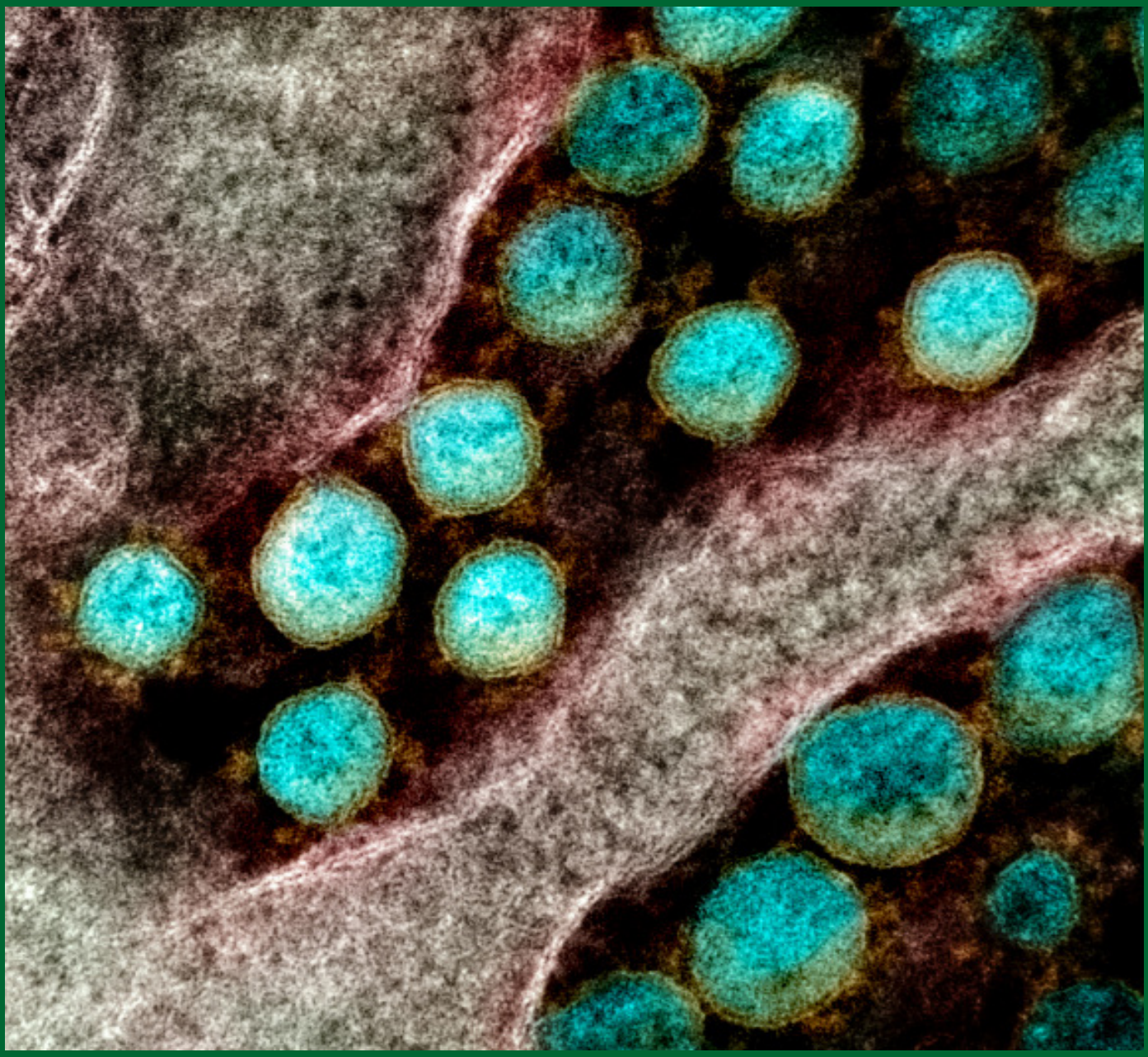
COVID-19
Rush Journal Club



NOVEL CORONAVIRUS SARS-COV-2. Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID Available at: https://www.flickr.com/photos/niaid/49597768397/in/album-72157712914621487/. Accessed April 19, 2020.

This document is a collection of efforts from students of Rush University. It provides brief reviews of research articles regarding COVID-19. We hope that this will be helpful to clinicans, students, community leaders, and the general public. This document, however, does not act as a replacement of the original source document. Please use the DOI on each page to read more.

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Is there a study you'd like us to review? Do you have questions or feedback? Please email leah_r_greenfield@rush.edu or Mohammed_AbdulSami@rush.edu

Reviews are provided by students at Rush University and edited by Rush faculty. Level of evidence in each study, if applicable, was assessed using the Oxford guidelines as presented below. More information can be found at: https://www.cebm.net/2016/05/ocebm-levels-of-evidence/

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

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Vaccine effectiveness against SARS-CoV-2 Infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish Cohort Study

Christian Holm Hansen et al.

medRxiv
December 20, 2021
DOI: https://doi.org/10.1101/2021.12.20.21267966

Purpose	To estimate vaccine effectiveness (VE) against the novel SARS-COV-2 Omicron variant up to five months after a primary vaccination series with BNT162b2 or mRNA-1273 vaccines.
Study design	Cohort Study
Level of evidence	Level 3
Methods	Data consisting of "complete residency", COVID-19 PCR test and vaccination data were studied. Whole genome sequencing or a novel variant specific PCR test were utilized to test for Omicron in all positive PCR cases. Results that were negative for Omicron were assumed to be Delta. The Vaccine Effectiveness (VE) was determined by comparing the rate of infection in unvaccinated to vaccinated individuals with two-does of BNT162b2 or mRNA-127s vaccine series. Previously SARS-Cov-2-PCR-positive individuals were excluded. Participants were studied at intervals of 30 days after full protection, 31-60 days, 61-90 days, and 91-150 days. VE was calculated as 1-Hazard Ratio (HR) using a Cox regression model adjusted for age, sex, geographical region and calendar time.
Findings	5,767 omicron cases were identified by December 12, 2021. VE against Omicron was 55.2% and 36.7% for the BNT162b2 and mRNA-1273 vaccines respectively for participants who completed primary vaccination. Participants 60 years and older and who received a booster dose 14 to 44 days earlier had a VE of 54.6% when compared to those with only a primary vaccination. After 3-5 months, VE against Omicron was shown to be -76.5% and -39.3% for BNT162b2 and mRNA-1273 respectively. VE against Delta remained positive after 3-5 months for both vaccines.
Clinical Implications	**Providers should be offering boosters only during seasonal peaks due to a limited window of VE against Omicron with the current BNT162b2 and mRNA-1273 vaccines to ensure maximal protection for their patients.** The medical community should be wary that the current vaccines may not provide adequate protection to emerging strains of SARS-Cov-2.
Limitations	This study is a preprint and has not undergone the peer-review process, limiting its ability to be used to guide clinical practice. Additionally, the study was performed in Denmark so findings may not be generalizable to other areas of the world. Furthermore, the study does not look at hospitalization and death statistics and does not measure behaviors amongst the groups studied.

Antibody Titers Before and After a Third Dose of the SARS-CoV-2 BNT 162b2 Vaccine in Adults ≥ 60 Years

Noa Eliakim-Raz, et al.

Signal Transduction and Targeted Therapy
May 5, 2020
DOI: https://doi.org/10.1038/s41392-020-0163-5

Purpose	To compare antibody titers before and after receiving a third dose of the SARS-CoV-2 BNT162b2 vaccine in adults who are at least 60 years of age.
Study design	Case series (n = 97)
Level of evidence	Level IV
Methods	Researchers utilized data from healthcare workers and their family members who were at least 60 years of age and were going to receive a third dose of the SARS-CoV-2 BNT162b2 vaccine. There were a total of 97 participants. It's been demonstrated that healthcare workers had waning immunity after 6 months from the 2nd vaccine administration, so they sought to compare titers before and after a third vaccination in this specific age population of healthcare workers. The exclusion criteria included prior known SARS-CoV-2 infection and malignancy. Anti-S IgG titers were determined between August 4-12 2021 and were reassessed 10-19 after receiving the third vaccination. A Quant assay was used to measure titers; they defined seropositivity as at least 50 arbitrary units (Au)/mL. The difference in titers before and after the third vaccine administration was evaluated utilizing the Wilcoxon signed rank test. A Spearman correlation was then used to assess the correlation between titer values and age. A multivariable analysis on a linear model of log IgG value was used with age, days from first vaccination, and other demographic/comorbidity data.
Findings	Median age of all participants was 70 years. 94/97 participants (97%) were seropositive prior to receiving the third vaccination. After receiving the third dose, and at 10-19 days after receiving it, all participants were seropositive with a median titer increase of 440 AU/mL ($P < 0.001$). No correlation between ages were found ($R = - 0.075$; $P < 0.47$). None of the other variables played a role in titer levels.
Clinical Implications	Given the waning immunity with the SARS-CoV-2 BNT162b2 vaccine, especially after 6 months from the 2nd dose, it was sought to see how titer levels would change. **The evidence suggests that receiving a third dose significantly increases titers.** This is extremely important to healthcare workers on the frontlines.
Limitations	The sample size was relatively small (< 100) and there was a lack of testing cellular immunity and neutralizing antibodies. Additionally, the follow-up time was short.

BNT162b2 Vaccine Booster and Mortality Due to Covid-19

Ronen Arbel et al.

The New England Journal of Medicine
December 23rd, 2021
DOI: 10.1056/NEJMoa2115624

Purpose	To assess the decrease in mortality rate associated with the BNT162b2 booster vs individuals who did not receive the booster
Study design	Case Control Trial
Level of evidence	Level 3
Methods	The Clalit Health Service (CHS) electronic medical records was queried on October 3, 2021 for members > 50 years of age that had received two doses of BNT162b2 booster > 5 months between the date of August, 6th, 2021 to September 29th, 2021. Participants were excluded if they received the booster before the start date and if they were infected with COVID-19 within 3 days before the effective booster date. 843,208 participants met the inclusion criteria. 758,118 participants (90%) received the booster within the study period. Primary analysis compared mortality rates of those who received the booster (at least 7 days earlier) versus those who did not. Secondary analysis compared COVID-19 infection rates of those in the booster group versus the non-booster group.
Findings	Mortality due to COVID-19 was much lower in the booster group (n= 65; 0.16 per 100,000 persons per day) compared to the non-booster group (n= 137; 2.97 per 100,000 persons per day). COVID-19 infection was lower in the booster group (n= 2888) compared to the non-booster group (n= 11,108). **Mortality and infection rates associated with COVID-19 were significantly lower in the boosted group when compared to non-boosted groups.**
Clinical Implications	The booster drastically reduces the mortality and infection rates of COVID-19 in the patients >50 who were fully vaccinated >5 months earlier. **The boosted group had a 90% lower mortality rate compared to those who did not receive it.**
Limitations	A longer study period is necessary to determine the long-term efficacy and safety profile of the vaccine.

Duration of Protection against Mild and Severe Disease by Covid-19 Vaccines

Nick Andrews et al.

New England Journal of Medicine
January 12, 2022
Doi: https://doi.org/10.1056/NEJMoa2115481

Purpose	To determine the effectiveness of 2 doses of the ChAdOx1-S, BNT162b2, and mRNA-1273 vaccines against symptomatic COVID19 infection, hospitalization, and death.
Study design	Case Control
Level of evidence	Level 4
Methods	Vaccination status was compared between adults with COVID symptoms and PCR confirmed infection, hospitalization within 14 days and death within 28 days of confirmed PCR testing. The control group was made up of adults with symptoms of COVID-19 but had a negative PCR test. Analysis was stratified to determine vaccine effectiveness against the alpha and delta variants. Analysis was adjusted for age, sex, socioeconomic status, race, care home residence status, geographic region, healthcare worker status , and status of being in a high risk group or a clinically vulnerable group.
Findings	Vaccine effectiveness against the delta variant decreased to 44.3% by 20 weeks with the ChAdOx1-S and to 66.3% with the BNT162b2 vaccine. Vaccine effectiveness decreased more significantly in those greater than 65 years old compared to 40-64. After 20 weeks, effectiveness against hospitalization decreased to 80% and 91.7% and effectiveness against death was decreased to 84.8% and 91.9% with the ChAdOx1-S and BNT162b2 vaccines. Vaccine effectiveness at prevention of hospitalization decreased more significantly in those greater than 65 years old and those 40-64 with underlying medical conditions compared to healthy adults. The mRNA vaccines were more effective than the ChAdOx1-S vaccine at preventing more severe outcomes, against the alpha variant, and among younger persons as compared with older persons.
Clinical Implications	**Vaccine effectiveness decreases after 20 weeks with the most significant decline those over the age of 65 years old or with underlying medical conditions.**
Limitations	They were only able to successfully match 85.2% of PCR tests to the vaccination database. Exclusion of those participants may have skewed the data. A higher proportion of non-White compared to White persons were not able to be matched to the vaccination database and exclusion of them may have led to results not representative of the population. Participants had to declare symptoms in order to obtain a test and some asymptomatic persons may have declared symptoms in order to access a test.

SARS-CoV-2 Antibody Response to 2 or 3 Doses of the BNT162b2 Vaccine in Patients Treated With Anticancer Agents

Charlotte Fenioux, MD et al.

JAMA Oncology
January 7, 2022
DOI: https://doi.org/10.1001/jamaoncol.2021.7777

Purpose	To assess the humoral response to 2 or 3 doses of the BNT162b2 (BioNTech; Pfizer) vaccine in patients treated with anticancer agents.
Study design	Prospective observational cohort study (n= 163)
Level of evidence	3
Methods	163 patients (median age, 66 [27-89] years; 53% men; 47% women) with solid tumors (digestive, urologic, breast, and other) receiving oncologic treatment and who had no history of COVID-19 were enrolled. 122 received chemotherapy (75%), 26 received targeted oral therapy (16%), and 15 received immunotherapy (9%). The humoral response to the BNT162b2 vaccine was evaluated with quantitative serologic testing for the anti–SARS-CoV-2 spike protein antibody. The primary end point of the study was sufficient humoral response which was set at a threshold of 1000 arbitrary units (AU)/mL.
Findings	Anti-S immunoglobulin G titer greater than 1000 AU/mL was found in 22 of the 145 (15%) at the time of the second vaccine administration and 92 of 142 (65%) 28 days after the second vaccination. 36 patients received a third dose due to poor antibody response and 75% (27 of 36) had an anti-S titer greater than 1000 AU/mL after the third dose. Humoral response was decreased 3 months after the second dose with 27 of 64 (42%) having titers less than 1000 AU/mL. Age, sex, cancer type, cancer category (neoadjuvant, adjuvant,metastatic first, or >1 line), lymphopenia, and use of corticosteroids before the vaccine were not associated with degree of humoral response. Chemotherapy schedule and timing of vaccine administration were not associated with lower humoral response. Lower anti-S were seen in patients treated with chemotherapy or targeted therapy compared to immunotherapy (odds ratio, 5.4; 95% CI, 1.5-20.2; P=.02).
Clinical Implications	**Sufficient antibody response after 2 or 3 vaccine doses is seen in patients receiving oncologic treatment for solid tumors**. There is evidence to use a third vaccine dose one month after the second dose for adequate antibody response. There was no relationship with the timing of vaccine administration and chemotherapy cycle.
Limitations	The study is limited by a small sample size which prevented comparative analysis between solid tumor types after the third dose of the vaccine.

Protection against Covid-19 by BNT162b2 Booster across Age Groups

Yinon M. Bar-On et al.

The New England Journal of Medicine
December 8th, 2021
DOI: 10.1056/NEJMoa2115926

Purpose	To compare the rates of confirmed COVID-19, severe illness and death between individuals that received the COVID-19 booster and those that did not
Study design	Case Control Trial
Level of evidence	Level 3
Methods	The Israel Ministry of Health database was queried on October 12, 2021 to include fully vaccinated individuals 16 and older at least 5 months prior to the study, have been fully vaccinated after January 16, 2021, and did not have a past positive PCR test for COVID-19. 4,696,865 individuals met the inclusion criteria. Primary analysis compared those that received the COVID-19 booster (at least 12 days earlier) versus those who did not, whereas secondary analysis compared the rates in the COVID-19 booster group versus those in the early booster group (patients that received the booster 3-7 days earlier). Confirmed infection, development of severe illness, and death were chosen for periods of 2, 7 and 35 days prior to the data query.
Findings	The rate of confirmed COVID-19 infection was lower in the booster group by 9-17.2 when compared to the non-boosted group, and 4.9-10.8 when compared to the early-boosted group across all age groups studied. **The rate of severe illness and COVID-19 associated death was also significantly lowered in the boosted group when compared to both the non-boosted group and early-boosted groups.** In all age groups, the rate of confirmed infection was lower in the early booster group than in the non booster group.
Clinical Implications	**The booster dose reduced the rate of confirmed COVID-19 infection and severe illness across each different age group studied.** Across all age groups, the booster is effective against the delta variant in at least the short term, offering protection for individuals against COVID-19.
Limitations	This study focused on a time period that did not include the Omicron COVID-19 variant, potentially limiting the current applicability to the current stage of the COVID-19 pandemic.

Comparative Effectiveness of BNT162b2 and mRBA-1273 Vaccines in U.S. Veterans

Barbra A. Dickerman et al.

The New England Journal of Medicine
January 13, 2022
DOI: https://doi.org/https://doi.org/10.1056/NEJMoa2115463

Purpose	To compare the effectiveness of two-dose messenger RNA (mRNA)-based vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), in U.S. Veterans.
Study design	Retrospective Observational Analysis
Level of evidence	Level 3
Methods	The electronic health records of U.S. veterans who received a first dose of the BNT162b2 or mRNA-1273 vaccine between January 4 and May 14, 2021 were used to compare effectiveness of the two vaccines. 219,842 recipients of each vaccine were matched in a 1:1 ratio according to risk factors. Outcomes included documented severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, symptomatic Covid-19 infection, hospitalization, admission to an ICU, or death from Covid-19 . A second analysis used veterans who received a first dose between July 1 and September 20, 2021 to assess the influence of the B.1.617.2 (Delta) variant.
Findings	When comparing documented infection, the estimated risk was 5.75 events per 1000 persons for the BNT162b2 group, and 4.52 events for the mRNA-1273 group. The excess number of events per 1000 persons when comparing BNT162b2 to mRNA-1273 was 1.23 for documented infection, 0.44 for symptomatic infection, 0.55 for hospitalization, 0.10 for ICU admission, and 0.02 for death from Covid-19. The excess risk for the 12 week follow-up period predominated by Delta-variant was 6.54 events per 1000 persons.
Clinical Implications	The risks of Covid-19 outcomes were low, regardless of which vaccine was received. **This study showed that risks were significantly lower with mRNA-1273 than with BNT162b2, across all studied outcomes and both the Alpha- and Delta-variant predominated periods.**
Limitations	This study provides evidence regarding potentially different effectiveness of the two vaccines, however it did not compare their safety. Currently head-to-head comparisons of BNT162b2 and mRNA-1273 vaccines for safety outcomes are lacking, however observational and surveillance efforts have confirmed the safety of both vaccines. This study showed similar results for both the Alpha- and Delta-variant time periods, however further studies continue to be needed for emerging variants such as Omicron. Finally, the study was limited to the VA health system records and outcomes could have been misclassified if veterans sought care outside the VA health system.

Homologous and Heterologous Covid-19 Booster Vaccinations

Robert Atmar et al.

The New England Journal of Medicine
January 26, 2022
DOI: https://doi.org/10.1056/NEJMoa2116414

Purpose	To determine the efficacy of homogeneous compared to heterogeneous boosters in fully vaccinated participants against breakthrough SARS-CoV-2 infection.
Study design	Open label non-randomized clinical trial (n=458)
Level of evidence	Level 3
Methods	Participants who had no history of SARS-CoV-2 infection received a booster of either mRNA-1273 (Moderna) (n=154), Ad26.COV2.S (Johnson & Johnson–Janssen) (n=150), or BNT162b2 (Pfizer–BioNTech) (n=153). The primary endpoints were safety, reactogenicity, and humoral immunogenicity on trial days 15 and 29.
Findings	For all 3 vaccines, antibody neutralizing titers increased by a factor of 4 to 73 whereas the binding titers increased by 5 to 55. Homogenous boosters increased neutralizing titers by a factor of 4 to 20 compared to heterologous boosters, which increased titers by a factor of 6 to 73. T-cells specific for spike protein increased in all but the Ad26.COV2.S group; the neutralizing antibodies were lowest after homologous Ad26.COV2.S boosting regardless of the interval between primary and booster vaccination. Heterogeneous boosting with Ad26.COV2.S vaccine increased spike specific CD8+ T-cells in the mRNA vaccine groups.
Clinical Implications	Homologous and heterologous booster vaccines had acceptable safety and immunogenicity. Heterologous vaccines offer practical benefits in simplifying the logistics of administering vaccines. Also, there was a greater increase in antibody titers after heterologous boosting compared to that of homologous boosting.
Limitations	This paper only studied the 'delta' and 'beta' COVID-19 variants. The sample size was insufficient for intergroup comparison or study if there were rare adverse effects. The demographic of the study population was not representative of the population of the United States. The follow-up period was not long enough to study if there were any long term risks. The interim between primary series and booster was variable between groups and was shorter than 6 months recommended in the mRNA group. The mRNA-1273 dose used in the study was higher than what is currently FDA recommended for boosting. Immunogenicity was only studied for T-cell response through day 15 and antibody response through day 21.

Safety and Efficacy of a Third Dose of BNT162b2 COVID-19 Vaccine

Edson D. Moreira Jr., et al.

The New England Journal of Medicine
March 23, 2022
DOI: 10.1056/NEJMoa2200674

Purpose	To determine the safety profile and efficacy of offering a third dose of the BNT162b2 (Pfizer-BioNTech) vaccine to individuals 16 years of age or older.
Study design	Randomized Clinical Trial (n=10,125)
Level of evidence	Level 2
Methods	Recruited participants were at least 16 years old and had received two doses of the BNT162b2 vaccine 19 to 42 days apart. Participants had received the second dose at least 175 days prior and had no previous diagnosis of COVID-19. They were randomly assigned to receive an IM injection of the third dose (30 µg per dose; n=5081) or the placebo (n=5044) via an interactive Web-based response system. The median interval between the second and the third dose was 10.8 and 10.7 months in the vaccine group and the placebo group, respectively. Both site personnel and participants were blinded to the trial-group assignments, except those who prepared, dispensed, or administered the injections. Vaccine safety and efficacy against COVID-19 started 7 days after the third dose.
Findings	**During a median follow-up of 2.5 months, participants with COVID-19 starting 7 days after the third dose numbered 6 in the vaccine group and 123 in the placebo group, corresponding to a relative vaccine efficacy of 95.3%.** The most common side effect from the third dose of the vaccine was injection site pain. Most reported side effects were low-grade. Moreover, there was no adverse event related to pericarditis (occurring among the younger population) or myocarditis and no new safety profiles were reported.
Clinical Implications	The third dose of the vaccine provides additional protection against COVID-19 on top of any residual protection from the first two-dose series according to this study covering more than ten thousand participants.
Limitations	There is a lack of data regarding participants who received the third dose with a longer interval between doses. Follow-up on placebo recipients was limited due to the unblinding the trial for those participants to receive the third dose. Researchers did not assess vaccine efficacy against transmissibility.

Association of COVID-19 Vaccination With Risk of COVID-19 Infection, Hospitalization, and Death in Heart Transplant Recipients

Laura L. Peters DNP, FNP, et

JAMA Cardiology
April 27, 2022
DOI: 10.1001/jamacardio.2022.0670

Purpose	To assess the safety and effectiveness of COVID-19 vaccination and associations with SARS-CoV-2 infection and clinical outcomes in a large population of adult orthotopic heart transplant (OHT) recipients.
Study design	Case Control (n=436)
Level of evidence	Level IV
Methods	Single-center retrospective study of 482 OHT recipients from March 23, 2020 to January 31, 2022. A total of 436 OHT recipients were included in the study after excluding 46 patients, who were infected with COVID-19 prior to receiving the vaccine. Primary outcomes were the number of COVID-19 infections, COVID-19 related hospitalizations, ICU admissions, and death between vaccinated and unvaccinated adult recipients of OHT.
Findings	Of the 436 patients included in the study, 366 patients were included in the vaccinated cohort and 70 patients in the unvaccinated cohort. Unvaccinated patients were younger, had better kidney function, and slightly higher diastolic blood pressure. COVID-19 vaccination lowered risk of COVID-19 infection (risk ratio, RR: 0.41; 95% CI, 0.30-0.56), hospitalization (RR: 0.29; 95% CI, 0.14-0.61), and death (RR: 0.19; 95% CI, 0.05-0.82). None of the 366 vaccinated patients had any echo evidence of changed LV function, rejection, or allosensitization at 6 months after receipt of the COVID-19 vaccine.
Clinical Implications	COVID-19 vaccination decreases symptomatic COVID-19 infection, hospitalizations and deaths with no heart transplant-specific adverse events for OHT recipients. Despite the decrease in immunogenic response to COVID-19 vaccination in immunosuppressed OHT recipients, it is extremely vital that all heart transplant recipients receive the COVID-19 vaccine.
Limitations	Single center analysis means there may be differences in geographical trends in COVID-19 infection rates as compared to the rest of the United States. The time points of vaccination were not consistent throughout the study in regards to the follow-up period.

Covid-19: Pfizer's Paxlovid is 89% Effective in Patients at Risk of Serious Illness, Company Reports

Elizabeth Mahase

British Medical Journal
November 8, 2021
DOI: 10.1136/bmj.n2713

Purpose	To assess the efficacy of Pfizer's randomized control trial for paxlovid, an oral
Study design	Randomized Control Trial, Double-Blind
Level of evidence	1
Methods	Interim analysis was performed on 1219 participants who had enrolled in the Evaluation of Protease Inhibition for COVID-19 (EPIC – SR) by 29 September 2021. Patients who had laboratory-confirmed diagnosis of SARS-CoV-2 infection within a five-day period with mild-moderate symptoms and had at least one underlying medical condition associated with increased risk of illness from COVID-19. The study was performed in North & South America, Europe, Africa & Asia, with 45% of participants in the U.S. Patients were randomized 1:1 and received paxlovid or placebo q12hr for five days.
Findings	Individuals who received paxlovid treatment within 3 days of confirmed SARS-CoV-2 infection, **the risk of hospitalization or death within 28 days after randomization from any cause was 89% lower than the respective risks associated with the placebo group.** Of the individuals treated with paxlovid, 0.8% (3/389) were admitted to the hospital, whereas 7% (27/385) of the individuals in the placebo group were admitted, along with 7 deaths ($p<.0001$). Of individuals treated with paxlovid within 5 days of symptom onset, 1% (6/607) were admitted to the hospital compared to 6.7% (41/612) with 10 deaths in the control group.
Clinical Implications	The data presented suggests that paxlovid is significantly effective at reducing hospitalizations in individuals treated within 3- and 5-days of symptom onset of COVID-19. Therefore, this medication may help reduce the hospital-patient burden by preventing moderate-to-severe symptoms and death.
Limitations	The data regarding the efficacy of paxlovid is specific to the cohort of individuals with mild to moderate disease, and therefore may not be effective in individuals with severe disease.

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

Angélica Jayke Bernal et al.

The New England Journal of Medicine
December 26, 2021
DOI: https://doi.org/10.1056/NEJMoa2116044

Purpose	To evaluate the safety and efficacy of molnupiravir in non-hospitalized unvaccinated adults with mild-to-moderate laboratory confirmed COVID-19 and at least one risk factor for severe illness.
Study design	Double-blind, randomized, placebo-controlled trial (n= 1433)
Level of evidence	Level 2
Methods	Within 5 days of symptom onset, participants were randomized to receive either 800 mg PO molnupiravir or a placebo twice daily for 5 days. The primary endpoint was the incidence of hospitalization for any cause or death at day 29. The secondary endpoint was improvement or progression of signs and symptoms of COVID-19.
Findings	At interim analysis (n= 775) the rate of hospitalization or death in the molnupiravir group was 7.3% (28 of 385 participants) compared to the placebo 14.1% (53 of 377) (difference, −6.8 percentage points; 95% confidence interval, −11.3 to −2.4; P=0.001). In the analysis of the entire study group, risk of hospitalization or death for the molnupiravir group was 6.8% (48 of 709) and for the control group it was 9.7% (68 of 699) [difference, −3.0 percentage points; 95% confidence interval, −5.9 to −0.1]. There was one death in the molnupiravir group and 9 in the control. Adverse effects were reported in 30.4% (216 of 710) in the molnupiravir group and 33% (231 of 701) in the control group. The most common adverse effects were COVID pneumonia, bacterial pneumonia, worsening COVID-19, and diarrhea. The molnupiravir group showed a greater improvement in COVID symptoms compared to the control group.
Clinical Implications	**Molnupiravir was found to decrease rates of hospitalization and death associated with COVID-19 in unvaccinated adults with risk factors for severe COVID infection.** There were no safety concerns associated with molnupiriavir.
Limitations	This study was limited by its sample size. Both groups had fairly low rates (6.8% vs 9.7%) of hospitalization or death limiting the analysis of the difference between the two groups. There were more women in the placebo group who have a lower risk for severe disease; however, post hoc analysis adjusted for sex was consistent with the primary analysis.

Early Remdesivir to Prevent Progression to Severe COVID in Outpatients

Robert Gottlieb et al.

The New England Journal of Medicine
December 22, 2021
DOI: 10.1056/NEJMoa2116846

Purpose	To determine if remdesivir is effective at preventing the progression of COVID-19 in non-hospitalized symptomatic patients with a high risk of disease progression.
Study design	Randomized controlled trial (n=562)
Level of evidence	Level 2
Methods	Patients were recruited from medical sites in the US, UK, Spain, and Denmark between September 2020 and and April 2021. All patients were ≥ 12 years old, had a confirmed COVID-19 infection with symptoms, were not hospitalized, had not received a COVID-19 vaccine, and had ≥ 1 risk factor making them susceptible to progression to severe disease. Risk factors for progression to severe disease included age ≥ 60, particular medical conditions, and obesity. Patients were separated into a treatment group (n=279) and placebo group (n=283). The treatment group received 200 mg IV remdesivir on the first day of the study and 100 mg IV remdesivir the following 2 days. Primary endpoints included hospitalization due to COVID-19 or death by day 28 and adverse events. The secondary endpoint was a medical visit due to COVID-19 or death by day 28.
Findings	Two patients (0.7%) in the treatment group experienced hospitalization due to COVID-19 compared to 15 patients (5.3%) in the placebo group (hazard ratio = 0.13, 95% CI 0.03-0.59). Four patients (1.6%) in the treatment group had a medical visit related to COVID-19 compared to 21 patients (8.3%) in the placebo group (hazard ratio = 0.19, 95% CI 0.07-0.56). Zero patients died by the 28th day. Within the treatment group, 42.3% of patients experienced an adverse event compared to 46.3% in the placebo group. **Overall, 3 days of remdesivir lowered the risk of hospitalization or death by 87% and lowered the risk of a medical visit related to COVID-19 by 81% compared to placebo.**
Clinical Implications	This study suggests that remdesivir is a safe and effective way to prevent progression to severe COVID-19 in non-hospitalized high-risk patients with symptomatic COVID-19.
Limitations	This study underrepresented Black and Asian patients, patients with chronic liver or kidney disease, patients with cancer, and immunocompromised patients. Additionally, a majority of patients were from the US, possibly limiting the generalizability of these findings. Furthermore, this study took place before the delta or omicron variants emerged and thus cannot speak to the effects of remdesivir against these variants. Finally, the study did not include patients vaccinated against COVID-19.

Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19

Alexandra C Apple et al.

Annals of Clinical and Translational Neurology
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Purpose	To identify salient clinical factors associated with cognitive post-acute sequelae of SARS-CoV-2 infection (PASC) after mild COVID-19 that may inform pathogenesis.
Study design	Case control
Level of evidence	Level 3
Methods	Participants underwent a structured interview covering COVID-19 illness, past medical history, pre-existing cognitive risk factors, medications, and the presence of cognitive symptoms since onset of COVID-19. Participants then underwent cognitive testing to evaluate memory, executive functioning, processing speed, attention and working memory, visuospatial abilities, and language based on the HIV-associated neurocognitive disorder (HAND) criteria, given no current testing criteria exists for PASC. Individuals consenting to LP had CSF and serum samples collected (n=13 PASC+, n=4 PASC- controls) and evaluated.
Findings	CSF was analyzed in 53% of participants (17/32), reflecting 59% (13/22) with cognitive PASC and 40% (4/10) of cognitive controls. Among those who underwent LP, cognitive PASC participants were older than cognitive controls (median of 47 vs. 28 years, $p = 0.03$) with no other groups differences. LPs were performed a median of 9.7 months (IQR: 6.9–13.9) after first COVID-19 symptom. Overall, 77% (10/13) of participants with cognitive PASC had a CSF abnormality compared with 0% (0/4) of cognitive controls ($p = 0.01$).
Clinical Implications	Cognitive symptoms identified in viruses (HIV, SARS, MERS, HCV and EBV) have been thought to be triggered by the overstimulated immune system. While the pathophysiology is not entirely understood, studies have shown a significant correlation. Researchers are now investigating the "brain fog" that has been a report of COVID-19+ patients via neurocognitive survey as well as biomarker assay. **While data is limited given sample size limitations, clinicians are encouraged to accept newly reported cognitive sx reported by COVID+ patients rather than require that they meet certain survey criteria.**
Limitations	There are several limitations of this study which include a small sample size decreasing the validity of results. Additionally, comparing cognitive performance of COVID patients using HIV references may not be as precise in identifying true change. Finally, age differences between cognitive PASC and cognitive control participants, although not significant, could have altered the presence of pre-existing cognitive risk factors.

Association of SARS-CoV-2 Infection With Serious Maternal Morbidity and Mortality From Obstetric Complications

Torri D. Metz et al.

Journal of American Medical Association
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DOI: https://doi.org/10.1001/jama.2022.1190

Purpose	To evaluate the risk of obstetric morbidity and mortality associated with SARS-CoV-2 infection
Study design	Retrospective cohort study (n=14,104)
Level of evidence	Level 3
Methods	Pregnant or postpartum patients with a positive PCR or an antigen test (n= 2352) were compared to those with a negative test result (n=11,752). The primary outcome was maternal death or serious morbidity due to hypertensive disorders of pregnancy, postpartum hemorrhage, or infection other than SARS-CoV-2. The secondary outcome was cesarean birth.
Findings	SARS-CoV-2 infection was associated with maternal morbidity and death (13.4% vs 9.2%; adjusted relative risk [aRR], 1.41; 95% CI, 1.23-1.61). All 5 maternal deaths were in the SARS-CoV-2 group. COVID-19 infection was not significantly associated with cesarean birth (34.7% vs 32.4%; 1.05; 95% CI, 0.99-1.11). Moderate or severe COVID-19 infection (n=586) when compared to those with a negative test was significantly associated with the primary outcome (26.1% vs 9.2%; 2.06; 95% CI, 1.73-2.46) and the major secondary outcome of cesarean birth (45.4% vs 32.4%; 1.17; 95% CI, 1.07-1.28). Mild or asymptomatic infection (n= 1766) was not significantly associated with the primary outcome (9.2% vs 9.2%; aRR, 1.11 [95% CI, 0.94-1.32]) or cesarean birth (31.2% vs 32.4%; 1.00; 95% CI, 0.93-1.07). COVID-19 severity was categorized as critical in 59 patients (2.5%), severe in 180 (7.7%), moderate in 347 (14.8%), mild in 728 (31.0%), and asymptomatic in 1038 (44.1%). Patients with a positive SARS-CoV-2 test were more likely to be younger, have a higher BMI, be Hispanic, and have public or no insurance. There was no association found between insurance status, race or ethnicity and SARS-CoV-2 for any of the outcomes.
Clinical Implications	**SARS-CoV-2 infection is associated with an increased risk of serious morbidity or mortality from obstetric complications.** Pregnant people with COVID-19 infection were also more likely to have a C-section, deliver preterm, or develop a postpartum hemorrhage.
Limitations	There is the possibility of false positive antigen tests, as 44.1% (1038) of the patients were asymptomatic. This study was performed prior to the delta variant which is known to be more virulent and may result in worse pregnancy outcomes. Sixteen of the 17 sites were academic hospitals which may limit the generalizability of the study.

Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021

Matthew E. Oster et al.

Journal of American Medical Association
January 25, 2022
DOI: 10.1001/jama.2021.24110

Purpose	This paper highlights the prevalence of reported vaccine-induced myocarditis cases for patients who received an mRNA-based COVID-19 vaccine in the USA.
Study design	Cross-Sectional Study
Level of evidence	Level 4
Methods	The research team analyzed Vaccine Adverse Event Reporting System (VAERS) to detect cases of myocarditis and pericarditis for persons 12 years and older who received an mRNA-based COVID-19 vaccine in the USA between 12/14/2020 and 8/31/2021 (n=192,405,448). Information collected consisted of age, sex, race, ethnicity, and vaccine type. In patients under 30 years old, the research team conducted medical review and clinician interviews to elicit more details about the clinical course. The team then compared myocarditis rates from the aforementioned time period to myocarditis rates of the population from 2017-2019 using the IBM MarketScan Commercial Research Database.
Findings	Authors found 1991 reports of myocarditis after mRNA-based COVID-19 vaccination during this time period and 1626 of these reports met the CDC criteria for myocarditis. 1195 (73%) of the 1626 cases occurred in patients under the age of 30 years old whereas 543 (33%) of the cases were younger than 18 (median age: 21 years). Utilizing only reports that included vaccine dose information, 82% of the myocarditis cases occurred after the second vaccination dose. The median time from vaccination to symptom onset for the first and second dose was 3 days and 2 days, respectively. The largest proportions of cases of myocarditis were among White persons (69%) and males were predominantly affected (82% of the cases).
Clinical Implications	Myocarditis is a rare but serious adverse effect of the mRNA-based COVID-19 vaccines. There is an inverse relationship between age and frequency of myocarditis. There is also a relationship between male sex and increased risk of myocarditis. Physicians should take age and sex as well as the risk of severe COVID-19 illness into account prior to recommending the COVID-19 vaccine.
Limitations	VAERS is a passive reporting system. Authors found that the quality of information varied on a report by report basis. It was unknown if these patients had prior SARS-COV-2 infection. Both underreporting and overreporting are possible, however underreporting is more likely. The authors did not compare rates of myocarditis after SARS-COV-2 infection to the vaccine rate.

Health Outcomes in People 2 Years After Surviving Hospitalisation with COVID-19: A Longitudinal Cohort Study

Lixue Huang et al.

JThe Lancet
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DOI: https://doi.org/10.1016/S2213-2600(22)00126-6

Purpose	To examine the long-term effects of COVID-19 infection and hospitalization 2 years after initial symptom onset.
Study design	Longitudinal cohort study (n=1192)
Level of evidence	Level 3
Methods	Patients who were hospitalized with COVID-19 at Jin Yin-tan hospital in Wuhan, China and subsequently discharged between January and May 2020 were recruited to participate. Questionnaires on physical and mental health symptoms, lab tests, and walking distance tests were administered 6 months, 1 year, and 2 years after the onset of COVID-19 symptoms. Primary outcomes were long-term symptoms, return to job, 6 minute walking distance, health-related quality of life, and modified British Medical Research Council (mMRC) dyspnea scale score.
Findings	At 6 months post-COVID infection, 777 patients (68%) reported at least one long-term symptom. This number decreased to 650 patients (55%) at 2 years post-COVID infection. Muscle weakness and fatigue (31%) were the most commonly reported long-term symptoms. 288 patients (26%) had a mMRC dyspnea scale score of 1 or more at 6 months. This number decreased to 168 patients (14%) at 2 years. At 6 months post-infection, 256 patients (23%) reported symptoms of anxiety or depression while only 143 patients (12%) reported these symptoms at 2 years. 438 patients (89%) had returned to their pre-infection job at 2 years. Patients still experiencing symptoms at 2 years post-infection had lower health-related quality of life and higher rates of healthcare usage and mental health complaints compared to patients without long-term symptoms.
Clinical Implications	This study suggests that the majority of patients hospitalized with COVID-19 will experience at least 1 long-term symptom that has a negative impact on their physical or mental health. Health providers should be cognizant of the prevalence and impact of long-term COVID-19 sequelae and provide support when possible.
Limitations	Being a single-institution study based in China, these results may not be generalizable to other locations. Additionally, this study was conducted near the beginning of the pandemic and thus may not be reflective of the COVID-19 variants that emerged later in the pandemic. Finally, it is not possible to determine if the findings from this study are specific to COVID-19 since patients were compared to controls without a respiratory infection rather than controls with a respiratory infection that is not COVID.

Association of Child Masking With COVID-19–Related Closures in US Childcare Programs

Thomas S Murray et al.

JAMA Network Open
January 27, 2022
Doi: 10.1001/jamanetworkopen.2021.41227

Purpose	To determine if child masking was associated with reduced child care program closures.
Study design	Prospective cross sectional survey
Level of evidence	Level 5
Methods	A total of 6,654 childcare professionals were surveyed to determine the association between child care program closure due to suspected or confirmed COVID-19 in children or staff and early adoption and continued child masking. Data were controlled for other risk mitigation strategies, physical distancing, as well as program (home-based vs center) and community (age, race, ethnicity, etc.) characteristics.
Findings	Early adoption of child masking was associated with a 13% lower risk of program closure (relative risk 0.87; 95% CI, 0.77-0.99, p=0.04) and an absolute risk reduction of 5.8% (95% CI, 0.9-10.7, p=0.02). Continued masking for 1 year was associated with a 14% lower risk (adjusted relative risk, 0.86; 95% CI, 0.74-1.00, p=0.04) and an absolute risk reduction of 6.4% (95% CI, 0.6-12.1 percentage points; p=0.03).
Clinical Implications	**This study showed that child masking is effective at preventing COVID-19 infections resulting in program closures.** Child masking may be an effective strategy at keeping childcare programs open.
Limitations	This study is limited by participant reports which were not independently confirmed. Closures due to COVID transmission within the center rather than an imported transmission were not differentiated. Adult and child behavior outside of the center was unknown including absence of masking in congregate settings or engagement in additional preventative measures which could have led to higher or lower likelihood of introduction of COVID infection to the childcare program. This study was conducted when the delta variant was less common and therefore may not be reflective of the power of masking against a more infectious variant.

Alcohol-Related Deaths During the COVID-19 Pandemic

Aaron M. White, Ph.D. et al.

The Journal of the American Medical Association
March 18, 2022
DOI:10.1001/jama.2022.4308

Purpose	To assess if alcohol related deaths increased during the COVID-19 pandemic
Study design	Retrospective chart review
Level of evidence	1
Methods	US mortality data from the National Center for Health Statistics in individuals 16 years or older in 2019 and 2020 was used to compare the number and rate of alcohol-related and all-cause deaths. Data from the Center for Disease Control (CDC) and Prevention Wide-range Online Data for Epidemiological Research was used to obtain data for the first half of 2021. This study used death certificates and assessed for alcohol as an underlying or contributing cause of death. Furthermore, age specific rates were calculated in addition to comparisons between rates in 2019 and 2020 by age group and sex.
Findings	Results implicate that Americans have been drinking more alcohol since the start of the COVID-19 pandemic to cope with pandemic-related stress. Deaths due to alcohol increased between 2019 and 2020 from 78,927 to 99,017 (25.5%) along with age-adjusted rate increase from 27.3 to 34.4 per 100,000 (25.9%). In addition, there was an increased rate amongst all age groups, with the largest increase occurring in individuals aged 35 to 44 years old (22.9 to 32.0 per 100,000; 39.7%). Rates were also increased in both males (from 42.1 to 52.6 per 100,000) and females (from 13.7 to 17.5 per 100,000) by 25.1% and 27.3%, respectively. In addition, there was an increase in deaths due to alcohol-associated liver disease from 24,106 to 29,504 (22.4%) and alcohol-related mental and behavioral disorders from 11,216 to 15,211 (35.1%). Finally, there was an increase from 6,302 to 10,032 (59.2%) in deaths due to alcohol-contributed synthetic opioid overdose .
Clinical Implications	The number of alcohol-related deaths and alcohol-contributing synthetic opioid overdose deaths increased significantly from 2019 to 2020.
Limitations	Limitations include possible inaccurate recording on death certificates. Also, data gathered for 2021 was based on provisional data which may be subjected to change over time.

Analysis of Firearm Violence During the COVID-19 Pandemic in the US

Sun Shengzhi PhD, et al.

The Journal of the American Medical Association Network
April 28, 2022
DOI: 10.1001/jamanetworkopen.2022.9393

Purpose	To determine the changes in interpersonal firearm violence during the first year of the COVID-19 pandemic in the United States.
Study design	Cross-Sectional Study
Level of evidence	Level 4
Methods	Firearm violence data for the US states and the District of Columbia was obtained via the Gun Violence Archive (GVA), which covers reports of non-suicidal deaths, injuries and threats involving guns between January 1, 2016 and February 28, 2021. The COVID-19 pandemic period was defined as March 1, 2020 to February 28, 2021. The excess burden parameter was divided into three types of events: firearm-related incidents, nonfatal injuries, and death.
Findings	Between January 1, 2016 and February 28, 2021, 295,280 identified firearm-related incidents, 165,335 firearm-related nonfatal injuries, and 83,491 firearm-related deaths were identified in the US. During the pandemic period, 62,485 identified firearm-related incidents, 40,021 firearm-related nonfatal injuries, and 19,818 firearm-related deaths were identified. **Compared to the baseline year, there was a 15.0% increase in firearm-related incidents, a 34.3% increase in firearm-related nonfatal injuries, and a 28.4% increase in firearm-related deaths during the pandemic period.** This excess burden was more pronounced between June to October 2020, especially in Minnesota and New York state.
Clinical Implications	These findings suggest that the pandemic has affected population health beyond direct morbidity and mortality caused by COVID-19 infection itself.
Limitations	It is difficult to attribute an increase in firearm violence solely to the pandemic as there were other changes during this period, such as civic unrest related to police violence and racism. Due to the lack of information provided by GVA, personal characteristics and types of death via firearm-related violence were not specified.

Review by Sarala Prabhu, MS1

Association of Social Determinants of Health and Vaccinations With Child Mental Health During the COVID-19 Pandemic in the US

Yunyu Xiao et al.

JAMA Psychiatry
April 27, 2022
DOI: 10.1001/jamapsychiatry.2022.0818

Purpose	To determine how social determinants of health and vaccinations play a role in the mental health outcomes of children in the US during the COVID-19 pandemic.
Study design	Prospective Longitudinal Cohort study (n=8493)
Level of evidence	Level 3
Methods	Researchers used baseline data previously established by the Adolescent Brain Cognitive Development (ABCD) study and created a longitudinal data set composed of ABCD COVID-19 Rapid Response wave surveys administered between May 16, 2020 and April 24, 2021. They further included ABCD COVID-19 geocoded data on individual level social determinants of health, ABCD child residential history, ABCD sociodemographics, dates of vaccine eligibility as per New York Times and US News & World Report, and the CDC COVID-19 vaccine tracker. Child mental health outcomes were measured by determining stress, COVID-19 related worry, sadness, and well-being using the Perceived Stress Scale (PSS) 5-point Likert scale.
Findings	Researchers found that there was a consistent mean decrease in stress, sadness and COVID-19-related worry after adult vaccinations started rolling out on December 13, 2020. COVID-19 worry was shown to be higher among Asian, Black, and Hispanic children compared to White children. Furthermore, higher stress scores were associated with disrupted mental health treatment, living in economically deprived neighborhoods and living with higher shares of adults working full-time who were unable to social distance. Lastly, increased trajectoires of sadness were seen in children with families experiencing pandemic-related food insecurity.
Clinical Implications	**Study suggested that adult COVID-19 vaccination status and socioeconomic factors impacted childrens' mental health during the COVID-19 pandemic**. It is important to consider how social determinants of health with emphasis on race can contribute to mental health disparities in children.
Limitations	The study used previous baseline data from the ABCD study which consisted of self report measures that could introduce social desirability and recall bias. Moreover, the study did not account for possible intersectionality effects between different social determinant factors such as gender, race, healthcare status and how those could possibly confound the data.

Association of COVID-19 Acute Respiratory Distress Syndrome With Symptoms of Posttraumatic Stress Disorder in Family Member After

Elie Azoulay MD, PhD, et al.

JAMA
February 18, 2022
DOI: 10.1001/jama.2022.2017

Purpose	To determine the association between patients hospitalized due to COVID-19 acute respiratory distress syndrome (ARDS) vs. ARDS of other causes and the risk for Posttraumatic Stress Disorder (PTSD)-related symptoms in family members.
Study design	Prospective Cohort (n=602 family members)
Level of evidence	Level IV
Methods	Participants were enrolled from 23 ICUs in France from January 2020 to June 2020 with final follow-up ending in October 2020. Primary outcome was PTSD symptoms at 90 days after ICU discharge measured by Impact of Events Scale-Revised score (PTSD symptoms defined by score >22). Secondary outcomes were symptoms of anxiety and depression at 90 days.
Findings	602 family members of 307 patients were prospectively enrolled. 517 family members and 273 patients completed the day-90 assessment. 303 family members were COVID-19 patient family members. 28% of all family members exhibited symptoms of PTSD related symptoms after ICU discharge, significantly more common in family members of patients with COVID-19 (35% vs. 19%, p<0.001). Symptoms of anxiety (41% vs. 34%) and depression (31% vs. 18%) were also significantly higher in the COVID-19 vs. non-COVID-19 group. PTSD symptoms significantly higher among bereaved family members of patients who passed away from COVID-19 vs. non-COVID-19 ARDS (63% vs. 39%, p=0.008), with fewer family members attending the funeral and the funeral not occurring as they expected. COVID-19 ARDS was significantly associated with an increased risk for PTSD-related symptoms in family members when adjusting for age, sex, and level of social support (odds ratio, OR: 2.05). There were non-significant differences for PTSD, anxiety and depressive symptoms for ICU survivors of COVID-19 ARDS vs. non-COVID-19 ARDS, as well as when compared to family members.
Clinical Implications	Family members of patients with COVID-19 ARDS have a significantly higher risk of PTSD, anxiety, and depressive symptoms at 90-days post discharge as compared to family members of non-COVID-19 ARDS patients. These symptoms were significantly increased in bereaved family members of COVID-19 patients as compared to non-COVID-19 ARDS patients.
Limitations	Possible variability in actions of ICU clinical staff that could contribute to the different experiences of family members. Study was conducted in early 2020 and may not reflect current strains of COVID-19.

Effect of Covid-19 Vaccination on Transmission of Alpha and Delta Variants

Joshua S. Gans,PhD et al.

JAMA Network
January 7, 2022
DOI: https://doi.org/10.1001/jama.2021.24355

Purpose	To investigate the incidence of false-positive COVID rapid antigen tests.
Study design	Retrospective, cohort study
Level of evidence	Level III
Methods	Asymptomatic employees were screened twice weekly using rapid antigen tests from January 11-October 13,2021 to assess as a screening for asymptomatic workers. Participants testing positive were referred for a confirmatory polymerase chain reaction (PCR) test that was completed within 24 hours. Data was verified by an audit process by external participant organizations.
Findings	903,408 rapid antigen tests were performed in over 537 workplaces. Of the 1,322 positive results, 1,103 patients received further evaluation by PCR. False positives, identified as a positive rapid antigen test followed by a negative confirmatory PCR test, was 426 (42%). Of the false positives, 278 (60%) occurred in two workplaces, which were drawn from a single batch of the "Abbott's Panbio COVID-19 Ag Rapid Test Device."
Clinical Implications	**This study indicates that the false positive results from COVID rapid antigen tests are low**. As many of the false positives were identified to be associated with one batch of tests, the false positives are more likely a result of manufacturing instead of an implementation issue. Therefore, it is important to identify faulty batches and to inform officials as well as manufacturing companies efficiency, to allow removal of defective tests and to return to employment.
Limitations	Limitations include convenience sampling for the different workplaces. Additionally, reporting the lot number and/or results of the confirmatory PCR tests were optional for the participants. Finally, this study was performed in Canada and therefore may not generalize to other parts of the world.

Efficacy of a Fourth Dose of Covid-19 mRNA Vaccine against Omicron

Gili Regev-Yochay, M.D.

New England Journal of Medicine
March 16, 2022
DOI: 10.1056/NEJMc2202542

Purpose	To assess the immunogenicity and durability of a 4th dose of the COVID-19 mRNA vaccine.
Study design	Open-label, non-randomized prospective intervention study (n = 300-400)
Level of evidence	Level 4
Methods	Volunteers will be tested before and after a 4th dose of COVID-19 vaccine (either BNT162b2 of Pfizer-BioNTech, n=154 or mRNA-1273 of Moderna, n=120), and followed for 180 days. This group will be contrasted to a control group of healthcare workers (who did not receive the 4th dose) with similar characteristics (308 controls for Pfizer group and 239 controls for Moderna group). Primary outcomes include serum IgG, pseudoneutralization, microneutralization, avidity and IgA as well as adverse event reportings via electronic survey. Secondary outcomes include T-cell and B-cell activity, as well as SARS-CoV-2 incidence, specifically Omicron variant.
Findings	Overall, 25.0% of the participants in the control group were infected with the Omicron variant, as compared with 18.3% of the participants in the BNT162b2 group and 20.7% of those in the mRNA-1273 group. Vaccine efficacy against any SARS-CoV-2 infection was 30% (95% confidence interval [CI], −9 to +55) for BNT162b2 and 11% (95% CI, −43 to +44) for mRNA-1273. Most infected health care workers reported negligible symptoms, both in the control group and the intervention groups. However, most of the infected participants were potentially infectious, with relatively high viral loads (nucleocapsid gene cycle threshold, ≤25). Vaccine efficacy was estimated to be higher for the prevention of symptomatic disease (43% for BNT162b2 and 31% for mRNA-1273).
Clinical Implications	The study provided evidence that a 4th dose of mRNA vaccine is immunogenic, safe, and somewhat efficacious against symptomatic disease. A comparison of the initial response to the 4th dose with the peak response to a 3rd dose did not show substantial differences in humoral response or in levels of Omicron-specific neutralizing antibodies. **Along with previous data showing the superiority of a 3rd dose to a 2nd dose, results suggest that maximal immunogenicity of mRNA vaccines is achieved after 3 doses and that antibody levels can be restored by a 4th dose.**
Limitations	The nonrandomized design and 1-week difference between enrollment in the two intervention groups generated potential biases. Older and vulnerable populations were not assessed and sample size was small.

Comparison of Home Antigen Testing With RT-PCR and Viral Culture During the Course of SARS-CoV-2 Infection

Victoria T. Chu, et al.

JAMA Internal Medicine
April 29, 2022
DOI: 10.1001/jamainternmed.2022.1827

Purpose	To compare the diagnostic performance of COVID-19 home antigen tests during the course of infection with RT-PCR and viral culture.
Study design	Prospective cohort study (n=225)
Level of evidence	Level 3
Methods	A sample of 225 individuals with RT-PCR confirmed SARS-CoV-2 infection and their household members were enrolled in this study for 15 days. Every household member was required to document symptoms and take 1 at-home antigen test daily. Nasopharyngeal (NP) swabs for RT-PCR and viral culture were collected by trained professionals from all participants at enrollment and 14 days later. A subset of participants underwent daily NP swab testing for 7 days after enrollment. NP swabs were collected from all household members when a previously uninfected individual became symptomatic or had a newly positive at-home test.
Findings	The 225 enrolled participants contributed 3044 home antigen tests and 642 NP swabs. At home antigen test sensitivity peaked 4 days after the illness onset compared to 3 days with RT-PCR and 2 days with viral cultures. The sensitivity of antigen tests was 64% compared to RT-PCR and 84% compared to viral cultures collected on the same day. Sensitivity improved when a second antigen test was performed 1 to 2 days later, particularly early in the illness course. Six days after illness onset, RT-PCR positivity was 86%, antigen test positivity was 61%, and culture positivity was 36%. At 11 days after illness onset, RT-PCR positivity remained at 86%, while antigen test positivity and culture positivity were 16% and 9%, respectively. Home antigen test positivity was consistently higher for unvaccinated cases compared with those who received at least 1 vaccine dose before infection.
Clinical Implications	Home antigen tests are moderately sensitive compared with RT-PCR (64%) but highly sensitive compared with viral culture (84%) collected on the same day. With the widespread availability, ease of use, and rapid turnaround time, home antigen tests may increase testing and identification of COVID-19 cases.
Limitations	The findings are limited to the SARS-CoV-2 lineages that were circulating at the time of the investigation. Participants were primarily non-Hispanic, White, younger, and unvaccinated. All participants were confirmed with SARS-CoV-2 before consenting to the study, limiting the use of home antigen kits to screen for infected individuals

Post-COVID Conditions Among Adult COVID-19 Survivors Aged 18-64 and ≥65 Years - United States, March 2020 - November 2021

Laura Bull-Otterson, PhD, et

Center for Disease Control and Prevention, Morbidity and Mortality Weekly Report

May 27, 2022

DOI: http://dx.doi.org/10.15585/mmwr.mm7121e1

Purpose	A growing number of persons previously infected with SARS-CoV-2, the virus that causes COVID-19, have reported persistent symptoms, or the onset of long-term symptoms, ≥4 weeks after acute COVID-19. These symptoms are commonly referred to as post-COVID conditions, or long COVID.
Study design	Case Control, EHR data review by CDC
Level of evidence	Level 1
Methods	Electronic health record (EHR) data during March 2020–November 2021, for persons in the United States aged ≥18 years were used to assess the incidence of 26 conditions often attributable to post-COVID among patients who had received a previous COVID-19 diagnosis (case-patients) compared with the incidence among matched patients without evidence of COVID-19 in the EHR (control patients). Follow-up period was 30 to 365 days after the index encounter.
Findings	Among all patients aged ≥18 years, 38% of case-patients experienced an incident condition compared with 16% of controls; conditions affected multiple systems including cardiovascular, pulmonary, hematologic, renal, endocrine, gastrointestinal, musculoskeletal, neurologic, and psychiatric signs and symptoms. By age group, the highest risk ratios (RRs) were for acute pulmonary embolism (RR=2.1 and 2.2 among persons aged 18–64 and ≥65 years, respectively) and respiratory signs and symptoms (RR=2.1 in both age groups). Among those aged 18–64 years, 35.4% of case-patients experienced an incident condition compared with 14.6% of controls. Among those aged ≥65 years, 45.4% of case-patients experienced an incident condition compared with 18.5% of controls. These findings translate to one in five COVID-19 survivors aged 18–64 years, and one in four survivors aged ≥65 years experiencing an incident condition that might be attributable to previous COVID-19.
Clinical Implications	**What is added by this report?** COVID-19 survivors have twice the risk for developing pulmonary embolism or respiratory conditions; one in five COVID-19 survivors aged 18–64 years and one in four survivors aged ≥65 years experienced at least one incident condition that might be attributable to previous COVID-19. **Implications for public health practice?** Implementation of COVID-19 prevention strategies, as well as routine assessment for post-COVID conditions among persons who survive COVID-19, is critical to reducing the incidence and impact of post-COVID conditions, particularly among adults aged ≥65 years.
Limitations	'Long-term' sequelae limited to several years timeline at most, due to recency of pandemic. Also, it is difficult to prove the causality but those with prior COVID-19 history were more than twice as likely experience these health events than those without prior infection.

Correlation Between Mask Compliance and COVID-19 Outcomes in Europe

Beny Spira

Cureus
April 19, 2022
DOI: 10.7759/cureus.24268

Purpose	To analyze the correlation between mask usage and morbidity and mortality among European countries during the 2020-2021 winter.
Study design	Retrospective Cohort Analysis
Level of evidence	3
Methods	The author used morbidity, mortality and mask usage data from Institute for Health Metrics and Evaluation at the University of Washington. The morbidity, mortality, and mask usage data over a six-month period (October 2020 to March 2021) of 35 European countries were analyzed. All European countries with more than one million inhabitants were selected. The author used Spearman's correlation analyses and Shapiro-Wilk normality checks as well as linear regressions to analyze the data.
Findings	All countries in the study underwent a peak of COVID-19 infection during the time period selected by the author. Weak positive correlations were observed when mask compliance was plotted against morbidity (cases/million) or mortality (death/million). There was not a negative correlation between mask usage and cases; however, there was a strong positive correlation between mask usage and deaths in Western Europe suggesting that the universal use of masks may have had harmful unintended consequences. Repeating the correlations after excluding countries with greater than 20 million people, the results did not change significantly. Rearranging countries into subgroups and performing the same analysis did not find a negative correlation between mask usage and cases or deaths.
Clinical Implications	If community masking was associated with decreased COVID-19 cases and deaths, the pattern should be able to be observed from a large retrospective cohort. This paper demonstrates how the evidence supporting the use of mask mandates and community masking to decrease cases and deaths associated with COVID-19 is weak. The lack of a negative correlation between mask usage and COVID-19 cases and deaths suggest that other preventive measures aside from masking should be studied to find an efficacious population wide strategy to decrease COVID-19 cases and deaths.
Limitations	When comparing an intervention among millions of people and various countries there is a possibility for confounding variables especially in regards to different cultures and laws. This paper takes into account mask mandates and mask usage in countries during the selected time period but does not control for other variables such as limiting capacity at public spaces. The author states that he did not control for vaccination rates among populations. This paper is reproducible due to low cost of performing statistical analyses and wide availability to COVID-19 data.