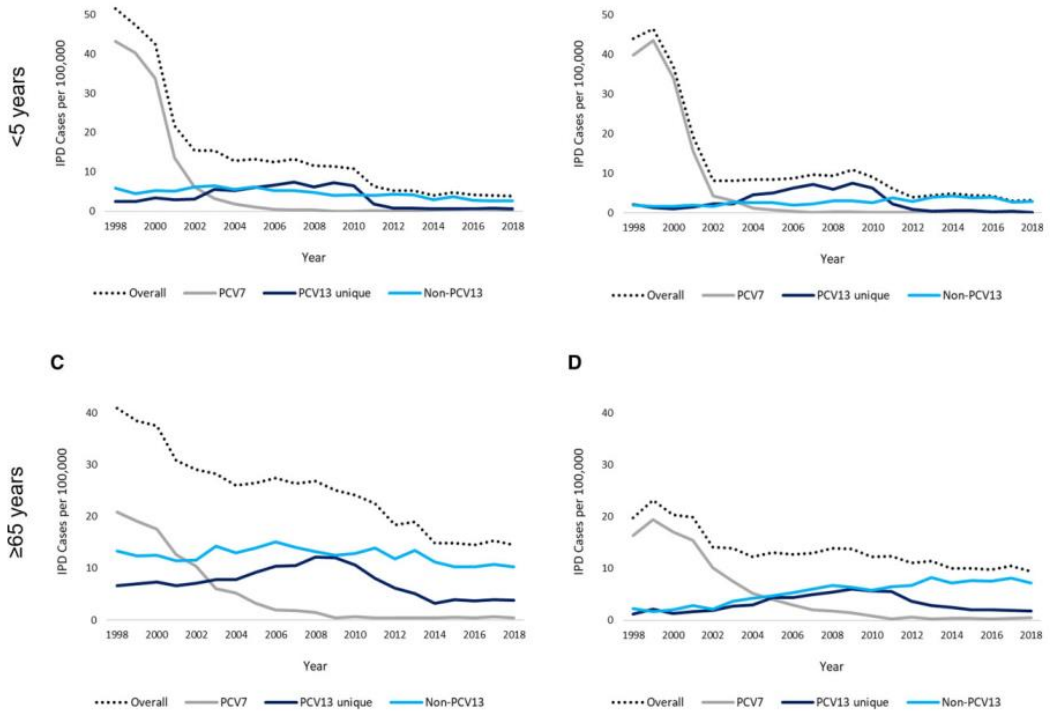


Figure 1. Annual incidence of invasive pneumococcal disease (IPD) per 100 000 persons in the United States by age group, antibiotic susceptibility, and serotype group, 1998–2018. (*A*) Susceptible, age <5 years; (*B*) nonsusceptible, age <years; (*C*) susceptible, age ≥65 years; (*D*) nonsusceptible, age ≥65 years. NOTE: Y-axis is different for each age group. PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

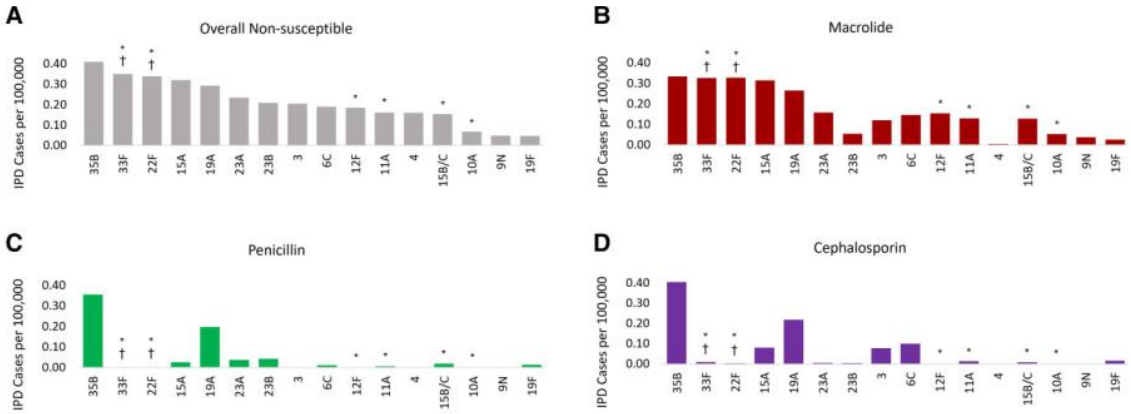


Figure 3. (*A–D*) Incidence of nonsusceptible invasive pneumococcal disease (NS-IPD) by antibiotic class and serotype, 2014–2018. (*A*) Nonsusceptible to any antibiotic class (antibiotic classes included antifolates [trimethoprim-sulfamethoxazole], carbapenems [meropenem], cephalosporins [cefuroxime, ceftriaxone, or cefotaxime], fluoroquinolones [levofloxacin], glycopeptides [vancomycin], lincosamides [clindamycin], macrolides [erythromycin], oxazolidinones [linezolid], penicillins [penicillin or amoxicillin], and tetracyclines [tetracycline]; (*B*) macrolide; (*C*) penicillin; and (*D*) cephalosporin (includes the most common serotypes with average NS-IPD incidence ≥0.05 cases per 100 000 persons). †New vaccine serotypes in 15-valent vaccine: 22F and 33F. *New vaccine serotypes in 20-valent vaccine: 10A,11A, 12F, 15B/C, 22F, and 33F.

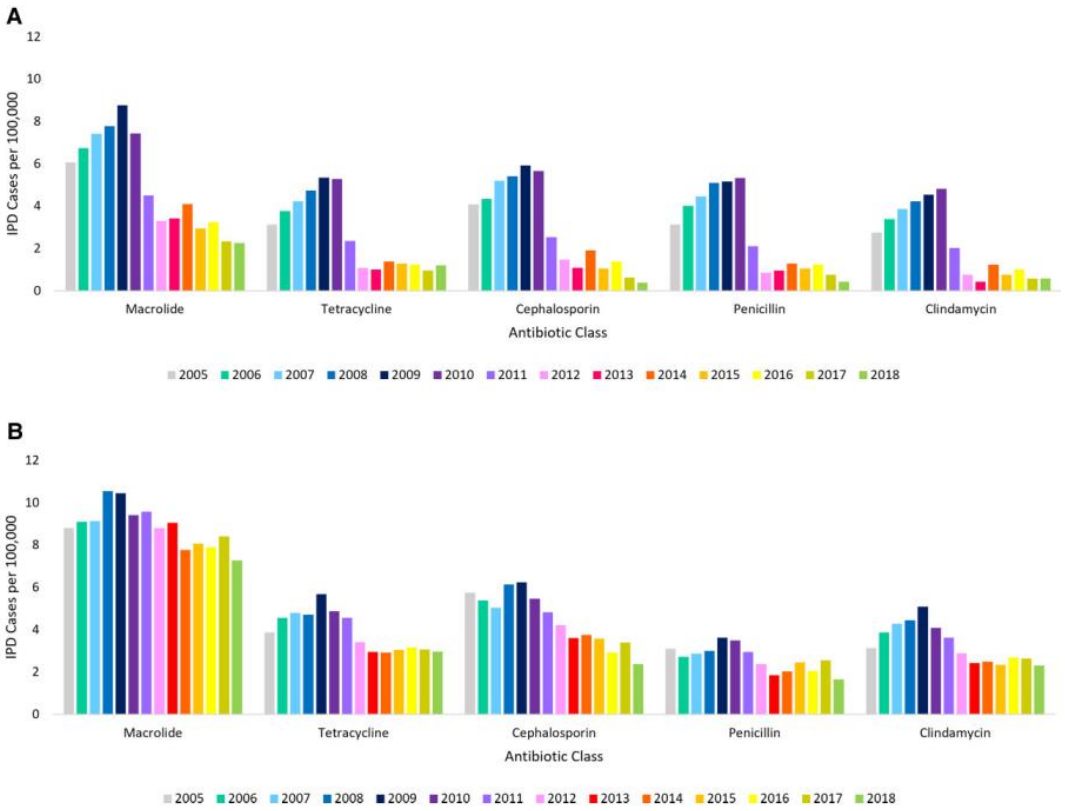


Figure 4. (*A* and *B*) Changes in the incidence of invasive pneumococcal disease (IPD) nonsusceptible to antibiotics by drug class among persons aged (*A*) <5 years and (*B*) ≥65 years, per 100 000 persons in the United States, 2005–2018.

Comment: Nonsusceptible IPD incidence decreased after PCV7 and PCV13 introduction in the United States. However, recent increases in NVT NS-IPD, most pronounced among older adults, have been observed. Increases in NVT NS-IPD observed after PCV7 and PCV13 introduction diminished the overall benefits on antibiotic-nonsusceptible disease. Probably the best example, data showed increases in infections associated with resistant strains of non-PCV7 serotype19A were observed shortly after PCV7 introduction; however, introduction of PCV13, which includes serotype 19A, led to further reductions in vaccine-type. New higher valency PCVs containing the most common nonsusceptible serotypes, including 22F and 33F, could help further reduce NS-IPD. The ABCs catchment population represents mostly urban areas in the US and does not collect individual-level information on prior antibiotic use. Little is known about prescribing differences between urban and rural areas. Less severe forms of pneumococcal illness, such as nonbacteremic pneumonia or otitis media, are not captured by ABCs; therefore, the full picture of nonsusceptible strains circulating in the community cannot be fully assessed.

Swine Influenza

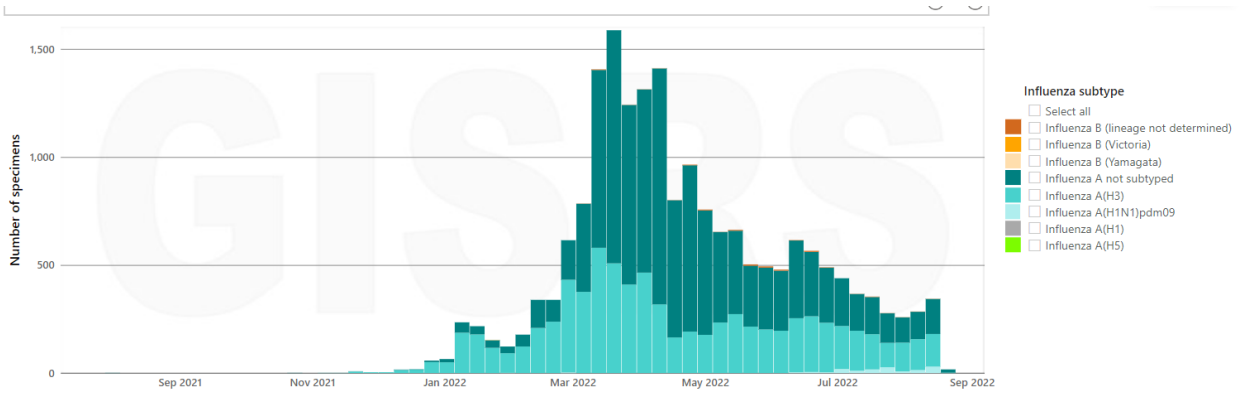
CDC last week urged health providers to ask patients with suspected flu infections outside of the regular flu season to ask about any recent exposure to pigs.

So far, five variant cases have been reported over the summer from three states, all but one of which occurred in people who were exposed to pigs or attended an agricultural fair. Three West Virginia cases involved variant H3N2 (H3N2v), and single cases from Ohio and Oregon involved variant H1N2 (H1N2v). All patients recovered, and no human-to-human spread was detected.

The CDC said fair settings allow swine influenza viruses to spread among pigs and from pigs to people, and it said it expects more cases to be reported as the agricultural fair season continues.

It recommends that clinicians who suspect flu in people with recent swine exposure obtain a nasopharyngeal swab and request testing at a state public health lab. The CDC also recommended that people at high risk for flu complications avoid exposure to pigs and swine barns this year.

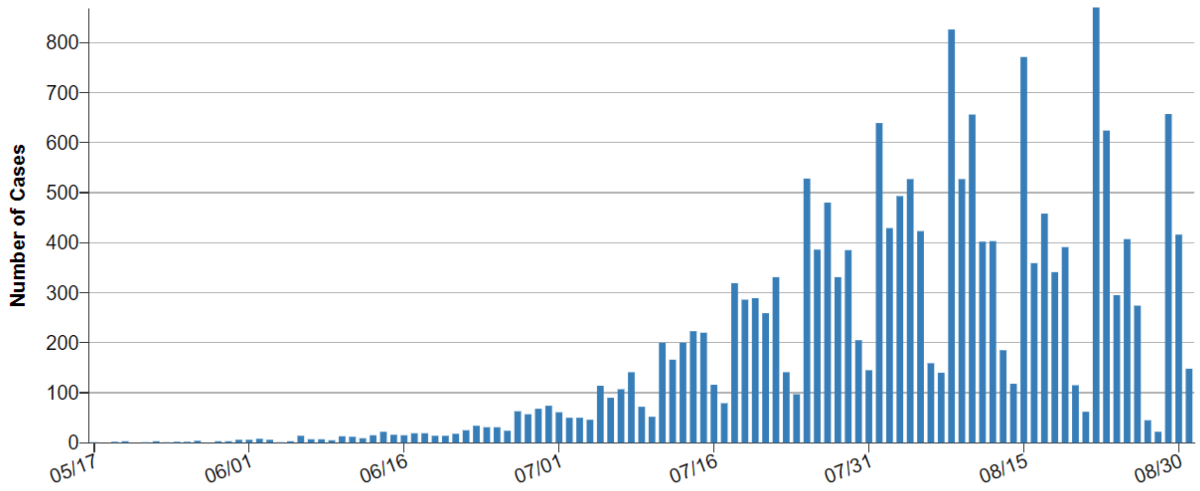
Comment: We have seen this situation in the past related to exposure to swine. To date no human-to-human spread has been documented. Below is influenza in the Southern Hemisphere indicating that unlike 2021, influenza has reemerged. This is a reminder that as Covid-19 numbers decline [hopefully] compared to 2020 and 2021, we may see a resurgence of influence this winter making influenza vaccination even more important since we are likely to see multiple respiratory viruses circulating this fall and winter.



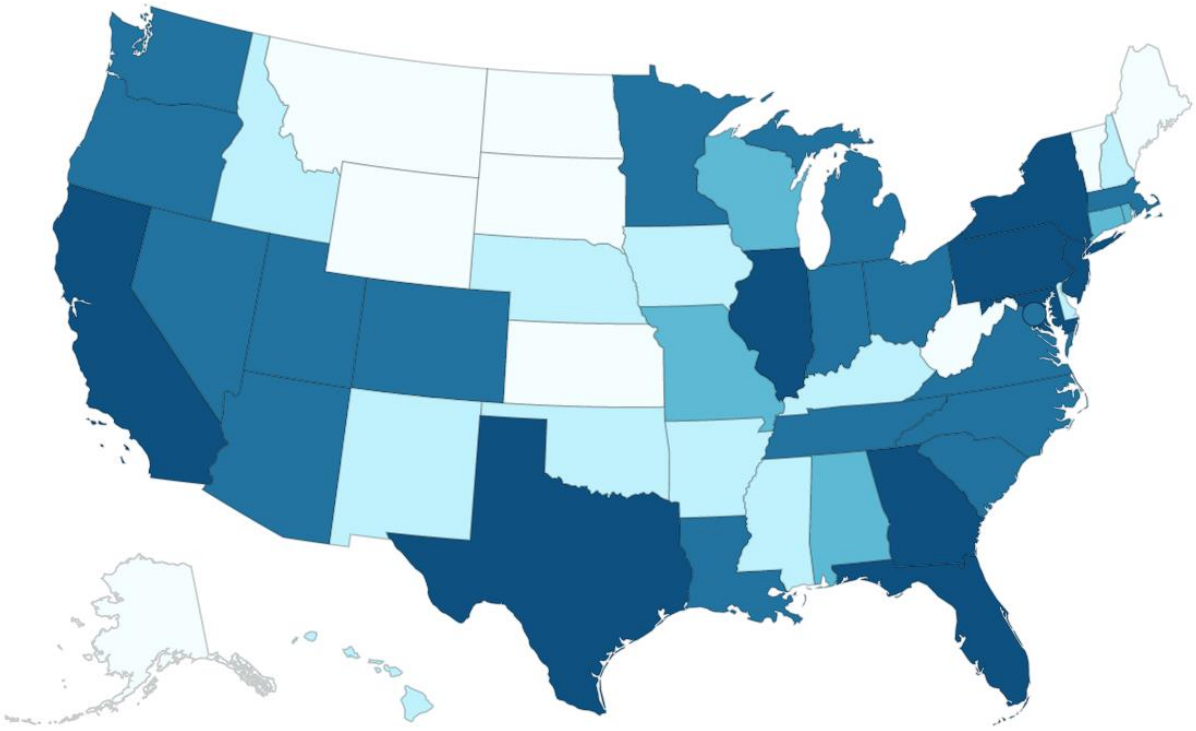
Monkeypox

Monkeypox by the Numbers

U.S. Monkeypox Case Trends Reported to CDC

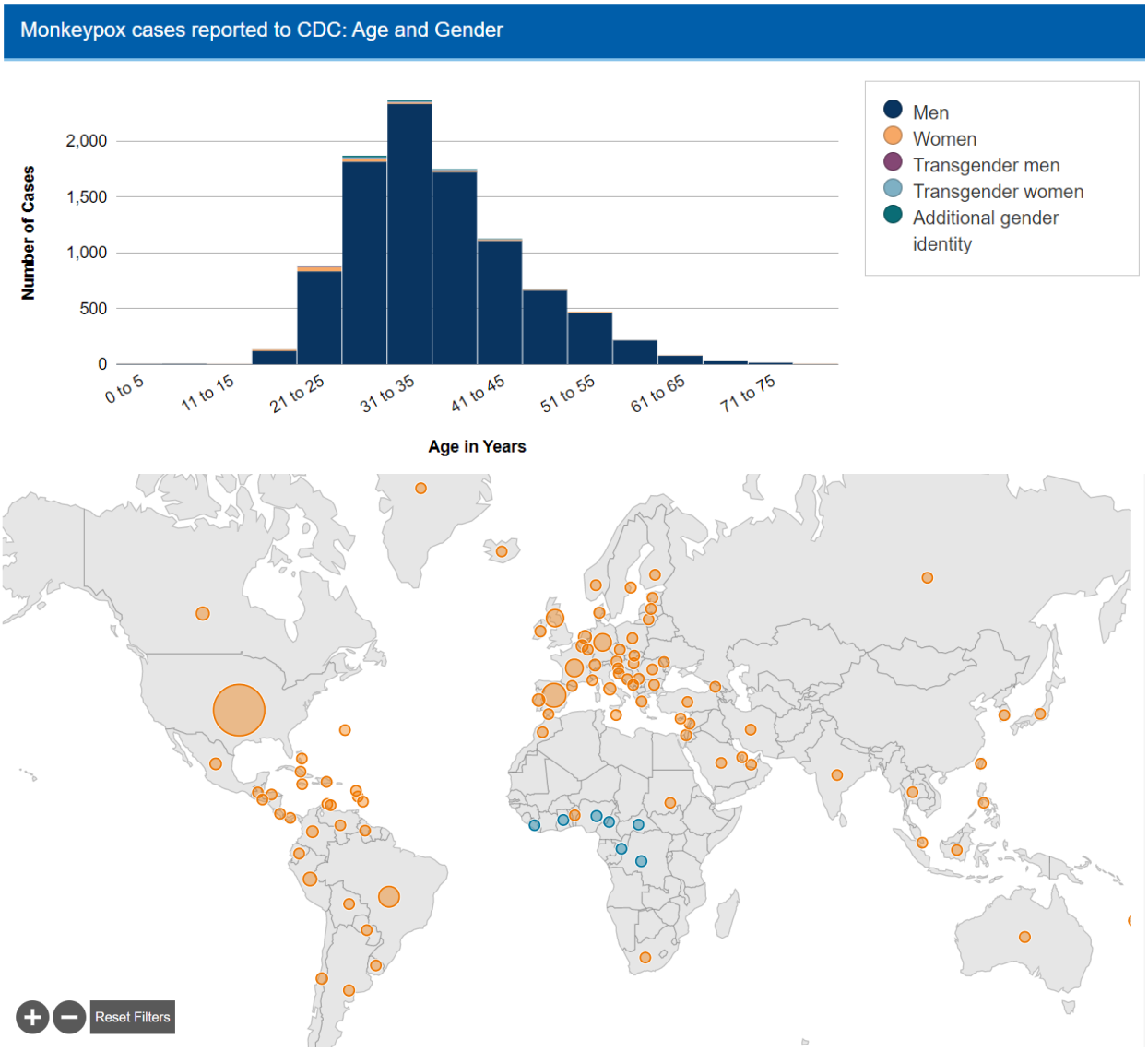


Cases Reported in 2022



Case Range

- 1 to 10
- 11 to 50
- 51 to 100
- 101 to 500
- >500



Comment: Latest numbers indicate the number of cases has begun to decline. California and NY both have over 3000 cases reported with Texas, Illinois, Georgia, and Florida with between 1000-2000 cases. Cases are predominantly men between 30-45. Globally cases are up to 53,000 cases. US is up to 20,000. As you can see from the global map the US has the most cases.

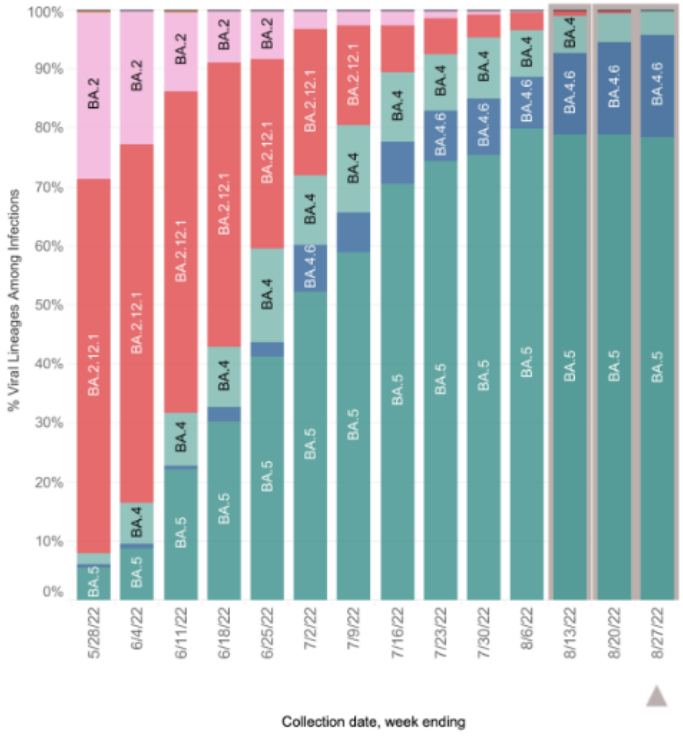
COVID-19

COVID-19 News

Covid Variant BA.4.6

The CDC weekly variant proportions data update on Wednesday offered a glimpse that a new Omicron strain dubbed BA.4.6 may be able to outcompete now-dominant BA.5 in the US.

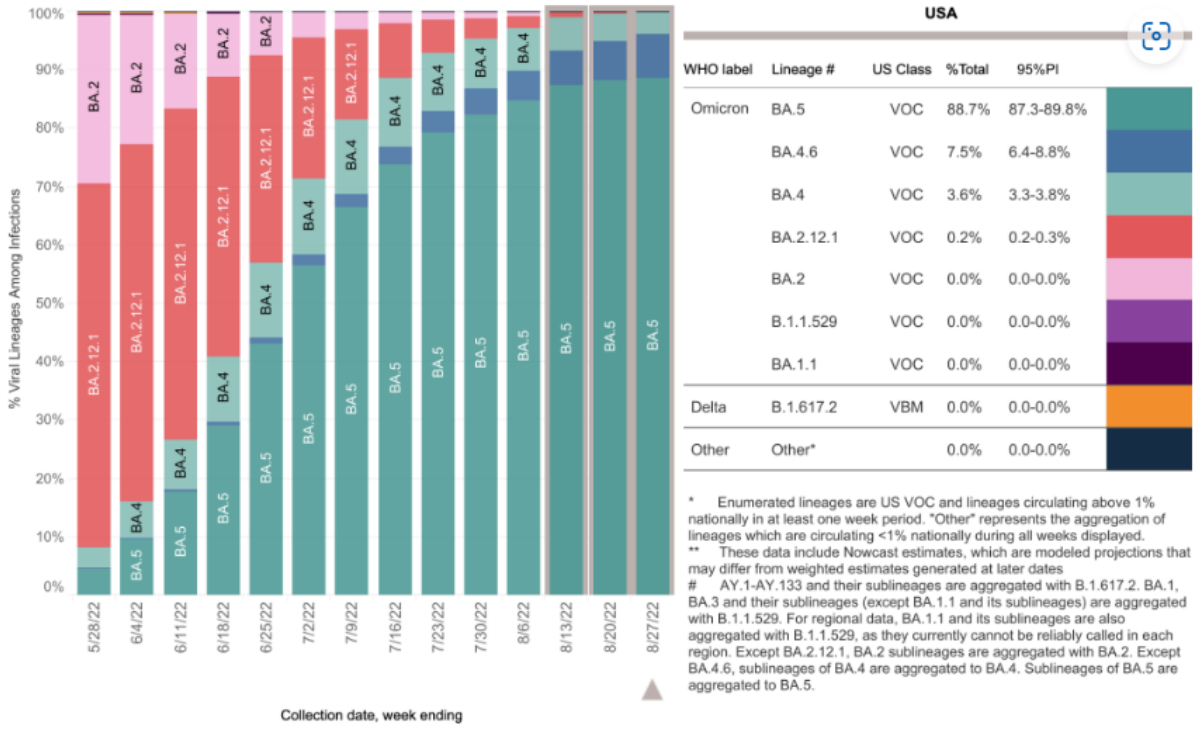
While BA.4.6 has been in the US since at least May, it remained below 2% of new cases sequenced until July, when it gradually began to rise, even as BA.5 continued to do the same. As of this week's CDC reporting, it currently stands at 7.5%. Looking deeper the variant proportions can be broken out regionally. In the area defined primarily by California, Arizona and Nevada, BA.4.6 lags behind even BA.4, with shares of 2.8% and 3.3%, respectively. BA.5 in the region stands at 93% and rising. Compare that to the CDC-grouped region of Nebraska, Iowa, Kansas and Missouri, where BA.4.6 has risen to 17.2% of all new cases sequenced, and BA.5 actually fell for the first time this past week to 78.5%. It peaked at 80% there in the first week of August and has fallen slightly in the three weeks since. During same that time frame BA.4.6 has nearly doubled in those states from 8.7%.



Region 7 - Iowa, Kansas, Missouri, and Nebraska

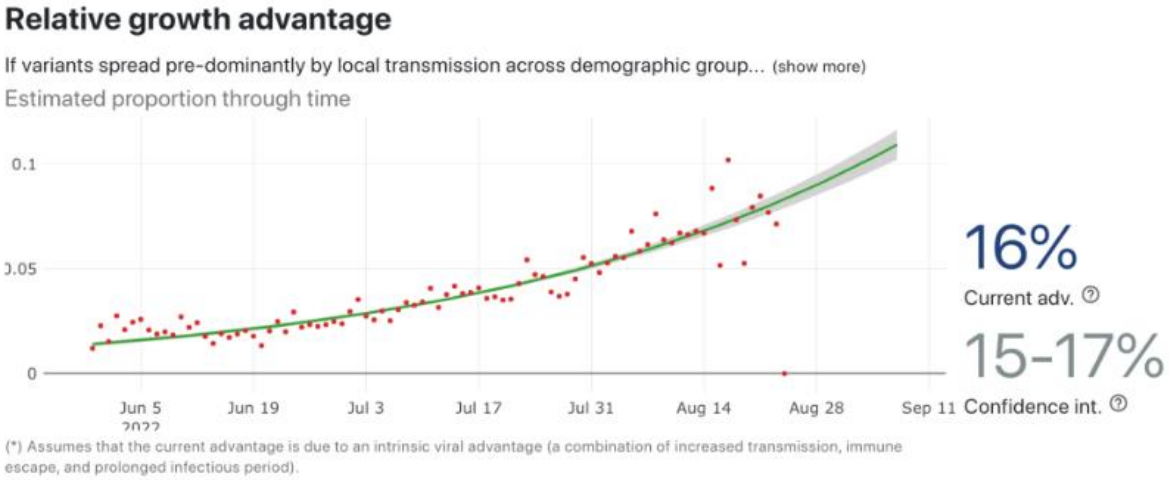
WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	78.5%	70.0-85.2%
	BA.4.6	VOC	17.2%	10.0-27.7%
	BA.4	VOC	3.9%	2.9-5.4%
	BA.2.12.1	VOC	0.3%	0.2-0.4%
	BA.2	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
\# AY.1-AY.133 and their sublineages are aggregated with B.1.617.2. BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. For regional data, BA.1.1 and its sublineages are also aggregated with B.1.1.529, as they currently cannot be reliably called in each region. Except BA.2.12.1, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Sublineages of BA.5 are aggregated to BA.5.

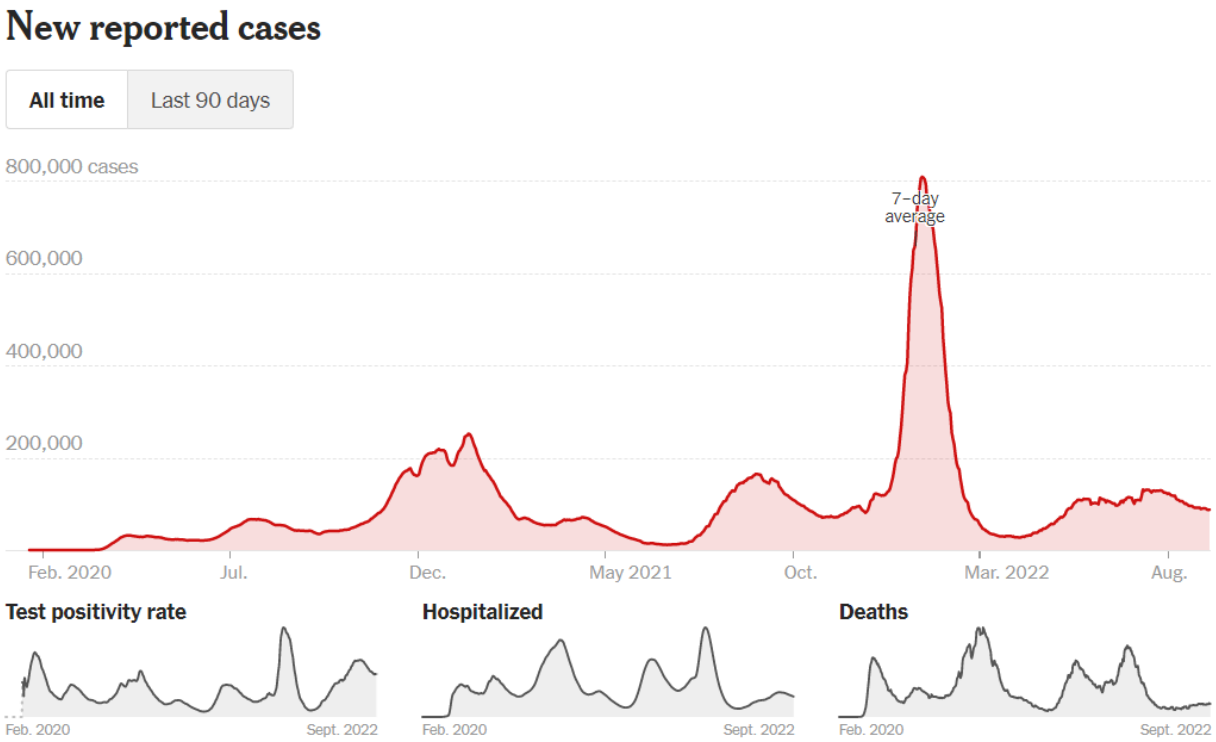


Variant growth across the U.S.

Comment: By one analysis of GISAID data, the new Omicron variant has a 16% growth advantage over BA.5, which makes it confusing that it has beat out BA.5 in some areas of the US while making little progress in others. The good news is that in all four of those states where BA.4.6 has risen Covid numbers are down across the board. Overall BA.4.6. is now 7.5% of all cases as of week ending August 27th.



COVID-19 by the Numbers



Comment: COVID-19 cases and hospitalizations continue to fall across the country, with more than 30 states seeing declines in the past two weeks. Hospitalizations have also seen improvement. Fewer than 40,000 people are currently in American hospitals with COVID-19, a decrease of 9 percent in the past two weeks.

FDA and CDC Approve Bivalent Vaccine

The FDA and then CDC recommended Thursday that millions of eligible Americans, can get the updated vaccine. The CDC's ACIP voted 13-1 to recommend updated vaccines from Moderna, for those 18 and older, and from Pfizer-BioNTech, for people 12 and older. The updated Omicron boosters are made with the same method as earlier mRNA vaccines and contain the same antigen load. The boosters can be given at least 2 months after primary vaccination or the last booster dose. CDC officials said to simplify the process, vaccinators will focus on the time since the last vaccine dose was given, not the number of earlier booster doses people have received. From modeling projections, the CDC estimates that broad uptake of the updated booster early this fall could prevent more than 100,000 hospitalizations.

Comment: Several advisory panel members expressed concern about the lack of clinical data about the reformulated boosters but also noted the potential harm in waiting for clinical data until November. The FDA did not convene their outside advisory panel. The FDA based its EUA

authorization on clinical data from the Omicron BA.1 bivalent booster, which has been approved in Europe. Early clinical studies have shown that boosting with bivalent mRNA vaccines containing both ancestral and omicron BA.1 spike immunogens induced peak omicron neutralizing antibody titers that were less than twice the peak titers induced by boosting with the original mRNA vaccines. This may be statistically significant but there are doubts that it is clinically significant. Current Covid-19 vaccines are less effective at blocking infection with the omicron variant than at blocking infection with prior variants, but protection against severe disease remains largely preserved. The most important goal of Covid-19 vaccination should be to provide long-term protection against severe disease, hospitalization, and death from current and future variants. Booster recommendations should therefore consider not only peak neutralizing antibody titers but also durable prevention of severe Covid-19 disease. To date all variants have conserved epitopes for cytotoxic B and T cells and are highly cross reactive against all variants and most likely has contribute substantially to protection against severe disease. T cell response appears to be long-lived. The discussion about frequent boosters may distracts from the critical goal of vaccinating the large number of unvaccinated persons. In addition, only 47% of eligible persons in the US have received any booster doses. Our goal should be to vaccinate all eligible persons with the initial two does and at least one booster. My recommendation for the new bivalent vaccine is to focus on the high-risk vulnerable population. [age >75, individuals with certain high-risk underlying medical conditions, and the immunocompromised] The FDA set the minimum wait time to be two months, but most feel it is better to wait longer closer to 4 months. In addition, if you are at high risk, vaccinated and boosted and recently had Covid-19 (assume BA.4/ BA.5) no booster is needed at this time. See article below.

COVID-19 Journal Review

Covid-19 Vaccines — Immunity, Variants, Boosters N Engl J Med published online August 31, 2022

DOI: 10.1056/NEJMra2206573

Summary Highlights

- Innate immune responses are the first line of defense against viruses and are rapidly triggered when cellular pattern-recognition receptors, such as toll-like receptors, recognize pathogen-associated molecular patterns. Innate antiviral immunity includes secretion of type I interferons, antiviral cytokines, and certain cellular responses, including neutrophils, monocytes and macrophages, dendritic cells, and natural killer cells.
- Adaptive immune responses, the second line of defense against viruses, involve antigen-specific recognition of viral epitopes. Adaptive immunity includes two complementary branches of the immune system: humoral immunity and cellular immunity.

- Humoral immunity to SARS-CoV-2 includes antibodies that bind the SARS-CoV-2 spike protein and either neutralize the virus or eliminate it through other effector mechanisms
- Cellular immunity to SARS-CoV-2 includes virus-specific B cells and T cells, which provide long-term immunologic memory and rapidly expand on reexposure to antigen. B cells produce antibodies, CD8+ T cells directly eliminate virally infected cells, and CD4+ T cells provide help to support the immune responses.
- For acute viral infections, including SARS-CoV-2, it is likely that neutralizing antibodies are critical for blocking acquisition of infection, whereas a combination of humoral and cellular immune responses most likely controls viral replication after infection and prevents progression to severe disease, hospitalization, and death-see Figure 1 below

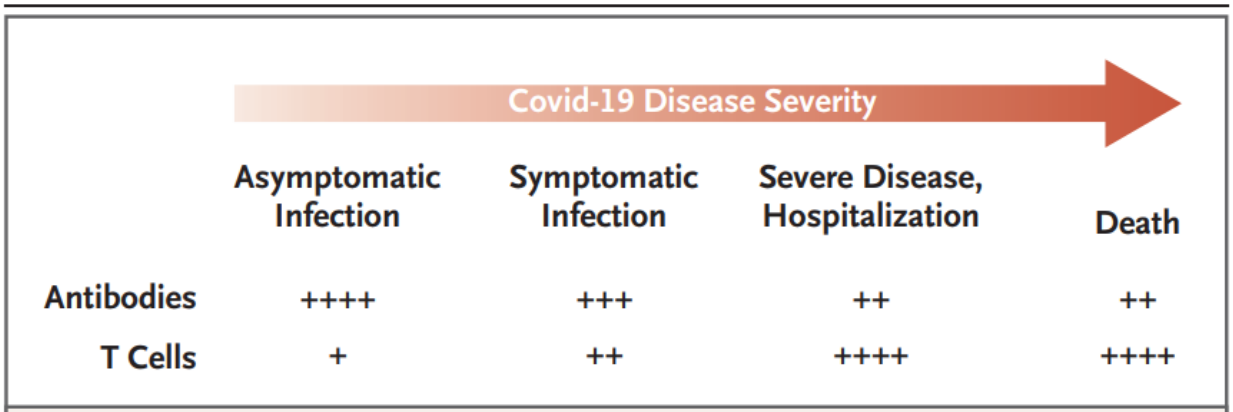


Figure 1. Immune Responses for Protection against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

- In the US, four vaccines have been authorized for either full approval or emergency use: the mRNA vaccines BNT162b2 (Pfizer) and mRNA-1273(Moderna), the adenovirus vector–based vaccine Ad26. COV2.S(J&J), and most recently the adjuvanted protein vaccine NVX-CoV2373(Novavax).
  - The FDA and the CDC have recently restricted the use of J&J vaccine in the US because of the rare but serious occurrence of vaccine-induced immune thrombotic thrombocytopenia (VITT), also called thrombosis with thrombocytopenia syndrome (TTS). VITT has developed in 54 persons (9 of whom died), reflecting a rate of 3 to 4 cases per 1 million vaccinated persons.
  - Myocarditis and pericarditis have been reported as complications with Pfizer and Moderna, at a rate of 52 to 137 cases per 1 million vaccinated adolescent boys and young men after the second dose, with at least 10 reported deaths. The incidence rate of myocarditis within 7 days after the second mRNA dose has been reported as 566 cases per 1 million person-years. Most cases of vaccine-induced myocarditis are mild; however, severe complications can occur. Both thrombosis and myocarditis occur far more frequently after natural Covid-19 infection than after Covid-19 vaccination.
  - The Pfizer and Moderna vaccines induce excellent short-term neutralizing antibody responses and protective efficacy. However, neutralizing antibody titers

induced by mRNA vaccines wane by 3 to 6 months and decline further by 8 months, with a half-life of approximately 60 days. In contrast to Pfizer and Moderna, J&J induces lower initial neutralizing antibody titers, but these neutralizing antibody responses and clinical effectiveness are durable for at least 8 months. In fact, at 6 to 8 months, antibody responses are similar with Pfizer, Moderna, and J&J.

- Multiple studies have shown that neutralizing antibodies induced by all primary vaccine regimens show little cross-reactivity with omicron but that boosting leads to a substantial increase in omicron neutralizing antibodies. However, after a third dose of mRNA vaccine it has been shown that increased neutralizing antibody titers, as well as clinical effectiveness wane by 4 months. After a fourth mRNA immunization, protection against infection with SARS-CoV-2 omicron has been reported to wane in just 4 weeks.
- Hybrid immunity from both vaccination and infection provides greater and more durable protection than either alone.

- Cellular immune responses are induced by both mRNA vaccines and adenovirus vector–based vaccines and have shown greater durability than serum antibody titers. CD8+ T-cell responses control viral replication after infection so that SARS-CoV-2 vaccines will continue to provide substantial protection against severe disease even after neutralizing antibody titers decline. In contrast with the limited cross-reactivity of vaccine-induced neutralizing antibodies to omicron, T-cell responses induced by vaccines have very good (>80%) cross-reactivity to omicron and to prior variants.
- In summary data suggest that neutralizing antibodies are primarily responsible for blocking acquisition of SARS-CoV-2 infection but that both antibody and CD8+ T-cell responses are critical for preventing severe disease.
- Boosting every 4 to 6 months to maintain high neutralizing antibody titers is not practical or a viable long-term strategy.
  - Boosting with mRNA vaccines is also not risk-free
  - Frequent boosting recommendations only worsen booster fatigue. To date only 47% of eligible persons in the US have received any booster dose.
  - Ideally, Covid-19 boosters should be recommended no more than annually similar to influenza.

Comment: This is an excellent overview on vaccines and boosters. I believe the pandemic appears to be transitioning to an endemic phase. Population immunity to SARS-CoV-2 will continue to increase due to vaccination and/or natural infection. In immunocompromised persons, both antibody and T-cell responses to Covid-19 vaccines may be reduced, with the degree of reduction dependent on the extent and type of immunosuppression. In these populations, additional vaccine doses and prophylactic treatment with monoclonal antibodies (tixagevimab| cilgavimab-[Evusheld]) are recommended.

Early Treatment of Favipiravir in COVID-19 Patients Without Pneumonia: A Multicentre, Open Labelled, Randomized Control Study Emerging Microbes & Infections published online August 23, 2022

DOI: 10.1080/22221751.2022.2117092

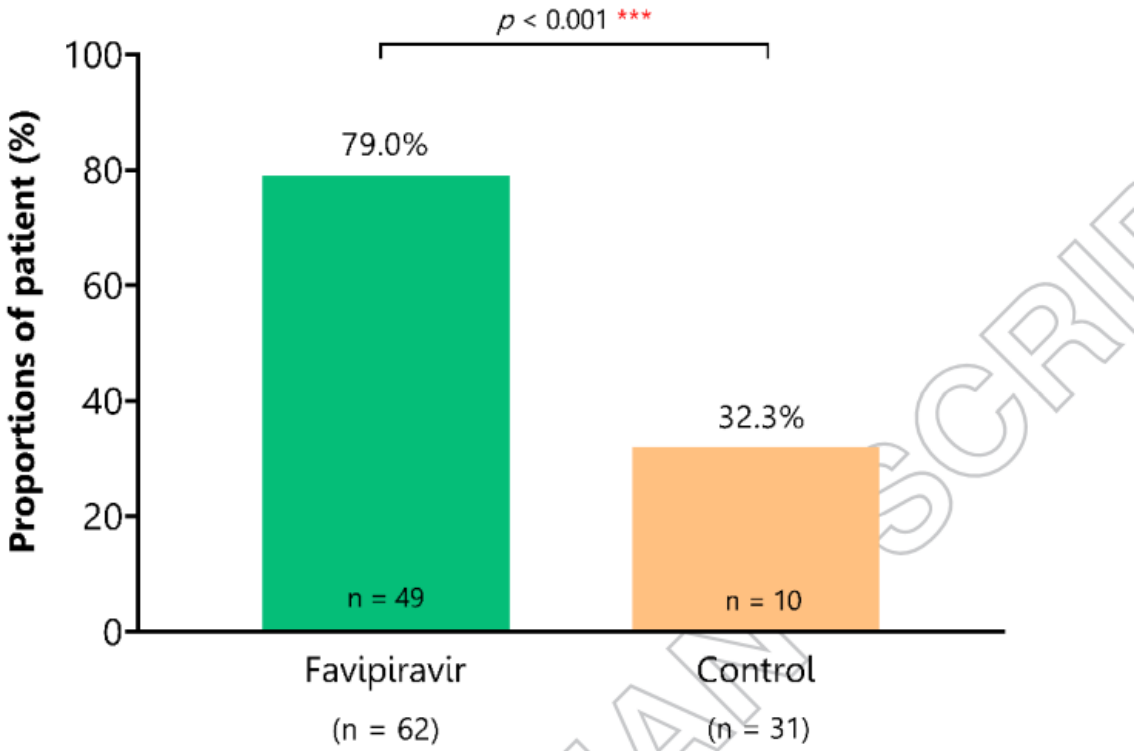
The multicenter, open-labelled, randomized prospective cohort, conducted from December 2020 to July 2021, enrolled PCR-confirmed SARS-CoV-2-infected patients who had mild-to-moderate symptoms, without pneumonia, within 10 days of symptom onset.

Of the 93 patients enrolled, 62 (median age, 32 years; 66.1% were female) received 1,800 mg FPV twice-daily (BID) on day 1 and 800 mg BID 5-14 days thereafter until negative viral detection, while the remaining 31 patients (median age, 28 years; 61.3% were female) received only supportive care. The primary endpoint was time to clinical improvement, defined by a National Early Warning Score (NEWS) of ≤ 1.

There were no significant between-group differences in the prevalence of underlying conditions, duration of COVID-19 symptoms before enrolment, and clinical presentations observed between the two arms. None of the patients received COVID-19 vaccines prior to being enrolled in the study. Overall, patients received treatment for an average 1.6 days after disease onset (90% before 4 days).

The median time to sustained clinical improvement, by NEWS, was 2 and 14 days for patients in the FPV and control arms, respectively (adjusted hazard ratio [aHR] 2.77, 95% confidence interval [CI] 1.57-4.88, $P < 0.001$). Patients who received FPV also had significantly higher likelihoods of clinical improvement within 14 days after enrolment by NEWS (79% vs 32%, $P < 0.001$), particularly among female patients (aOR 6.35, 95% CI 1.49-27.07, $P < 0.001$).

Additionally, 8 (12.9%) and 7 (22.6%) patients in FPV and control arms developed mild pneumonia at a median of 6.5 and 7 days after treatment, respectively ($P = 0.316$). All recovered well without complications.



Cumulative proportion of patients who experienced clinical improvement

Comment: Using the NEWS clinical severity assessment system, the investigators found that patients (females in particular) treated with FPV were significantly more likely than controls to experience clinical improvement from COVID-19 within 14 days. The findings in this article support previous literature that early administration of FPV in mild COVID-19 expedites recovery and is relatively safe for short-term usage. This is relevant to only patients who are affected by mild COVID-19. This is a small series in young adults and further studies are needed to confirm in older persons with high-risk underlying medical problems.

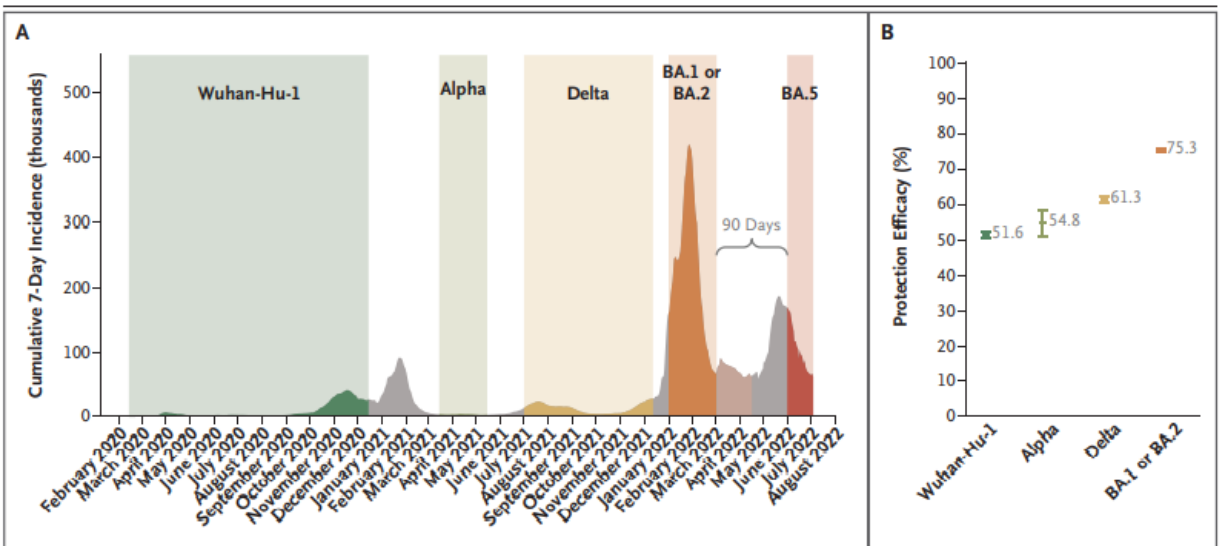
Risk of BA.5 Infection among Persons Exposed to Previous SARS-CoV-2 Variants

N Engl J Med published online August 31, 2022

DOI: 10.1056/NEJMc2209479

The authors used a national registry of COVID-19 cases to determine which variant likely caused infection based on date and variant predominance. Cases in patients age 12 and older were used. They identified all persons who had a first infection in periods of dominance of each variant, to calculate their infection risk during the period of BA.5 dominance.

The researchers found that while natural infections from 2020 and 2021 (when the wild-type strain and the Delta variant were predominant) offered some protection against BA.5, people infected with the BA.1 and BA.2 variants, at the beginning of 2022, who were also vaccinated had four times the protection as those who were only vaccinated.



Comment: This study demonstrates, in the period of time analyzed, that previous infection in vaccinated people (the so-called hybrid immunity) continues to confer protection for the variants that are known for their ability to evade the immune response, such as the subvariant currently dominant. The study design could not eliminate all confounders.

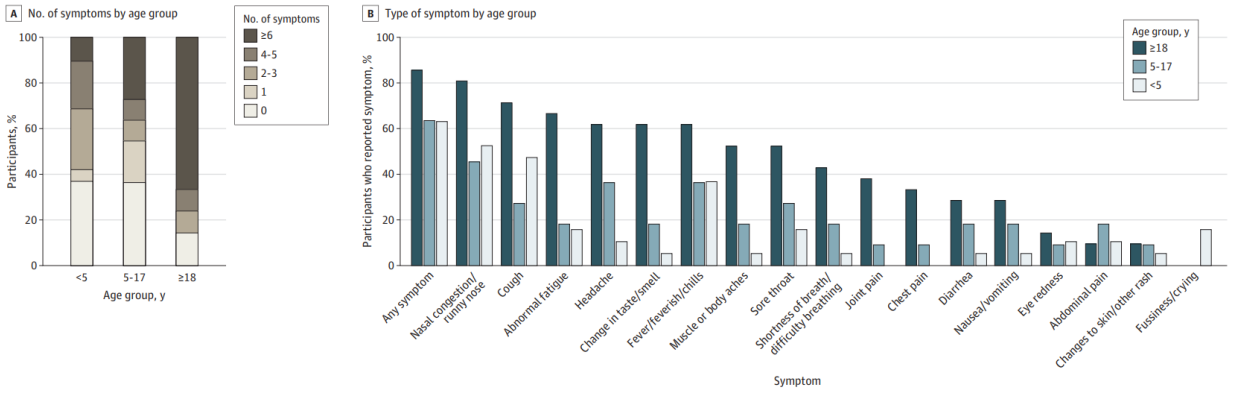
Assessment of Clinical and Virological Characteristics of SARS-CoV-2 Infection Among Children Aged 0 to 4 Years and Their Household Members JAMA Netw Open 2022;5(8):e2227348.

doi:10.1001/jamanetworkopen.2022.27348

Investigators analyzed weekly symptom questionnaires, self-collected nasal swabs, and sera from 690 participants in 175 Maryland households with one or more children younger than 5 years from November 24, 2020, to October 15, 2021. They prospectively examined the incidence and clinical features of SARS-CoV-2 household infection, with a focus on children aged 0 to 4 years. They used a novel study design, including courier pickup of self-collected nasal swabs from symptomatic and asymptomatic household members for weekly monitoring of SARS-CoV-2 by qualitative rapid-turnaround PCR testing, blood samples for serological assessment at enrollment and during the study period, and weekly web-based symptom surveys of the entire household to assess infection among participants of all ages.

54 incident SARS-CoV-2 infections were detected in 8.6% of children aged 0 to 4 years, 11.0% of children aged 5 to 17 years, and 6.3% of adults. Children were more frequently asymptomatic or mildly symptomatic than adults; highest detected viral loads correlated with the number of symptoms in adults but not in young children.

Figure 3. SARS-CoV-2 Symptoms by Age Group



Comment: In this study, SARS-CoV-2 infections were frequently asymptomatic among children aged 0 to 4 years; the presence and number of symptoms did not correlate with viral load. These findings suggest that symptom screening may be insufficient to prevent outbreaks involving young children. There are however several important limitations of the study. The first was that the study does not necessarily represent the general population with over 85% of the study population self-reported their race as White, and household members required online access to enter study data. Second, there was a relatively small number of patients and households with SARS-CoV-2 infection. The combination of a homogeneous population and a small number of infections makes generalization to a large population difficult. Third, the study period only included Alpha and Delta but since Omicron variants were not circulating. Given the higher rate of transmissibility and infectivity of the Omicron variant, it is difficult to make direct associations between findings reported during this study period and those present in the current era during which the Omicron variant is circulating. However, the higher rates of asymptomatic infection observed among children in this study are likely to be consistent with those observed for current and future viral variants. Lastly, this study did not address other social characteristics potentially associated with viral transmission, such as characteristics of childcare or school attendance, or evaluate factors including masking or social distancing, screening approaches outside the home, or the number of individuals per class among children attending school or childcare. During the pandemic, childcare centers as well as schools have relied on symptom-based screening and temperature checks as the main mitigation strategies for young children. The current study highlights the limitations of symptom-based screening for SARS-CoV-2, especially in the toddler age group. In June 2022, the FDA and CDC approved EUA for vaccination in children under age 5. Vaccination against SARS-CoV-2 infection is considered the best strategy to diminish the spread of virus and prevent severe disease/MIS-C in children. However, just over 5% of eligible babies and toddlers nationwide have received their first dose. Last month the CDC updated their recommendations for schools. They now recommend that the routine use of tests for general surveillance to understand disease spread should be stopped and we should not be using this to screen asymptomatic children from coming to school.