Infectious Diseases Watch

January 23, 2023

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General Infectious Diseases

Efficacy and safety of azithromycin versus placebo to treat lower respiratory tract infections associated with low procalcitonin: a randomised, placebo-controlled, double-blind, non-inferiority trial

Lancet Infect Dis published online December 13, 2022

doi.org/10.1016/ S1473-3099(22)00735-6

The investigators conducted a randomized, placebo-controlled, double-blind, non-inferiority trial at five health centers in the US. Adults aged 18 years or older with clinically suspected non-pneumonia lower respiratory tract infection and symptom duration from 24 h to 28 days were eligible for enrollment. Participants with a procalcitonin concentration of ≤0·25 ng/mL were randomly assigned (1:1), in blocks of four with stratification by site, to receive oral azithromycin 250 mg or matching placebo (two capsules on day 1 followed by one capsule daily for 4 days). Participants, non-study clinical providers, investigators, and study coordinators were masked to treatment allocation. The primary outcome was efficacy of azithromycin versus placebo in terms of clinical improvement at day 5 in the intention-to-treat population. The non-inferiority margin was –12·5%. Solicited adverse events (abdominal pain, vomiting, diarrhea, allergic reaction, or yeast infections) were recorded as a secondary outcome.

499 patients were enrolled and randomly assigned to receive azithromycin (n=249) or placebo (n=250). Clinical improvement at day 5 was observed in 148 (63%, 95% CI 54 to 71) of 238 participants with full data in the placebo group and 155 (69%, 61 to 77) of 227 participants with full data in the azithromycin group in the intention-to-treat analysis (between-group difference –6%, 95% CI –15 to 2). The 95% CI for the difference did not meet the non-inferiority margin. Adverse events and the severity of adverse events were not significantly different between groups at day 5, except for increased abdominal pain associated with azithromycin (47 [23%, 95% CI 18 to 29] of 204 participants) compared with placebo (35 [16%, 12 to 21] of 221; between-group difference –7% [95% CI –15 to 0]; p=0·066).

Comment: Azithromycin has several immunomodulatory effects, not linked to the antibacterial effect. These effects might have led to improving the clinical state of the active patients without this being linked to procalcitonin or bacterial infection. Patients with CAP have been shown to

have an earlier clinical improvement when randomly assigned to receive immunomodulatory drugs; such effects could also be present when using azithromycin. Prespecified sample size was adjusted, and eventually the trial was closed prematurely due to the Covid-19 pandemic.

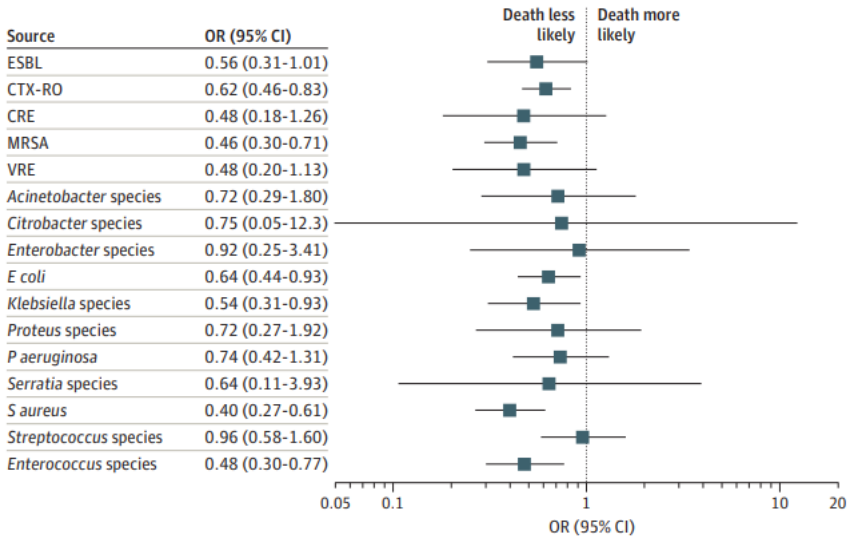
Simple measurement of a biomarker does not solve the problem. Procalcitonin could, however, be a part of the solution in combination with education of physicians and patients to change our prescription culture, which is still too liberal. It is reasonable, among outpatients with lower respiratory tract infection, to implement procalcitonin-guided reduction of antimicrobial prescriptions as in the current trial.

Association of Appropriate Empirical Antimicrobial Therapy With In-Hospital Mortality in Patients With Bloodstream Infections in the US JAMA Netw Open . 2023;6:e2249353.

doi:10.1001/jamanetworkopen.2022.49353

This retrospective cross-sectional study used data from the Premier Healthcare database from 2016 to 2020. The analysis included 32,100 adult patients (aged ≥18 years) with BSIs from 183 US hospitals who received at least 1 new systemic antimicrobial agent within 2 days after blood samples were collected during the hospitalization. Patients with polymicrobial infections were excluded from the analysis. Multilevel logistic regression models were used to estimate the association between receipt of appropriate initial empirical antimicrobial therapy and in-hospital mortality for patients infected with gram-negative rods (GNRs), gram-positive cocci (GPC), and Candida species.

The most common pathogens were E. coli (58.4%) and S. aureus (31.8%). Among patients infected with S aureus, MRSA was isolated in 43.6%. The crude proportions of appropriate empirical therapy use were 94.4% for GNR, 97.0% for GPC, and 65.1% for Candida species. The proportions of appropriate therapy use for resistant organisms were 55.3% for carbapenem-resistant Enterobacterales species and 60.4% for vancomycin-resistant Enterococcus species. Compared with inappropriate empirical therapy, receipt of appropriate empirical antimicrobial therapy was associated with lower in-hospital risk of death for 3 pathogen groups (GNR: adjusted odds ratio [aOR], 0.52 [95% CI, 0.42-0.64]; GPC: aOR, 0.60 [95% CI, 0.47-0.78]; Candida species: aOR, 0.43 [95% CI, 0.21-0.87]).



Comment: The investigators found that the proportions of appropriate empirical therapy were generally higher (94.4% for GNRs and 97.0% for GPC) than previous studies. A prior study using the Cerner database from 2005 to 2014, reported that patients infected with resistant organisms were more likely to receive inappropriate empirical antibiotic therapy. [Lancet Infect Dis. 2021; 21:241-251] In the last ID Watch [January 1, 2023] a study was reviewed that provided evidence supporting rapid diagnostic tests' role in antibiotic stewardship and, more importantly, demonstrates improvement in patient outcomes when the pathogen was a resistant GNR [Clin Infect Dis 2022; 75:2066–75] In this paper, the investigators were unable to obtain specific illness severity scores, detailed information on the time to adequate source control, or the time to antimicrobial administration. Lastly, the data sets did not allow them to account for appropriate doses of prescribed antimicrobial agents. Bottom line, advances in diagnostic approaches, including molecular diagnostic testing as well as implementation of ASPs, plays an important role in ensuring that patients receive adequate treatment in a timely fashion.

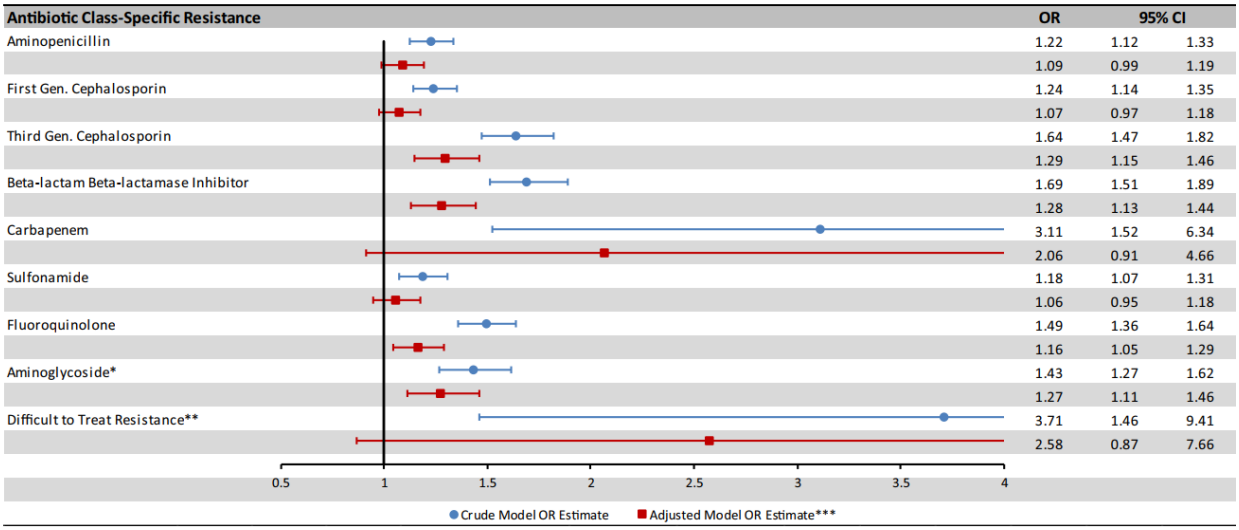
Antimicrobial resistance and mortality following E. coli bacteremia. eClinMed 2023; 56:101781

doi.org/10.1016/j.eclinm.2022.101781

The investigators examined all episodes of E. coli bloodstream infection in Ontario, Canada between 2017 and 2020, and measured 90-day mortality among those with resistant versus sensitive isolates for each of 8 commonly used antibiotic classes and a category of difficult to treat resistance (DTTR). They used multivariable logistic regression to calculate an adjusted odds of mortality associated with AMR, after accounting for patient demographics, comorbidities, and prior healthcare exposure.

Among 14,548 eligible episodes of E. coli BSI, resistance was most common to aminopenicillins (46.8%), followed by first generation cephalosporins (38.8%), fluoroquinolones (26.5%), sulfonamides (24.1%), third generation cephalosporins (13.8%), aminoglycosides (11.7%), beta-lactam-beta-lactamase-inhibitors (9.1%) and carbapenems (0.2%). Only 18 (0.1%) episodes exhibited DTTR. For each class of antimicrobial agents, they detected much higher crude

mortality associated with resistant versus susceptible E. coli. After accounting for patient characteristics including age, sex, comorbidities, test location, and especially healthcare exposure, the associations between resistance and mortality were greatly attenuated but many remained statistically significant. The point estimates for the adjusted odds ratio of AMR associated mortality remained highest for DTTR and individual antibiotic classes most commonly used in empiric treatment (third generation cephalosporins, beta-lactam beta-lactamase inhibitors and carbapenems). See figure below



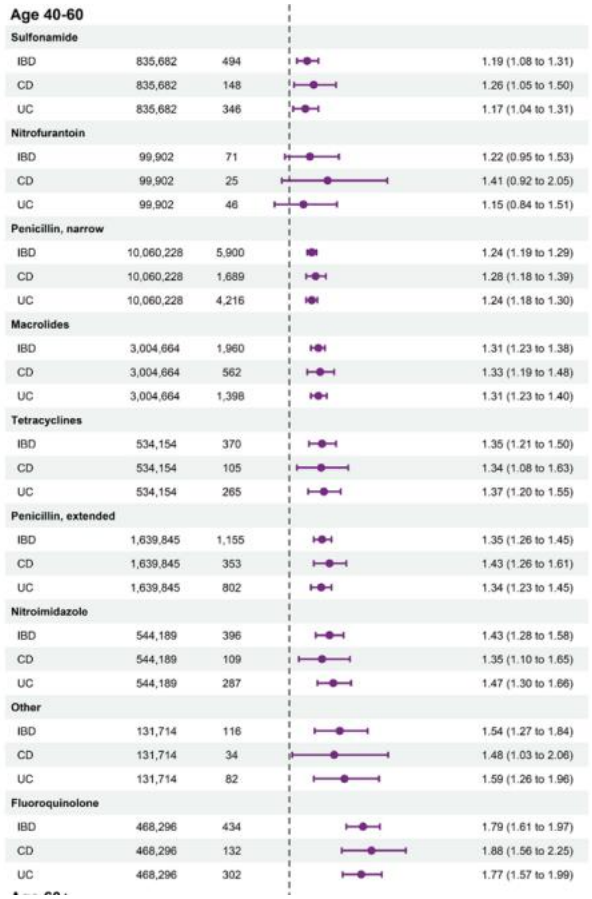
Comment: The study findings bolster the Antimicrobial Resistance Collaboration's current estimate of 1 million deaths per year attributable to AMR, [Lancet. 2022; 399:629–655] by demonstrating a strong association between AMR and mortality. Their analyses are potentially underpowered for carbapenem resistance and DTTR because of low local rates of resistance. Another limitation of this study is lack of access to information on the empiric and targeted antibiotic agents used to treat these BSIs. This information would have been helpful to determine the extent to which selection of inadequate treatment regimens mediates the impact of resistance on outcomes. AMR significantly increased during the pandemic further emphasizing the global and local efforts are essential to help control AMR. Strong ASPs and infection prevention are critical tools in our fight against AMR.

Antibiotic use as a risk factor for inflammatory bowel disease across the ages: a population-based cohort study Gut published online January 9, 2023

doi:10.1136/ gutjnl-2022-327845

Antibiotics have been associated with development of IBD in younger populations, but their influence on IBD risk in adults is uncertain. To assess the impact of antibiotic exposure, including dose–response, timing, and antibiotic class, on the risk of IBD in all individuals aged ≥10 years the investigators used the Denmark nationwide registries, a population-based cohort of residents aged ≥10 years was established between 2000 and 2018. Incidence rate ratios (IRRs) for IBD following antibiotic exposure were calculated using Poisson regression.

There was a total of 6,104,245 individuals, resulting in 87,112,328 person-years of follow-up, and 52,898 new cases of IBD. Antibiotic exposure was associated with an increased risk of IBD as compared with no antibiotic exposure for all age groups, although was greatest among individuals aged 40–60 years and ≥60 years (age 10–40 years, IRR 1.28, 95%CI 1.25 to 1.32; age 40–60 years, IRR 1.48, 95%CI 1.43 to 1.54; age ≥60 years, IRR 1.47, 95%CI 1.42 to 1.53). For all age groups a positive dose–response was observed, with similar results seen for both ulcerative colitis and Crohn's disease. The highest risk of developing IBD was seen 1–2 years after antibiotic exposure, and after use of antibiotic classes often prescribed to treat gastrointestinal pathogens. Nitrofurantoin was the only class of antibiotics not found to be associated with the development of IBD across all age. The highest risk were the nitroimidazoles [mostly metronidazole](age 10–40, IRR 1.31, 95%CI 1.19 to 1.42; age 40–60, IRR 1.43, 95%CI 1.28 to 1.58; age≥60, IRR 1.61, 95%CI 1.41 to 1.83) and FQ (age 10–40, IRR 1.76, 95%CI 1.60 to 1.93; age 40–60, IRR 1.79, 95%CI 1.61 to 1.97; age≥60, IRR 1.54, 95%CI 1.41 to 1.69), which are commonly used to target gastrointestinal pathogens.



Comment: The association between antibiotic exposure and the development of IBD underscores the importance of antibiotic stewardship as a public health priority and suggests the gastrointestinal microbiome as an important factor in the development of IBD, particularly among older adults. although antibiotic classes were obtained, specific indications relating to antibiotic use, as well as the potential pathogen, are not publicly available within the data registries. Although complete data regarding outpatient antibiotic prescriptions can be obtained,

inpatient antibiotic use and medication adherence cannot be confirmed. Although they adjusted for age, sex, time, degree of urbanization, socioeconomic index, PPI use, antiviral and antifungal use, as well as prior antibiotic courses, the possibility of additional confounders may still exist.

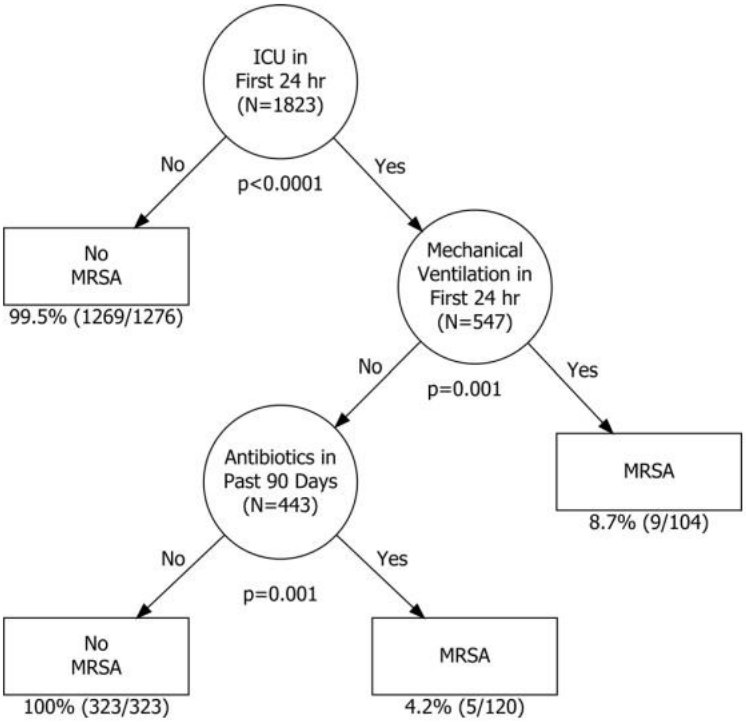
Machine Learning To Stratify Methicillin-Resistant Staphylococcus aureus Risk among Hospitalized Patients with Community-Acquired Pneumonia. Antimicrob Agents Chemotherapy published online December 6, 2022

doi.org/10.1128/aac.01023-22

MRSA is an uncommon but potentially life-threatening cause of CABP (community acquired bacterial pneumonia). While comprising <1% of CABP cases, rates have increased during years when circulating influenza and other respiratory viruses cause a high burden of community illness. IDSA/ATS guidelines offer nebulous recommendations on when MRSA coverage should be included in empiric antibiotic therapy for CABP, resulting in disproportionately high use of vancomycin.

Investigators analyzed electronic health records from 1823 patients hospitalized with CABP at a large academic hospital from 2014 to 2018 [prepandemic], and the data were applied to a machine learning model to obtain early predictive features of MRSA. In all, 21 patients (1.2%) had MRSA in blood or respiratory cultures within 72 hours of admission. Of these 21 cases, 7 were among the 1276 that were *not* admitted to the intensive care unit (ICU) in the first 24 hours (0.5%) and 14 were among the 547 that *were* admitted to the ICU within 24 hours (2.6%). Of those 14 in the ICU, 9 were among the 104 that were intubated within 24 hours (8.7%) and 5 were not ventilated. Of those 5, all had received antibiotics for other indications within 90 days. Of 323 patients who did not receive recent antibiotics, early ICU admission, or early ventilation, none had MRSA.

Data were evaluated using a machine learning approach. Cases were CAP patients with MRSA isolated from blood or respiratory cultures within 72 hours of admission; controls did not have MRSA CAP. The Classification Tree Analysis algorithm was used for model development. Model predictions were evaluated in sensitivity analyses. The final machine learning model was moderately accurate (receiver operating characteristic [ROC] area = 0.775). ICU admission, receipt of mechanical ventilation within 24 hours of admission, and receipt of antibiotics within 90 days are all predictors of MRSA in patients with CABP.



Comment: This study demonstrated that even though MRSA is an uncommon pathogen to cause CABP, patients with severe illness (ICU admission, receipt of mechanical ventilation within 24 hours of admission) are at increased risk for MRSA and antibiotic coverage for MRSA should be considered. The study did not look at seasonality. Along that line, the study could be enhanced by an assessment of the relationship of MRSA pneumonia and respiratory viral infections. The sample size of cases was relatively small.

Defining the Optimal Duration of Therapy for Hospitalized Patients with Complicated Urinary Tract Infections and Associated Bacteremia Clin Infect Dis published online January 12, 2023

DOI: 10.1093/cid/ciad009

This is a retrospective cohort study, looking at 1,099 adult patients treated at 24 US hospitals in 2019 who had gram-negative cUTIs and associated BSIs and received either 7 (265 patients), 10 (382), or 14 (452) days of antibiotic exposure. The primary outcome was recurrent infection up to 30 days after the discontinuation of antibiotic therapy. Propensity scores were generated for an inverse probability of treatment weighted analysis. Highly bioavailable agents included in the highly bioavailable agent category included: (1) ciprofloxacin 500-750 orally every 12 hours, (2) levofloxacin 500-750 orally every 24 hours, (3) trimethoprim-sulfamethoxazole [TMP-SMX] ≥5 mg/kg/day(TMP compenent)[SMX-DS contains 160 mg TMX and 800 mg SMX], (4) amoxicillin 1000 mg PO every 8 hours, (5) amoxicillin clavulanate 875-1000 mg PO every 8 hours, or (6) cephalexin 1000 mg PO every 6 hours.

The most identified pathogens were as follows: E coli (59%), K pneumoniae (16%), P mirabilis (8%), and P aeruginosa (6%); Overall 143 (13%) patients were infected with ESBL-producing organisms.

There was no difference in the odds of recurrent infection for 382 (46%) patients receiving 10 days and 452 (54%) patients receiving 14 days of therapy (aOR 0.99, 95% CI, 0.52-1.87). An increased odds of recurrence was observed in 265 (37%) patients receiving 7 days versus 452 (63%) patients receiving 14 days of treatment (aOR 2.54, 95% CI, 1.40-4.60). When limiting the 7-day versus 14-day analysis to the 627 patients who remained on intravenous beta-lactam therapy or were transitioned to highly bioavailable oral agents, differences in outcomes no longer persisted: aOR 0.76, 95% CI, 0.38-1.52. Of 76 patients with recurrent infections, 2 (11%), 2 (10%), and 10 (36%) in the 7, 10, and 14-day groups, respectively, had drug-resistant infections (p=0.10).

Comment: 7 days of antibiotic therapy was associated with more clinical failures compared to 14 days, except in the subgroup of patients receiving highly bioavailable agents. However, suboptimal dosages were used for most patients transitioned to oral beta-lactam agents. More aggressive dosing may have led to different outcomes. However, the findings still suggest that 7 days of antibiotics may be sufficient for bacteremic patients with cUTI when IV beta-lactams are used for the entire treatment course or when antibiotics are transitioned to highly bioavailable agents. The high bioavailability and sustained serum concentrations of oral fluoroquinolones and TMP-SMX support the basis for these findings, however, resistance to these agents reserve this option for targeted therapy and not empiric therapy. Although FQ and TMP-SMX are associated with adverse events they nonetheless represent an oral option that can enable hospitalized patients to continue care in the outpatient setting and avoid complications from IV catheters. The use of IPTW incorporating propensity scores mitigates – but may not eliminate - baseline differences between treatment groups in observational studies; and differences between treatment groups beyond day 1 which likely influence final treatment durations, are generally not addressed. More data are needed to determine if patients treated with oral beta-lactam agents administered at dosages and frequencies that mimic IV beta-lactam agents can also be successfully treated with 7 days of antibiotics.

Risk Factors Associated With Antimicrobial Resistance and Adverse Short-Term Health Outcomes Among Adult and Adolescent Female Outpatients With Uncomplicated Urinary Tract Infection OFID published online November 21, 2022

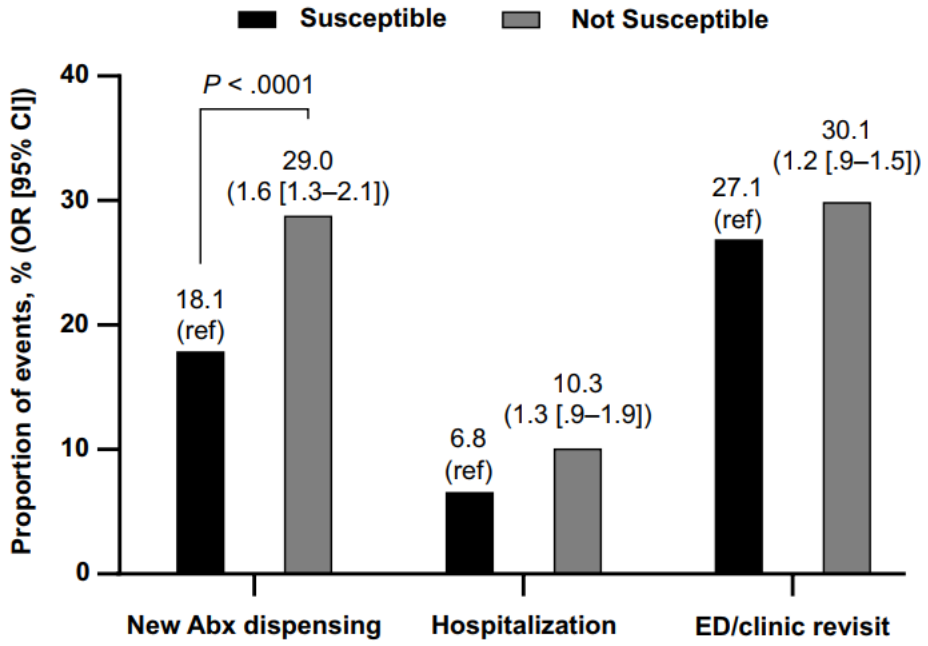
doi.org/10.1093/ofid/ofac623

This is a retrospective cohort study using data from female outpatients aged ≥12 years, with a positive urine culture and dispensing of an oral antibiotic ±1 day from index culture. Isolate susceptibility to the antimicrobial initially dispensed, patient age, and history of antimicrobial exposure, resistance, and all-cause hospitalization within 12 months of index culture were evaluated for associations with adverse outcomes during 28-day follow up. Outcomes assessed were new antimicrobial dispensing, all-cause hospitalization, and all-cause outpatient ED/clinic visits. Urine cultures were collected between January 1, 2015, and December 31, 2019.

Of 2366 uUTIs, 1908 (80.6%) were caused by isolates susceptible and 458 (19.4%) by isolates not susceptible (intermediate/resistant) to initial antimicrobial treatment. Within 28 days, patients

with episodes caused by not susceptible isolates were 60% more likely to receive a new antimicrobial versus episodes with susceptible isolates (29.0% vs 18.1%; 95% confidence interval, 1.3–2.1; *P* < .0001). Other variables associated with new antibiotic dispenses within 28 days were older age, prior antimicrobial exposure, or prior nitrofurantoin nonsusceptible uropathogens (*P* < .05). Older age, prior antimicrobial resistant urine isolates, and prior hospitalization were associated with all-cause hospitalization (*P* < .05). Prior fluoroquinolone resistant isolates or oral antibiotic dispensing within 12 months of index culture were associated with subsequent all-cause outpatient visits (*P* < .05). Patients with ESBL+ isolates at index were more likely to be hospitalized compared with patients with non-ESBL+ isolates, which may have impacted ED and clinic visit results.

E coli was the most common pathogen (78.5%) followed by K pneumoniae (11.3%). Nitrofurantoin (34.3%) was most frequent initially prescribed antimicrobial, followed by TMP/SMX (22.5%), cephalexin (20.4%), and FQ (18.4%).



Comment: This study evaluated the associations between inadequate antibiotic coverage of the organism causing uUTI (where the organism was not susceptible to initial treatment) in female patients. New antimicrobial dispensing within the 28-day follow-up period was significantly more likely in patients who were initially treated with empiric therapy that did not cover the causative pathogen compared with those where initial therapy was adequate for the uropathogen. However, 69% of patients with isolates not susceptible to the antimicrobial dispensed at index did not require a new antimicrobial. This suggests that either many uUTIs are self-limiting or that the high concentration of antibiotics in the urine was sufficient to overcome bacterial resistance in some cases. Since E coli was the most commonly isolated pathogen, rate of isolates that were not susceptible to SXT and FQ in the US has been reported in the 25-30% range yet

~40% of patients initially received either TMP/SMX or a FQ. A recent study found patients with UTIs caused by isolates not susceptible to the antibiotic prescribed were significantly less likely to have their symptoms resolved within 3 days of receipt, compared with patients with susceptible isolates (45% not susceptible vs 67% susceptible) [J Clin Microbiol 2019; 57:e00143–19]. The use of microbiology data to confirm prior nonsusceptible uropathogens, pharmacy prescription history to confirm prior treatments, and records of previous healthcare exposure(s) may help predict non susceptibility. In another recent article, the investigators linked a 10-year longitudinal data set of over 700,000 community-acquired UTIs with over 5,000,000 individually resolved records of antibiotic purchases. They identified strong associations of antibiotic resistance with the demographics, records of past urine cultures and history of drug purchases of the patients. When combined, these associations allow for machine-learning-based personalized drug-specific predictions of antibiotic resistance, thereby enabling drug-prescribing algorithms that match an antibiotic treatment recommendation to the expected resistance of each sample. Applying these algorithms retrospectively, over a 1-year test period, they greatly reduced the risk of mismatched treatment compared with the current standard of care. [Nat Med 2019; 25:1143-1152] Lastly, given that initial uUTIs are typically treated empirically, without the use of urine culture to inform choice of therapy, the inclusion only of patients with a positive urine culture may have biased the study population towards inclusion of patients with recurrent uUTI and potentially a higher percentage of not susceptible isolates, reducing the generalizability of the study results.

Association of Pneumococcal Conjugate Vaccine Use With Hospitalized Pneumonia in Medicare Beneficiaries 65 Years or Older With and Without Medical Conditions, 2014 to 2017. JAMA Intern Med. 2023;183:40-47.

doi:10.1001/jamainternmed.2022.5472

In this cohort study, investigators determined the association between PCV13 use and hospitalization for pneumonia among 24 million Medicare beneficiaries (age, ≥65) between 2014 and 2017. Five million people received PCV13 only, and 11 million received no pneumococcal vaccine; people who received the 23-valent pneumococcal polysaccharide vaccine (PPS23; with or without PCV13) were excluded from this analysis.

The percentage of beneficiaries who received PCV13 increased from 1% in 2014 to 42% in 2017. After adjustment for comorbidities, PCV13 use was associated with relative reductions of 6.7% for hospitalized pneumonia, 4.7% for hospitalized non–healthcare-associated pneumonia, and 5.8% for hospitalized lobar pneumonia. It was estimated that PCV13 use averted an estimated 35,000 hospitalizations for pneumonia, 25,000 hospitalizations for non–healthcare-associated pneumonia, and 1300 hospitalizations for lobar pneumonia, with the largest number of averted cases among participants with immunocompromising and chronic medical conditions.

Comment: This study results suggest that PCV13 use was associated with reduced pneumonia hospitalization among Medicare beneficiaries 65 years or older, many of whom had underlying medical conditions. In late 2021, the ACIP recommended PCV15 followed by PPS23 or PCV20 alone in adults ≥65 and in younger adults with certain underlying chronic medical conditions. [Ann Intern Med 2022; 175:432] It is hoped that the use of the newer vaccines will further decrease the risk of pneumonia is older adults. Misclassification of PCV13 vaccination

status, including missing doses given outside of Medicare Part A or B settings, remains a possibility, which could bias the VE estimates toward the null. As with any observational study, and especially those using administrative data, residual confounding may be present due to unmeasured factors, despite adjustment made for several potential confounders.

Proposed HHS National Action Plan

HHS has proposed new 5-year targets for reduction rates for certain HAIs. All goals will begin with 2023 as the baseline year with the goals achieved by 2028. The proposed HAI reduction rates are:

- Reduce central line-associated bloodstream infections (CLABSI) in intensive care units and ward-located patients by 40% from 2023-2028
- Reduce catheter-associated urinary tracts infections (CAUTI) in intensive care units and ward-located patients by 25% from 2023-2028
- Reduce hospital-onset MRSA bacteremia by 40% from 2023-2028
- Reduce hospital-onset *Clostridioides difficile* infections (CDI) by 20% from 2023-2028

HHS is not recommending an SSI target due to the instability of SSI data collection in 2020-2022.

Comment: Up until the Covid-19 pandemic there was significant progress in reducing HAIs. However, the pandemic resulted in extraordinary challenges for infection prevention in hospitals. Increases HAIs were observed throughout 2020 and 2021 as hospitals responded to increased patient volumes, increased patient acuity levels, and staffing challenges. The Compendium is being updated with 2 section already published [CLABSI and VAP; NV-HAP) Now that Covid-19 is entering into a different phase, I hope we can return to basics and apply evidenced-based strategies to reduce HAIs.

Antibiotic concentrations and antibiotic resistance in aquatic environments of the WHO Western Pacific and South-East Asia regions: a systematic review and probabilistic environmental hazard assessment Lancet Planet Health 2023; 7: e45–54

The investigators examined the levels of antibiotic residues that are likely to contribute to antibiotic resistance from different aquatic sources in the Western Pacific Region (WPR) and the South-East Asia Region (SEAR), regions as defined by the World Health Organization. These regions include China and India, which are among the world's largest producers and consumers of antibiotics.

The investigators then performed a systematic review of the literature published between 2006 and 2019, including 218 relevant reports from the WPR and 22 from the SEAR. They also used a method called Probabilistic Environmental Hazard Assessment to determine where the concentration of antibiotics is high enough to likely contribute to antibiotic resistance.

Ninety-two antibiotics were detected in the WPR, and forty-five in the SEAR. Antibiotic concentrations exceeding the level considered safe for resistance development (Predicted No Effect Concentrations, PNECs) were observed in wastewater, influents and effluents of wastewater treatment plants and in receiving aquatic environments. The highest risk was

observed in wastewater and influent of wastewater treatment plants. The relative impact of various contributors, such as hospital, municipal, livestock, and pharmaceutical manufacturing was also determined.

In receiving aquatic environments, the highest likelihood of levels exceeding the threshold considered safe for resistance development was observed for the antibiotic ciprofloxacin in drinking water in China and the WPR.

Comment: Antibiotic residues in wastewater and wastewater treatment plants may serve as hot spots for the development of antibiotic resistance in these regions and pose a potential threat to human health through exposure to different sources of water, including drinking water. Limitations to be considered when interpreting the results are the lack of data on the environmental occurrence of antibiotics from many of the countries in the regions and the fact that only studies written in English were included. Nonetheless this maybe another target for wastewater surveillance. In addition if confirmed in other countries, this might help in prioritizing future areas of research on antibiotics and antibiotic resistance in aquatic environments.

Uganda's Ebola Outbreak

The WHO on January 11th declared the latest Ebola epidemic in Uganda over, closing the chapter on a deadly outbreak that lasted nearly four months and killed dozens of people. The outbreak had spread to nine districts, including the capital, Kampala, raising fears of its snowballing across the East African region. It was the worst Ebola outbreak in Uganda in more than two decades, and the second deadliest in the country's history, with 142 confirmed cases and 55 deaths, and an additional 22 deaths also linked to the outbreak, according to the W.H.O. Seven of those who died were health workers.

Comment: The WHO considers an epidemic over when no confirmed or probable cases are reported for 42 days, twice the incubation period for Ebola infections. I think we are all relieved.

FDA OKs Tdap Shot in Pregnancy to Protect Newborns From Pertussis

The FDA has approved another Tdap vaccine option for use during pregnancy to protect newborns from pertussis. The agency on January 9th licensed Adacel (Sanofi Pasteur) for immunization during the third trimester to prevent pertussis in infants younger than 2 months old. The FDA in October approved a different Tdap vaccine, Boostrix (GlaxoSmithKline), for this indication. Boostrix was the first vaccine specifically approved to prevent a disease in newborns whose mothers receive the vaccine while pregnant.

The CDC recommend that women receive a dose of Tdap vaccine during each pregnancy, preferably during gestational weeks 27-36 – and ideally toward the earlier end of that window – to help protect babies from *Bordetella pertussis*.

Comment: Acellular pertussis vaccine if given in the third trimester confers passive immunity to the baby. It also reduces the likelihood that the mother will get pertussis and pass it on to the

infant. Studies have found that providing Tdap vaccination during gestational weeks 27-36 was 85% more effective at preventing pertussis in infants younger than 2 months old, compared with providing Tdap vaccination to mothers in the hospital postpartum. [Clin Infect Dis 2017; 64:3–8]

Vaccination Coverage with Selected Vaccines and Exemption Rates Among Children in Kindergarten — United States, 2021–22 School Year MMWR 2023; 72;26–32

This report summarizes data collected by state and local immunization programs on vaccination coverage and exemptions to vaccination among children in kindergarten in 49 states and the District of Columbia and provisional enrollment or grace period status for kindergartners in 27 states for the 2021–22 school year.

Nationwide, vaccination coverage with 2 doses of MMR was 93.5%; with the state-required number of DTaP doses was 93.1%; with poliovirus vaccine was 93.5%; and with the state-required number of varicella vaccine doses was 92.8%. Compared with the 2020–21 school year, vaccination coverage decreased 0.4–0.9 percentage points for all vaccines. Although 2.6% of kindergartners had an exemption for at least one vaccine, an additional 3.9% who did not have an exemption were not up to date with MMR.

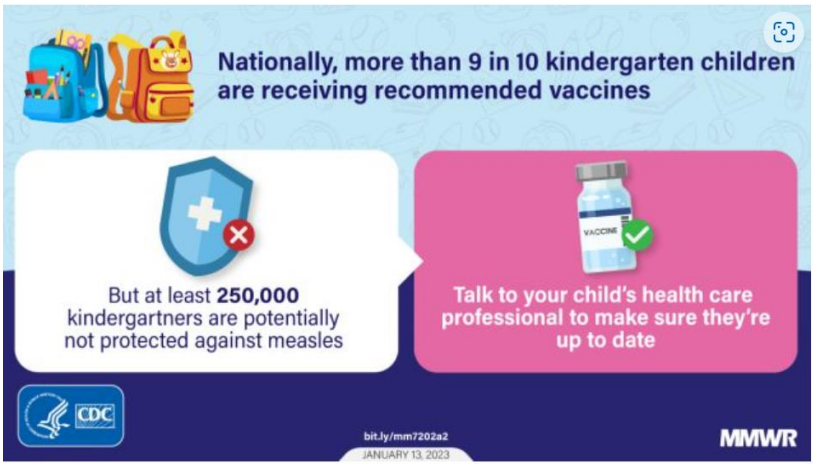
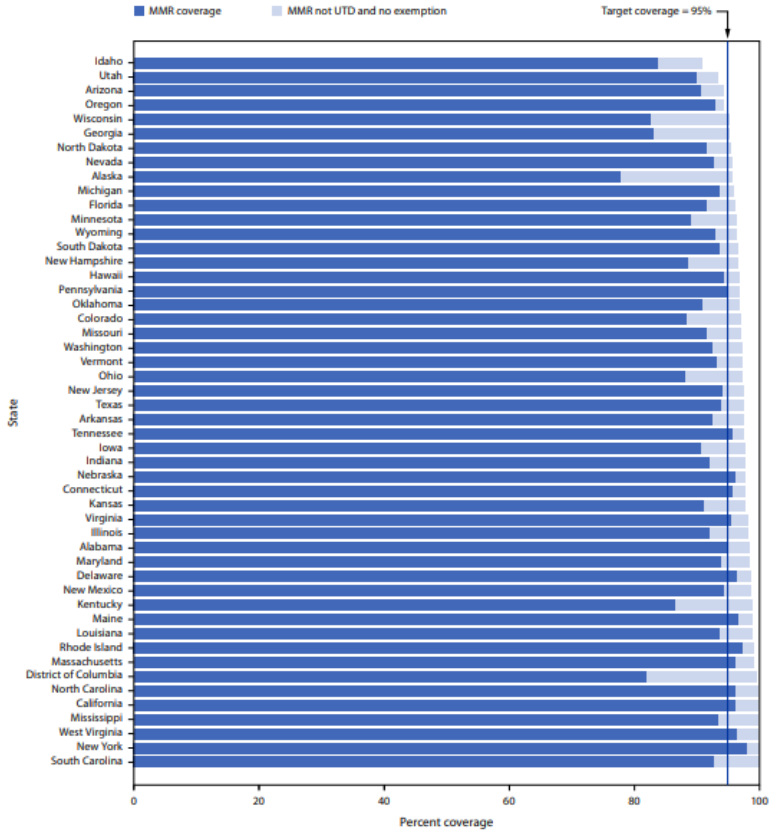


FIGURE 2. Potentially achievable coverage*,† with measles, mumps, and rubella vaccine among kindergartners, by state — United States, 2021–22 school year



Comment: Despite widespread return to in-person learning, Covid-19–related disruptions continued to affect vaccination coverage and assessment for the 2021–22 school year, preventing a return to prepandemic coverage. Vaccination coverage among kindergarten students remains below prepandemic levels; pockets of under vaccinated children within larger areas of high vaccination coverage can lead to outbreaks. We have seen outbreaks of measles in Ohio and polio in NY in under vaccinated populations. This is another unintended consequence of the pandemic.

Moderna Reports RSV Vaccine Cuts Risk of Respiratory Diseases in Older Adults

Moderna's Phase 3 trial, which started early last year, enrolled about 37,000 people ages 60 and older in 22 countries including the US. About half were given a single dose of Moderna's RSV vaccine, and others received a placebo. Moderna's vaccine was 82.4% effective at preventing severe RSV cases with three or more symptoms present. Vaccine's efficacy appeared to hold up for at least six months and could be longer pending follow-up analyses. Researchers found that using a certain method to target a protein on the surface of the virus could be effective at triggering the desired immune response.

Comment: Unlike influenza and Covid-19, there is no approved vaccine against RSV. Each year RSV infections result in about 58,000 hospitalizations of children under 5 years old and

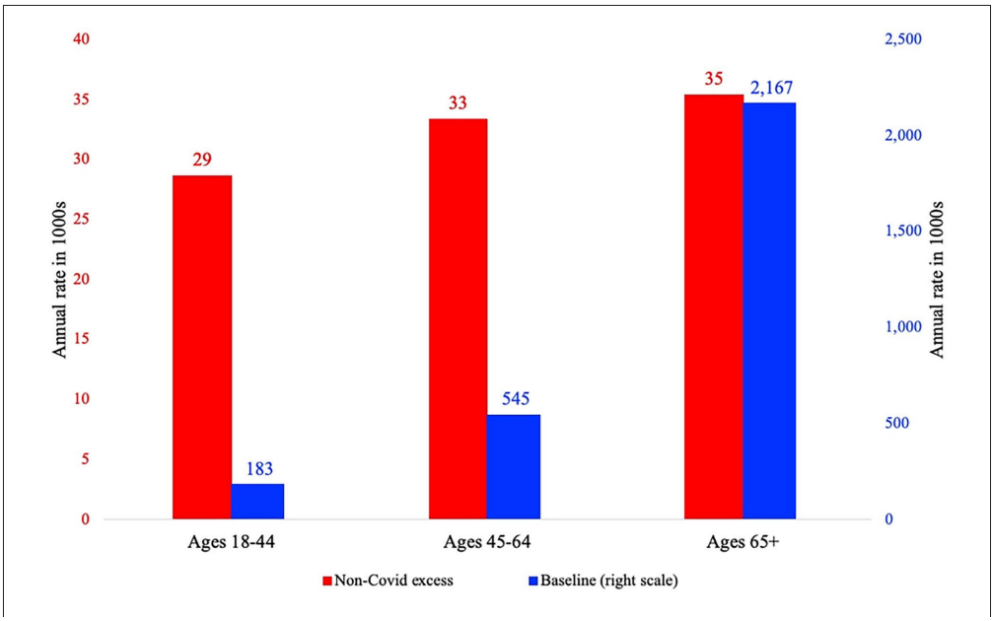
177,000 hospitalizations of adults 65 and older, according to the CDC. While most children survive, RSV still kills up to 500 children in the US each year and about 14,000 older adults annually. Moderna envisions the RSV vaccine as a once-yearly shot ahead of the typical RSV season in the fall and winter in the Northern Hemisphere. GSK, Pfizer, and Johnson & Johnson are also developing RSV vaccines. Pfizer and GSK have applied for FDA approval of their respective RSV vaccines in adults 60 and older and expect FDA decisions in May. Meanwhile, Sanofi and AstraZeneca have co-developed an antibody-based drug to be used for the prevention of RSV in infants. They applied for FDA approval of the drug and expect a decision in the third quarter of 2023.

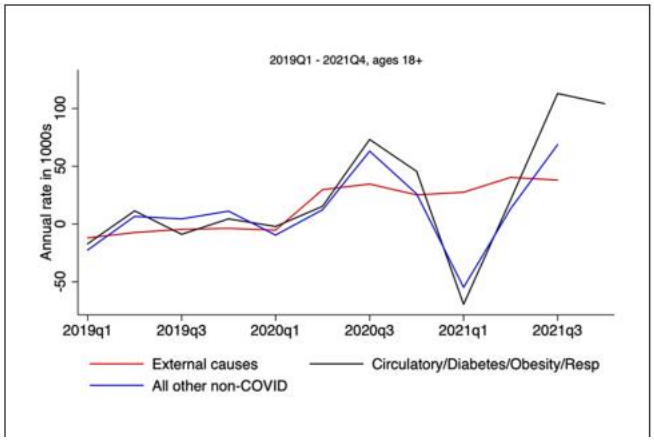
The Young were not Spared: What Death Certificates Reveal about Non-Covid Excess Deaths. J Health Care published online December 15, 2022 suggested by Joe Anzaldua

doi.org/10.1177/00469580221139016

The investigators used monthly fatalities are measured using the on-line CDC Wonder tools, sponsored by the CDC, for tabulating every death certificate filed with a US state or District of Columbia. States provide the death certificates to the CDC on a rolling basis.

During the first two years of the pandemic, “excess deaths”—the death toll above the historical trend—markedly exceeded the number of deaths attributed to Covid-19. From April 2020 through at least the end of 2021, Americans died from non-Covid causes at an average annual rate of 97 000 more than previous trends. Hypertension and heart disease deaths combined were elevated 32,000. Diabetes or obesity, drug-induced causes, and alcohol-induced causes were each elevated 12,000 to 15,000 above previous trends. Drug deaths especially followed an alarming trend, only to significantly exceed it during the pandemic to reach 108,000 for calendar year 2021. Homicide and motor-vehicle fatalities combined were elevated almost 10,000. However, Covid-19 deaths did disproportionately afflict senior citizens. Absolute numbers of non-Covid-19 excess deaths are similar for each of the 18 to 44, 45 to 64, and over-65 age groups, with essentially no aggregate excess deaths of children. Mortality from all causes during the pandemic was elevated 26% for working-age adults (18-64), as compared to 18% for the elderly.





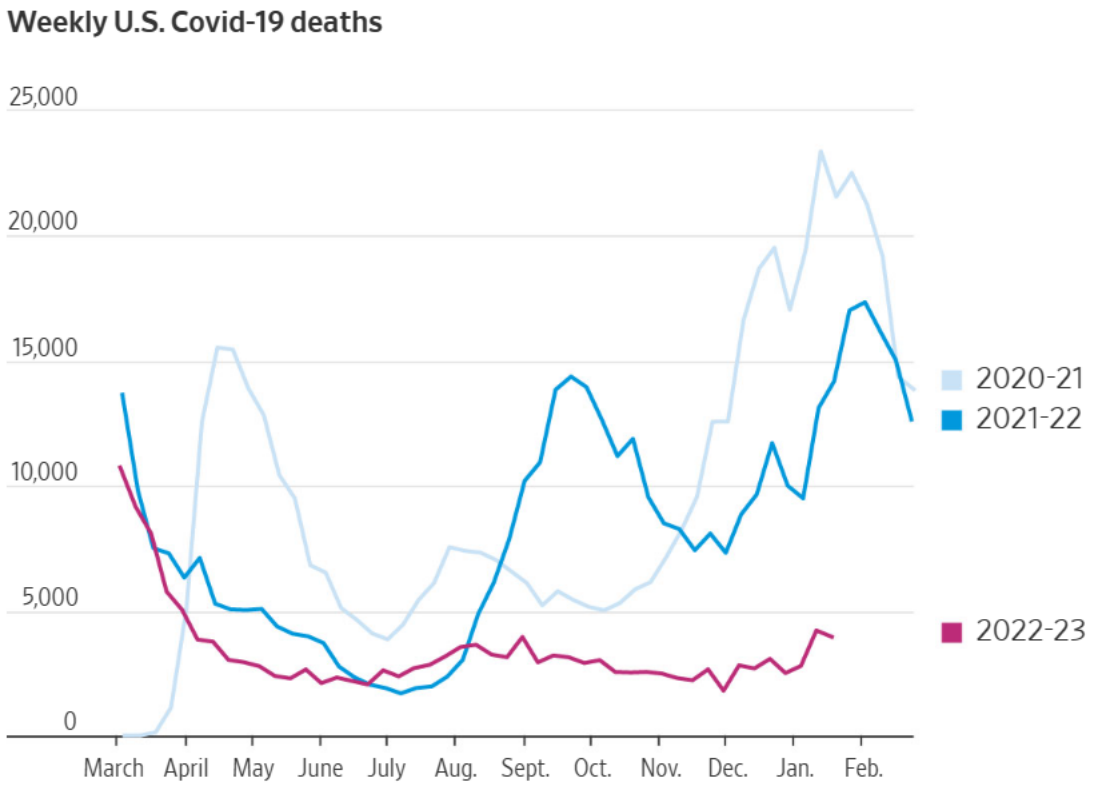
Comment: While deaths from hypertension, heart disease and diabetes dominate non-Covid-19 excess deaths for senior citizens, the other causes—accidents, overdoses, alcoholism and homicide—skew younger, poorer and with a disproportionate effect on minorities. It also bears mention that these young-adult deaths, running 27% above historical trends, The CDC data show the rate of non-Covid-19 excess deaths in the first half of 2022 was even higher than 2020 or 2021. These deaths disproportionately among young adults. Other data on drug addictions, non-fatal shootings, weight gain, and cancer screenings point to a historic, yet largely unacknowledged, health emergency. What we are witnessing are multiple healthcare crises, but resources and attention are still directed toward Covid-19. We have seen the same patterns in increased HAIs as resources were directed at Covid-19 and away from basic evidenced-based practices. The pandemic response involved wholesale disruption of ordinary life. Now that we are in a different phase of the pandemic, the public-health community should pivot and focus on its effects on the millions of Americans we knew suffered from drug addiction, diabetes, and many other potentially lethal health conditions. The time is now to begin to alleviate the collateral damage from Covid-19 policies.

COVID-19

VII Commentary-Covid-19 Year 4

As we enter the fourth of the pandemic where do things stand.

- Despite a recent climb in hospitalizations and Covid-19 wastewater surveillance reports—two key measures that predict trends—it now appears to have leveled off and even beginning to decline even following the quick rise of the Omicron XBB.1.5 subvariant. In fact, wastewater now shows a downward trend nationally in recent weeks following an upswing during the holiday season. These wastewater declines include the Northeast, where XBB.1.5 has been most prevalent.
- We are in a very different place in part due to significant community immunity due to natural infection and/vaccination.
- Winters have been the deadliest: In January 2021, the US reached a peak of nearly 23,400 deaths reported in a single week, according to the CDC. The second-most deadly surge came about a year later, when the CDC reported about 17,350 deaths in the week of February 2, 2022. Reported deaths have trended slightly up lately, tracking the recent increase in infections, but the most recent weekly tally was about 3,950, according to the CDC, about 72% lower than a year ago.



- The seven-day average for patients in hospitals with confirmed Covid-19 was about 33,870 on Thursday, down from levels above 41,000 as recently as January 9th comparted to levels of more than 151,000 at the same time last year. New Covid-19-

positive patient admissions have also been declining. These numbers include many patients hospitalized with Covid-19 not because of Covid-19 (test positive during routine screening but admitted for other reasons). (See Washington Post article below)

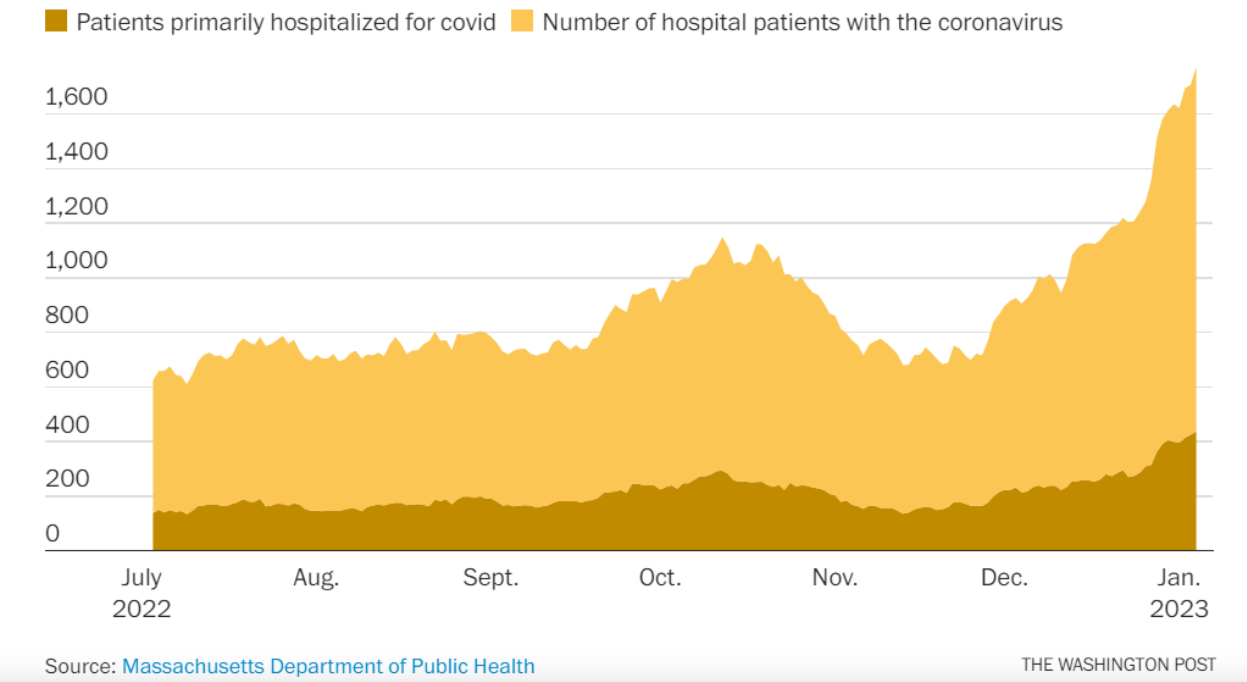
- The virus has had other impact beyond Covid-19 infections. Here are a few:
    - Drug overdoses have surged to record numbers
    - Increased mental illnesses
    - Stress from pandemic has contributed to rising crime
    - Learning loss for our children in schools
    - Increased deaths due to chronic disease and lower life expectancy
    - HCW burnout leading to staffing shortages

Additional Comment: Despite the fact we are in a much better place than last year, the virus is not done with us quite yet. We all have Covid-19 fatigue. Vaccine uptake for the bivalent booster has been inadequate and politics and consistent messaging is holding us back. Beyond boosters, the use of medical grade masks for high-risk individuals in public indoor settings, testing before large gatherings, stay home if sick, improved ventilation and filtration are other tools we have to reduce risk of infection. (See updated WHO Guidelines below)

On a good note, hospitalization rates for both influenza and RSV, have also dropped in the past several weeks.

Are Americans dying from Covid-19 or with Covid-19? Washington Post January 13, 2023

The data from Massachusetts is an example. Massachusetts changed its hospitalization reporting a year ago to include both total hospitalizations with Covid-19 and those that received dexamethasone as a good surrogate measure for hospitalizations due to the Covid-19. In recent months, only about 30 percent of total hospitalizations with Covid-19 were primarily attributed to the virus. -see graph below



Comment: Earlier in the pandemic, a large proportion of Covid-19-positive hospitalizations were due to Covid-19. But as more people developed some immunity through vaccination and/or natural infection, fewer patients were hospitalized because of it. This is a gray zone in the data in which Covid-19 might not be the primary cause of death but could have contributed to it. To be clear even if the Covid-19 death count turns out to be 30-50% of what's currently reported, that's still too high.

WHO's Covid-19 updated guidelines. January 13, 2023

- WHO has said that if Covid-19 patients are displaying symptoms of the virus they will have to be isolated for at least 10 days from the date of onset of the symptoms
    - WHO also states that if a Covid patient tests negative with an antigen-based rapid test, they can be discharged early from isolation
    - Asymptomatic Covid patients or individuals who have tested positive for the virus, but do not experience any symptoms, should be isolated for 5 days
- The WHO recommends the use of masks irrespective of the local epidemiological situation, given the current spread of the Covid-19 globally. WHO also says that one should wear masks in the following situations:
    - If one has recently been exposed to Covid-19
    - When someone has or suspects they have Covid-19
    - When someone is at high-risk of severe Covid-19
    - Anyone in a crowded, enclosed, or poorly ventilated space
- WHO has extended its strong recommendation for the use of nirmatrelvir-ritonavir
- WHO also reviewed the evidence on two other medicines, sotrovimab and casirivimab-imdevimab, and maintains strong recommendations against their use for treating Covid-19

US renews health emergency.

HHS today renewed the public health emergency for Covid-19 that has been in place since January 2020 and has now been extended again.

Comment: What this action indicates is that Covid-19 is not done with us yet!

NIH Updates Regarding the Use of Bebtelovimab December 28, 2022

Due to the increasing prevalence of SARS-CoV-2 Omicron subvariants that are anticipated to be resistant to bebtelovimab (i.e., BQ.1, BQ.1.1, XBB), bebtelovimab is not currently authorized by the FDA for the treatment of COVID-19 in any region of the US. The Panel **recommends against** the use of **bebtelovimab** for the treatment of nonhospitalized patients with COVID-19 who are at high risk of progressing to severe COVID-19 **(AIII)**

Activity of Select Monoclonal Antibodies Versus Omicron

Neutralization color coding is based upon synthesized available data regarding change in in vitro neutralization relative to that of an ancestral variant: green <10-fold reduction, yellow 10-100-fold reduction, orange >100-fold reduction.

Change in neutralizing activity adapted from NIH COVID-19 Treatment Guidelines.

Lineage	Tixagevimab and cilgavimab (Evusheld®) in vitro neutralization	Bebtelovimab in vitro neutralization
BA.5†		
BQ.1*		
BA.4		
BA.4.6		
BA.2†		
XBB*		
BA.1 BA.1.1		

In vitro activity may not correlate to real-world effectiveness and is only one component of clinical decision-making.

†Sublineages exhibiting additional mutations such as at spike positions 346, 444, 460, and/or 486 (e.g., BA.2.75.2, BN.1 [a BA.2 sublineage], or BF.7 [a BA.5 sublineage]) may show further in vitro immune evasion of tixagevimab and cilgavimab.

*This asterisk denotes that the category encompasses other members of the sublineage (such as BQ.1.1 and XBB.1.5).

This resource was funded in part by a cooperative agreement with the Centers for Disease Control and Prevention (grant number NU50CK000574). The Centers for Disease Control and Prevention is an agency within the Department of Health and Human Services (HHS). The contents of this resource do not necessarily represent the policy of CDC or HHS, and should not be considered an endorsement by the Federal Government.

COVID-19 Real-Time Learning Network
Brought to you by CDC and IDSA

Comment: Tixagevimab plus cilgavimab (Evusheld) is still the only anti-SARS-CoV-2 mAb product that is currently authorized for use as pre-exposure prophylaxis (PrEP) in people who are not expected to mount an adequate immune response to Covid-19 vaccination or those with contraindications for Covid-19 vaccines. Many Omicron subvariants, including the dominant Omicron subvariants in the US, are less susceptible to tixagevimab plus cilgavimab. The FDA said they did not expect Evusheld to provide protection against the XBB.1.5 variant. In the absence of an alternative option for PrEP, the NIH Panel still recommends the use of tixagevimab 300 mg plus cilgavimab 300 mg administered as 2 consecutive 3-mL intramuscular (IM) injections **(BIIb)** as SARS-CoV-2 PrEP for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection and who have not been recently exposed to an individual with SARS-CoV-2 infection. The decision to administer tixagevimab plus cilgavimab should be based on the regional prevalence of the resistant subvariants. Individuals who received tixagevimab plus cilgavimab as PrEP should continue to

take precautions to avoid infection. If they experience signs and symptoms consistent with Covid-19, they should be tested for SARS-CoV-2 and, if infected, promptly seek medical attention to see if they are eligible for antiviral treatment such as ritonavir-nirmatrelvir**.**

CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older January 13, 2023

Following the availability and use of the updated (bivalent) Covid-19 vaccines, CDC's Vaccine Safety Datalink (VSD), a near real-time surveillance system, met the statistical criteria to prompt additional investigation into whether there was a safety concern for ischemic stroke in people ages 65 and older who received the Pfizer bivalent Covid-19 Vaccine. Rapid-response investigation of the signal in the VSD raised a question of whether people 65 and older who have received the Pfizer Covid-19 Vaccine, Bivalent were more likely to have an ischemic stroke in the 21 days following vaccination compared with days 22-44 following vaccination. This preliminary signal has not been identified with the Moderna bivalent Covid-19 Vaccine.

There may be other confounding factors contributing to the signal identified in the VSD that merit further investigation. Furthermore, it is important to note that, to date, no other safety systems have shown a similar signal and multiple subsequent analyses have not validated this signal. See below

- A large study of updated (bivalent) vaccines (from Pfizer and Moderna) using the CMS database revealed no increased risk of ischemic stroke.

- A preliminary study using the Veterans Affairs database did not indicate an increased risk of ischemic stroke following an updated (bivalent) vaccine.
- The Vaccine Adverse Event Reporting System (VAERS) managed by CDC and FDA has not seen an increase in reporting of ischemic strokes following the updated (bivalent) vaccine.
- Pfizer's global safety database has not indicated a signal for ischemic stroke with the updated (bivalent) vaccine.
- Other countries have not observed an increased risk for ischemic stroke with updated (bivalent) vaccines.

Comment: CDC continues to recommend that everyone ages 6 months of age and older stay up to date with Covid-19 vaccination; this includes individuals who are currently eligible to receive an updated (bivalent) vaccine. Preliminary Data have shown an updated Covid-19 vaccine reduces the risk of hospitalization from Covid-19 by nearly 3-fold compared to those who were previously vaccinated but have not yet received the updated vaccine especially in the elderly and high-risk population. CDC and FDA will continue to evaluate additional data from

these and other vaccine safety systems. These data and additional analyses will be discussed at the upcoming January 26th meeting of the FDA's Vaccines and Related Biological Products Advisory Committee.

Based on above data sets (CMS, VA, VAERS etc.), it seems unlikely that the signal in VSD represents a true clinical risk, however, I agree with decision to be transparent and honest with the public. The challenge is to be honest without causing additional fear and confusion.

Combined IDSA/SHEA Statement: U.S. Must Consider Broader Measures to Mitigate COVID-19 Transmission January 5, 2023

The US government's new policy of requiring pre-flight Covid-19 testing for all travelers from China will likely have limited impact on transmission and will not provide the necessary data to fully assess the increasing number of cases globally. In addition, the policy could unintentionally fuel anti-Asian bias and xenophobia.

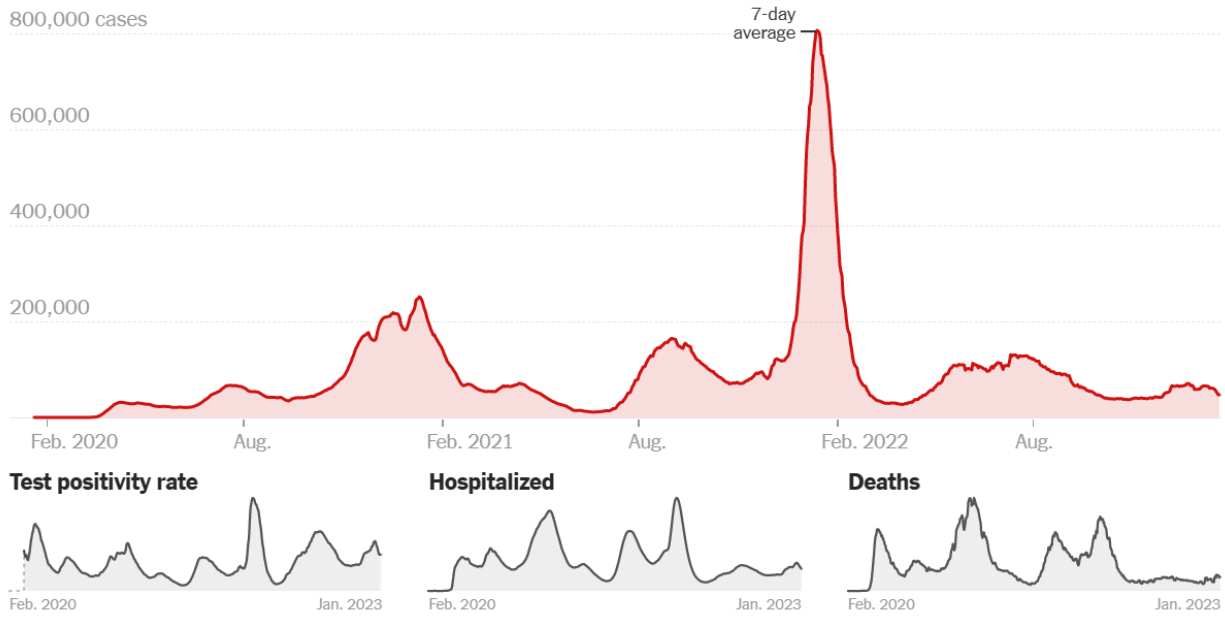
To improve surveillance and obtain more useful data, the Administration should consider expanding broader testing strategies that are not defined by a narrow geographic scope. However, testing alone is unlikely to prevent transmission of the virus in the US.

As Covid-19 and other respiratory viruses continue to affect our communities and strain hospitals this winter, it is critical that we continue to protect ourselves and others by practicing basic public health precautions: stay home when ill, get all recommended vaccinations and boosters, and mask when appropriate.

The CDC, the Biden Administration and governors across the country should also be prepared to strengthen mitigation measures as necessary if the situation continues to worsen. In addition, it is critical that the Biden Administration continue its efforts to improve our diplomatic communications with China to ensure transparency regarding Covid-19 infection data.

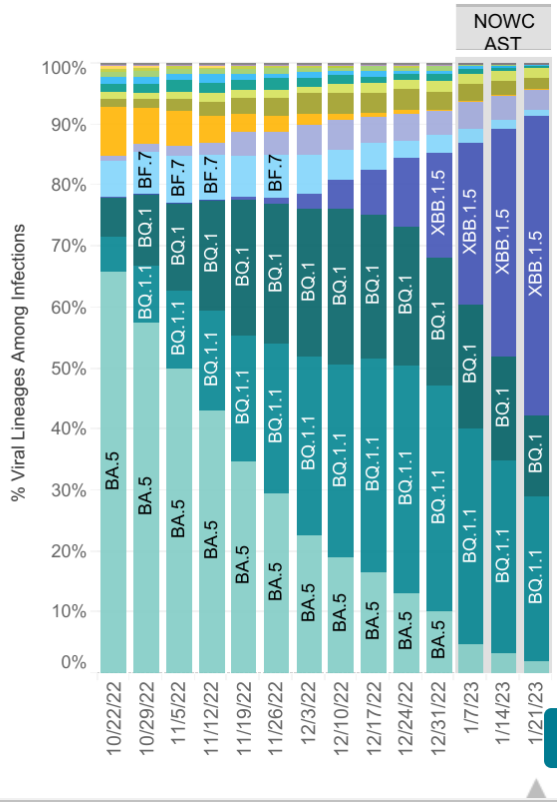
Comment: This is a timely statement and supports the ID Watch comment from January 1, 2023: "We have tried testing and travel restrictions in the past with questionable success." ID Watch continues to recommend being up to date with vaccinations, staying home when ill, and masking in public indoor settings especially if you are in a high-risk group.

COVID-19 by the Numbers



USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	XBB.1.5	VOC	49.1%	37.5-60.8%
	BQ.1.1	VOC	26.9%	20.9-33.9%
	BQ.1	VOC	13.3%	10.1-17.4%
	XBB	VOC	3.3%	2.7-4.1%
	BA.5	VOC	2.0%	1.5-2.8%
	BN.1	VOC	1.8%	1.4-2.5%
	BA.2.75	VOC	1.6%	1.2-2.2%
	BF.7	VOC	1.0%	0.8-1.4%
	BA.5.2.6	VOC	0.4%	0.3-0.5%
	BA.2	VOC	0.2%	0.1-0.3%
	BF.11	VOC	0.2%	0.1-0.2%
	BA.4.6	VOC	0.1%	0.0-0.1%
	BA.2.75.2	VOC	0.0%	0.0-0.1%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.4	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%



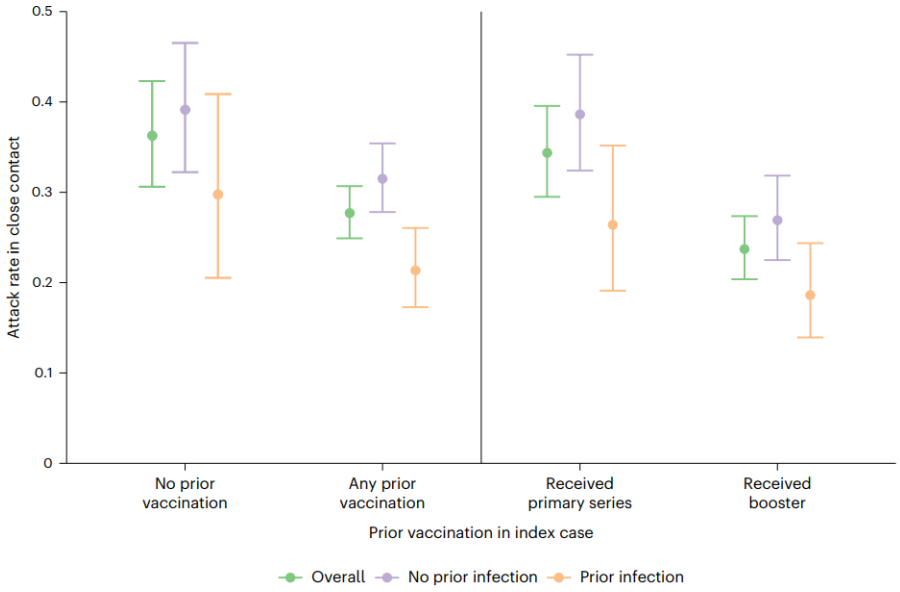
Comment: Although XBB.1.5 is gaining prevalence nationwide, Covid-19 cases are flat and hospitalizations have dipped. In the last two weeks, daily average Covid-19 cases have sat at 18 per 100,000, while hospitalizations have decreased by 8 percent. Covid-19 hospital admissions are projected to remain stable or have an uncertain trend over the next four weeks, with 2,500 to 13,100 new daily admissions likely to be reported on February 3rd, according to the CDC's forecast from 14 modeling groups. A high level of population immunity, paired with an uptick in public health awareness amid the severe virus season, may have helped the US avoid a significant winter surge.

Infectiousness of SARS-CoV-2 breakthrough infections and reinfections during the Omicron wave. Nat Med published online January 2, 2023

doi.org/10.1038/s41591-022-02138-x

Investigators studied 111,687 inmates in 35 prisons populated mostly by men (97%) from Dec 15, 2021, to May 20, 2022. Despite 81% uptake of the primary COVID-19 vaccine series, breakthrough infections were common. The rate of severe disease was low, however; of the 22,334 inmates tested positive, only 31 were hospitalized, and none died.

Unvaccinated, infected inmates had an estimated 36% risk of spreading the virus, compared with 28% among infected vaccinees. After adjustment, any vaccination, previous infection alone, and both vaccination and previous infection cut the risk of SARS-CoV-2 transmission by 22%, 23%, and 40%, respectively. Booster doses and more recent vaccination further lowered contagiousness among vaccinated inmates, with each dose conferring an 11% risk reduction; the risk of transmission rose 6% for every 5 weeks that had elapsed since the last shot.



Comment: Only 59% of inmates and 41% of staff were up to date with vaccination and only 73% of them had completed the primary series. This study underscores the benefit of vaccination to reduce, but not eliminate, transmission in congregant living.

Protection against symptomatic infection with delta (B.1.617.2) and omicron (B.1.1.529) BA.1 and BA.2 SARS-CoV-2 variants after previous infection and vaccination in adolescents in England, August, 2021–March, 2022: a national, observational, test-negative, case-control study.

Lancet Infect Dis published online November 24, 2022

doi.org/10.1016/ S1473-3099(22)00729-0

The investigators conducted an observational, test-negative, case-control study using national SARS-CoV-2 testing and COVID-19 mRNA vaccination data in the UK. Symptomatic adolescents aged 12–17 years who were unvaccinated or had received primary Pfizer immunization at symptom onset and had a community SARS-CoV-2 PCR test were included. Vaccination and previous SARS-CoV-2 infection status in adolescents with PCR-confirmed COVID-19 (cases) were compared with vaccination and previous infection status in adolescents who had a negative SARS-CoV-2 PCR test (controls). Vaccination data were collected from the National Immunization Management System and were linked to PCR testing data. The primary outcome was protection against SARS-CoV-2 delta and omicron infection.

Between August 9, 2021, and March 31, 2022, 1, 161,704 SARS-CoV-2 PCR tests were linked to COVID-19 vaccination status, including 390467 positive tests with the delta variant and 212,433 positive tests with the omicron variants BA.1 and BA.2. In unvaccinated adolescents, previous SARS-CoV-2 infection with wildtype, alpha (B.1.1.7), or delta strains provided greater protection against subsequent delta infection (>86·1%) than against subsequent omicron infection (<52.4%); previous delta or omicron infection provided similar protection against omicron reinfection (52·4% [95% CI 50·9–53·8] vs 59·3% [46·7–69·0]). In adolescents with no previous infection, vaccination provided lower protection against omicron infection than against delta infection, with omicron protection peaking at 64·5% (95% CI 63·6–65·4) at 2–14 weeks after dose two and 62.9% (60.5–65.1) at 2–14 weeks after dose three, with waning protection after each dose. Adolescents with hybrid immunity from previous infection and vaccination had the highest protection, irrespective of the SARS-CoV-2 strain in the primary infection. The highest protection against omicron infection was observed in adolescents with vaccination and previous omicron infection, reaching 96.4% (95% CI 84.4–99.1) at 15–24 weeks after vaccine dose two.

Comment: This study for the first time in adolescents, demonstrated the additional protection afforded by hybrid immunity. This study is consistent with emerging literature in adults, which has demonstrated that hybrid immunity provided the most robust protection against SARS-CoV-2 infection [N Engl J Med 2022; 386: 2201–12; N Engl J Med 2022; 387: 21–34]. Vaccination provides low-to-moderate protection against symptomatic omicron infection, with waning protection after each dose, while hybrid immunity provided the most robust protection. Because most adolescents were vaccinated before omicron began circulating, they were unable to assess protection beyond 2–14 weeks after one vaccine dose for this cohort. It is possible, due to using real-world data, that differences not adjusted for in their multivariable analysis might be present between groups compared, as well as differences in behaviors in those who were

tested versus those who chose not to test when unwell. Although more data are needed to investigate longer-term protection and protection against infection with new variants [now BQ and XBB], these data question the need for additional booster vaccine doses for adolescents in populations with already high protection against SARS-CoV-2 infection. We need to consider natural/hybrid immunity in our guidance.

Enhanced transmissibility of XBB.1.5 is contributed by both strong ACE2 binding and antibody evasion bioRxiv posted January 3, 2023

doi.org/10.1101/2023.01.03.522427

XBB.1.5 is growing rapidly in the United States, carrying an additional Ser486Pro substitution compared to XBB.1 and outcompeting BQ.1.1 and other XBB sublineages. [see above] Using vesicular stomatitis virus (VSV)-based pseudovirus neutralization assays, tjhey evaluated the neutralization titers against XBB.1.5 of convalescent plasma from individuals who had received 3 doses of CoronaVac prior to BA.1, BA.5, or BF.7 breakthrough infection (BTI). A cohort of convalescents from BA.5 BTI who had received at least two doses of Pfizer or Moderna was also included in the analysis. Human ACE2 (hACE2)-binding affinity of XBB.1.5 receptor-binding domain (RBD) was also examined by surface plasmon resonance (SPR) assays, in comparison to that of XBB.1, BQ.1.1, and BA.2.75.

XBB.1.5 exhibits a substantially higher hACE2-binding affinity compared to BQ.1.1 and XBB/XBB.1. Convalescent plasma samples from BA.1, BA.5, and BF.7 breakthrough infection are significantly evaded by both XBB.1 and XBB.1.5, with XBB.1.5 displaying slightly weaker immune evasion capability than XBB.1. Evusheld and Bebtelovimab could not neutralize XBB.1/XBB.1.5, while Sotrovimab was weakly reactive.

Comment: The fact that XBB.1 and XBB.1.5 showed comparable antibody evasion but distinct transmissibility suggests enhanced receptor-binding affinity would indeed lead to higher growth advantages. The strong hACE2 binding of XBB.1.5 could also enable its tolerance of further immune escape mutations, which should be closely monitored.

Neutralisation sensitivity of the SARS-CoV-2 XBB.1 lineage. Lancet Infect Dis published online January 5, 2023

doi.org/10.1016/ S1473-3099(22)00831-3

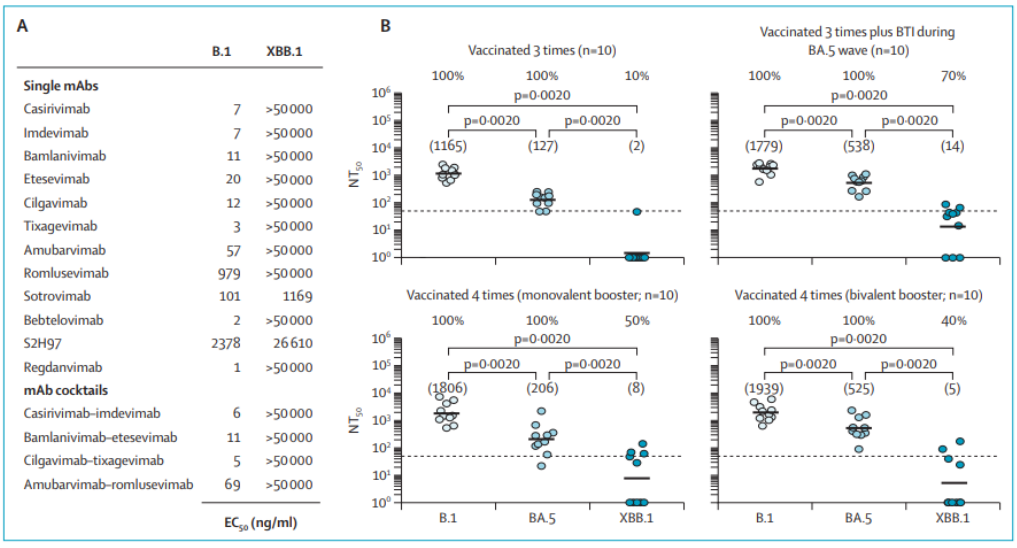
The XBB lineage is the result of recombination of two omicron variant sublineages, BJ.1 and BM.1.1.1, and the breakpoint is located in the gene for the spike protein which is responsible for host cell entry and constitutes the target of neutralizing antibodies.

The investigators report an initial assessment of the ability of the SARS-CoV-2 XBB.1 lineage to enter host cells and to evade antibody-mediated neutralization. For this, we used spike-protein carrying pseudovirus particles (pp) that represent a suitable model to study host-cell entry of SARS-CoV-2 and its neutralization. Particles pseudotyped with the spike protein of the ancestral

B.1 (B.1pp) or the currently dominating omicron BA.5 (BA.5pp) lineage were used for comparison.

They assessed the sensitivity of XBB.1pp to neutralization by antibodies induced by vaccination or vaccination plus breakthrough infection. Plasma of triple vaccinated individuals had almost no detectable neutralizing activity against XBB.1pp (neutralizing titer 50 [NT50] 2), whereas the neutralizing activity against B.1pp was high (NT50 1165) and against BA.5pp was moderate (NT50 127). Next, they measured the plasma of triple vaccinated individuals with breakthrough infection during the BA.5 wave in Germany (June to November 2022). The plasma samples showed high neutralizing activity against B.1pp (NT50 1779), moderate neutralizing activity against BA.5pp (NT50 538), and low neutralizing activity against XBB.1pp (NT50 14). Similar findings were made for plasma from triple vaccinated individuals who received either monovalent or bivalent (i.e., B.1 or B.1 plus BA.5) booster vaccination: B.1pp NT50 1806 for B.1 or 1939 for B.1 plus BA.5; BA.5pp NT50 206 for B.1 or 525 for B.1 plus BA.5; and XBB.1pp NT50 8 for B.1 or 5 for B.1 plus BA.5.

The investigators team also noted that all the analyzed mAbs and mAb cocktails effectively neutralized $B.1_{pp}$ while $XBB.1_{pp}$ was neutralized by only sotrovimab and S2H97. Also, the efficiency of $XBB.1_{pp}$ neutralization decreased by over 10 times compared to $B.1_{pp}$ neutralization.



A

	B.1	XBB.1
Single mAbs		
Casirivimab	7	>50000
Imdevimab	7	>50000
Bamlanivimab	11	>50000
Etesevimab	20	>50000
Cilgavimab	12	>50000
Tixagevimab	3	>50000
Amubarvimab	57	>50000
Romlusevimab	979	>50000
Sotrovimab	101	1169
Bebtelovimab	2	>50000
S2H97	2378	26610
Regdanvimab	1	>50000
mAb cocktails		
Casirivimab–imdevimab	6	>50000
Bamlanivimab–etesevimab	11	>50000
Cilgavimab–tixagevimab	5	>50000
Amubarvimab–romlusevimab	69	>50000
	EC_{50} (ng/ml)	

B

Comment: Overall, the study findings showed that the SARS-CoV-2 XBB.1 lineage has an exceptionally robust antibody evasion activity. The researchers believe that the finding that $XBB.1_{pp}$ was not neutralized by mAbs highlights the need for novel mAbs for Covid-19 treatment along with additional therapeutic options for locations with high cases of XBB lineage infections. CP (convalescent plasma) may be an option. See next article.

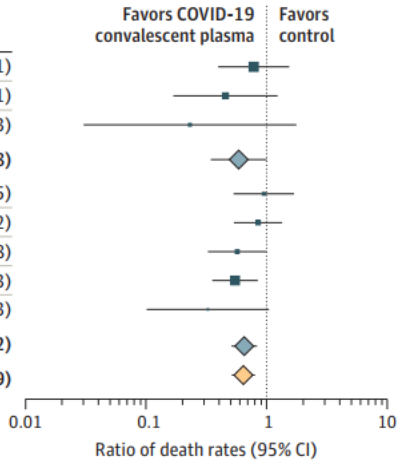
COVID-19 Convalescent Plasma for the Treatment of Immunocompromised Patients: A Systematic Review and Meta-analysis JAMA Network Open. 2023;6:e2250647

doi:10.1001/jamanetworkopen.2022.50647

RCTs, matched cohort studies, and case report or series on Covid-19 convalescent plasma(CP) use in patients who are immunocompromised were included. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Data were extracted by 3 independent reviewers in duplicate and pooled. The end point was all-cause mortality after COVID-19 CP transfusion; exploratory subgroup analyses were performed based on putative factors associated with the potential mortality benefit of CP.

This systematic review and meta-analysis included 3 RCTs enrolling 1487 participants and 5 controlled studies. Additionally, 125 case series or reports enrolling 265 participants and 13 uncontrolled large case series enrolling 358 participants were included. Separate meta-analyses, using models both stratified and pooled by study type (i.e., randomized clinical trials and matched cohort studies), demonstrated that transfusion of Covid-19 CP was associated with a decrease in mortality compared with the control cohort for the amalgam of both RCTs and matched cohort studies (risk ratio [RR], 0.63 [95% CI, 0.50-0.79]).

	Deaths/patients (%)		
Source	CCP group	Usual care group	RR (95% CI)
Denkinger et al,[30] 2022	12/68 (18)	15/65 (23)	0.77 (0.39-1.51)
Lacombe et al,[31] 2022	4/22 (18)	11/27 (41)	0.45 (0.17-1.21)
Bar et al,[29] 2021	1/15 (7)	5/17 (29)	0.23 (0.03-1.73)
RCT total	**17/105 (16)**	**31/109 (28)**	**0.58 (0.34-0.98)**
Cristell et al,[33] 2021	13/58 (22)	28/116 (24)	0.93 (0.52-1.65)
Lanza et al,[36] 2022	19/79 (24)	46/159 (29)	0.83 (0.52-1.32)
Hueso et al,[35] 2022	13/61 (21)	29/76 (38)	0.56 (0.32-0.98)
Thompson et al,[34] 2021	19/143 (13)	204/823 (25)	0.54 (0.35-0.83)
Biernat et al,[32] 2021	3/23 (13)	9/22 (41)	0.32 (0.10-1.03)
MCT total	**67/364 (18)**	**316/1196 (26)**	**0.64 (0.50-0.82)**
Overall	**84/469 (18)**	**347/1305 (27)**	**0.63 (0.50-0.79)**



Comment: This review suggest that transfusion of Covid-19 CP may be associated with a mortality benefit for patients who are immunocompromised who are susceptible to refractory infection. Several scientific societies like IDSA have recently revised their guidelines to recommend the use of Covid-19 CP in patients who are immunocompromised, especially after concerns related to the prevalence of monoclonal antibody-resistant SARS-CoV-2 variants. IDSA states among ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who have no other treatment options [e.g., nirmatrelvir/ritonavir, three-day treatment with remdesivir], the IDSA guideline panel suggests FDA-qualified high-titer Covid-19 CP within 8 days of symptom onset rather than no high-titer COVID-19 CP. The NIH states there is insufficient evidence for the Panel to recommend either for or against the use of high-titer Covid-19 CP for the treatment of Covid-19 in hospitalized or nonhospitalized patients who are immunocompromised. The Panel concluded that there is insufficient evidence for a definitive

recommendation. However, given the need for treatment of Covid-19 in people who are immunocompromised, some Panel members would use CP in certain situations.

Effectiveness of the Bivalent mRNA Vaccine in Preventing Severe Covid-19 Outcomes: an observational cohort study Lancet posted online January 3, 2023

The study by investigators from Israel has not yet been peer reviewed.

They found an 81% reduction in hospitalizations among people aged 65 and older who had received the booster against those who had previously received at least two Covid-19 vaccinations, but not the bivalent vaccine. The study was carried out from the end of September until mid-December and looked at 622,701 people aged 65 and over who were eligible for the bivalent booster. Among them, 85,314, or 14%, had received it.

Hospitalization due to Covid-19 occurred in 6 bivalent recipients and 297 participants who did not receive the booster. Death due to Covid-19 occurred in 1 bivalent recipient and 73 participants who did not. This decrease in mortality was statistically borderline because of the relatively low death rates in the country, but it was nonetheless significant.

Comment: Participants who received the bivalent vaccine had lower hospitalization and mortality rates due to Covid-19 than non-recipients up to 70 days after vaccination. While the bivalent vaccine targets the original strain and its BA.4/BA.5 Omicron subvariant, investigators have been closely watching the XBB.1.5 variant, which is now rapidly spreading in the US. Preliminary CDC data shows that persons who received the bivalent vaccine have a much lower risk of hospitalizations. The bivalent vaccine is not as good against the new XBB.1.5 but most feel it should provide some benefit. Unfortunately, the uptake of the bivalent booster has been very low.

Impaired CD4+ T cell response in older adults is associated with reduced immunogenicity and reactogenicity of mRNA COVID-19 vaccination Nat Aging published online January 12, 2023

doi.org/10.1038/s43587-022-00343-4

Using a vaccinated cohort (n = 216), the investigators demonstrated that older adults (aged ≥65 years) had fewer vaccine-induced spike-specific CD4+ T cells including CXCR3+ circulating follicular helper T cells and the TH1 subset of helper T cells after the first dose, which correlated with their lower peak IgG levels and fewer systemic adverse effects after the second dose, compared with younger adults. Moreover, spike-specific TH1 cells in older adults expressed higher levels of programmed cell death protein 1, a negative regulator of T cell activation, which was associated with low spike-specific CD8+ T cell responses. Thus, an inefficient CD4+ T cell response after the first dose may reduce the production of helper T cytokines, even after the second dose, thereby lowering humoral and cellular immunity and reducing systemic reactogenicity.

Comment: This study demonstrated enhancing CD4+ T cell response following the first vaccine dose is key to improving vaccine efficacy especially in older adults who tend to have a defect in the process. The investigators demonstrated the characteristics of immune responses to the two doses of Pfizer mRNA vaccine in older individuals (aged ≥ 65 years), revealing a lower induction and early contraction of antigen-specific T cells. The mechanisms underlying lower CD4+ T cell responses after the first dose in older adults remain to be determined.

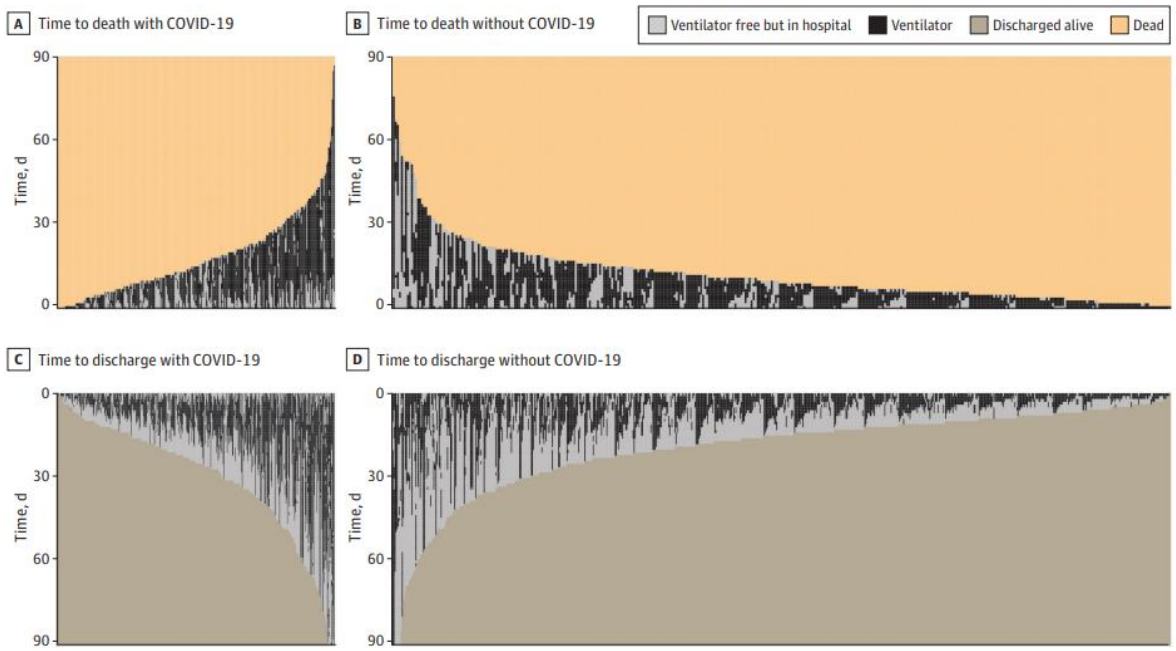
Outcomes Among Mechanically Ventilated Patients With Severe Pneumonia and Acute Hypoxemic Respiratory Failure From SARS-CoV-2 and Other Etiologies

JAMA Network Open. 2023;6(1):e2250401.

doi:10.1001/jamanetworkopen.2022.50401

This retrospective cohort study was conducted at the Johns Hopkins Healthcare System among adult patients (aged ≥18 years) with pneumonia who required mechanical ventilation in the first 2 weeks of hospitalization. Clinical, laboratory, and mechanical ventilation data were extracted from admission to hospital discharge or death. The primary outcome was 90-day in-hospital mortality. Secondary outcomes were time to liberation from mechanical ventilation, hospital length of stay, static respiratory system compliance, and ventilatory ratio. Unadjusted and multivariable-adjusted logistic regression, proportional hazards regression, and doubly robust regression were used in propensity score–matched sets to compare clinical outcomes.

Overall, 719 patients (mean age 61.8 years; 442 [61.5%] were male; 460 [64.0%] belonged to a minoritized racial group and 253 [35.2%] were White) with severe Covid-19 pneumonia and 1127 patients (mean [SD] age, 60.9 years; 586 [52.0%] were male; 459 [40.7%] belonged to a minoritized racial group and 655 [58.1%] were White) with severe non–Covid-19 pneumonia. In unadjusted analyses, patients with Covid-19 pneumonia had higher 90-day mortality (odds ratio, 1.21, 95% CI 1.04-1.41), longer time on mechanical ventilation, and lower compliance (32.0 vs 28.4 mL/kg PBW/cm H2O; P < .001) when compared with those with non–Covid-19 pneumonia. In propensity score–matched analyses, patients with Covid-19 pneumonia were equally likely to die within 90 days as those with non–Covid-19 pneumonia (odds ratio, 1.04; 95% CI, 0.81 to 1.35; P = .85), had similar respiratory system compliance (mean difference, 1.82 mL/cm H2O; 95% CI, −1.53 to 5.17 mL/cm H2O; P = .28) and ventilatory ratio (mean difference, −0.05; 95% CI, −0.22 to 0.11; P = .52), but had lower rates of liberation from mechanical ventilation (0.81; 95% CI, 0.65 to 1.00) when compared with those with non–Covid-19 pneumonia. Patients with Covid-19 pneumonia had somewhat lower rates of being discharged from the hospital alive at 90 days (0.83; 95% CI, 0.68 to 1.01) than those with non–Covid-19 pneumonia; however, this was not statistically significant.



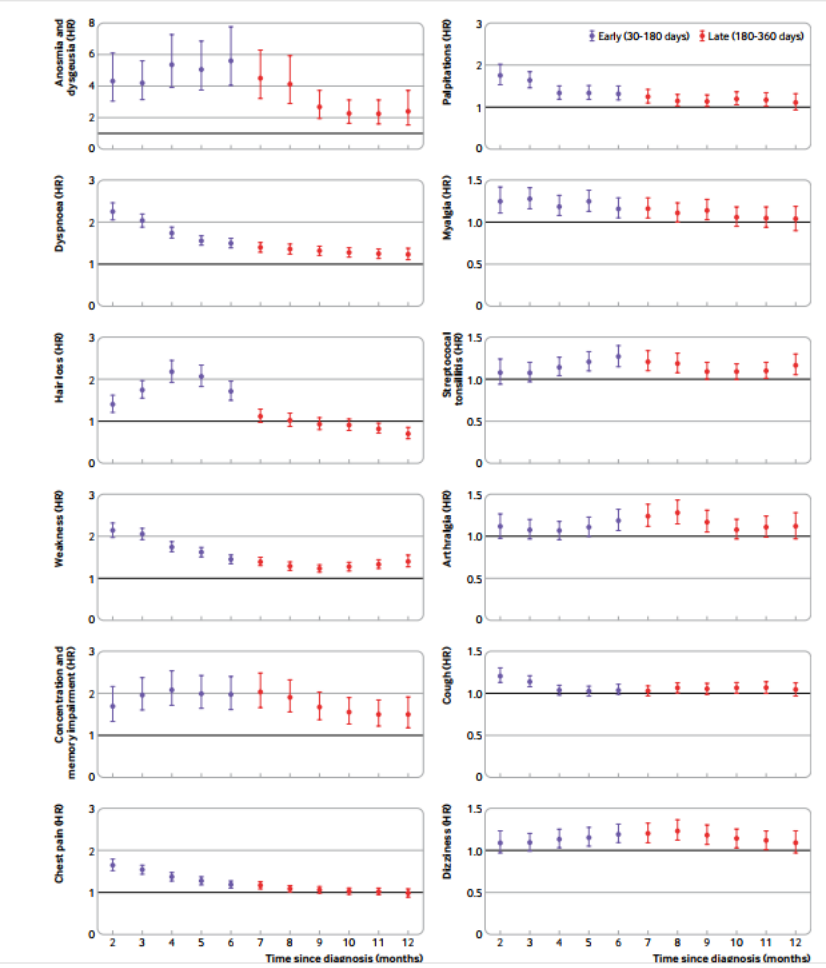
Comment: In this cohort study of 1846 patients with pneumonia, Covid-19 pneumonia had similar mortality rates and physiologic phenotypes as other causes of pneumonia. However, Covid-19 pneumonia has been associated with longer duration of mechanical ventilation than H1N1 and other etiologies of ARDS. [Ann Am Thorac Soc. 2021;18:1202-1210] Reasons why patients with Covid-19 pneumonia have longer ventilator courses are likely multifactorial due to both pathophysiology and clinical practice. Emerging evidence suggests SARS-CoV-2 may cause persistent and slower-to-resolve alveolar inflammation that could contribute to a longer duration of mechanical ventilation. [Nature. 2021;590(7847):635-641] As with any retrospective study of EHR data, despite careful measures to account for data missingness and data validation, there may be unidentified differential patterns of data errors or missingness that may introduce bias. The investigators did not systematically capture differences in management, such as therapies for ARDS (e.g., compliance with low tidal volume ventilation, or use of prone positioning). Lastly, even though propensity score analyses aim to achieve balance in covariates between groups, remaining unmeasured confounders may still be present.

Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. BMJ 2023;380: e072529

doi.org/10.1136/ bmj-2022-072529

The objective of this study was to determine the clinical sequelae of long Covid-19 for a year after infection in patients with mild disease and to evaluate its association with age, sex, SARS-CoV-2 variants, and vaccination status. The data set was the electronic medical records from an Israeli nationwide healthcare organization to include all ages who did a polymerase chain reaction test for SARS-CoV-2 between 1 March 2020 and 1 October 2021. Long Covid-19 was defined as symptoms persisting or new symptoms appearing beyond four weeks from the primary diagnosis of Covid-19.

Covid-19 infection was significantly associated with increased risks in early and late periods for anosmia and dysgeusia (hazard ratio 4.59 (95% CI 3.63 to 5.80), risk difference 19.6 (95% CI 16.9 to 22.4) in early period; 2.96 (2.29 to 3.82), 11.0 (8.5 to 13.6) in late period), cognitive impairment (1.85 (1.58 to 2.17), 12.8, (9.6 to 16.1); 1.69 (1.45 to 1.96), 13.3 (9.4 to 17.3)), dyspnea (1.79 (1.68 to 1.90), 85.7 (76.9 to 94.5); 1.30 (1.22 to 1.38), 35.4 (26.3 to 44.6)), weakness (1.78 (1.69 to 1.88), 108.5, 98.4 to 118.6; 1.30 (1.22 to 1.37), 50.2 (39.4 to 61.1)), and palpitations (1.49 (1.35 to 1.64), 22.1 (16.8 to 27.4); 1.16 (1.05 to 1.27), 8.3 (2.4 to 14.1)) and with significant but lower excess risk for streptococcal tonsillitis and dizziness. Hair loss, chest pain, cough, myalgia, and respiratory disorders were significantly increased only during the early phase. Male and female patients showed minor differences, and children had fewer outcomes than adults during the early phase of Covid-19, which mostly resolved in the late period. Findings remained consistent across SARS-CoV-2 variants. Vaccinated patients with a breakthrough SARS-CoV-2 infection had a lower risk for dyspnea and similar risk for other outcomes compared with unvaccinated infected patients.



Comment: This study suggests that patients with mild Covid-19 are at risk for a small number of health outcomes, most of which are resolved within a year from diagnosis. Children had fewer outcomes, which mostly resolved in the late period. The risk for lingering dyspnea was reduced in vaccinated patients with breakthrough infection compared with unvaccinated people, while risks of all other outcomes were comparable. The investigators could not rule out potential behavioral and environmental differences between infected and uninfected people,

which might cause overestimation of the incidence among the infected population. They also admit there could be under-reporting of symptoms in the later periods when patients had reported the outcomes close to diagnosis of Covid-19 and did not continue reporting them as time from diagnosis advanced. Their definition varies with others who classify long Covid-19 as symptoms beyond 3 months.

Long COVID: major findings, mechanisms and recommendations Nat Rev Microbiol published online January 13, 2023

doi.org/10.1038/s41579-022-00846-2

At least 65 million individuals worldwide are estimated to have long Covid-19, with cases increasing daily. Biomedical research has made progress in identifying various pathophysiological changes and risk factors and in characterizing the illness; further, similarities with other viral-onset illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome and postural orthostatic tachycardia syndrome have laid the groundwork for research in the field. In this review, the authors explore the current literature and highlight key findings, the overlap with other conditions, the variable onset of symptoms, long Covid in children and the impact of vaccinations. Below I highlight a few sections.

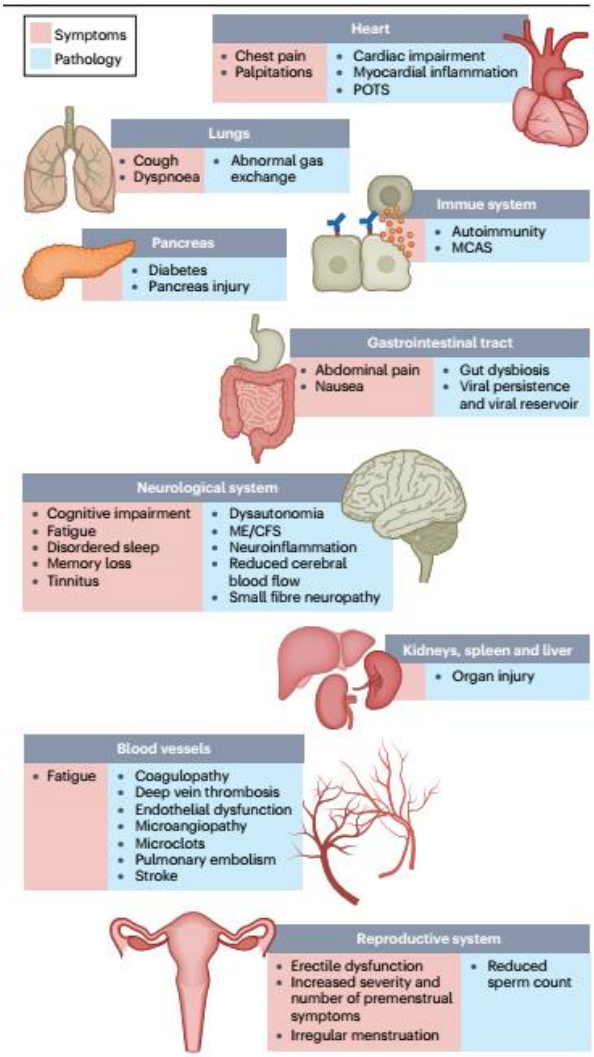
Under major findings they review immunology and virology. They report studies looking at immune dysregulation in individuals with long Covid who had mild acute Covid-19 have found T cell alterations, including exhausted T cells, reduced CD4+ and CD8+ effector memory cell numbers and elevated PD1 expression on central memory cells, persisting for at least 13 months. A comprehensive study comparing patients with long Covid with uninfected individuals and infected individuals without long Covid found increases in the numbers of non-classical monocytes, activated B cells, double-negative B cells, and IL-4- and IL-6-secreting CD4+ T cells and decreases in the numbers of conventional dendritic cells and exhausted T cells and low cortisol levels in individuals with long Covid at a median of 14 months after infection. Reactivated viruses, including EBV and HHV-6, have been found in patients with long Covid.

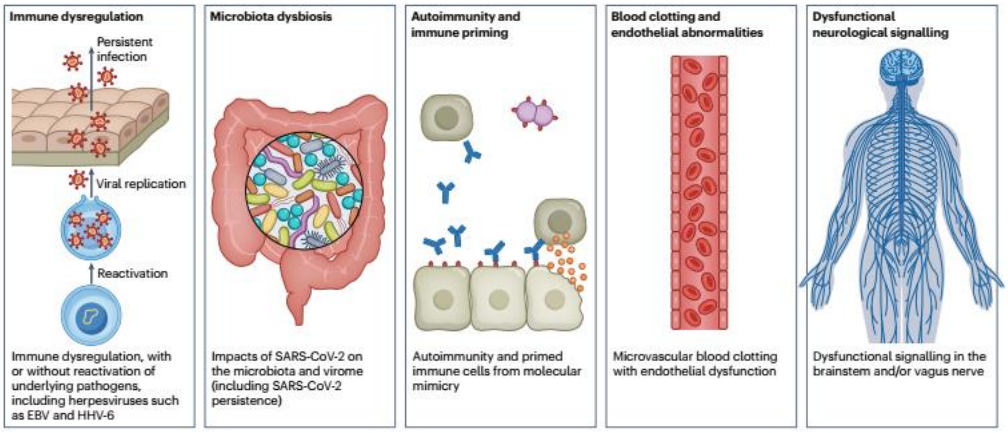
Under vascular issues and organ damage they write although Covid-19 was initially recognized as a respiratory illness, SARS-CoV-2 has capability to damage many organ systems. The damage that has been demonstrated across diverse tissues has predominantly been attributed to immune-mediated response and inflammation, rather than direct infection of cells by the virus. Circulatory system disruption includes endothelial dysfunction and subsequent downstream effects, and increased risks of deep vein thrombosis, pulmonary embolism, and bleeding events.

Under neurological and cognitive systems, they found neurological and cognitive symptoms are a major feature of long Covid-19, including sensorimotor symptoms, memory loss, cognitive impairment, paresthesia, dizziness and balance issues, sensitivity to light and noise, loss of (or phantom) smell or taste, and autonomic dysfunction, often impacting activities of daily living. Audiovestibular manifestations of long Covid can include tinnitus, hearing loss and vertigo. Possible mechanisms for these neuropathologies include neuroinflammation, damage to blood vessels by coagulopathy and endothelial dysfunction, and injury to neurons. Studies have found Alzheimer disease-like signaling in patients with long Covid-19, peptides that self-assemble into amyloid clumps which are toxic to neurons, widespread neuroinflammation, brain and brainstem hypometabolism correlated with specific symptoms and abnormal cerebrospinal fluid findings in

non-hospitalized individuals with long Covid-19 along with an association between younger age and a delayed onset of neurological symptoms.

Respiratory conditions are a common phenotype in long Covid, and in one study occurred twice as often in Covid-19 survivors as in the general population. Shortness of breath and cough are the most common respiratory symptoms and persisted for at least 7 months in 40% and 20% of patients with long Covid, respectively. Several imaging studies that included non-hospitalized individuals with long Covid demonstrated pulmonary abnormalities including in air trapping and lung perfusion. An immunological and proteomic study of patients 3–6 months after infection indicated apoptosis and epithelial damage in the airway but not in blood samples. Further immunological characterization comparing individuals with long Covid with individuals who had recovered from Covid-19 noted a correlation between decreased lung function, systemic inflammation, and SARS-CoV-2-specific T cells.





Comment: This review is an excellent starting point in our current understanding of current knowledge. It is impossible to do justice to this article, but I have inserted key figures as representative examples of the information in this article. Although these key findings are critical to understanding long Covid-19, current diagnostic and treatment options are lacking, and clinical trials must be prioritized that address leading hypotheses. Additionally, to strengthen long Covid-19 research, future studies must account for biases and SARS-CoV-2 testing issues, build on viral-onset research, and meaningfully engage patients throughout the research process. We also need a common definition.