Infectious Diseases Watch

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General Infectious Diseases

In critically ill patients, anti-anaerobic antibiotics increase risk of adverse clinical outcomes

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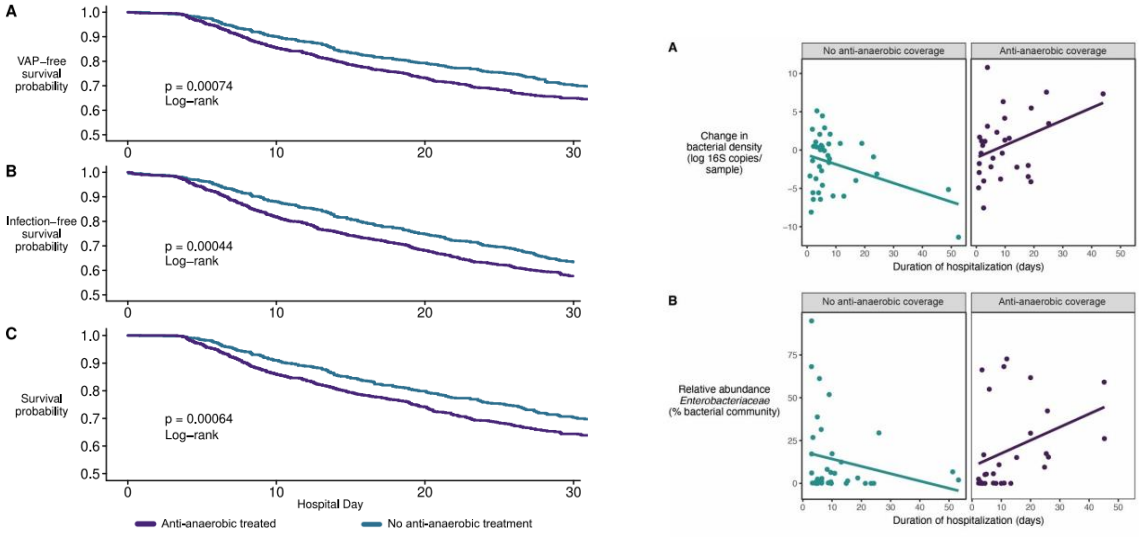
The anaerobic gut flora has important protective properties that may be depleted by antibiotics with anaerobic activity, thereby allowing proliferation of bacteria capable of causing opportunistic infections. Is this effect clinically relevant in critically ill patients?

Investigators conducted a retrospective observational cohort study of 3032 critically ill patients, all of whom received parenteral antibiotics within 72 hours of mechanical ventilation. They compared clinical outcomes and respiratory microbiology in patients who did and did not receive anti-anaerobic antibiotics early in their hospital stay They compared ICU outcomes VAP-free survival, infection-free survival, overall survival in all patients plus changes in gut microbiota in a 116-patient subcohort. Piperacillin tazobactam was the most common antimicrobial administered with anaerobic coverage. They also used a murine model, to study the effects of anaerobe depletion in infectious (*K. pneumoniae* and *S. aureus* pneumonia) and noninfectious (*hyperoxia*) injury.

In multivariate adjusted analysis, use of anti-anaerobic antibiotics was significantly associated with decreased VAP-free survival (hazard ratio, 1.24, 95% CI 1.06 - 1.45), infection-free survival (HR, 1.22, 95% CI 1.09 - 1.38), and overall survival (HR, 1.14, 95% CI 1.02 - 1.28). Patients who received anti-anaerobic antibiotics had decreased initial gut bacterial density (p=0.00038), increased microbiome expansion during hospitalization (p=0.011), and domination by *Enterobacteriaceae* spp. (p=0.045) Mechanically ventilated patients who died were more likely to die of infection-related causes if they had received anti-anaerobic antibiotics. Analysis of the gut microbiota in 116 patients revealed decreased gut bacterial density shortly after administration of anti-anaerobic antibiotics followed by later expansion of the microbiome dominated by *Enterobacteriaceae* spp., providing an explanation for the higher proportion of VAP caused by these pathogens in patients receiving anti-anaerobic antibiotics. In murine models, treatment with anti-anaerobic antibiotics increased susceptibility to *Enterobacteriaceae* pneumonia ($p<0.05$) and increased the lethality of hyperoxia (p=0.0002).



Comment: Mechanically ventilated patients showed expansion of gut Enterobacterales and excess risk for pneumonia and death associated with anti-anaerobic antibiotics. This study suggests that disruption of anaerobic gut flora play a role in risk of VAP. Clinicians routinely prescribe empiric antibiotics with anti-anaerobic activity. [J Hosp Med 2020: 15(12): 754-756] This widespread practice has recently been called into question given the infrequency of anaerobic pathogens among hospitalized patients even including patients with aspiration pneumonia. [Chest 2021: 159: 58-72]

While anti-anaerobic antibiotic exposure was associated with increased risk of VAP overall differences in survival could not be totally explained by increased infection rates alone. Most deaths were due to non-infectious causes in both treatment groups, and the overall survival difference (7% unadjusted, 3.9% adjusted) exceeds the anticipated 1% attributable mortality of VAP. The murine animal experimentation similarly showed that anaerobe depletion both a direct effect of increased susceptibility to *Enterobacterales pneumonia and* markedly increased lethality of hyperoxia. These findings parallel results from the randomized clinical trials of anaerobe-sparing SDD, which has a mortality benefit that exceeds the attributable mortality of VAP[*JAMA* 2014: 312(14): 1429-1437 *; The Cochrane database of systematic reviews* 2021: 1(1): CD000022.]. These findings suggest that the protective effects of gut anaerobes are multifaceted and do not simply represent colonization resistance against potential pathogens. See next two articles

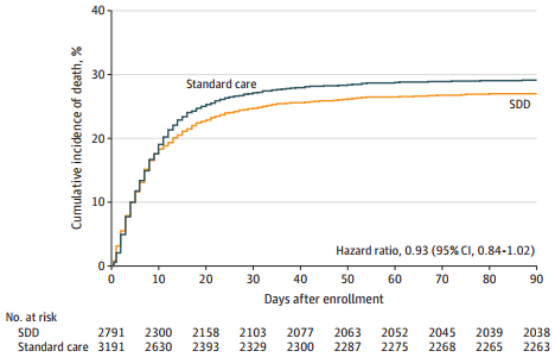
Effect of Selective Decontamination of the Digestive Tract on Hospital Mortality in Critically Ill Patients Receiving Mechanical Ventilation: A Randomized Clinical Trial
JAMA. 2022; 328:1911-192

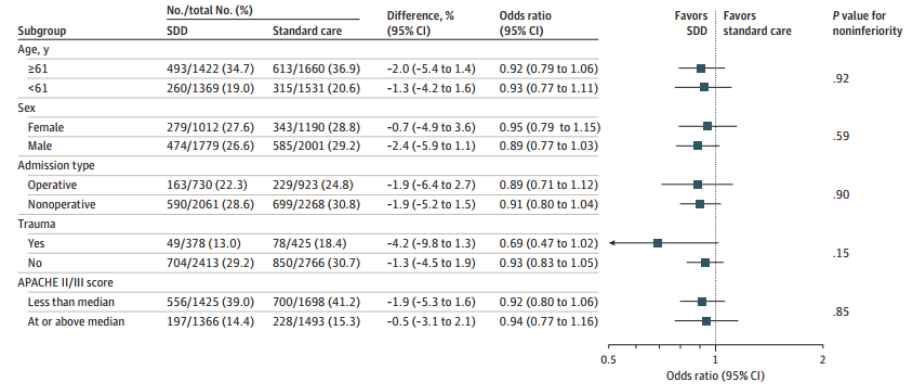
doi:10.1001/jama.2022.17927

Many ICU HO– infections of the respiratory tract, are caused by gram negative bacteria and S. *aureus* usually resulting from colonization of the upper and lower GI tract (mouth, stomach, and intestines). SDD aims to improve patient outcomes by reducing the incidence of ICU-acquired infections through eradicating and preventing colonization of the GI tract with the organisms mentioned above. SDD involves application of topical, nonabsorbable antimicrobial agents (usually colistin, tobramycin, and nystatin) that— selectively—spare the anaerobic flora. (see article above) Apart from the topical prophylaxis patients may receive, intravenous antibiotics, usually with a second- or third-generation cephalosporin which may empirically treat respiratory tract infections that may be incubating at the time of ICU admission.

This study is a cluster, crossover, randomized clinical trial that recruited 5982 mechanically ventilated adults from 19 intensive care units (ICUs) in Australia between April 2018 and May 2021 (final follow-up, August 2021). This trial was named the Selective Decontamination of the Digestive Tract in the Intensive Care Unit (SuDDICU). ICUs were randomly assigned to adopt or not adopt a SDD strategy for 2 alternating 12-month periods, separated by a 3-month interperiod gap. Patients in the SDD group (n = 2791) received a 6-hourly application of an oral paste and administration of a gastric suspension containing colistin, tobramycin, and nystatin for the duration of mechanical ventilation, plus a 4-day course of an intravenous antibiotic with a suitable antimicrobial spectrum. [cefotaxime or ceftriaxone] Patients in the control group (n = 3191) received standard care. The primary outcome was in-hospital mortality within 90 days. There were 8 secondary outcomes, including the proportion of patients with new positive blood cultures, antibiotic-resistant organisms (AROs), and *Clostridioides difficile* infections. For the ecological assessment, a noninferiority margin of 2% was prespecified for 3 outcomes including new cultures of AROs.

There were 753/2791 (27.0%) and 928/3191 (29.1%) in-hospital deaths in the SDD and standard care groups, respectively (mean difference, -1.7% [95% CI, -4.8% to 1.3%]; odds ratio, 0.91 [95% CI, 0.82-1.02]; *P* = .12). Of 8 prespecified secondary outcomes, 6 showed no significant differences. In the SDD vs standard care groups, 23.1% vs 34.6% had new ARO cultures (absolute difference, -11.0%; 95% CI, -14.7% to -7.3%), 5.6% vs 8.1% had new positive blood cultures (absolute difference, -1.95%; 95% CI, -3.5% to -0.4%), and 0.5% vs 0.9% had new *C difficile* infections (absolute difference, -0.24%; 95% CI, -0.6% to 0.1%). In 8599 patients enrolled in the ecological assessment, use of SDD was not shown to be noninferior with regard to the change in the proportion of patients who developed new AROs (-3.3% vs -1.59%; mean difference, -1.71% [1-sided 97.5% CI, - to 4.31%] and 0.88% vs 0.55%; mean difference, -0.32% [1-sided 97.5% CI, - to 5.47%]) in the first and second periods, respectively.





Comment: The use of SDD did not significantly reduce ICU mortality, the duration of mechanical ventilation, or the duration of ICU and hospital admission. There was a significant reduction in positive blood cultures and cultures of antibiotic resistant organisms and no significant increase in new *C difficile* infections in patients who received SDD. The use of SDD was not associated with an increased incidence of adverse events. While protocol adherence for the use of SDD approached 90% over the duration of the inception period and more than 130,000 doses of SDD were administered, prolonged use of SDD in long-term ventilated patients declined over time due to nonpalatability of the oral paste and reduced access to the upper gastrointestinal tract for the gastric suspension. Due to the overall low rate of antimicrobial resistance and relatively short period of observation, the ecological assessment had limited power to confirm or refute noninferiority of SDD compared with standard care and did not assess changes in microbiological outcomes at a hospital level or changes in ecology that might be associated with longer-term use of SDD. The authors do conclude that although mortality was not statistically significant, the authors conclude that the confidence interval includes a clinically relevant benefit. See next article

Association Between Selective Decontamination of the Digestive Tract and In-Hospital Mortality in Intensive Care Unit Patients Receiving Mechanical Ventilation:A Systematic Review and Meta-analysis JAMA. 2022; 328:1922-1934

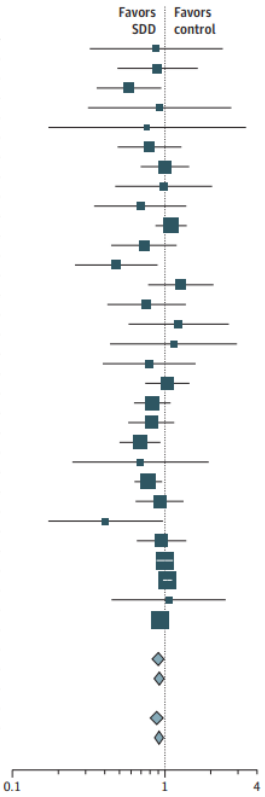
doi:10.1001/jama.2022.19709

The primary search was conducted using MEDLINE, EMBASE, and CENTRAL databases until September 2022 which included the article above. Studies included were RCTs including adults receiving mechanical ventilation in the ICU comparing SDD vs standard care or placebo. The primary analysis was conducted using a bayesian framework. The primary outcome was hospital mortality. Subgroups included SDD with an intravenous agent compared with SDD without an intravenous agent. There were 8 secondary outcomes including the incidence of ventilator-associated pneumonia, ICU-acquired bacteremia, and the incidence of positive cultures of antimicrobial-resistant organisms.

There were 32 randomized clinical trials including 24,389 participants in the analysis. The median age of participants in the included studies was 54 years (IQR, 44-60), and the median proportion of female trial participants was 33% (IQR, 25%-38%). Data from 30 trials including 24,034 participants contributed to the primary outcome. The pooled estimated risk ratio (RR) for mortality for SDD compared with standard care was 0.91 (95% credible interval [CrI], 0.82-0.99; I^2 = 33.9%; moderate certainty) with a 99.3% posterior probability that SDD reduced hospital mortality. The beneficial association of SDD was evident in trials with an intravenous agent (RR, 0.84 [95% CrI, 0.74-0.94]), but not in trials without an intravenous agent (RR, 1.01 [95% CrI, 0.91-1.11]) (*P* value for the interaction between subgroups = .02). SDD was associated with reduced risk of ventilator-associated pneumonia (RR, 0.44 [95% CrI, 0.36-0.54]) and ICU-acquired bacteremia (RR, 0.68 [95% CrI, 0.57-0.81]). Available data regarding the incidence of positive cultures of antimicrobial-resistant organisms were not amenable to pooling and were of very low certainty.

Figure 2. Forest Plot for Hospital Mortality for the Comparison Between Selective Decontamination of the Digestive Tract (SDD) Compared With Standard Care

Study	SDD Dead	SDD Alive	Control Dead	Control Alive	Risk ratio (95% CI)[a]	Weight, %
Unertl et al,[55] 1987	5	14	6	14	0.88 (0.32-2.40)	0.9
Kerver et al,[54] 1988	14	35	15	32	0.90 (0.49-1.65)	2.0
Ulrich et al,[53] 1989	15	33	28	24	0.58 (0.36-0.95)	2.8
Rodríguez-Roldán et al,[52] 1990	4	9	5	10	0.92 (0.31-2.73)	0.8
Aerdts et al,[51] 1991	2	15	6	33	0.76 (0.17-3.41)	0.4
Blair et al,[50] 1991	24	137	32	138	0.79 (0.49-1.28)	2.9
Gaussorgues et al,[49] 1991	29	30	29	30	1.00 (0.69-1.44)	4.1
Pugin et al,[48] 1991	10	28	11	30	0.98 (0.47-2.04)	1.5
Cockerill et al,[47] 1992	11	64	16	59	0.69 (0.34-1.38)	1.6
Gastinne et al,[46] 1992	88	132	82	143	1.10 (0.87-1.39)	6.2
Jacobs et al,[45] 1992	14	22	23	20	0.73 (0.44-1.19)	2.8
Rocha et al,[44] 1992	10	37	24	30	0.48 (0.26-0.89)	2.0
Korinek et al,[43] 1993	27	69	21	74	1.27 (0.78-2.09)	2.8
Wiener et al,[41] 1995	11	19	15	16	0.76 (0.42-1.37)	2.1
Quinio et al,[40] 1996	13	63	10	62	1.23 (0.58-2.63)	1.4
Abele-Horn,[39] 1997	11	47	5	25	1.14 (0.44-2.97)	0.9
Palomar et al,[38] 1997	10	31	13	29	0.79 (0.39-1.59)	1.6
Verwaest et al,[37] 1997	89	355	40	167	1.04 (0.74-1.45)	4.5
Sánchez García et al,[36] 1998	51	80	66	74	0.83 (0.63-1.09)	5.4
Bergmans et al,[35] 2001	30	57	59	80	0.81 (0.57-1.15)	4.3
Krueger et al,[34] 2002	52	213	75	187	0.69 (0.50-0.93)	4.9
Pneumatikos et al,[33] 2002	5	26	7	23	0.69 (0.25-1.94)	0.8
de Jonge et al,[32] 2003	113	353	146	322	0.78 (0.63-0.96)	6.7
Camus et al,[31] 2005	39	91	41	85	0.92 (0.64-1.33)	4.1
de La Cal,[30] 2005	6	47	15	39	0.41 (0.17-0.97)	1.1
Stoutenbeen et al,[28] 2007	42	159	44	156	0.95 (0.65-1.38)	4.0
de Smet et al,[27] 2009	1249	2700	632	1358	1.00 (0.88-1.13)	8.3
Wittekamp et al,[9] 2018	1661	2645	782	1326	1.04 (0.97-1.11)	9.2
Papoti et al,[26] 2019	8	27	8	29	1.06 (0.45-2.51)	1.1
SuDDICU,[10] 2022	753	2038	928	2263	0.93 (0.82-1.04)	8.4
Bayesian						
Vague priors					0.91 (0.82-0.99)	
Semi-informative priors					0.92 (0.85-0.99)	
Frequentist						
Sidik-Jonkman					0.88 (0.80-0.97)	
DerSimonian-Laird					0.92 (0.86-0.98)	



Comment: Among adults in the ICU treated with mechanical ventilation, the use of SDD compared with standard care or placebo was associated with lower hospital mortality. Beneficial effects were only obtained when pooling studies in which SDD included the intravenous component. [without an intravenous component called selective oropharyngeal decontamination (SOD)]

Additional Comment: The debate on SDD is now enhanced with another large cluster-randomized study suggesting outcome benefit for ICU patients (albeit without demonstrating a statistically significant effect) and another meta-analysis providing more evidence of benefit. Does the cumulative evidence coming from clinical SDD studies and meta-analyses provide sufficient evidence that SDD improves patient outcomes? The answer is probably yes in settings with relatively low prevalence of MDROs, such as ICUs in the Netherlands, Australia, and New Zealand where most of the studies have been done. In addition, there is no evidence that implementation of SDD in such settings negatively impacts resistance. What should be the criteria for starting SDD? In the Netherlands, SDD became the recommended standard care for patients with an expected length of mechanical ventilation of at least 48 hours or an expected length of stay in the ICU of at least 72 hours.

A more important question: Does the cumulative evidence coming from clinical SDD studies and meta-analyses also justify widespread implementation of SDD? For settings with higher prevalence of MDROs, there is only 1 cluster-randomized study that I am aware, and that trial did not provide evidence for better patient outcomes. [JAMA. 2018; 320:2087-2098] In summary, I do think important questions regarding the utility of SDD in critically ill patients receiving mechanical ventilation have been answered in settings with a low prevalence of antibiotic resistance. However, large-scale studies are still needed to determine effectiveness in settings with a high prevalence of MDROs.

The recently updated: Strategies to prevent ventilator-associated pneumonia, ventilator-associated events, and nonventilator hospital-acquired pneumonia in acute-care hospitals: 2022 Update [ICHE 2022; 43:687-713] puts SDD under additional approaches. “Consider using selective decontamination of the oropharynx and digestive tract to decrease microbial burden in ICUs with low prevalence of antibiotic-resistant organisms. Antimicrobial decontamination is not recommended in countries, regions, or ICUs with high prevalence of antibiotic-resistant organisms (Quality of Evidence: HIGH).” No consensus on low prevalence, but many use <5% of bloodstream infections caused by ESBL producing Enterobacterales.

FDA OKs First Fecal Transplant Therapy for Recurrent *C difficile*

The FDA has approved the first fecal microbiota product to prevent recurrence of *Clostridioides difficile* infection (CDI) in people aged 18 years and older. Rebyota (fecal microbiota, live-jslm), from Ferring Pharmaceuticals, is intended for use after an individual has completed antibiotic treatment for recurrent CDI given via enema. It is not indicated for the first occurrence of CDI. See article that follows

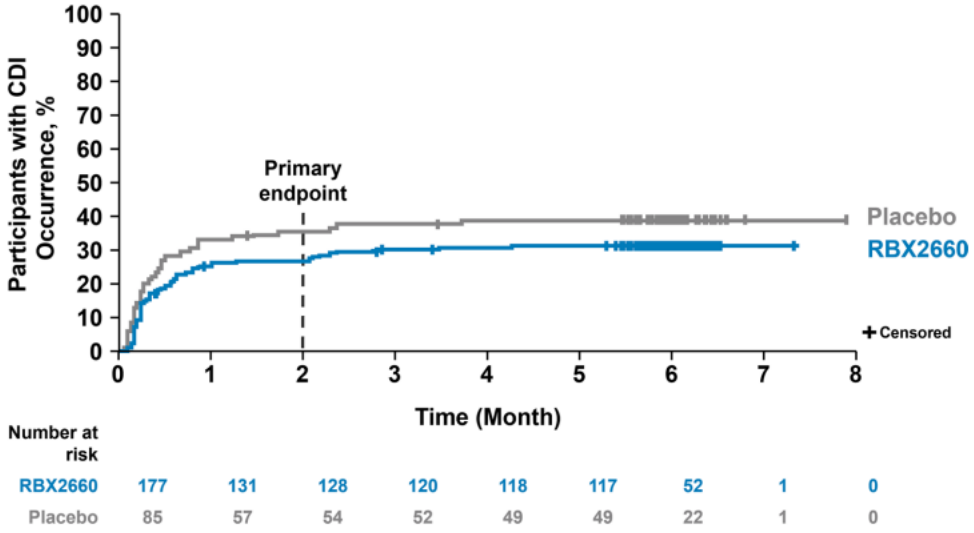
Efficacy and Safety of RBX2660 in PUNCH CD3, a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial with a Bayesian Primary Analysis

for the Prevention of Recurrent Clostridioides difficile Infection Drugs 2022; 82:1527–1538

doi.org/10.1007/s40265-022-01797-x

A randomized, double-blind, placebo-controlled, phase III study, with a Bayesian primary analysis integrating data from a previous phase IIb study, was conducted. Adults who had one or more C. difficile infection recurrences with a positive stool assay for C. difficile and who were previously treated with standard-of-care antibiotics (vancomycin alone, vancomycin in combination with another antibiotic, fidaxomicin alone, or other) were randomly assigned 2:1 to receive a subsequent blinded, single-dose enema of RBX2660 or placebo. RBX2660 is an investigational microbiota-based live biotherapeutic. RBX2660 consists of a broad consortium of live microbes prepared from human stool collected from rigorously screened healthy donor. The primary endpoint was treatment success, defined as the absence of C. difficile infection diarrhea within 8 weeks of study treatment.

Of the 320 patients screened, 289 were randomly assigned and 267 received blinded treatment (n = 180, RBX2660; n = 87, placebo). Original model estimates of treatment success were 70.4% versus 58.1% with RBX2660 and placebo, respectively. More than 90% of the participants who achieved treatment success at 8 weeks had sustained response through 6 months in both the RBX2660 and the placebo groups. Overall, RBX2660 was well tolerated, with manageable adverse events. The incidence of treatment-emergent adverse events was higher in RBX2660 recipients compared with placebo and was mostly driven by a higher incidence of mild gastrointestinal events. Conclusions RBX2660 is a safe and effective treatment to reduce recurrent C. difficile infection following standard-of-care antibiotics with a sustained response through 6 months.



Comment: Placebo response in this trial was higher than expected. However, even with a high placebo response rate, RBX2660 demonstrated superiority as a treatment to reduce CDI recurrence. Although the PCR assay is commonly used diagnostic tool in clinical practice in the US and was used in >70% of study participants, it can result in a false positive. This may have led to the inclusion of patients who do not actually have CDI and therefore also impact treatment

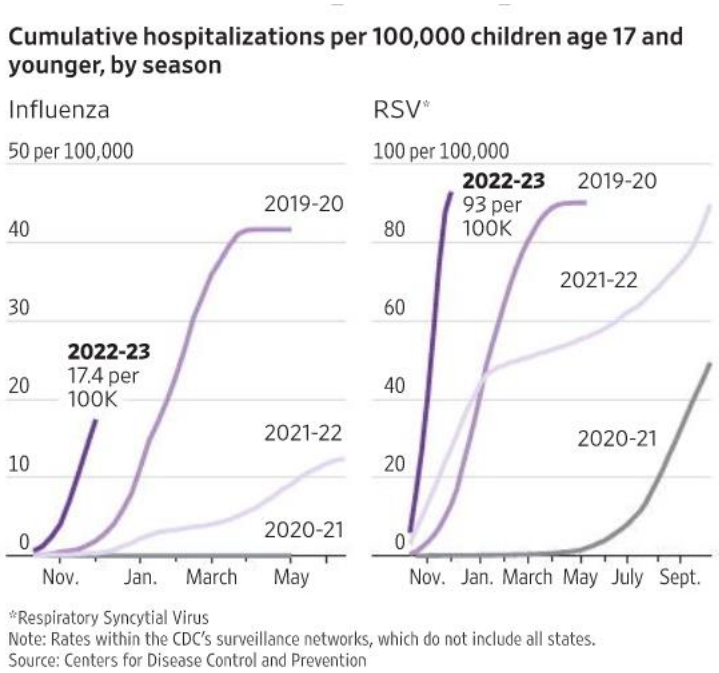
response rates. Another possible explanation for the higher placebo effect is that approximately one-third of participants were enrolled after only one CDI recurrence. As the risk of recurrence increases with each subsequent infection, some placebo participants may have had a lower risk of recurrence because of less severe dysbiosis. While the study population represents the general recurrent C. difficile population, the small number of non-White participants and the lack of participants with irritable bowel syndrome and inflammatory bowel disease, and immunocompromised patients limit the ability to broadly generalize these data.

Progress Toward Regional Measles Elimination — Worldwide, 2000–2021 MMWR 2022; 71:1489-1495

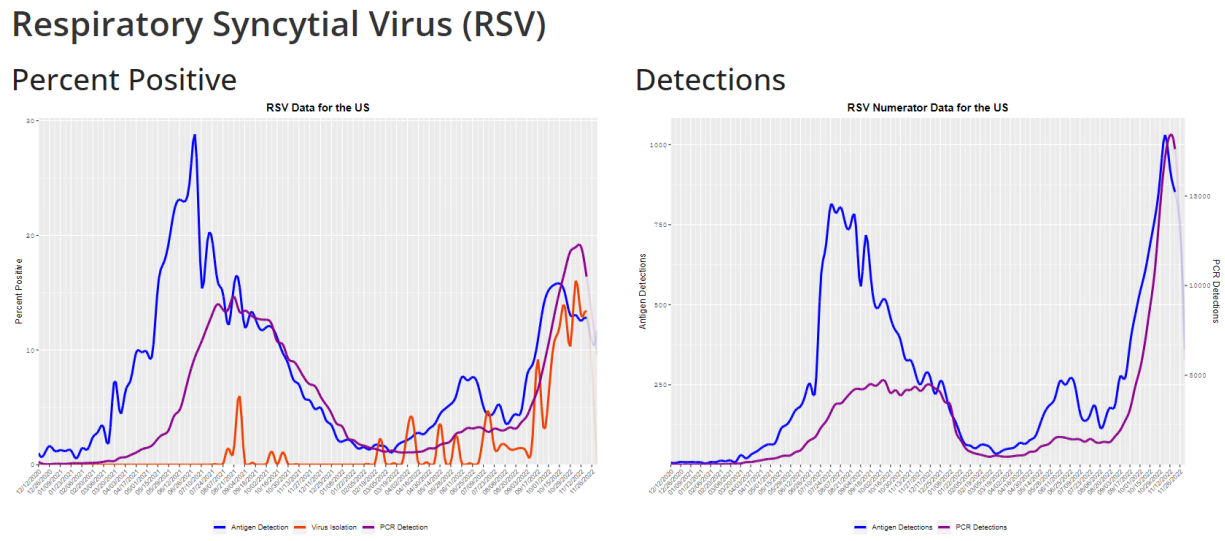
According to this new report, by investigators from WHO, the CDC and universities in the US and UK, in 2021, 25 million children missed their first measles vaccine (MCV) dose and 14.7 million missed their second dose. WHO and UNICEF use data from 1) administrative coverage (calculated by dividing the number of vaccine doses administered by the estimated target population reported annually), 2) country estimates, and 3) vaccination coverage surveys to estimate MCV1 and second dose MCV (MCV2) coverage through routine immunization services (i.e., not mass campaigns). Also in 2021, there were approximately 9 million cases and 128,000 deaths from measles across the globe. Only 81% of children received their first dose of measles. According to the report, from 2000 to 2021, estimated global coverage for a first measles vaccine dose increased from 72% to a peak of 86% in 2019, but during the COVID-19 pandemic, this number decreased from 83% in 2020 to 81% in 2021.

Comment: Measles surveillance continues to be suboptimal, and large and disruptive outbreaks were reported in 22 countries. Reaching all children with 2 doses of measles vaccine and strengthening measles surveillance is critical to close immunity gaps and prevent outbreaks. Unvaccinated children are at the center of an outbreak of measles in central Ohio that now numbers over 32 cases. Immunizations in US have also suffered during the pandemic. Not all countries report complete, or any, data for SIAs (supplementary immunization activities) and outbreak response activities; therefore, the numbers on these activities provided in this report could be underestimated.

Respiratory Viruses

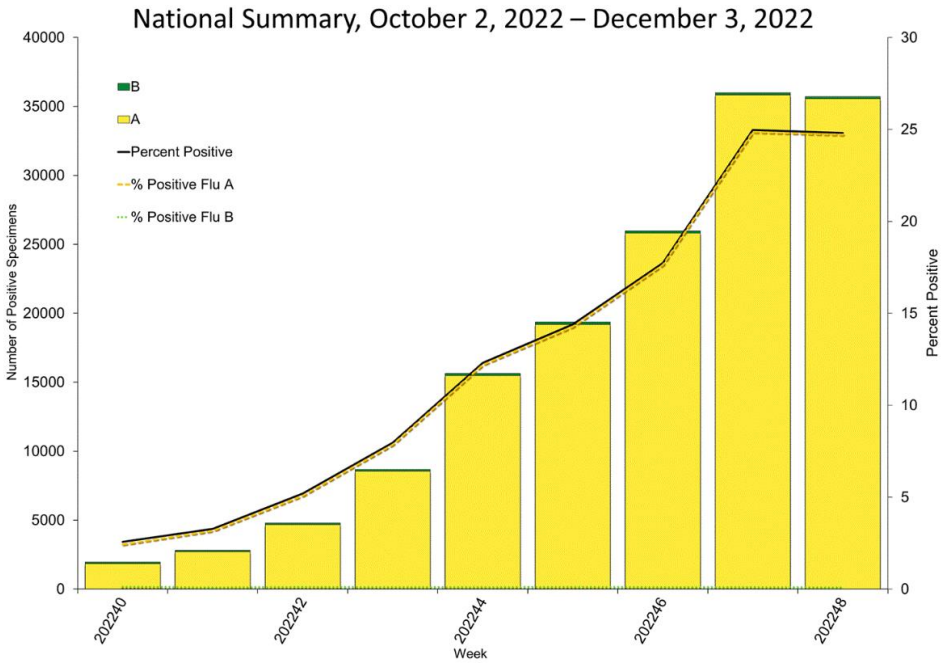


RSV by the Numbers



Comment: It now appears for many areas RSV has peeked, but cases are still usually high for this time of year.

Influenza by the Numbers



Comment: Seasonal influenza remains high across the US. 76% are H3N2 and 24% are H1N1. So far there have been 13 million illnesses and 120,000 hospitalizations, and 7300 deaths. No resistance has been demonstrated to antivirals. [oseltamivir, zanamivir, and baloxavir]

Additional Comments: Health officials recommend that people stay updated on Covid-19 and influenza vaccines. The influenza vaccine formulation appears to be a very good match. Stay home if sick, and frequently wash their hands, and consider wearing masks and get tested early. There isn't an approved RSV vaccine available in the U.S., but several candidates are in trials.

Effectiveness of Influenza Vaccination of Pregnant Women for Prevention of Maternal and Early Infant Influenza-Associated Hospitalizations in South Africa: A Prospective Test-Negative Study OFID published online October 19, 2022

doi.org/10.1093/ofid/ofac552

During 2015–2018, influenza vaccination campaigns targeting pregnant women were augmented at selected antenatal clinics; these were coupled with prospective hospital-based surveillance for acute respiratory or febrile illness in infants aged <6 months and cardiorespiratory illness among pregnant or postpartum women. Vaccine effectiveness (VE) was assessed using a test-negative case-control study.

Overall, 71 influenza-positive and 371 influenza-negative infants were included in the analysis; mothers of 26.8% of influenza-positive infants were vaccinated during pregnancy compared with 35.6% of influenza-negative infants, corresponding to an adjusted VE (aVE) of 29.0% (95% confidence interval [CI], -33.6% to 62.3%). When limited to vaccine-matched strains, aVE was 65.2% (95% CI, 11.7%–86.3%). For maternal hospitalizations, 56 influenza-positive and 345 influenza-negative women were included in the analysis, with 28.6% of influenza-positive women being vaccinated compared with 38.3% of influenza negatives, for an aVE of 46.9% (95% CI, -2.8% to 72.5%).

Comment: In this study covering 4 consecutive influenza seasons, influenza vaccination during pregnancy had an estimated effectiveness of 65% against influenza-associated hospital admissions in young infants, although VE was only demonstrated against influenza viruses considered to be vaccine matches. In this study, maternal influenza vaccination did not demonstrate effectiveness against hospitalization in WLWH (women living with HIV).

A multivalent nucleoside-modified mRNA vaccine against all known influenza virus subtypes Science 2022; 378:899-904

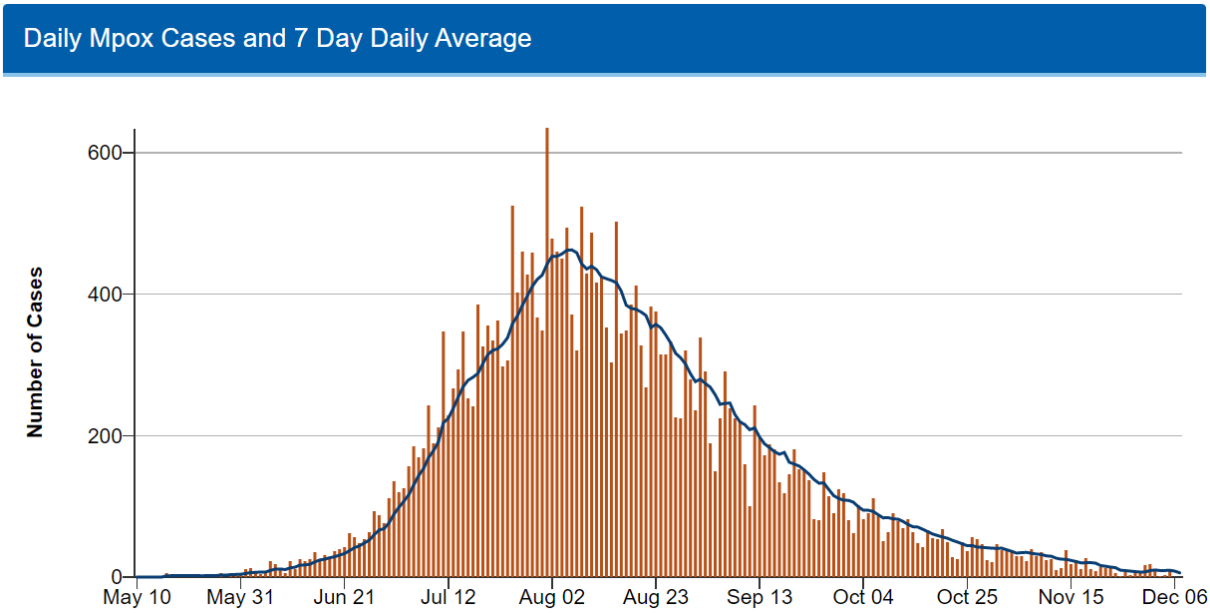
DOI: 10.1126/science.abm027

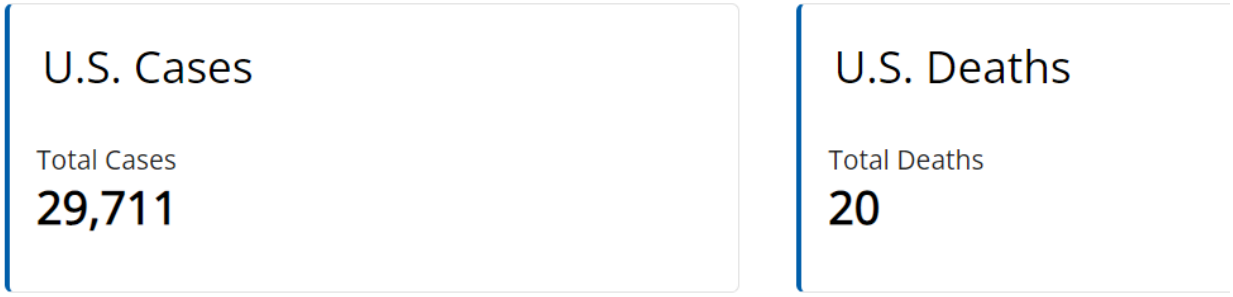
Investigators at the University of Pennsylvania developed an mRNA vaccine that simultaneously immunized against all 20 subtypes of flu virus with one injection. In mice and ferrets, it produced robust antibody production against the specific HA antigens from each of the 20 flu subtypes. Unimmunized animals became ill and died when challenged with an H1N1 virus; immunized animals displayed few or no clinical signs of infection — even when they were challenged with a "mismatched" strain (an avian flu whose HA was not included in the vaccine).

Comment: This effect is reminiscent of how SARS-CoV-2 vaccines that were based on the first variants have protected humans from severe disease caused by later variants. This study shows that an mRNA vaccine allows a single shot to protect against multiple different strains in animals. mRNA vaccines are faster to manufacturer and less expensive than current methods. More importantly a vaccine like this could be more effective than current annual influenza shots in humans.

Mpox

Mpox by the Numbers





Comment: As the graph demonstrates Mpox is down to very low numbers. This is a very encouraging trend.

Single and 2-dose vaccinations with modified vaccinia Ankara-Bavarian Nordic® induce durable B cell memory responses comparable to replicating smallpox vaccines J Infect Dis published online November 21, 20212

doi.org/10.1093/infdis/jiac455

Participants naïve to smallpox vaccination were randomized to 1 dose MVA-BN (1×MVA, N=181), 2 doses MVA-BN (2×MVA, N=183), or placebo (N=181). Participants with

previous smallpox vaccination received 1 MVA-BN booster (HSPX+, N=200). Subsets of the formerly naïve groups (~75 each) received an MVA-BN booster 2 years later.

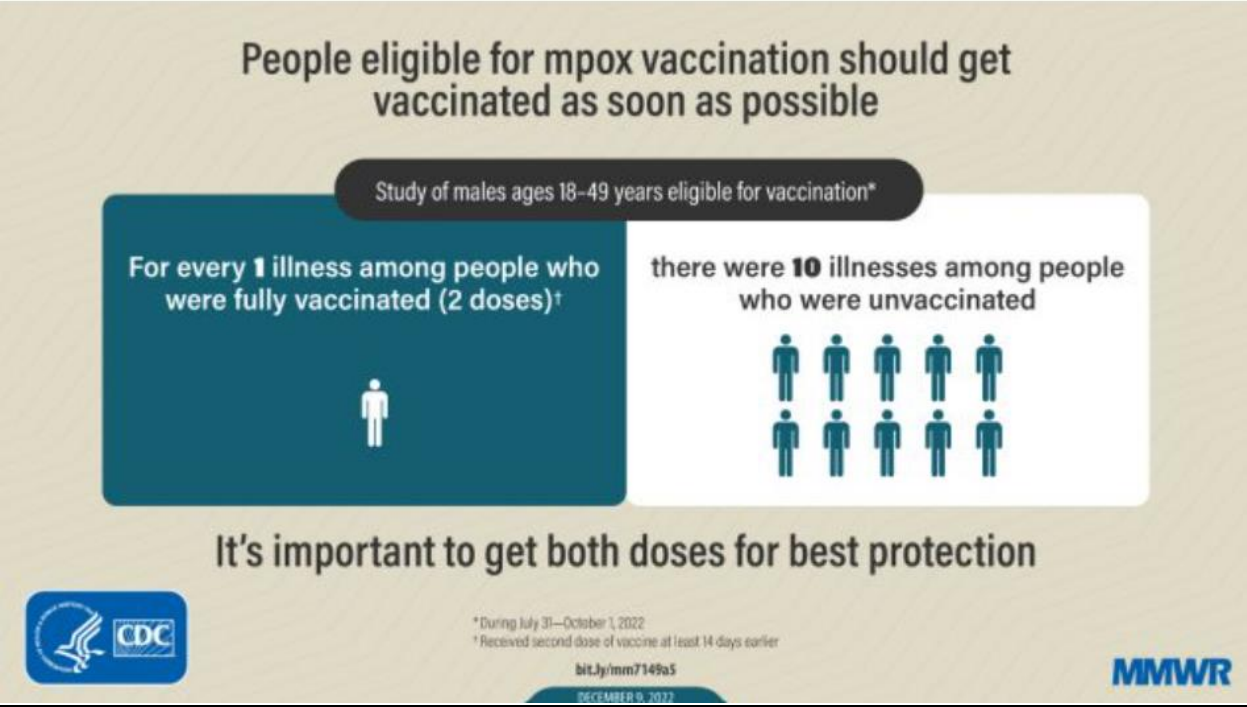
Neutralizing antibody (nAb) geometric mean titers (GMTs) increased from 1.1 (baseline, both naïve groups) to 7.2 and 7.5 (Week 4, 1×MVA and 2×MVA, respectively), and further to 45.6 (Week 6, 2×MVA after second vaccination). In HSPX+, nAb GMT rapidly increased from 21.6 (baseline) to 175.1 (Week 2). At 2 years, GMTs for 1×MVA, 2×MVA, and HSPX+ were 1.1, 1.3, and 10.3, respectively. After boosting in the previously naïve groups, nAb GMTs increased rapidly in 2 weeks to 80.7 (1×MVA) and 125.3 (2×MVA), higher than after primary vaccination and comparable to boosted HSPX+ subjects. Six months after boosting, GMTs were 25.6 (1×MVA) and 49.3 (2×MVA).

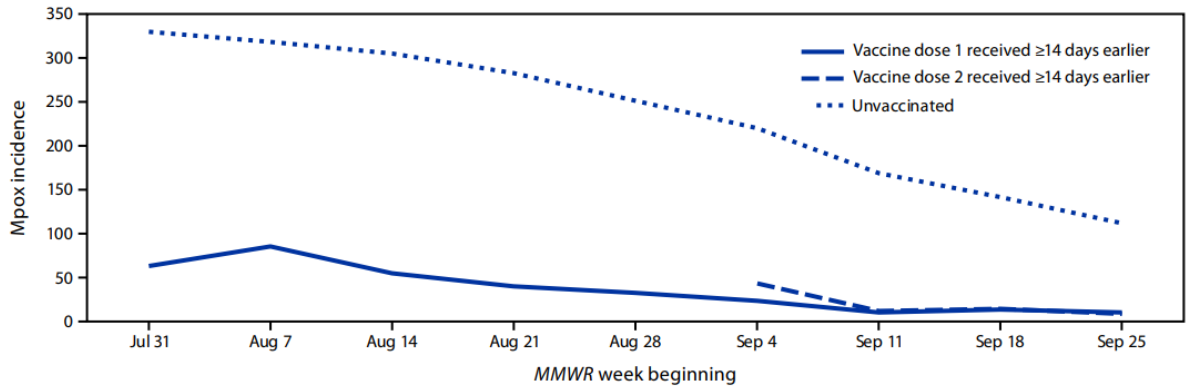
Comment: Priming with either 1 or 2 doses of MVA-BN induced durable immune memory, as boosting 2 years later elicited a rapid and sizable anamnestic response comparable to boosting following immunization in the distant past with older generation replicating smallpox vaccines. Because reports of myopericarditis were reported in military personnel administered replicating smallpox vaccines, cardiac events have been intensively monitored throughout the MVA-BN clinical development program. No safety concerns were identified. The study was conducted in a single European site, with very little racial or ethnic, however, other MVA-BN studies that enrolled a more diverse population have not revealed any racial difference in immunogenicity or safety. Another limitation is that the antigens used in the immune assays were based on vaccinia, and not on Monkeypox.

Reduced Risk for Mpox After Receipt of 1 or 2 Doses of JYNNEOS Vaccine Compared with Risk Among Unvaccinated Persons — 43 U.S. Jurisdictions, July 31–October 1, 2022. MMWR 2022; 71:1560-1564

This study was based on case data collected from 9,544 reported mpox cases among men aged 18 to 49 years from July 31 to October 1, 2022, from 43 US jurisdictions, and separated by vaccination status.

According to the study, 8,320 mpox infections (87.2%) occurred in unvaccinated men and 1,224 (12.8%) in vaccinated men, including 218 (17.8%) in those without a known vaccination date. Among cases in vaccinated men whose vaccination date was known, 614 (61%) were in those whose illness onset occurred 13 days or less after receipt of dose 1 and 392 (39%) in men with illness onset 14 days or more after receipt of dose 1. Among this group, 48 cases (12.2%) (0.5% of all cases) were among persons with illness onset 14 days or more after receipt of dose 2, the authors said. There was no difference in outcomes for subcutaneous or intradermal vaccine recipients.





Comment: The study as well as other studies reviewed in ID Watch show mpox cases were 9.6 times higher among unvaccinated men compared to those who had received two vaccine doses, and 7.4 times higher than in those who had received only the first dose. This analysis was unable to control for possible differences in testing or behaviors that affect the risk for Monkeypox virus exposure (e.g., reducing number of sexual partners), or possible differences in risk of infection because of patient characteristics (e.g., age, underlying medical conditions, and HIV-associated immune suppression); therefore, attribution of these results to vaccination cannot be definitively concluded from these data. The temporality of exposures that result in infection is not known, nor was it possible to determine whether vaccination was administered as postexposure or preexposure prophylaxis. Further study is needed to determine the magnitude and durability of protection, but evidence clearly indicates that JYNNEOS vaccination provides protection against Mpox.

COVID-19

FDA Authorizes Updated Covid-19 Vaccines for Children as Young as 6 Months

Under the decision, certain children 6 months through 5 years can get the updated bivalent vaccine. The latest authorization only applies to certain children. It clears use of the bivalent vaccine in children who got two doses of Moderna's original Covid-19 vaccine, or who got the first two doses of Pfizer's original vaccine. It does not apply to children who got all three initial doses of the Pfizer-BioNTech vaccine, however. The FDA said it is still evaluating extending the updated booster to those children. The reformulated vaccines will be given at the same dosages as earlier versions of the vaccine.

Comment: The uptake of the bivalent vaccines has been very disappointing. Vaccines in young children has also lagged older children and adults. Through November, only 1.8 million US children ages 6 months to 4 years have received at least one dose of a Covid-19 shot, about 10% of that age group, according to AAP. Polls have found large numbers of parents of children under 5 years opposed to vaccinating them. Roughly half of parents surveyed said they definitely won't vaccinate their children who are under 5 years, according to a poll published in September by the Kaiser Family Foundation. The FDA extended the authorizations of the boosters without results from testing in young children. Instead, the FDA said it relied on data from studies evaluating the bivalent shots in adults against certain substrains of Omicron, as well as information from previous studies about Covid-19 vaccines in children and adults.

Here we go again!

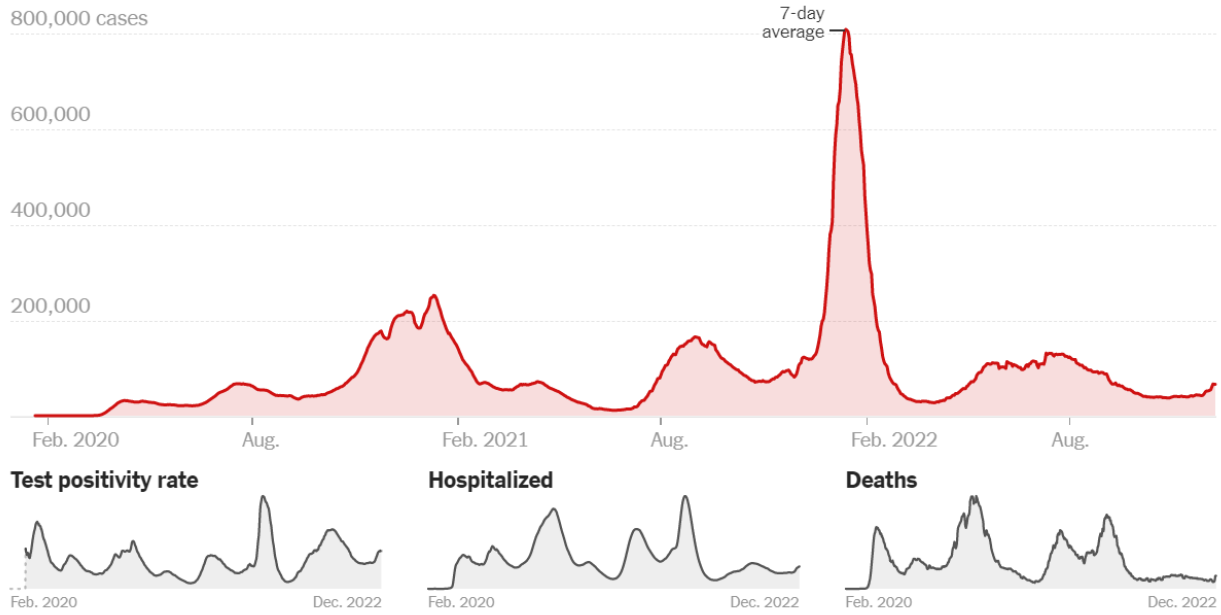
CDC recommends masks again in NYC and LA as well as other communities with increasing cases of Covid-19. A growing number of communities are now seeing Covid-19 cases and hospitalizations at levels high enough to warrant indoor masking and other measures to curb the virus, according to the CDC Thursday. According to the CDC's weekly update, 13.7% of Americans now live in communities now rated at "high" Covid-19 Community Levels, up from 4.9% of the population last week. An additional 38.1% of Americans are in "medium" areas and 48.2% are in "low" areas. More than 10 large counties are now in the "high" category:

- Los Angeles County, California (10,039,107 residents)
- Maricopa County, Arizona (4,485,414)
- Kings County, New York (2,559,903)
- Queens County, New York (2,253,858)
- San Bernardino County, California (2,180,085)
- Santa Clara County, California (1,927,852)
- New York County, New York (1,628,706)
- Suffolk County, New York (1,476,601)

- Bronx County, New York (1,418,207)
- Nassau County, New York (1,356,924)
- Pima County, Arizona (1,047,279)

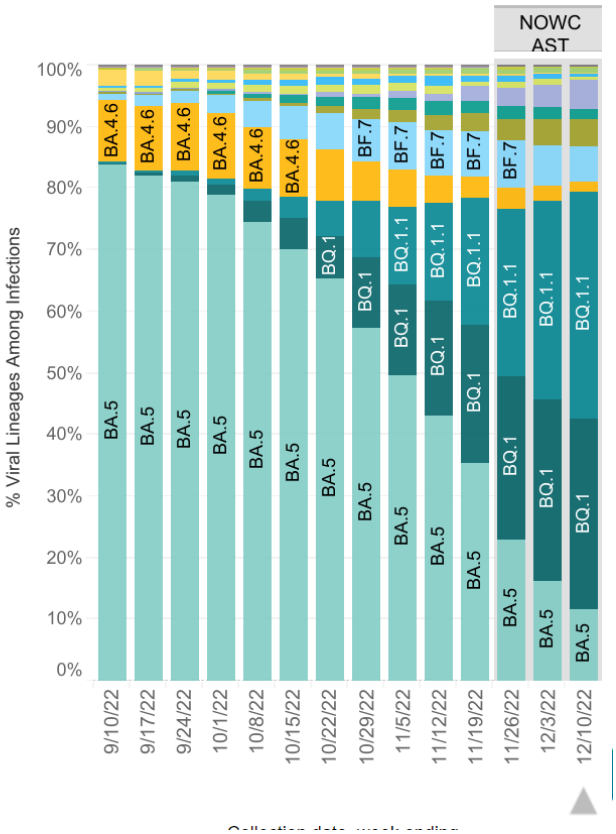
Comment: The list includes almost all of the New York metro area. Officials in the state recently urged schools to return to indoor masking to curb the spread of Covid-19 as well as the respiratory virus RSV and influenza. Authorities in Los Angeles have also warned that indoor masking rules might return there as cases have increased. The updated numbers come as CDC officials say they have been mulling new "pan-respiratory" benchmarks to measure the spread of all three currently circulating viruses. Roughly two in three cases are now estimated to be the BQ.1 or BQ.1.1 variants. See below Only around 15% of adults and 34% of seniors now have an updated bivalent booster. By comparison, CDC survey data estimates only 60% of seniors had an annual flu shot through November.

Covid-19 By the Numbers



USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BQ.1.1	VOC	36.8%	34.1-39.6%
	BQ.1	VOC	31.1%	29.0-33.4%
	BA.5	VOC	11.5%	10.3-12.7%
	BF.7	VOC	5.7%	5.0-6.5%
	XBB	VOC	4.7%	2.6-8.1%
	BN.1	VOC	4.3%	3.8-4.9%
	BA.5.2.6	VOC	1.7%	1.4-2.0%
	BA.4.6	VOC	1.6%	1.4-1.9%
	BF.11	VOC	0.8%	0.6-1.0%
	BA.2	VOC	0.7%	0.5-1.1%
	BA.2.75	VOC	0.6%	0.5-0.7%
	BA.2.75.2	VOC	0.4%	0.3-0.5%
	BA.4	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
	B.1.1.529	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%
Other	Other*		0.0%	0.0-0.1%



Comments: Conditions are worsening across the country, with reported cases and hospitalizations up more than 25 percent in the past two weeks and test positivity rates rising quickly. Since Thanksgiving, all but four states have seen hospitalization counts increase. The current surge is milder so far than at this point in previous winter waves, but its nationwide scope is concerning. So far deaths have not changed in the past two weeks and currently sit just below 350 per day. This increase has been driven by the increase in BQ.1 and BQ.1.1 which together now account for almost 70% of cases. The updated booster should offer some protection, but not optimal. Compared to BA.4 and BA.4, booster protection levels go down against the BQ pair. See reviews below

Bebtelovimab Update

The FDA announced on November 30, 2022, that bebtelovimab is no longer currently authorized for emergency use in the US because it is not expected to neutralize Omicron subvariants BQ.1 and BQ.1.1. Nowcast data from the CDC (see below) published last week estimates that the combined proportion of COVID-19 cases caused by the Omicron BQ.1 and BQ.1.1 subvariants to be above 57% nationally, and already above 50% in all individual regions but one, and data shows a sustained trend of increasing prevalence across all regions. Given that a COVID-19 infection is likely to be caused by a non-susceptible SARS-CoV-2 variant, and consistent with the terms and conditions of the Letter of Authorization, bebtelovimab is not currently authorized for emergency use in any U.S. region at this time.

Comment: Clinicians should use other approved or authorized products that are expected to retain activity against BQ.1 and BQ.1.1. which currently include the following:

- Nirmatrelvir-ritonavir is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.
- RDV is approved for the treatment of adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.
- Molnupiravir is authorized for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.
- COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is still authorized for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings. COVID-19 convalescent plasma is not authorized to treat immunocompetent patients with COVID-19.

Association of COVID-19 with diabetes: a systematic review and meta-analysis

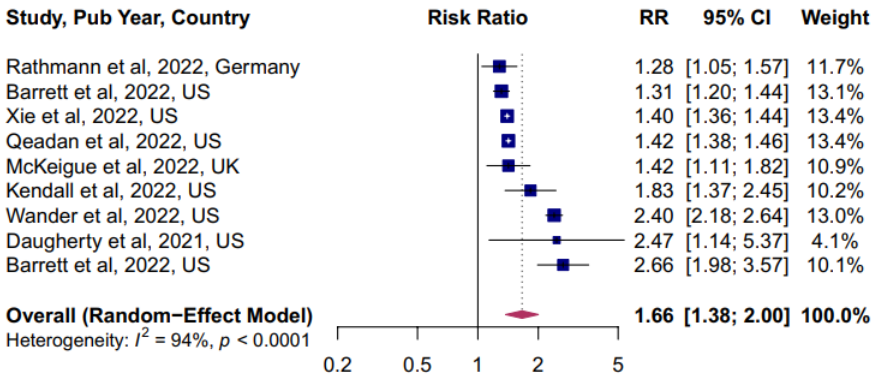
Scientific Reports 2022 12:20191

doi.org/10.1038/s41598-022-24185-7

Emerging evidence suggests that Covid-19 may lead to new onset of diabetes. [MMWR 2022 71: 59–65; Lancet Diabetes Endocrinol. 2021; 9:786–798] The exact mechanisms for incident diabetes in survivors of Covid-19 are not well understood, but it is likely that complex interrelated processes are involved, including previous stress hyperglycemia, steroid induced hyperglycemia, and direct or indirect effects of SARS-CoV-2 on the β-cells of pancreatic islets.

[Annu. Rev. Med. 2022; 73:129–147] A previous study with more than 180,000 veterans found that patients who survived Covid-19 were 40% more likely to develop diabetes than those who were never diagnosed with Covid-19. [Lancet Diabetes Endocrinol*. 2022;* 10: 311–321] Moreover, another study found that up to 14% of people hospitalized for COVID-19 were diagnosed with diabetes later. A previous systematic review and meta-analysis was limited to only a proportion of newly diagnosed diabetes after COVID-19 with no comparison groups. [Diabetes Obes. Metab.2021; 23:870–874] This systemic review is aimed to fill a possible knowledge gap by conducting a systematic review and meta-analysis to determine if their truly is an association of Covid-19 with new onset diabetes.

In this systematic review and meta-analysis of 8 cohort studies including over 47 million participants, Covid-19 was associated with a 66% higher risk of diabetes compared to the controls without Covid-19. The risk was not modified by age, sex, and study quality. The risk of bias assessment was low. Their findings are consistent with the previous meta-analysis that assessed the proportion of Covid-19 survivors with incident diabetes.



Comment: Potential mechanisms of new-onset diabetes are multifaceted and not fully understood. SARS-CoV-2 is known to bind to angiotensin-converting enzyme 2 and transmembrane serine protease 2 receptors, which are expressed in key metabolic organs and tissues, including pancreatic beta cells, adipose tissue, the small intestine, and the kidneys. [Front. Cell Infect. Microbiol*.* 2021; 11: 678482–678482] Furthermore, it has been demonstrated that SARS-CoV-2 infection attenuates pancreatic insulin levels and secretion and induces β cell apoptosis. [Cell Metab 2021; 33:1565-1576.e1565] SARS-CoV-2 is not the only virus associated with diabetes. A significant number of other viruses are associated with type 1 diabetes through molecular mimicry, including Coxsackievirus B, and cytomegalovirus. The studies chosen demonstrated a high degree of heterogeneity, which could have been caused by pooling studies from different sociodemographic populations. Due to the limited number of studies included in the present meta-analysis, they could not categorize the risk by the type of diabetes such as type 1 and type 2. Moving forward it seems reasonable to actively monitoring glucose after recovery from Covid-19.

The free fatty acid–binding pocket is a conserved hallmark in pathogenic β-coronavirus spike proteins from SARS-CoV to Omicron Sci. Adv.2022; 8: eadc9179 article suggested by Carlos Plasencia

DOI: 10.1126/sciadv.adc9179

In this new study investigators examined the spike structure conserved for all coronaviruses. Their research discovered a tailor-made pocket feature in the SARS-CoV-2 spike protein, first discovered in 2020, is present in all serious coronaviruses, including MERS and Omicron. In striking contrast, the pocket feature is not present in coronaviruses which cause mild infection with cold-like symptoms. In their earlier work they identified the presence of a small molecule, linoleic acid, buried in a tailor-made pocket within the SARS-Cov-2 glycoprotein, known as the spike protein, which binds to the human cell surface, allowing the virus to penetrate the cells and start replicating, causing widespread damage.

The investigators showed that binding linoleic acid in the pocket could stop virus infectivity, suggesting an anti-viral treatment. This initial work was with the original Wuhan strain. Since then, a whole range of SARS-CoV-2 variants have emerged, most recently Omicron. They then tested every new variant of concern and asked whether the pocket function is still present. The team applied high-resolution electron cryo-microscopy, cutting-edge computational approaches, and cloud computing. Their results showed that SARS-CoV and MERS-CoV also had the pocket, and could bind the ligand, linoleic acid, by a virtually identical mechanism.

These findings suggest that the pocket, which binds a small molecule, linoleic acid-an essential fatty acid indispensable for many cellular functions including inflammation and maintaining cell membranes in the lungs so that we can breathe properly-could now be exploited to treat all serious coronaviruses, at the same time rendering them vulnerable to a linoleic acid-based treatment targeting this pocket.

Comment: Omicron has undergone many mutations, enabling it to escape immune protection offered by vaccination or antibody treatments. Despite the mutations the investigators found that the pocket remained virtually unaltered, also in Omicron. These results could establish FFA binding as a hallmark of pathogenic β-CoV infection and replication, setting the stage for FFA-based antiviral strategies to overcome Covid-19.

Shifting Mortality Dynamics in the United States During the COVID-19 Pandemic as Measured by Years of Life Lost Ann Intern Med published online November 29, 2022

doi:10.7326/M22-2226

The investigators set out to quantify this downward age shift in COVID-19–involved deaths, which required an age-weighted metric. Unlike the mortality metric, the measure of years of life lost (YLL) offers an indicator of premature mortality based on the estimated number of years a person would have lived if they had not died prematurely. Mortality data from March to December in 2020 and 2021 were obtained from CDC WONDER(Centers for Disease Control and Prevention Wide-ranging ONlineData for Epidemiologic Research), an integrated system of public-use data sets spanning public health topics . Age-specific standard life expectancies were obtained from the 2017 World Population Prospects and WHO Global Health Estimate, providing frontier-period life expectancy projections for the year 2050 to represent lifespans thought to be achieved by a substantial number of people alive at the time of this analysis. For the 15 leading causes of death, YLL were estimated, comparing March to December 2020 with March to December 2021 to minimize the effects of seasonal variation in mortality on the comparator intervals.

The 15 leading causes of US death were the same in both 10-month intervals and accounted for approximately 80% of deaths. Unsuppressed data were available for 99.95% of deaths. The YLL associated with most of the leading causes of US. Deaths were stable across intervals. Three of the four causes of death that exhibited larger than 10% changes in deaths across the study intervals had concordant changes in YLL. Specifically, YLL due to unintentional injuries increased by 10.5%, comparable to the 11.0% increase in unintentional injury deaths. Large and similar decreases in YLL and deaths were observed for influenza and pneumonia (YLL, -14.6%; deaths, -16.0%) and Alzheimer disease (YLL, -12.6; deaths,-14.2%). In contrast, despite 20.8%fewer COVID-19 deaths during March to December 2021 than during March to December 2020, YLL due to COVID-19 increased by 7.4% as the age distribution of decedents shifted downward (that is, to relatively younger persons); the median (interquartile range) age of COVID-19–involved deaths decreased from 78 years (68 to 87 years) to 69 years (59 to 80 years). Accordingly, YLL per COVID-19 death increased by 35.7%; YLL per death did not change by more than 2.2% for any other cause.

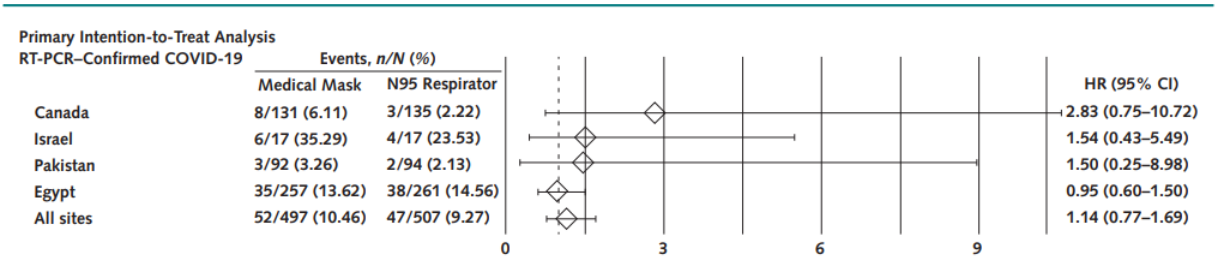
Medical Masks Versus N95 Respirators for Preventing COVID-19Among Health Care Workers Ann Intern Med published online November 29, 2022

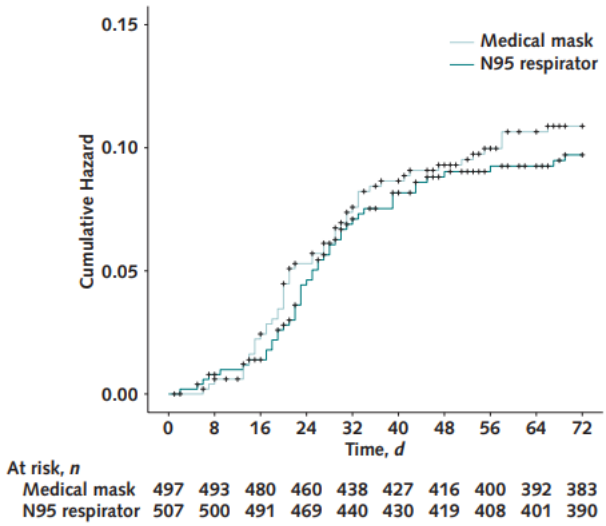
doi:10.7326/M22-1966

This is a randomized trial which tracked COVID-19 infections among 1,009 HCWs directly caring for infected patients at 29 hospitals in Canada, Israel, Pakistan, and Egypt from May 4, 2020, to March 29, 2022. HCWs were randomly assigned to wear either medical masks or a fit-tested N95 filtering facepiece respirator (FFR) for 10 weeks (the fit-testing protocol wasn't defined). HCWs were instructed to wear a mask or respirator when caring for patients with confirmed or suspected COVID-19, according to the current policy at their hospital. HCWs in Canada were allowed to make their own decisions about whether to don a mask or N95, regardless of which intervention they were assigned to.

COVID-19 infection was confirmed using PCR in 52 of 497 (10.46%) HCWs in the medical mask group, compared with 47 of 507 (9.27%) in the N95 group (hazard ratio [HR], 1.14; 95% confidence interval [CI], 0.77 to 1.69).

A subgroup analysis showed that 8 of 131 (6.11%) HCWs in the medical mask group and 3 of 135 (2.22%) in the N95 group were infected in Canada (HR, 2.83; 95% CI, 0.75 to 10.72), as were 6 of 17 (35.29%) versus 4 of 17 (23.53%) in Israel (HR, 1.54; 95% CI, 0.43 to 5.49), 3 of 92 (3.26%) versus 2 of 94 (2.13%) in Pakistan (HR, 1.50; 95% CI, 0.25 to 8.98), and 35 of 257 (13.62%) versus 38 of 261 (14.56%) in Egypt (HR, 0.95; 95% CI, 0.60 to 1.50).





Comment: The study is underpowered but ruled out a doubling of hazard for use of medical masks. Meaning the surgical masks were not statistically less effective than N95s in preventing COVID-19 infections in HCWs looking after patients with COVID-19. The investigators cautioned that HCWs could have been infected outside of the hospital and that the results may not apply to other countries because of differences in treatment effects. Also, wide confidence intervals [see above Forest plot] indicating a high degree of uncertainty, Differences in self-reported adherence and baseline SARS-CoV-2 antibody status, and between-country differences in vaccination coverage and dominant circulating variants may have distorted the results. The study, however, did show a general trend to N95s being superior to surgical masks at all sites except Egypt. The study also noted that both study arms used an N95 respirator for aerosol-generating procedures, and the intervention was tested only for periods of care outside of such procedures. In addition, another problem with this study is that many HCWs are infected by patients with unrecognized Covid-19. [J Infect Dis 2022; 226:191-194] In addition, only 81% of N95 users reported using them all the time. A previously published study showing that N95s must be worn continuously during a shift to be effective—including while caring for patients assumed to be non-infectious and conducting non-patient care activities—consistent with ubiquitous airborne transmission risk in healthcare settings. [AJRCCM 2013; 187:960-966] About a quarter of participants reported never caring for COVID patients yet were still included in the analysis The noninferiority threshold set in the study may be unacceptable to HCWs (5% absolute increase in COVID-19 infections, a doubling of risk with medical masks). A commentary pointed out: "There was substantial heterogeneity in outcomes by country. A post hoc analysis stratified by country reported hazard ratios that ranged from 0.95 in Egypt (where participants were enrolled later in the pandemic and seroprevalence was high) to 2.83 in Canada (where participants were enrolled early in the pandemic and seroprevalence was low). Among the factors that could contribute to this heterogeneity are differences in vaccine types, vaccination rates, infection control measures, local transmission dynamics, and enrollment during periods when different variants were predominantly circulating. This heterogeneity warrants caution in the interpretation of the trial findings." Despite the results in this study that medical masks may be similar to N95 masks in the Omicron-era with high local immunity I would say at best these results are not definitive given all the weaknesses of this study outlined above.

Association of Initial SARS-CoV-2 Test Positivity With Patient-Reported Well-being 3 Months After a Symptomatic Illness

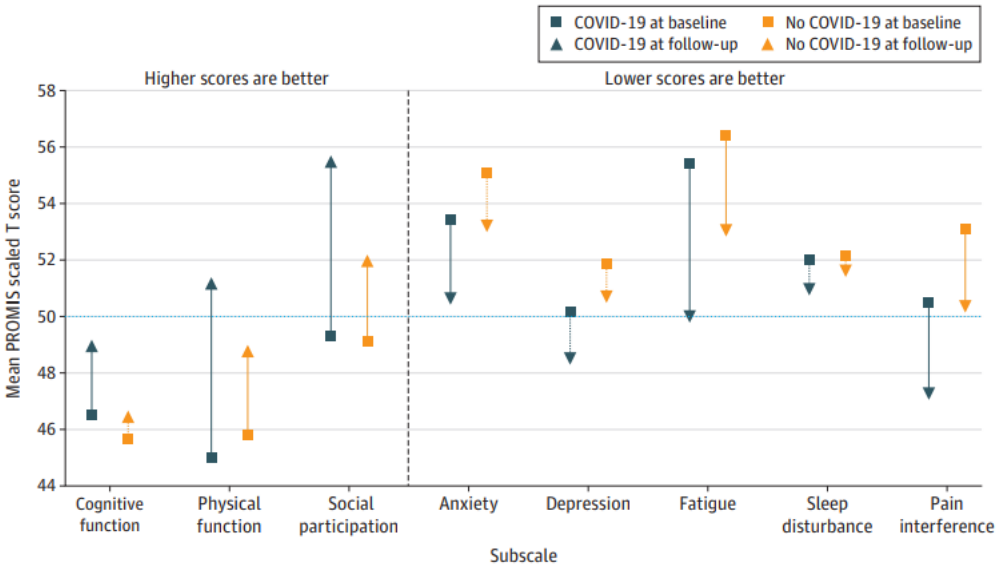
JAMA Netw Open published online December 1, 2022. JAMA Network Open. 2022;5(12):e2244486.

doi:10.1001/jamanetworkopen.2022.44486

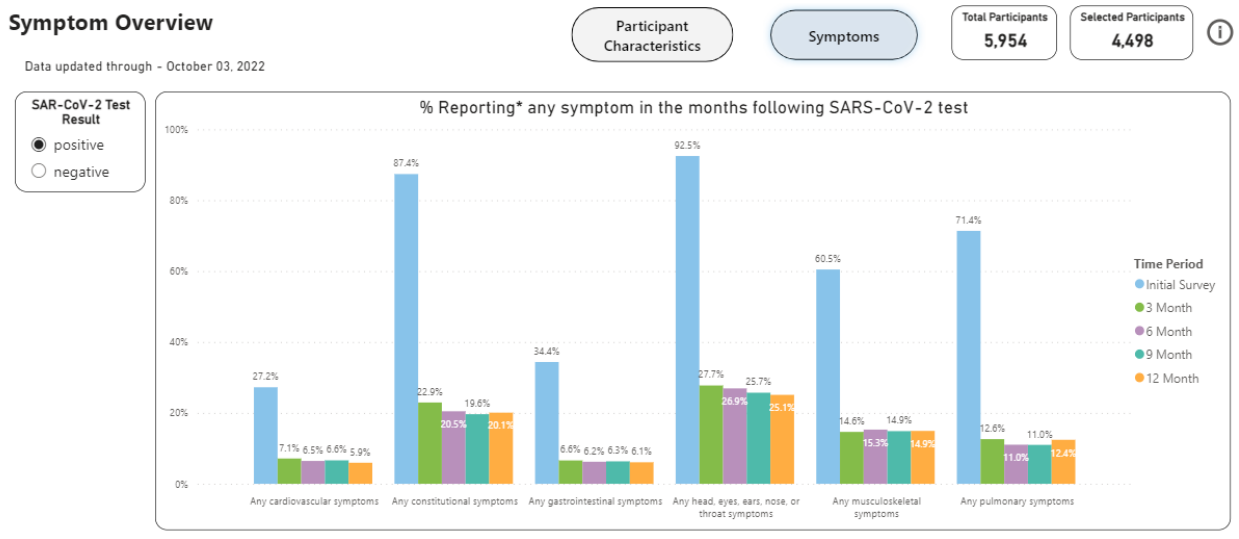
The purpose of this study was to compare patient-reported outcomes of physical, mental, and social well-being among adults with symptomatic illness who received a positive vs negative test result for SARS-CoV-2 infection. Participants were enrolled from December 11, 2020, to September 10, 2021, and comprised adults (aged 18 years) with acute symptoms suggestive of SARS-CoV-2 infection at the time of receipt of a SARS-CoV-2 test approved by the FDA. The analysis included the first 1000 participants who completed baseline and 3-month follow-up surveys consisting of questions from the 29-item Patient-Reported Outcomes Measurement Information System (PROMIS-29; 7 subscales, including physical function, anxiety, depression, fatigue, social participation, sleep disturbance, and pain interference) and the PROMIS Short

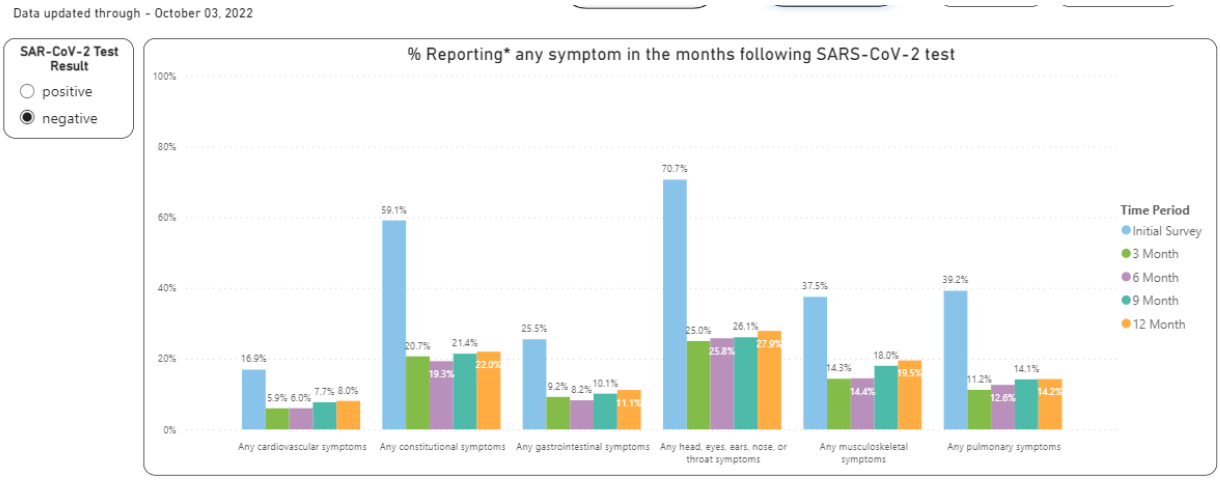
Form–Cognitive Function 8a scale, for which population-normed T scores were reported. Mean PROMIS scores for participants with positive Covid-19 tests vs negative Covid-19 tests were compared descriptively and using multivariable regression analysis.

Among 1000 participants, 722 (72.2%) received a positive COVID-19 result and 278 (27.8%) received a negative result; 406 of 998 participants (40.7%) were aged 18 to 34 years, 644 of 972 (66.3%) were female, 833 of 984 (84.7%) were non-Hispanic, and 685 of 974 (70.3%) were White. A total of 282 of 712 participants (39.6%) in the Covid-19–positive group and 147 of 275 participants (53.5%) in the Covid-19–negative group reported persistently poor physical, mental, or social well-being at 3-month follow-up. After adjustment, improvements in well-being were statistically and clinically greater for participants in the Covid-19–positive group vs the Covid-19– negative group only for social participation (β = 3.32; 95% CI, 1.84-4.80; *P* < .001); changes in other well-being domains were not clinically different between groups. Improvements in well-being in the Covid-19–positive group were concentrated among participants aged 18 to 34 years (e.g., social participation: β = 3.90; 95% CI, 1.75-6.05; *P* < .001) and those who presented for Covid-19 testing in an ambulatory setting (e.g., social participation: β = 4.16; 95% CI, 2.12-6.20; *P* < .001).



Comment: In this study, participants in both the Covid-19–positive and Covid-19–negative groups reported persistently poor physical, mental, or social well-being at 3-month follow-up. Although this study aimed to recruit a diverse population across the US, the requirement for access to a verifiable Covid-19 test, existing electronic health record system, and internet-enabled devices to administer study components may have biased the sample. Finding an appropriate comparison group for Covid-19–positive participants is difficult, and comparison with participants with symptomatic illness who test negative provides information on the ways in which infection with SARS-CoV-2 may differ from acute infection with other viruses; however, comparison with this Covid-19–negative group may underestimate the decrement in well-being compared with the general population who do not experience illness. In addition, participants recruited through September 2021, so findings may not be applicable to later variants. Their analyses only include data from participants who completed both the baseline survey and the 3-month follow-up survey; 3-month postbaseline assessment represents short-term observation of changes in well-being. Longer follow-up is necessary. These findings may reflect the impact of infection severity at presentation and emphasize the importance of comparing Covid-19–positive participants with a concurrent control group of COVID-19–negative. Covid-19 tests may yield false-negative or false-positive results, therefore, they cannot exclude the possibility that some participants may have been misclassified. Below is from CDC Covid-19 tracker. The graphs below represent longitudinal multicenter, observational cohort of adults with acute Covid-like symptoms who test positive for SARS-CoV-2 and a comparison group of adults with acute Covid-like symptoms who test negative for SARS-CoV-2. Participants are being followed-up every 3 months for a maximum of 18 months.





Symptoms reported at 3, 6, 9, 12, 15, and 18 months:
- Any cardiovascular symptoms (chest pains, palpitations)
- Any constitutional symptom (tired, chills, feeling hot, fever, shakes)
- Any gastrointestinal symptoms (diarrhea, nausea/vomiting, abdominal pain)
- Any head, eyes, ears, nose, or throat symptom (headache, runny nose, loss of smell, loss of taste, sore throat, loss of hair)
- Any musculoskeletal symptoms (aches, joint pains)
- Any pulmonary symptoms (cough, shortness of breath, wheezing)

*Participants can report symptoms in more than one group. Estimates are not adjusted for common demographic and clinical characteristics (e.g. age, co-morbidities). Follow-up and data collection are on-going and missing data is not presented.

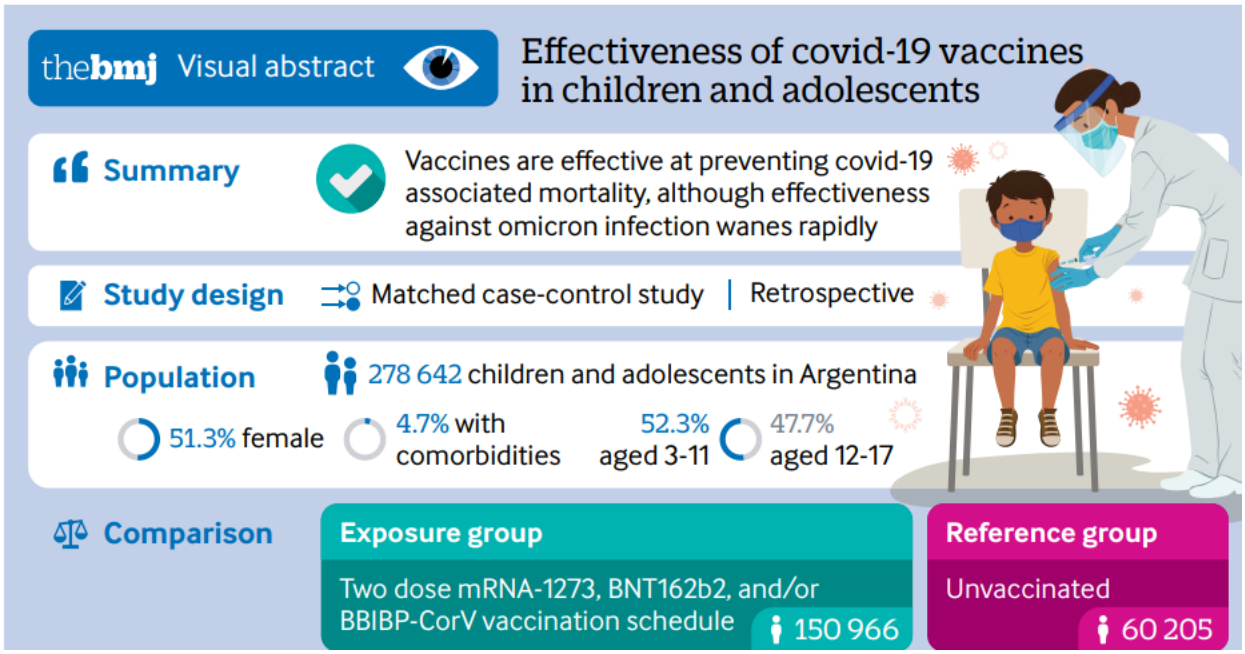
COVID + participants had COVID-like symptoms and tested positive for SARS-CoV-2 infection within 42 days of enrollment

In summary in this cohort study and data from the CDC Tracker, SARS-CoV-2 infection was not associated with worse physical, mental, and social well-being (as measured through PROMIS scores) at 3-month follow-up compared with no SARS-CoV-2 infection among adults with symptomatic illness. These findings emphasize the importance of including a concurrent control group when studying sequelae of Covid-19 illness.

Effectiveness of mRNA-1273, BNT162b2, and BBIBP-CorV vaccines against infection and mortality in children in Argentina, during predominance of delta and omicron covid-19 variants: test negative, case-control study BMJ2022;379: e073070

doi.org/10.1136/ bmj-2022-073070

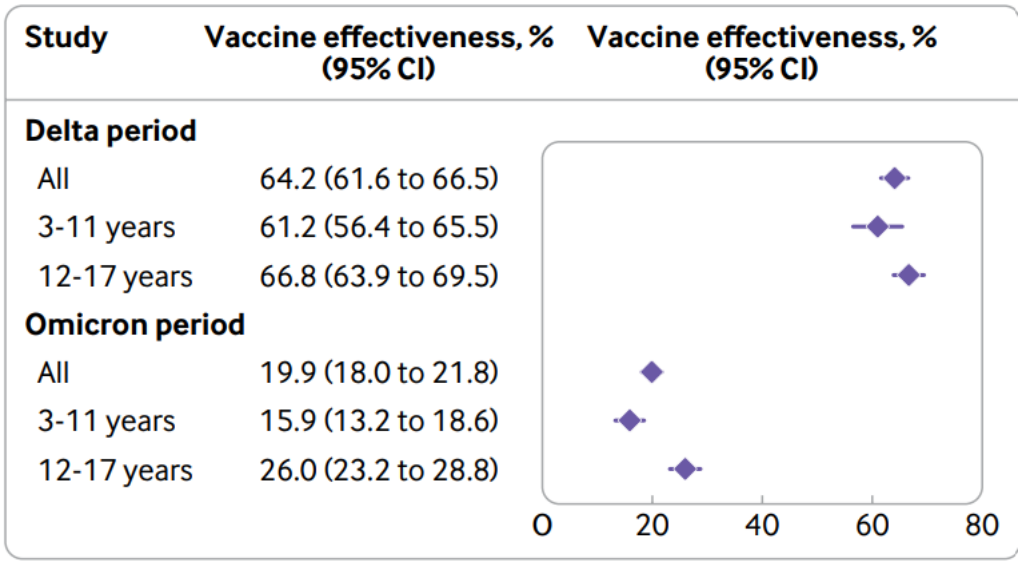
Thea objective of this study was to estimate the effectiveness of a two dose vaccine schedule (mRNA-1273, BNT162b2, and BBIBPCorV-Sinopharm) against SARS-CoV-2 infection and covid-19 related death and short term waning of immunity in children (3-11 years old) and adolescents (12-17 years old) during periods of delta and omicron variant.



844,460 children and adolescents without previous SARS-CoV-2 infection were eligible to receive primary vaccination schedule who were tested for SARS-CoV-2 by PCR or rapid antigen test from September 2021 to April 2022. After matching with their corresponding controls, 139,321 (60.3%) of 231,181 cases remained for analysis. Main outcomes were SARS-CoV-2 infection and Covid-19 related deaths.

Estimated vaccine effectiveness against SARS-CoV-2 infection was 61.2% (95% confidence interval 56.4% to 65.5%) in children and 66.8% (63.9% to 69.5%) in adolescents during the delta dominant period and 15.9% (13.2% to 18.6%) and 26.0% (23.2% to 28.8%), respectively, when omicron was dominant. Vaccine effectiveness against death related to SARS-CoV-2 infection during omicron predominance was 66.9% (6.4% to 89.8%) in children and 97.6% (81.0% to 99.7%) in adolescents. Heterologous mRNA schedules showed comparable to superior VE in comparison with homologous schedules. VE in preventing mortality in children vaccinated with BBIP-CoV was lower than in adolescents vaccinated with mRNA vaccines.

Vaccine effectiveness declined over time, especially during the omicron period, from 37.6% (34.2% to 40.8%) at 15-30 days after vaccination to 2.0% (1.8% to 5.6%) after ≥60 days in children and from 55.8% (52.4% to 59.0%) to 12.4% (8.6% to 16.1%) in adolescents.



Comment: Vaccine effectiveness in preventing mortality remained high in children and adolescents regardless of the circulating variant. Vaccine effectiveness in preventing SARS-CoV-2 infection in the short term after vaccination was lower during omicron predominance and decreasing significantly over time. Although prior studies suggest a reduction in VE for SARS-CoV-2 infection over time, observational studies have shown that VE against severe disease is higher and more stable. Limitations of this study include that some information, such as symptoms and hospital admissions, was incomplete and was consequently not included in any analysis. Each age group used different vaccines, so any conclusion based on their differences should not be attributed exclusively to the vaccine technology or to age related factors. Finally, information about variants could not be established at an individual level, and so they used the prevalent variant from surveillance data when analyzing the results.

SARS-CoV-2 viral load and shedding kinetics Nat Rev Microbiol published online December 2, 2022

Doi.org/10.1038/s4579-022-00822-W

Highlights

Viral shedding is influenced by biological characteristics of the virus, host factors and pre-existing immunity (previous infection and/or vaccination) of the infected individual. Although the process of human-to-human transmission is multifactorial, viral load substantially contributed to human-to-human transmission, with higher viral load posing a greater risk for onward transmission. Emerging SARS-CoV-2 variants of concern have further complicated the picture of virus shedding. As underlying immunity in the population through previous infection and/or vaccination has rapidly increased after almost 3 years of the pandemic, viral shedding patterns have become more distinct from those of the strain. Understanding the factors and mechanisms that influence infectious virus shedding and the period during which individuals infected with SARS-CoV-2 are contagious is crucial to guide public health measures and limit transmission.

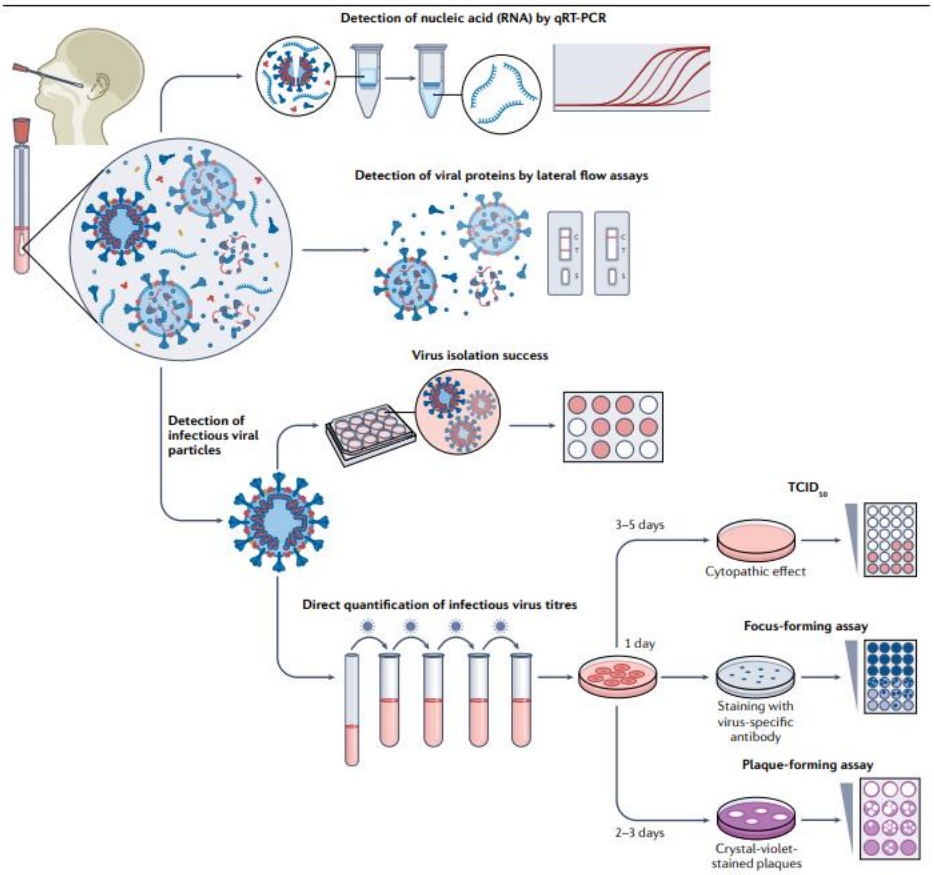
Furthermore, diagnostic tools to demonstrate the presence of infectious virus from routine diagnostic specimens are needed.

The gold standard for laboratory diagnosis of a respiratory tract infection is demonstration of viral RNA with a virus-specific (semi-)quantitative RT-PCR from material collected from the respiratory tract. The most used materials are swab specimens from the nasopharynx or oropharynx. Viral load as determined by RT-PCR is either expressed as the number of viral RNA copies per milliliter of viral transport medium or per swab, or by the arbitrary test-specific Ct value. By contrast, infectiousness is determined by qualitative or quantitative assessment of infectious virus in a clinical specimen by replication of virus in cell culture.

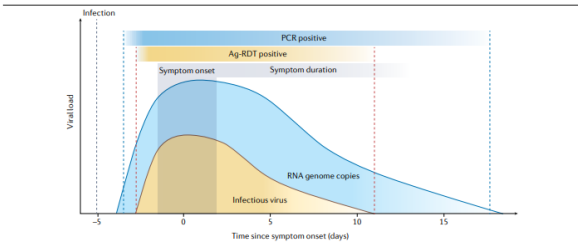
Techniques for detecting viral RNA by RT-PCR were quickly established at the beginning of the pandemic. The high specificity and sensitivity of RT-PCR make it the gold standard for diagnosing SARS-CoV-2 infections. Quantitative RT-PCR assays provide a Ct value, which is inversely correlated with the concentration of the target viral RNA in the clinical sample (that is, the higher the value, the lower the target RNA in the sample).

Most lateral flow tests are designed to detect SARS-CoV-2 nucleocapsid protein, as a proxy for infectious virus, in nasal or nasopharyngeal swabs. Indeed, most studies on Ag-RDT detection show good concordance with RT-PCR positivity when Ct values are below 25–30, a viral load compatible with the presence of infectious virus, whereas higher Ct values give less reliable results. see figure below

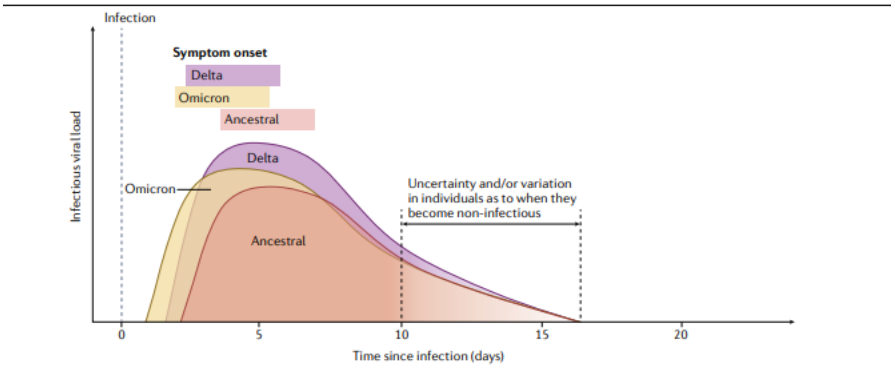
On average, the first positive Ag-RDT results are obtained about 1–2 days later than positive PCR results, whereas the highest sensitivity in patients was shown during the first 7 dpos(post-onset of symptoms) in the studies with ancestral SARS-CoV-2. Antigen tests show highest sensitivity for specimens containing infectious virus and with Ct values below 25, and their positivity highly correlates with the presence of infectious virus. By contrast, Ag-RDTs are less sensitive to low RNA viral loads (which have higher Ct values). Several studies have demonstrated a strong correlation between Ag-RDT positivity and the period in which infectious virus can be detected, indicating that Ag-RDTs can add an additional safety layer for deciding when to end isolation. [JAMA Intern. Med. 2022;182, 701–709]



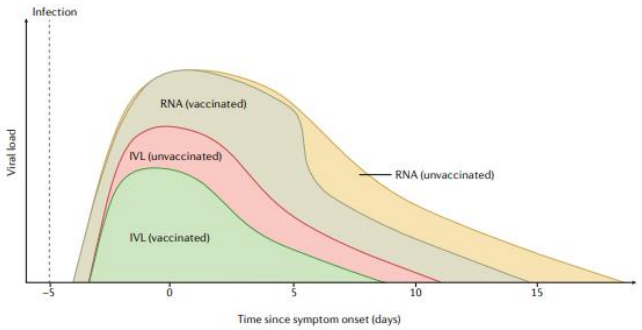
Studies showed peak viral loads at the time of symptom onset or even shortly before. RNA viral loads gradually declined over the course of the disease in the nasopharyngeal and throat swabs, reaching low or undetectable levels 2 weeks after symptom onset. (see below) Declining RNA viral load is associated with resolution of clinical symptoms and gradual increase in antibody titers. However, ongoing detection of viral RNA has been described for prolonged periods up to 28 dpos in otherwise healthy individuals. Infectious virus shedding of the ancestral SARS-CoV-2 strain, as determined by virus isolation in cell culture, was reported to correlate with high RNA viral load in the early acute phase after symptom onset [Clin. Infect. Dis. 2020 71, 2663–2666. Importantly, daily longitudinal sampling of respiratory specimens from individuals with mild disease or asymptomatic infection revealed that infectious virus can already be detected before the onset of symptoms. [Nat. Microbiol.2022; 7: 640–652] Successful infectious virus isolation was reported within the first 8–10 dpos, but culture probability after this time period rapidly declined. [J. Infect. Dis.2021; 224: 771–776] Prolonged detection of viral RNA was also reported in immunocompromised patients.



Viral evolution of SARS-CoV-2 over time has led to the emergence of numerous variants. Combined with increasing population immunity due to vaccination or natural infection, this has led to a need to reassess our knowledge of viral shedding patterns. Delta reportedly led to an even higher increase in RNA viral load compared to Alpha or ancestral strain.: one study reported a 1,000× increase relative to the ancestral virus, and other studies reported 1.7× or 6.2× higher viral load than Alpha. Furthermore, Delta demonstrated elevated probability of cell culture isolation and higher infectious virus titers than Alpha. Although Omicron was shown to be highly transmissible, lower RNA viral loads, lower cell culture isolation probability and lower infectious virus titers 25 were observed in patients infected with Omicron BA.1 than in those infected with Delta. Even within the Omicron clade, there are differences between sub-lineages, with infection with Omicron BA.2 leading to higher levels of RNA viral loads and longer time to viral clearance than with Omicron BA.1 [Preprint at medRxiv 2022; https://doi.org/10.1101/2022.04.02.22273333]. Studies have also shown differences in the duration of viral shedding. Analysis of Ct values in respiratory specimens found that Delta showed longer persistence of viral RNA than ancestral SARS-CoV-2 . Another study demonstrated that there was not significant difference in the mean duration of viral RNA presence in Delta and Omicron BA.1 infection. The duration of infectious virus shedding appears to be similar to that observed with ancestral SARS-CoV-2, with culturable virus obtained at 5 dpos85 and no replication-competent virus isolated beyond 10 dpos in patients infected with Delta and Omicron BA.1. [Emerg. Infect. Dis. 2022; 28, 998–100] See below



It is also important to note that pre-existing immunity to SARS-CoV-2, either from infection and/or vaccination, might influence the duration of infectious virus. Viral loads continue to play a key role in the SARS-CoV-2 transmission. The host including the role of vaccination or/and previous infection and viral factors (SARS-CoV-2 variants) greatly influence viral load dynamics and therefore may further impact viral transmission. Overall, vaccination has been found to lead to reduced viral load. See below



Infectious viral loads (IVLs)

Shedding of other Respiratory Viruses

RSV

The virus is transmitted by contact with nasal secretions or large aerosols. Viral loads and symptoms increased simultaneously, reaching a peak at 5.4 days. In human challenge trials, RSV titers were detectable for an average of 4.6 days. Viral RNA could be still detected up to 9 dpos, whereas infectious virus titers could be detected from 1 to 8 dpos in adults and up to 9 dpos in children.

Influenza

In symptomatic patients, RNA viral loads start to be detectable by PCR 2 days before the onset of symptoms and peak at 1 dpos. Human challenge trials with influenza A viruses show that viral loads already sharply increase at 1-day post-inoculation, reach a peak at 2 days post-inoculation and become undetectable at 8 days post-inoculation. The mean duration of viral shedding for influenza viruses is 4.8 days, and the maximum duration is between 6 and 7 days. Kinetics of infectious viral titers were similar to the viral load trends detected by PCR for different strains of influenza. Lower RNA viral loads and shorter infectious viral shedding were noted in asymptomatic patients.

MERS-CoV

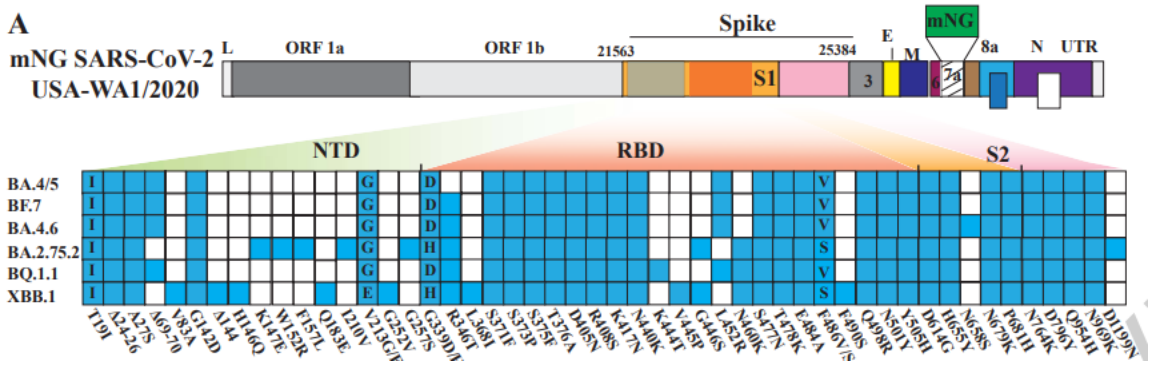
The virus is capable of airborne transmission and has low transmissibility among humans, with a maximum estimated reproduction number below 1. Viral shedding starts with onset of symptoms. Higher RNA viral loads were detected in the LRT than in the URT. Estimated mean shedding duration is 15.3 days in the URT and 16.3 days in the LRT. Prolonged PCR positivity and higher RNA viral loads in the URT and LRT were associated with increased disease severity. Viral RNA was also detected in the urine, stool and serum. One study reported detection of viral RNA in the blood for 34 days and showed that presence of viral RNA in the blood is associated with higher mortality; however, another study failed to isolate virus from PCR-positive serum samples.

Comment: This is an excellent review and worth the read.

Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1, and XBB.1 by parental mRNA vaccine or a BA.5-bivalent booster. Nat Med published online December 6, 2022

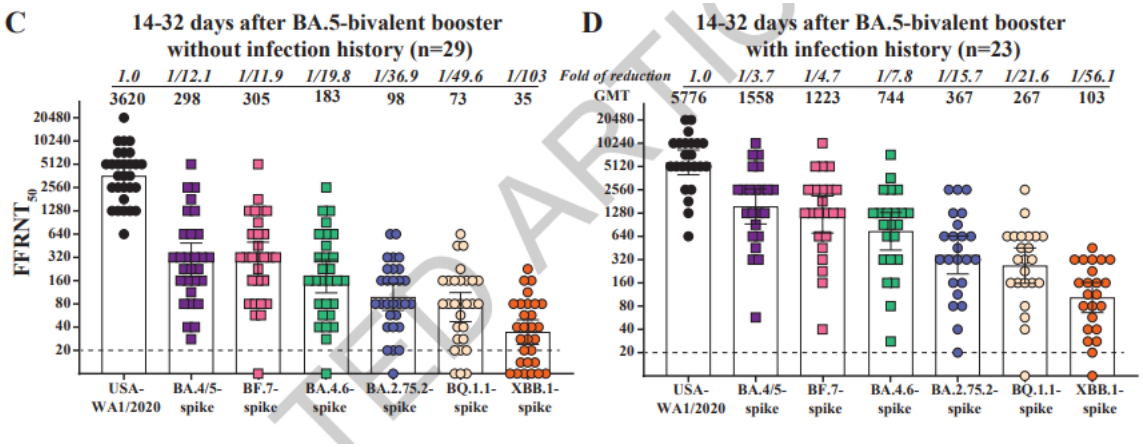
doi.org/10.1038/ s41591-022-02162-x

The newly emerged SARS-CoV-2 Omicron sublineages, including the BA.2-derived BA.2.75.2 and the BA.5-derived BQ.1.1 and XBB.1, have accumulated additional spike mutations that may affect vaccine effectiveness.



The investigators report neutralizing activities of three human serum panels collected from individuals 23–94 days after dose 4 of a parental mRNA vaccine, 14–32 days after a BA.5-bivalent-booster from individuals with 2–4 previous doses of parental mRNA vaccine, or 15–32 days after a BA.5-bivalent-booster from individuals with previous SARS-CoV-2 infection and 2–4 doses of parental mRNA vaccine.

The results showed that a BA.5-bivalent-booster elicited a high neutralizing titer against BA.4/5 measured at 14- to 32-day post-boost; however, the BA.5-bivalent-booster did not produce robust neutralization against the newly emerged BA.2.75.2, BQ.1.1, or XBB.1. Previous infection significantly enhanced the magnitude and breadth of BA.5-bivalent-booster-elicited neutralization.



Fluorescent focus reduction neutralization titers (FFRNT)

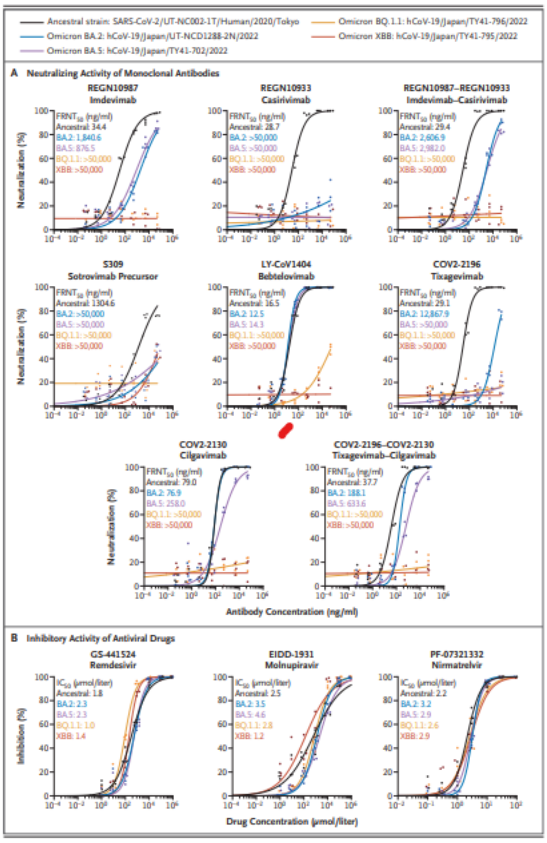
Comment: The neutralization results support two conclusions. First, the newly emerged Omicron sublineages continue to increase their immune evasion of vaccine- and/or infection-elicited neutralization. Among tested Omicron sublineages, BA.2.75.2, BQ.1.1, and XBB.1 exhibit the greatest evasion against vaccine-elicited neutralization, suggesting the potential of these new sublineages will be the dominant variants. Second, individuals with SARS-CoV-2 infection history develop higher and broader neutralization against the current circulating Omicron sublineages after the BA.5-bivalent booster. The investigators did not examine the antiviral roles of non-neutralizing antibodies and cell-mediated immunity. These two immune components, together with neutralizing antibodies, have been shown to protect patients from severe disease and death. Most T cell epitopes after vaccination or natural infection are preserved in Omicron spikes. They did not define the spike mutations that contribute to the observed immune evasion of the newly emerged Omicron sublineages. It is unclear how neutralizing titers related to protection against infection. This study supports a vaccine update strategy that future boosters should match newly emerged circulating SARS-CoV-2 variants if it could be done in timely manner.

Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB N Engl J Med published online December 7, 2022 article suggested by Yasser Alsafadi

DOI: 10.1056/NEJMc2214302

Three sublineages of the B.1.1.529 (omicron) variant of SARS-CoV-2 have serially transitioned into globally dominant forms — first BA.1, then BA.2, and then BA.5. As of October 2022, most circulating omicron variants belong to BA.5. However, the prevalence of BQ.1.1 (a BA.5 subvariant) and XBB (a BA.2 subvariant) is increasing rapidly in several countries, including the US and India. BA.2 and BA.5 variants have been shown to have less sensitivity to certain monoclonal antibodies than previously circulating variants of concern. In addition, as compared with BA.5 and BA.2, BQ.1.1 and XBB carry additional substitutions in the receptor-binding domain of the spike (S) protein, which is the major target for vaccines and therapeutic monoclonal antibodies for Covid-19.

The investigators assessed the efficacy of therapeutic monoclonal antibodies against omicron BQ.1.1 and XBB, which were isolated from patients. To examine the reactivity of monoclonal antibodies against these subvariants, they determined the 50% focus reduction neutralization test (FRNT50) titer of the monoclonal antibodies by using a live-virus neutralization assay. The results (shown below) suggest that imdevimab–casirivimab, tixagevimab–cilgavimab, sotrovimab, and bebtelovimab may not be effective against BQ.1.1 or XBB in the clinical setting. They also tested 3 antiviral drugs. The results suggest that remdesivir, molnupiravir, and nirmatrelvir are still efficacious against both BQ.1.1 and XBB in vitro. See below



Comment: This study and others suggest that the omicron sublineages BQ.1.1 and XBB have immune-evasion capabilities that are greater than those of earlier omicron variants, including BA.5 and BA.2. The continued evolution of omicron variants reinforces the need for new therapeutic monoclonal antibodies for Covid-19. Antivirals drugs maintain activity to all sublineages to date.

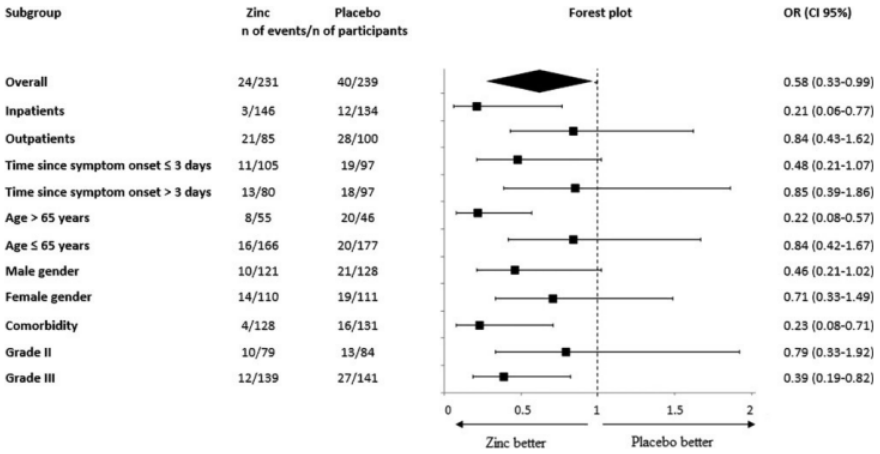
Twice-Daily Oral Zinc in the Treatment of Patients With Coronavirus Disease 2019: A Randomized Double-Blind Controlled Trial Clin Infect Dis published online November 4, 2022

doi.org/10.1093/cid/ciac807

The investigators conducted a prospective, randomized, double-blind, placebo-controlled multicenter trial. Patients who tested positive for COVID-19 without end-organ failure were randomized to oral zinc (n=231) or matching placebo (n=239) for 15 days. The primary combined outcome was death due to COVID-19 or intensive care unit (ICU) admission ≤30 days after randomization. Secondary outcomes included length of hospital stay for inpatients and duration of COVID-19 symptoms with COVID-19–related hospitalization for outpatients. Patients enrolled in the zinc group received 25 mg of elemental zinc twice a day for 15 days.

190 patients (40.4%) were ambulatory, and 280 patients (59.6%) were hospitalized. Mortality at 30 days was 6.5% in the zinc group and 9.2% in the placebo group (OR: .68; 95% CI .34–1.35); ICU admission rates were, respectively, 5.2% and 11.3% (OR: .43; 95% CI .21–.87). Combined

outcome was lower in the zinc group versus the placebo group (OR: .58; 95% CI .33–.99). Consistent results were observed in prespecified subgroups of patients aged.



Comment: This study included two different groups: IP with severe disease or OP with mild to moderate disease. Including both groups makes interpretation of their results more challenging. I would not substitute zinc for proven treatments for Covid-19; however, one could argue that if a clinician wishes to try zinc in addition to recommended treatments there appears to be little downside and now perhaps some scientific support. Lastly it may be difficult in this country to duplicate this trial at least in the IP setting since we are fortunately not seeing nearly as many ICU admissions and deaths.

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