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Infectious Diseases Watch

January 31, 2022

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VII Perspective: Is it Time to Pivot?

Initial strategies to control COVID-19 have often been based on limited data and have tended to be slow to evolve as new evidence emerges. Yet knowledge about COVID-19 has grown exponentially, and the expanding rollout of vaccines presents further opportunity to reassess the response to the pandemic more broadly. COVID-19 vaccines have proven to be highly effective at preventing severe disease and mortality and, to a lesser extent, milder symptomatic and asymptomatic cases. However, highly transmissible variants, such as Omicron which is immune evasive, has led to high numbers of asymptomatic or mild infections even among the vaccinated.[see Journal Review below] These breakthrough infections should not be considered "vaccine failures". Instead, they should be recognized as the characteristic of a highly effective vaccine that is operating precisely as intended—to prevent serious illness or death. The time is right to reexamine existing mitigation approaches to adapt to emerging evidence on effectiveness and to minimize unintended consequences by implementing common-sense policies. With the arrival of Omicron, we need more realistic goals and need to pivot from a Delta mindset to a new framework accepting COVID as an endemic disease. We must be sure that Americans understand this is a very different time from March 2020, especially in highly vaccinated regions. This hopefully can help move us beyond the continuous cycle of removing and reinstating COVID restrictions based on measures that are no longer clinically relevant.

As the Omicron surge peaks, there's bad news and good news. The bad news is that the main strategies for slowing its spread—mass testing, masks, isolation and quarantine and vaccine boosters— have had limited impact on spread, however, the vaccine still has a high VE against severe disease and death and boosters do reduce risk of infection as well as hospitalization from Omicron. The good news is that the new variant is relatively mild and so many people now have some immunity from vaccines, prior infection or both. The number of Omicron deaths seems to be similar in most countries to the level of a bad influenza season. Therefore, a new strategy of examining who is at risk of severe breakthroughs and protecting that population will help us make this critical transition.

The new strategy also means using different measures as the basis for COVID-19 restrictions. CDC currently uses cases/100,000 and percent positivity. In a vaccinated population, the relationship between case counts and hospitalizations has been uncoupled especially with Omicron. Because so many vaccinated individuals may test positive for COVID-19 with few or no symptoms, the number of infections in a community no longer predicts the number of hospitalizations or deaths. This uncoupling means that we should no longer focus on the number of COVID-19 infections as

predictive of the need for lockdowns, physical distancing, or mask use. Instead, we should change the metrics from cases to hospitalization and deaths for both protecting the country's population and to avoid unnecessary restrictions and lockdowns. We should set new targets that would trigger emergency measures. A word of caution, although reported numbers of "COVID hospitalizations" are up nationally, these figures include patients admitted for other reasons who incidentally test positive. Based on data from several states and the UK, it appears that roughly half these admissions likely aren't caused by COVID-19.

What does the new strategy look like? First, we need facts over fear and consistent messaging with compassion. Even with the continuing emergence of viral variants, widespread vaccination remains the quickest and most powerful way to reduce the toll from COVID-19 and continue returning toward a greater sense of normality. Our time should be spent on vaccinating the unvaccinated and boosting as soon as possible the most vulnerable, such as residents of nursing homes, persons over age 65, and those with high-risk underlying medical conditions. Shame and fear are not motivating strategies. This new strategy highlights the need for the CDC to increase its tracking and reporting of severe breakthrough infections by the health status of individuals so that the most vulnerable can be rapidly identified and prioritized for life saving treatment, such as Paxlovid, MCA and other powerful antiviral therapies as they become available.

As for masking, the CDC recently admitted that cloth masks do relatively little to prevent spread. That has led to calls for mandatory N95-type masks, which are more effective but harder to use. Use of N95, KN95, KF94, FFP2, or even double masking, should be encouraged among select high-risk populations, but perpetual masking of entire populations is not sustainable or necessary. Masking was a necessary intervention early on and during surges especially before vaccination. Our children, a group at lowest risk of serious COVID-19 illness, continue to endure more hours of uninterrupted masking than higher risk adults leading to psycho-social and other harms. COVID-19 poses very little threat of serious disease for students in highly vaccinated communities. Although masks should be part of nonpharmaceutical strategy especially when indoors in crowded, poorly ventilated areas during times of high transmission, it is time to stop exaggerated the efficacy of masks in ending this pandemic. The adult population now has had access to highly effective vaccines for over a year, and more recently, all children ages 5 and older became eligible for vaccination. Some scientists have even suggested that Omicron may be nature's vaccine increasing herd immunity against serious illness from future variants. With this level of immunity and access to new antiviral medications such as Paxlovid universal mandates for masking should be reexamined. Access to testing must be part of this strategy to rapidly identify high-risk people in a timely manner to provide effective antivirals to prevent progression of disease.

Finally, we need to update our thinking around natural immunity which both CDC and NIH have avoided addressing. Last week, the CDC released data from New York and California, which demonstrated natural immunity was 2.8 times as effective in preventing hospitalization and 3.3 to 4.7 times as effective in preventing COVID-19 infections compared with vaccination. [see Journal Review below] Natural immunity developed from prior variants reduced the risk of infection with the Omicron variant. Meanwhile, the effectiveness of the two-dose Moderna vaccine against infection (not severe disease) declines to 61% against Delta and 16% against Omicron at six months, according to a recent study. [see Journal Review below] A large study

from Israel reviewed last year demonstrated that natural immunity confers longer lasting and stronger protection against infection, symptomatic disease and hospitalization caused by the Delta variant, compared to the Pfizer two-dose vaccine-induced immunity. Individuals who were both previously infected with SARS-CoV-2 and given a single dose of the vaccine gained additional protection against the Delta variant. [doi.org/10.1101/2021.08.24.21262415] Natural immunity should count, and we should revise our policy and encourage persons who have natural immunity to receive at least one dose of an mRNA vaccine. This new roadmap will also give recognition to natural immunity from prior infection when implementing vaccine mandates (such as recommending 1 dose after natural infection to boost immunity but minimize side effects). This policy would increase public trust, particularly among more vaccine hesitant communities, as a more accurate reflection of the evidence to date.

It's past time we pivot from a zero-infection policy to protecting the most vulnerable from severe disease directly through vaccination and other evidence-based interventions. Modifying mask mandates, deemphasizing quarantine and isolation, and encouraging vaccination ought to be a compromise most of us can live with. We must continue to de-escalate fear around getting COVID-19 and apply focused protection measures to protect community members who remain at high risk. The future will also depend on our risk tolerance, both as individuals and as a community. Even though the Omicron tends to be milder, this contagious variant has wreaked havoc on our health care system and beyond due to the sheer volume of cases. Since it is unlikely that COVID-19 will disappear, and herd immunity now seems like a dream, SARS-CoV-2 is likely to become endemic especially since our population's immunity against the virus will remain imperfect. Although I am cautiously optimistic the future also depends on a wild card: new variants! There is still a significant vaccination gap across the globe, which can lead to more variants emerging. Now and in the future, we need to build back public confidence in competence and public health. To understand the term, it is not only skill but also judgment, humility, and empathy.

General Infectious Diseases

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

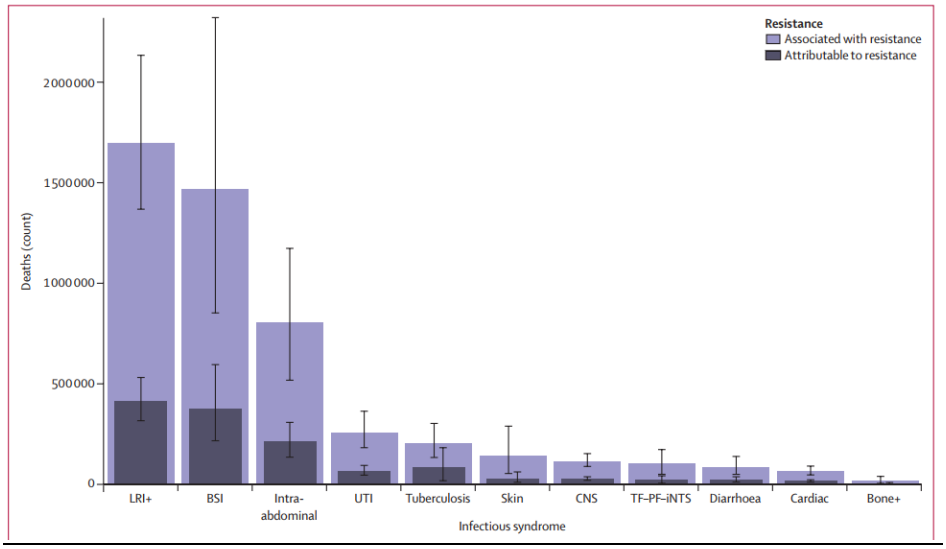
Lancet published online January 20, 2022

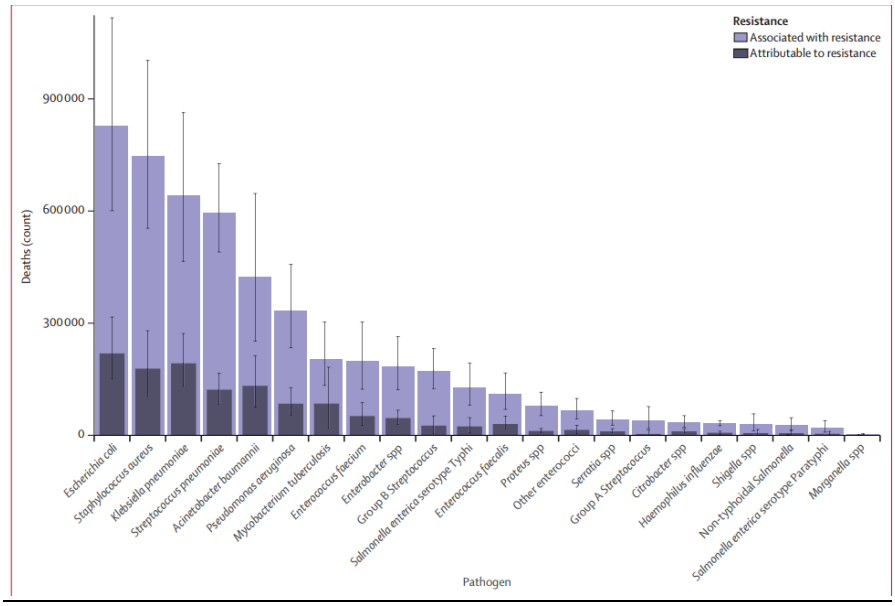
doi.org/10.1016/ S0140-6736(21)02724-0

The authors estimated deaths and disability-adjusted life-years (DALYs) attributable to and associated with bacterial AR for 23 pathogens and 88 pathogen–drug combinations in 204 countries and territories in 2019. They obtained data from systematic literature reviews, hospital systems, surveillance systems, and other sources, covering 471 million individual records or isolates and 7585 study-location-years. They used predictive statistical modelling to

produce estimates of AR burden for all locations, including for locations with no data. They divided the analysis into five broad components: (1) number of deaths where infection played a role, (2) proportion of infectious deaths attributable to a given infectious syndrome, (3)proportion of infectious syndrome deaths attributable to a given pathogen, (4)the percentage of a given pathogen resistant to an antibiotic of interest, and (5)the excess risk of death or duration of an infection associated with this resistance. They based their anaylsis on two counterfactuals: deaths attributable to AR (based on an alternative scenario in which all drug resistant infections were replaced by drug-susceptible infections), and deaths associated with AR (based on an alternative scenario in which all drug-resistant infections were replaced by no infection).

On the basis of their models, they estimated 4·95 million (3·62–6·57) deaths associated with bacterial AR in 2019, including 1·27 million (95% UI 0·911–1·71) deaths attributable to bacterial AR. At the regional level, they estimated the all-age death rate attributable to resistance to be highest in western sub-Saharan Africa, at 27·3 deaths per 100,000 (20·9–35·3), and lowest in Australasia, at 6·5 deaths (4·3–9·4) per 100,000. Lower respiratory infections accounted for more than 1·5 million deaths associated with resistance in 2019, making it the most troublesome infectious syndrome. The six leading pathogens for deaths associated with resistance (*Escherichia coli*, followed by *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*) were responsible for 929,000 (660,000–1,270,000) deaths attributable to AR and 3·57 million (2·62–4·78) deaths associated with AR in 2019. One pathogen–drug combination, MRSA, caused more than 100,000 deaths attributable to AR in 2019, while six more each caused 50,000–100,000 deaths: multidrug-resistant excluding extensively drug-resistant tuberculosis, third-generation cephalosporin-resistant *E coli*, carbapenem-resistant *A baumannii*, fluoroquinolone-resistant *E coli*, carbapenem-resistant *K pneumoniae*, and third-generation cephalosporin-resistant *K pneumoniae*.





Comment: These estimates indicate that bacterial AR is a major health problem whose magnitude is at least as large if not larger than other major diseases such as HIV, TB, and malaria. Bacterial AR is a problem in all regions including high income North America. Prevention of infections with vaccinations, sanitation, infection prevention, and antimicrobial stewardship across the continuum of care are important tools in our battle to combat AR. There are a few limitations. The estimates of the proportion of infections that were community acquired versus hospital acquired for lower respiratory infections and urinary tract infections were based on the coding of data from multiple causes of death and hospital discharge data. This approach could have led to misclassification. Additionally, no universal laboratory standard exists to demarcate resistance versus susceptibility, and we often had to defer to laboratory interpretation to classify the isolates in their data, resulting in heterogeneous classification. Lastly, there is a possibility of selection bias in passive microbial surveillance data, particularly if cultures are not routinely drawn. This study was done before the pandemic with initial reports demonstrating increased AR in the last two years. New drug development and new approaches such as phages should be supported.

Changes in outpatient antibiotic prescribing for acute respiratory illnesses, 2011 to 2018 Antimicrob Stewardship & Healthcare Epidemiol (2021), 1, e66, 1–8

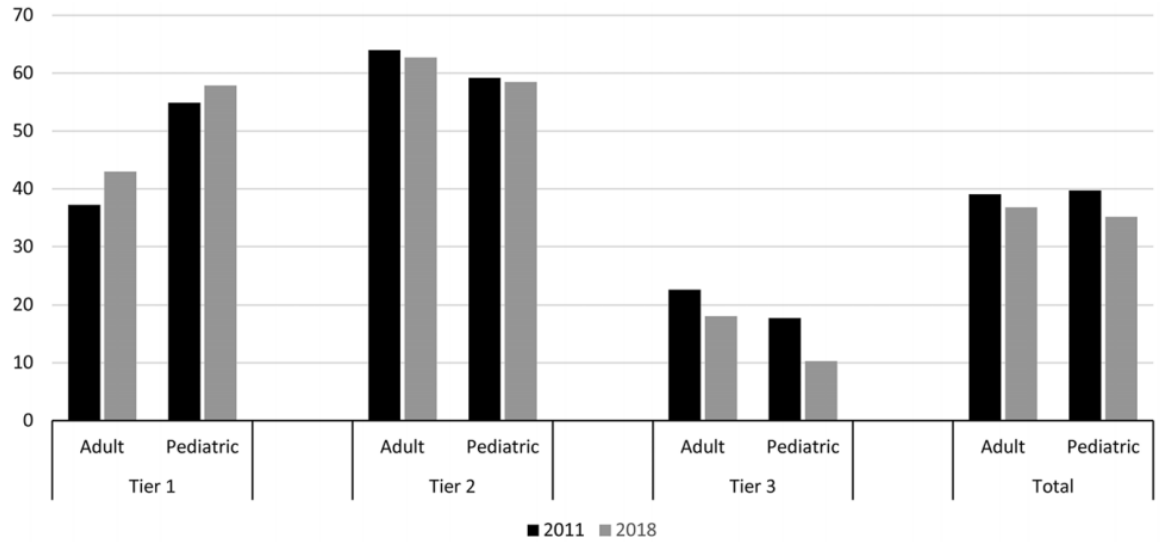
doi:10.1017/ash.2021.230

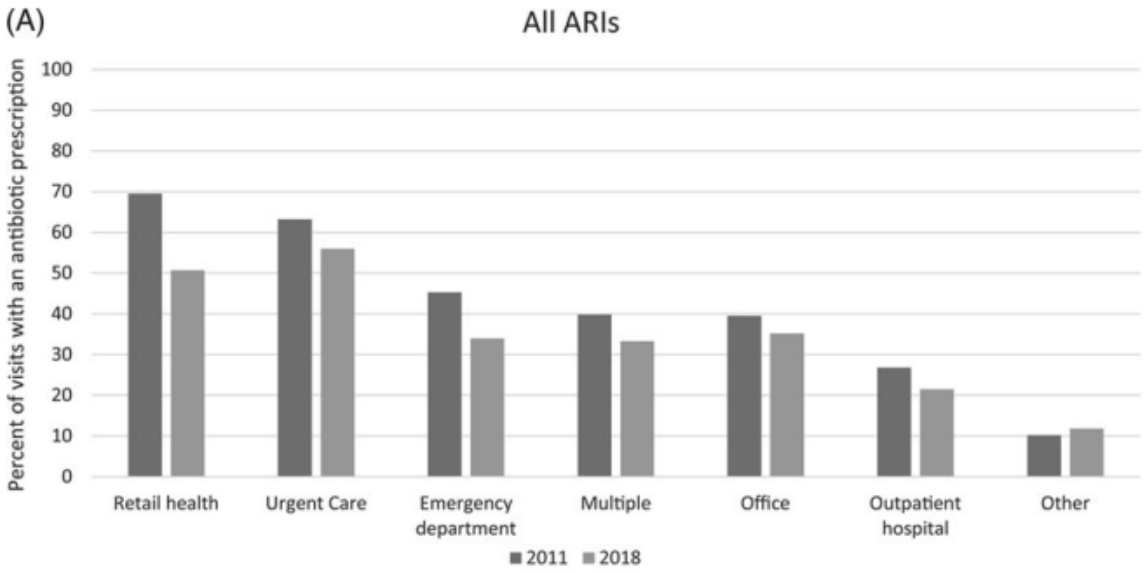
The authors used outpatient medical and pharmacy claims captured in the IBM MarketScan commercial database, a national convenience sample of privately insured individuals aged <65 years for acute respiratory illnesses (ARI) visits and antibiotic prescriptions in 2011 and 2018. They then calculated the annual number of ARI visits and visits with oral antibiotic prescriptions per 1,000 enrollees overall and by age category, sex, and setting in 2011 and 2018. Tier 1 contains conditions for which antibiotics are almost always indicated (pneumonia, urinary tract infection, miscellaneous bacterial infection). Tier 2 contains conditions for which antibiotics are

sometimes indicated (sinusitis, acute otitis media [AOM], pharyngitis, acne, skin and soft tissue infections, gastrointestinal infections). Tier 3 contains conditions for which antibiotics are almost never indicated (antibiotic inappropriate ARIs: bronchitis and bronchiolitis, asthma and allergy, viral upper respiratory infection [URI], influenza, nonsuppurative otitis media) and other conditions.

There were 829 ARI visits per 1,000 enrollees in 2011 compared with 760 ARI visits per 1,000 enrollees in 2018. In 2011, 39.3% of ARI visits were associated with ≥1 oral antibiotic prescription versus 36.2% in 2018. In 2018 compared with 2011, overall ARI visits decreased 8% (PRR, 0.92; 99.99% confidence interval [CI], 0.92–0.92), whereas visits with antibiotic prescriptions decreased 16% (PRR, 0.84; 99.99% CI, 0.84–0.85). Visits for antibiotic-inappropriate ARIs decreased by 9% (PRR, 0.91; 99.99% CI, 0.91–0.92), and visits with antibiotic prescriptions for these conditions decreased by 32% (PRR, 0.68; 99.99% CI, 0.67–0.68) from 2011 to 2018.

Percentage of acute respiratory illness visits with antibiotic prescriptions by patient age group and antibiotic-indication tier, 2011 and 2018





Comment: Both the rate of antibiotic prescriptions per 1,000 enrollees and the percentage of visits with antibiotic prescriptions decreased in 2018 compared with 2011. These decreases were greatest for antibiotic inappropriate ARIs (tier 3), suggesting a decrease in unnecessary antibiotic prescribing. However, in 2018 antibiotics were still prescribed in >15% of visits for antibiotic inappropriate ARIs. Antibiotic prescriptions for ARIs decreased across outpatient settings, and the percentage of visits with antibiotic prescriptions was highest in urgent care. This study was conducted using a sample of commercially insured individuals aged <65 years and may not be generalizable to other populations. Second, the analysis used diagnostic codes from claims to assign a single diagnosis to each visit and had no additional clinical information and no sample chart audit. They only examined 2 years (2011 and 2018), so they could not evaluate trends that occurred between those years. However, national outpatient antibiotic prescriptions did show consistent decreases during this period. Although reductions in inappropriate prescribing are encouraging, the decrease observed from 2011 to 2018 was still disappointing given the focus on ARI for almost two decades. As with prior studies pediatrics has outperformed adults.

COVID-19

COVID-19 News

“Stealth” Omicron Variant (BA.2)

A new subvariant of Omicron has emerged, which some have begun calling "son of Omicron," but public health officials say it's too soon to tell what kind of real threat, if any, this new strain will present. Initial reports suggest it may be more transmissible than BA.1 with boosters providing better protection against BA.2 than BA.1. This new subvariant does not appear to be more virulent. The subvariant has now been identified across at least 40 countries, including three cases reported in Houston and several in Washington state. To date BA.2 accounts for only a small minority of reported cases so far, including 5% in India, 4% of those in the United Kingdom, and 2% each of cases in Sweden and Singapore. The one exception is Denmark, a country with robust genetic sequencing abilities, where estimates range from 50% to 81% of cases.

Comment: BA.2 is not a new sublineage. It is called “stealth” because it did not have the same S-gene target failure on PCR testing that BA.1 did. That's because it lacks the spike deletions 69-70 in BA.1, so S-gene targets still turn up positive. Studies have used amplification failure of the spike gene (S gene target failure [SGTF]) on the TaqPath PCR assay as a proxy for the omicron variant. SGTF is a reasonable marker for the omicron variant given that other circulating variants did not have this characteristic. Since the BA.2 doesn't have a special signal that tells labs it's Omicron, labs now must go to genetic sequencing to identify variants. PCR and rapid antigen tests will pick up both BA.1 and BA.2. While BA.1 had about 60 mutations, BA.2 has about 85 mutations to date, BA.2 does not look that from Omicron (BA.1) in a meaningful way.

FDA Suspends Use of Two MCA Treatments to Fight COVID

The FDA deauthorized the use of two monoclonal antibody treatments to fight COVID-19 due to observed ineffectiveness against the omicron variant, which is now estimated to make up more than 99% of all U.S. cases. The MCA combinations bamlanivimab/etesevimab and casirivimab/imdevimab should only be used for COVID-19 patients exposed to variants other than Omicron because they are ineffective against the dominant Omicron variant. HHS notified state health officials that it has halted distribution of the” combination antibody medications made by Regeneron Pharmaceuticals [casirivimab and imdevimab] and Eli Lilly [bamlanivimab and etesevimab].

Comment: Sotrovimab is now the MCA of choice which retains activity against Omicron. The NIH list sotrovimab in order of preference behind Nirmatrelvir/ritonavir (Paxlovid) for outpatient treatment for mild to moderate Covid-19 in high-risk individuals. [see ID Watch Issue 2]

FDA Approves Remdesivir for outpatient treatment

Last week the FDA expanded its approval for the use of remdesivir to treat non-hospitalized patients 12 years and older for the treatment of mild-to-moderate COVID-19 disease with high risk of hospitalization. The drug was previously limited to patients requiring hospitalization.

Comment: This expansion is based on the NEJM article December 22, 2021, reviewed in the Daily Briefing December 27, 2021(now ID Watch). The NIH lists this as the third preference

behind nirmatrelvir/ritonavir and sotrovimab in part because it requires 3 daily infusions. [see ID Watch Issue 2]

COVID-19 by The Numbers

Children and COVID-19: State Data Report January 20, 2022

Cumulative Number of Child COVID-19 Cases

- 10,603,034 total child COVID-19 cases reported, and children represented 18.4% (10,603,034/57,745,512) of all cases

- Overall rate: 14,087 cases per 100,000 children in the population

Change in Child COVID-19 Cases

- 1,150,543 child COVID-19 cases were reported the past week from 1/13/22-1/20/22 (9,452,491 to 10,603,034) and children represented 25.5% (1,150,543/4,514,692) of the weekly reported cases

- Over two weeks, 1/6/22-1/20/22, there was a 25.2% increase in the cumulated number of child COVID-19 cases (2,132,031 cases added (8,471,003 to 10,603,034))

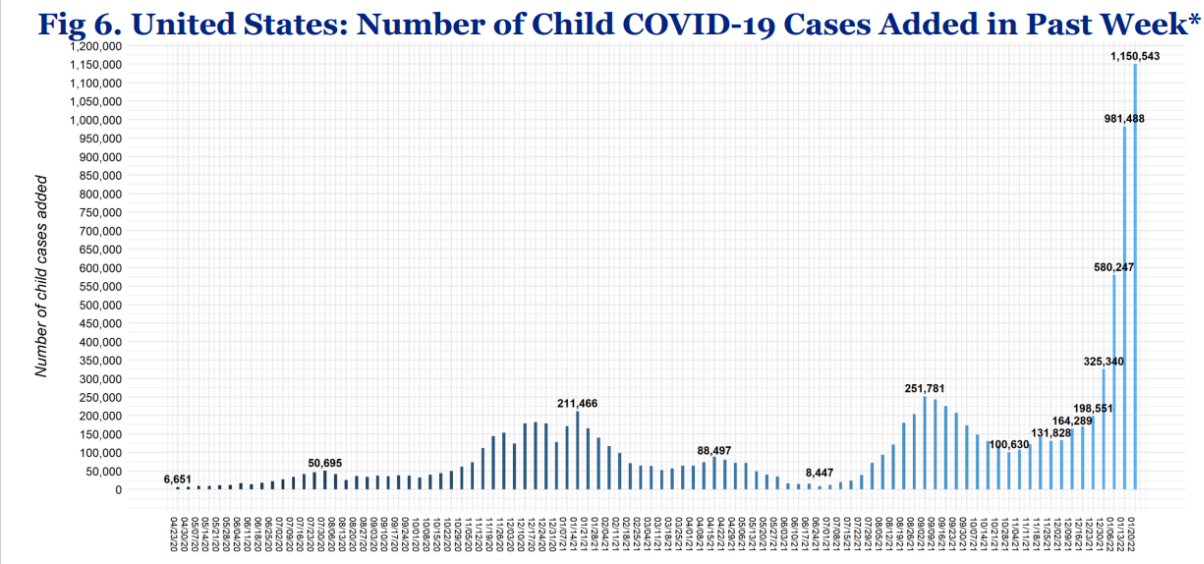
Cumulative Hospitalizations (24 states and NYC reported)

- Among states reporting, children ranged from 1.7%-4.4% of their total cumulated hospitalizations, and 0.1%-1.5% of all their child COVID-19 cases resulted in hospitalization

Cumulative Mortality (46 states, NYC, PR and GU reported)

- Among states reporting, children were 0.00%-0.26% of all COVID-19 deaths, and 4 states reported zero child deaths

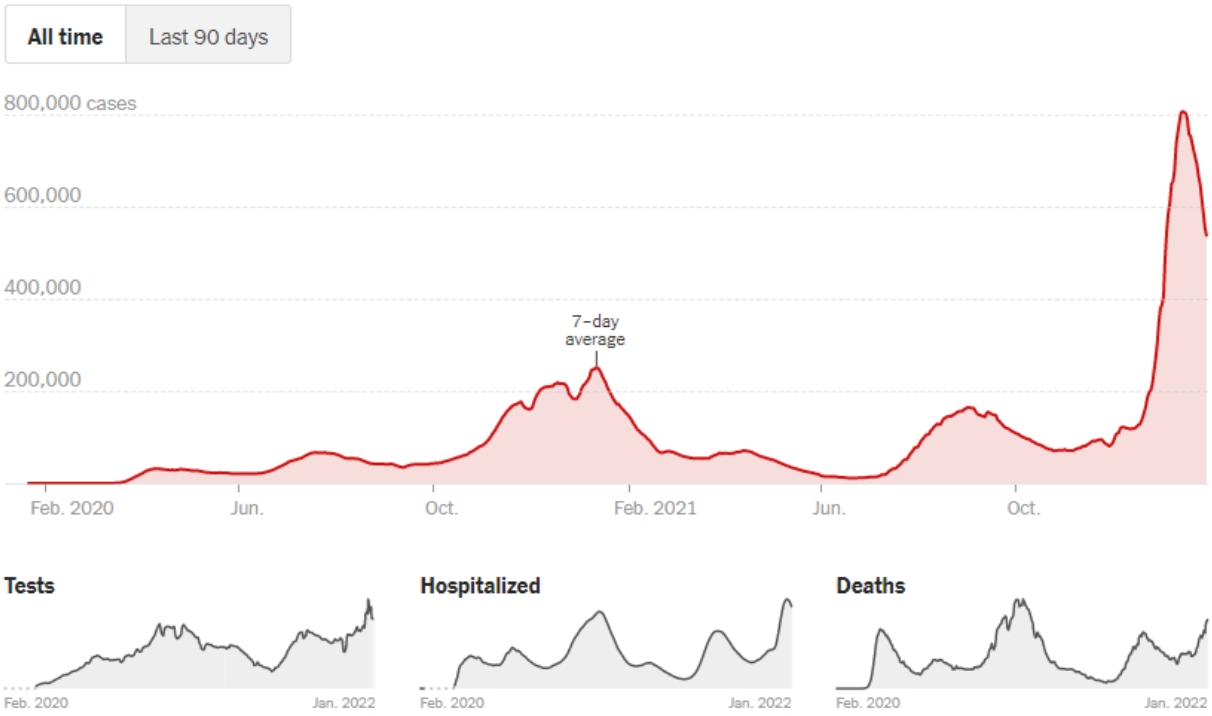
- In states reporting, 0.00%-0.02% of all child COVID-19 cases resulted in death



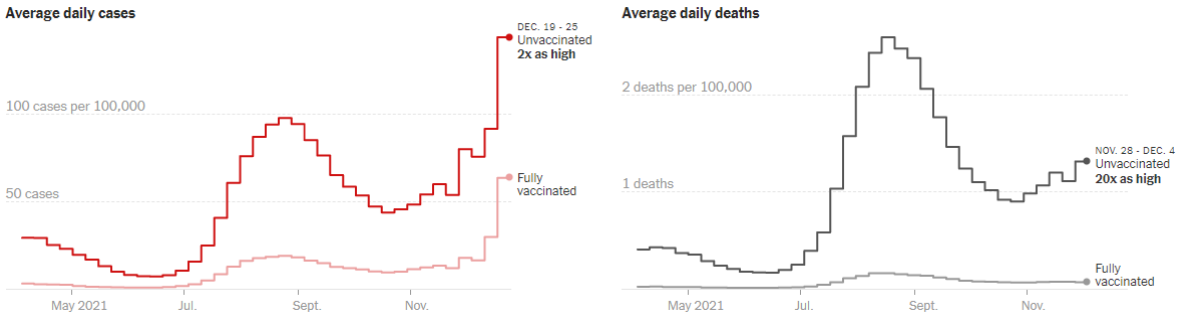
Comment: According to the latest update from the AAP, nearly 1,151,000 child COVID-19 cases were reported from Jan 13 to 20, a 17% increase over the previous week.

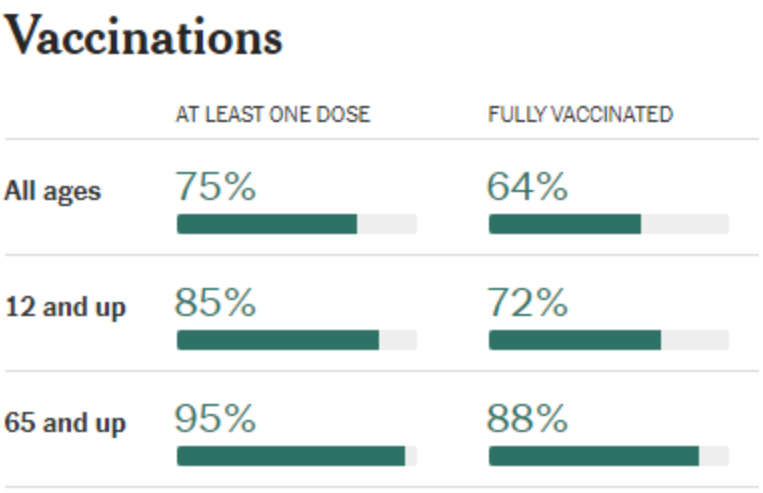
Over 10.6 million children have tested positive for COVID-19 since the onset of the pandemic; Over 2 million of these cases have been added in the past 2 weeks. The good news ≤0.02% of all infections in children result in death. Only 25% of children ages 5-11 have had at least one dose and only 18% are fully vaccinated.

New reported cases



	DAILY AVG. ON JAN. 29	14-DAY CHANGE	TOTAL REPORTED
Cases	537,784	-33%	74,211,771
Tests	2,070,685	+4%	—
Hospitalized	146,787	-5%	—
Deaths	2,572	+29%	882,964





Comment: For US as a whole, cases are declining and as well as hospitalizations. Death which is a delayed indicator has increased in large part due to volume of infections due to Omicron, however the deaths/100,000 is lower than with Delta. Almost all deaths are in the unvaccinated. (See above) In terms of vaccinations, the percent represent fully vaccinated and may not reflect the percentage that are "up-to-date." We still have opportunities for ages 5-17.

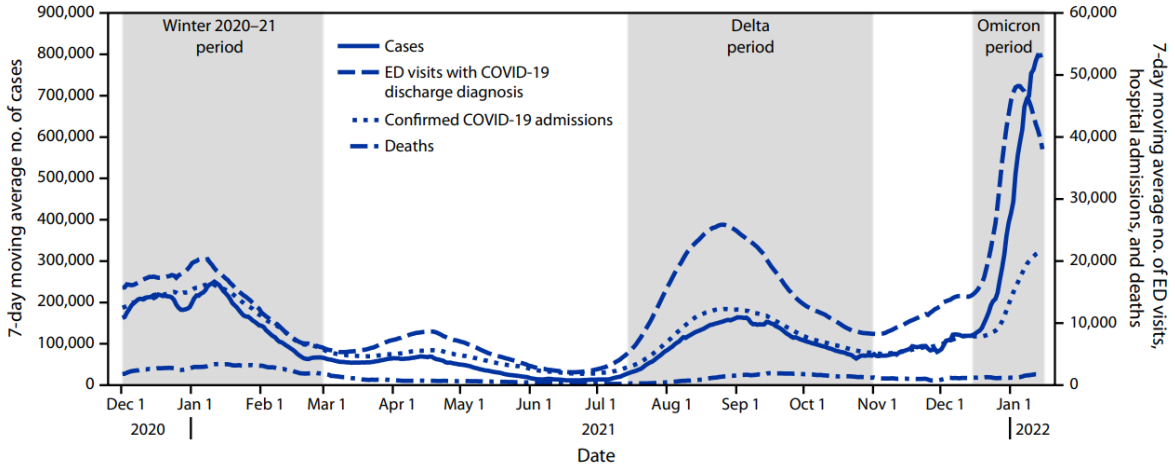
Journal Review

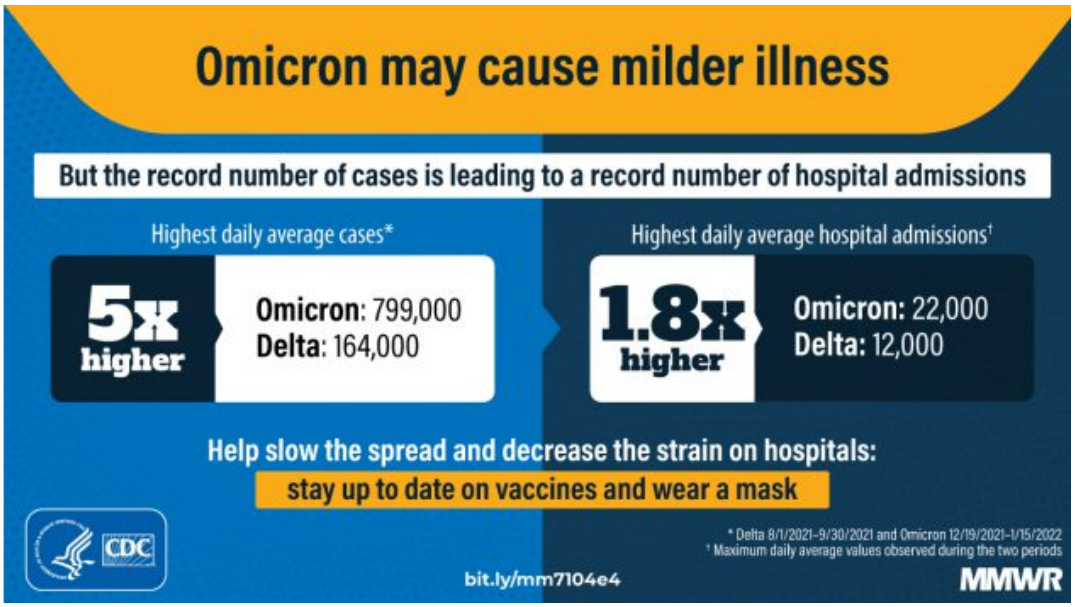
Trends in Disease Severity and Health Care Utilization During the Early Omicron Variant Period Compared with Previous SARS-CoV-2 High Transmission Periods — United States, December 2020–January 2022 MMWR 2022; 71:146–152

Omicron was first confirmed in the United States on Dec 1, 2021, and as of Jan 15, 2022, represented 99.5% of all sequenced viruses in the country. To gauge the severity of cases, the CDC compared that 6-week timeframe with cases and outcomes from Dec 1, 2020, through Feb 28, 2021 (winter 2020-21, when the wild-type strain was predominant), and Jul 15 to Oct 31, 2021, when Delta was the most dominant variant.

The highest daily 7-day moving average to date of cases (798,976 daily cases during January 9–15, 2022), emergency department (ED) visits (48,238), and admissions (21,586) were reported during the Omicron period, however, the highest daily 7-day moving average of deaths (1,854) was lower than during previous periods. The ratio of peak emergency department visits, hospital admissions, and deaths to case, were all lower in Omicron than other variants. In addition to lower ratios of ED visits, hospitalizations, and deaths to cases observed during the Omicron period, disease severity indicators were also lower among hospitalized COVID-19 patients, including ICU admission, receipt of IMV, length of stay, and in-hospital death. Among children aged < age 18, in-hospital severity indicators, including length of stay and ICU admission, were similar to and lower, respectively, during the Omicron period compared with those during previous high-transmission periods. However, high relative increases in ED visits and hospitalizations were observed among children during the Omicron period, which might be

related to lower vaccination rates in children compared with those in adults, especially among children aged 0–4 years who are currently not eligible for vaccination.





Comment: Although disease severity appears lower with the Omicron variant, the high volume of ED visits and hospitalizations can strain local health care systems in the US, and the average daily number of deaths remains substantial (almost all unvaccinated). This apparent decrease in disease severity is thought to be related to multiple factors, most notably increases in vaccination among high-risk persons, and the use of vaccine boosters among recommended subgroups. During the Omicron period, 207 million persons were fully vaccinated compared with 178 million persons and 1.5 million persons during the Delta and the winter 2020–21 periods, respectively. Further, during the Omicron period, 78 million persons had received vaccine boosters compared with 1.6 million persons during the Delta period; boosters were not recommended during winter 2020–21. Other key factors for lower disease severity include increased natural immunity, and potential lower virulence of the Omicron variant. The variation in vaccination coverage during the three periods assessed was not considered when comparing severity indicators. This limitation is most relevant when comparing the Omicron period to the winter 2020-21 period, when vaccines were just becoming available in the US. In addition,

person-level vaccination status was not available to compare severity indicators based on being up to date on vaccinations.

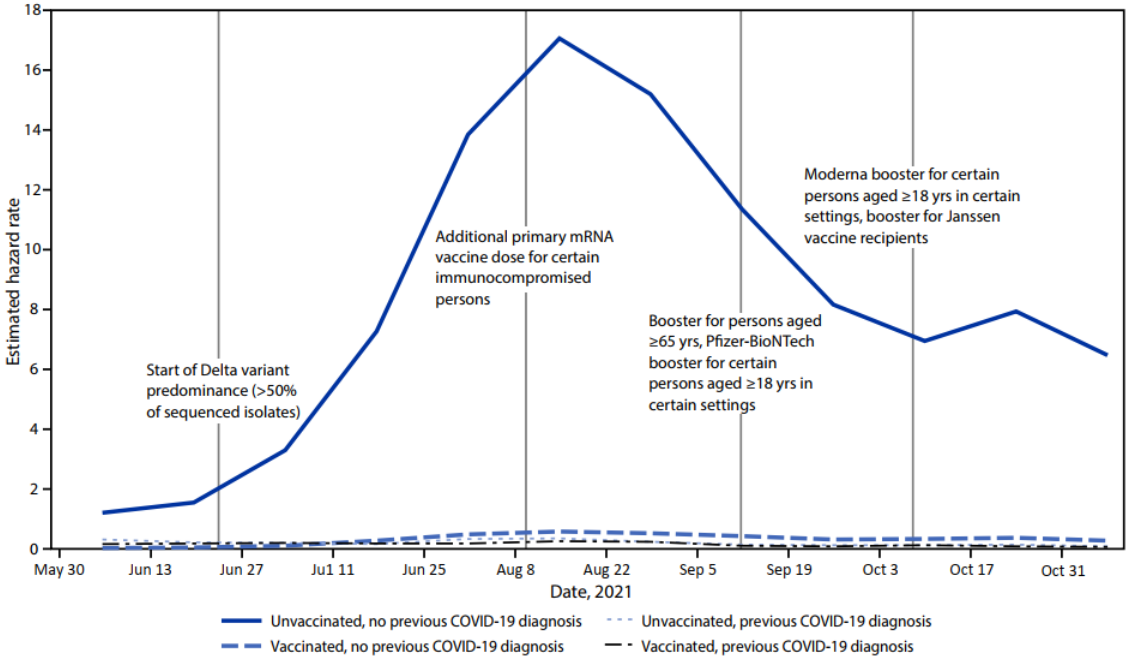
COVID-19 Cases and Hospitalizations by COVID-19 Vaccination Status and Previous COVID-19 Diagnosis — California and New York, May–November 2021

MMWR January 19, 2022

CDC analyzed the impact of primary COVID-19 vaccination and previous SARS-CoV-2 infection on COVID-19 incidence and hospitalization rates, using statewide testing, surveillance, and COVID-19 immunization data from California and New York (which account for 18% of the U.S. population) Four cohorts of adults aged ≥18 years were considered: persons who were 1) unvaccinated with no previous laboratory-confirmed COVID-19 diagnosis, 2) vaccinated (14 days after completion of a primary COVID-19 vaccination series) with no previous COVID-19 diagnosis, 3) unvaccinated with a previous COVID-19 diagnosis, and 4) vaccinated with a previous COVID-19 diagnosis. Age-adjusted hazard rates of incident laboratory-confirmed COVID-19 cases in both states were compared among cohorts, and in California, hospitalizations during May 30–November 20, 2021, were also compared.

Not surprisingly, during the study period, COVID-19 incidence in both states was highest among unvaccinated persons without a previous COVID-19 diagnosis compared with that among the other three groups. During the week beginning May 30, 2021, compared with COVID-19 case rates among unvaccinated persons without a previous COVID-19 diagnosis, COVID-19 case rates were 19.9-fold (California) and 18.4-fold (New York) lower among vaccinated persons without a previous diagnosis; 7.2-fold (California) and 9.9-fold lower (New York) among unvaccinated persons with a previous COVID-19 diagnosis; and 9.6-fold (California) and 8.5-fold lower (New York) among vaccinated persons with a previous COVID-19 diagnosis. hospitalization rates followed a similar pattern. These relationships changed after the Delta variant became predominant in late June and July. Compared with COVID-19 cases rates among unvaccinated persons without a previous COVID-19 diagnosis, case rates among vaccinated persons without a previous COVID-19 diagnosis were 6.2-fold (California) and 4.5-fold (New York) lower; rates were substantially lower among both groups with previous COVID-19 diagnoses, including 29.0-fold (California) and 14.7-fold lower (New York) among unvaccinated persons with a previous diagnosis, and 32.5-fold (California) and 19.8-fold lower (New York) among vaccinated persons with a previous diagnosis of COVID-19.

FIGURE. Incident laboratory-confirmed COVID-19–associated hospitalizations among immunologic cohorts defined by vaccination and previous diagnosis histories — California, May 30–November 13, 2021*,†



Comment: These results demonstrate that vaccination protects against COVID-19 and related hospitalization, and that surviving a previous infection protects against a reinfection and related hospitalization. Notably, infection-derived protection was higher after the Delta variant became predominant possibly a time when vaccine-induced immunity for many persons declined. In all, data from NY and CA demonstrated natural immunity was 2.8% as effective in preventing hospitalization and 3.3 to 4.7 times as effective in preventing infections compared to vaccination. Israel also found that natural immunity was more effective than vaccine immunity in preventing symptomatic illness. [doi.org/10.1101/2021.08.24.21262415] In this report, analyses were not stratified by time since vaccine receipt, but only by time since previous diagnosis. Potential exists for bias related to unmeasured confounding (e.g., behavioral, or geographic differences in exposure risk) and uncertainty in the population size of the unvaccinated group without a previous COVID-19 diagnosis. Data accounting for booster doses and as new variants, including Omicron, circulate will need to be assessed. However, studies are emerging indicating the importance of natural immunity not only in term of protection but also duration of protection. As my Perspective indicates, it is time for the CDC and NIH to address the importance of natural immunity. [see Perspective above]

Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study Lancet published online January 19, 2022

doi.org/10.1016/ S0140-6736(22)00017-4

The investigators used data linkages for national, South African COVID-19 case data, SARS-CoV-2 laboratory test data, SARS-CoV-2 genome data, and COVID-19 hospital admissions data. For individuals diagnosed with COVID-19 via TaqPath PCR tests, infections were designated as either SGTF or non-SGTF. [see above discussion on BA.2-there wasn't any BA.2 at the time] The delta variant was identified by genome sequencing. They compared individuals

with SGTF versus non-SGTF infections diagnosed between Oct 1 and Nov 30, 2021, and they further assessed disease severity by comparing SGTF-infected individuals diagnosed between Oct 1 and Nov 30, 2021, with delta variant-infected individuals diagnosed between April 1 and Nov 9, 2021.

The investigators report data from more than 11 000 individuals (>80·0% aged 19–59 years; 55·9% women) with COVID-19 in South Africa. They report significantly reduced odds of hospital admission for patients infected with the omicron SARS-CoV-2 variant versus other SARS-CoV-2 variants during the same period (Oct 1–Nov 30, 2021; adjusted odds ratio [aOR] 0·2, 95% CI 0·1–0·3) and significantly reduced odds of severe disease among patients infected by the omicron variant than among patients infected with the delta variant in earlier epidemic waves (496 [62·5%] of 793 *vs* 57 [23·4%] of 244; aOR 0·3, 95% CI 0·2–0·5). However, this study found the odds of previous infection were around 23-times higher in omicron infected versus delta variant-infected patients, which could be due to the omicron variant's capacity for immune escape that could increase the proportion of milder reinfection.

Comment: This study suggests a significantly reduced odds of hospitalization among individuals with omicron versus other variant infections diagnosed during the same time period. Omicron infected individuals had a significantly reduced odds of severe disease compared with individuals infected earlier with the Delta variant. Immunity (due to previous infection, vaccination, or both) in individuals infected with the omicron variant could, in part, account for this reduced severity. [see above] This article is consistent with other recent publications on Omicron including in the US. [ID Watch Issue 3]

Post-peak dynamics of a national Omicron SARS-CoV-2 epidemic during January 2022
prepublication posting January 26, 2022

Among 3,582 people who tested positive for COVID-19 in England between Jan. 5 and Jan. 20, nearly 65 percent said they had a prior bout with the virus that was confirmed by a test, according to this preprinted article. The findings are part of Imperial College London's ongoing COVID-19 monitoring study, known as REACT, and are based on the results of 100,607 polymerase chain reaction test results from Jan. 5 to Jan. 20, 2022. About 3,582 participants out of 4,011 who had positive results reported their previous history of COVID-19 infection; of these, about 65 percent had previously had COVID-19. However, these results are based on self-reported data and therefore it's uncertain what proportion of these are reinfections or recent infections picked up due to the sensitivity of PCR testing.

During this period in January, the study found 1 in 23 people or 4.41 percent were infected, the highest prevalence of positive test results since the study began in May 2020. Investigators found 99 percent of 1,406 positive test swabs that were sequenced were omicron, while just 1 percent were delta, and they found a high prevalence of infection among children aged 5 to 17.

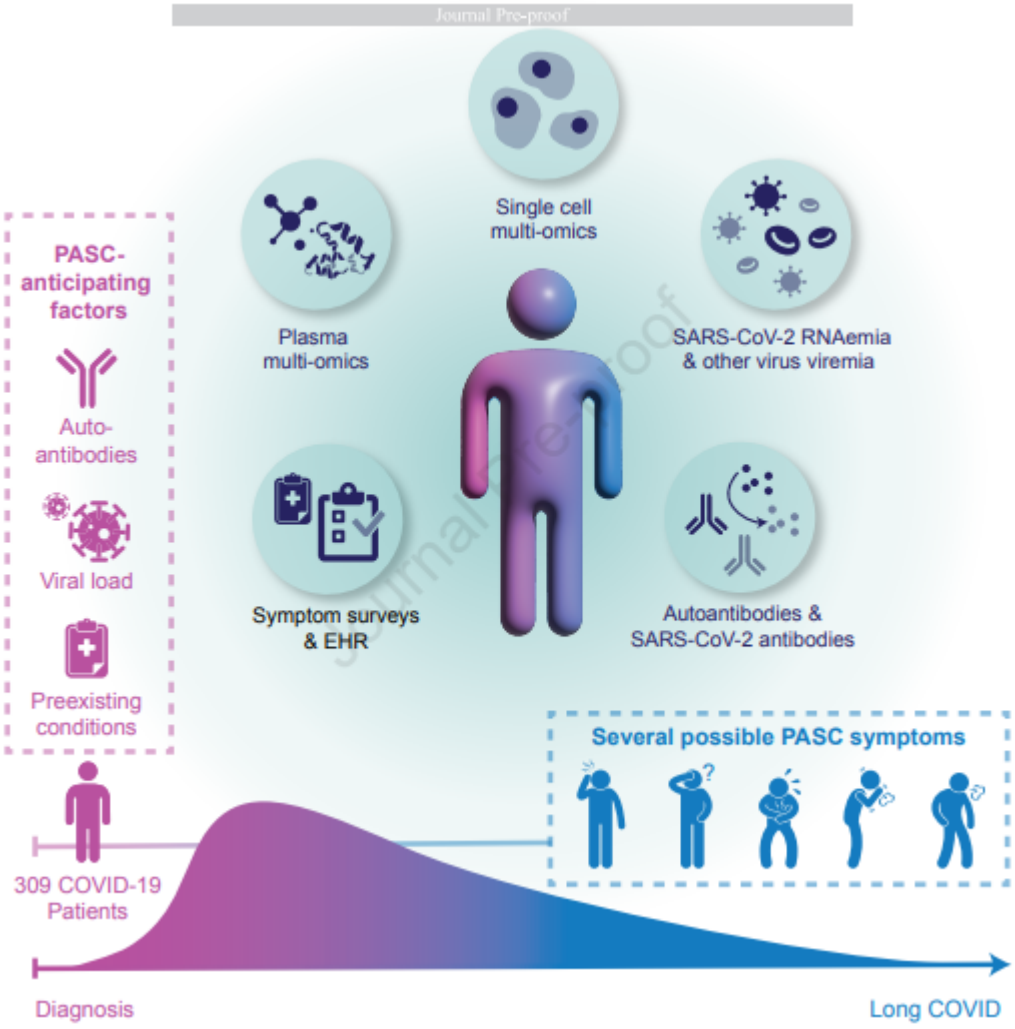
Comment: The comparison of infection prevalence data from REACT-1 and public data on hospitalizations and deaths indicate that although trends in these serious outcomes continue to track infections (albeit with an extended time lag) this is at a lower level than previously before widespread rollout of the vaccination campaign in England. As other studies have shown Omicron is immune evasive and can infect individuals who are immune by either natural immunity or vaccination especially if they have not been boosted. Nonetheless, it will be

important to monitor hospitalizations and deaths, which are lagging indicators, closely over the coming weeks in view of the continued high levels of infection, including among the older population, and as restrictions are lifted in England and elsewhere. Further measures beyond vaccination with boosters may be required if the very high rates of Omicron infection persist, despite the fact that Omicron appearing to cause less severe disease. [see above]

Multiple Early Factors Anticipate Post-Acute COVID-19 Sequelae Cell published online January 25.2022

doi.org/10.1016/j.cell.2022.01.01

Risk factors for post-acute sequelae of Covid-19 (PASC) and their biological associations are remain unclear. The investigators in this publication performed a deep multi-omic, longitudinal investigation of 309 COVID-19 patients from initial diagnosis to convalescence (2-3 months later), integrated with clinical data, and patient-reported symptoms. They found four PASC-anticipating risk factors at the time of initial COVID-19 diagnosis: type 2 diabetes, SARS-CoV-2 RNAemia, EBV viremia, and specific autoantibodies. In patients with gastrointestinal PASC, SARS-CoV-2-specific and CMV-specific CD8+ T cells exhibited unique dynamics during recovery from COVID-19. Analysis of symptom-associated immunological signatures revealed coordinated immunity polarization into four endotypes exhibiting divergent acute severity and PASC. They found that immunological associations between PASC factors diminish over time leading to distinct convalescent immune states. They had found that there was an association between these factors and long Covid (PASC) whether the initial infection was serious or mild. Detectability of most PASC factors at COVID-19 diagnosis emphasizes the importance of early disease measurements for understanding emergent chronic conditions and which may lead to specific PASC treatment strategies.



Comment: In this publication the investigators identified four major factors. Each is biologically plausible, consistent with theories that other investigators are pursuing, and importantly, each is potentially actionable. If these pathways are confirmed, clinicians can actually design interventions to reduce the risk of PASC. One of the four factors identified is the level of SARS-CoV-2 in the blood early in the infection, an indicator of viral load. Another is the presence of certain autoantibodies. A third factor is the reactivation of Epstein-Barr virus, a virus that infects most people, often when they are young, and then usually becomes latent. The final factor is having Type 2 diabetes. It might turn out that diabetes is only one of several medical conditions that increase the risk of long Covid**.** Of interest, patients reporting three or more symptoms, 95 percent had one or more of the four biological factors identified in this study. The most influential factor appeared to be autoantibodies, which were associated with two-thirds of the cases of long Covid. Each of the other three factors showed up in about a third of the cases with considerable overlap, with several factors identified in some patients. A major weakness of this study is the fact that patients had been followed for only two to three months which I believe is too short a time frame and the sample size is small. One potential conclusion is the suggestion that because patients with high viral loads early on often developed long Covid, giving people antivirals soon after diagnosis might help prevent long-term symptoms. With the EUA of drugs like Nirmatrelvir/ritonavir (Paxlovid) this may become a reality. Some patients

had reactivated EBV and its reactivation has been linked to conditions like chronic fatigue syndrome, which some cases of long Covid resemble, and multiple sclerosis. In the end it might be possible to give antivirals or immunotherapy to patients with reactivated Epstein-Barr virus.

If the result of this study is confirmed, the findings might suggest ways to prevent or treat some cases of long Covid, including the possibility of giving people antiviral medications soon after an infection has been diagnosed.