COVID-19 Literature Review
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1. Odds of contracting COVID in unvaccinated individuals is 5.5 fold higher than in vaccinated individuals.
2. Vaccination reduces the risk of delta variant infection and accelerates viral clearance. however, secondary attack rate and peak viral loads DO NOT differ between vaccinated and unvaccinated individuals.
3. Individuals with prior SARS-CoV-2 infection followed by 2 doses of mRNA vaccine develop higher spike antibody measurements than individuals with vaccination alone
4. A 3rd dose of mRNA increases seropositivity and antibody levels reducing rates of COVID infections and severe illness.
5. SARS-CoV-2 spike specific IgA antibody complexes are found in infants born to COVID positive mothers at 48 hours postpartum and at 2 months conferring passive immunity and stimulating neonatal immune system.
6. Vaccine efficacy of 91% reported for children 5 - 11 years of age after vaccination with mRNA with no vaccine-related serious side effects reported.
7. mRNA vaccination was 77% effective against COVID related hospitalization in immunocompromised adults compared to immunocompetent adults at 90%. A 3rd jab is highly recommended if immunosuppressed.
8. Sleep-related hypoxia was not associated with increased SARS-CoV-2 positivity; however, it was an associated risk factor for detrimental COVID-19 outcomes
9. With the exception of rituximab, there was no increased risk of mechanical ventilation or in-hospital death for pts admitted to the hospital while on immunosuppressive medicines.
10. Concomitant vaccination with AstraZeneca or mRNA vaccine plus an age-appropriate influenza vaccine raises no safety concerns and preserves antibody responses to both vaccines
11. In patients with COVID-19 who received invasive mechanical ventilation for moderate-to-severe ARDS, IVIG did not improve clinical outcomes at day 28 and tended to be associated with an increased frequency of serious adverse events, although not significant.
12. Humoral immunity following a second dose of mRNA vaccine was not impaired by methotrexate or targeted biologics.
13. Case study of immunosuppressed patient with sustained infective SARS-CoV2 x 8 months.
14. Based on a meta-analysis investigating 23 RCTs (3300 pts), Ivermectin did not show a statistically significant effect on survival or hospitalizations
15. A study with 3.5 million controls and >16,000breakthrough infections, demonstrates that there are increased risks of death and post-acute sequalae in people with breakthrough COVID-19 after vaccination

CDC - 10/29/2021 - vaccine efficacy	• Among COVID-19–like illness hospitalizations among adults aged ≥18 years whose previous infection or vaccination occurred 90–179 days earlier, the adjusted odds of laboratory-confirmed COVID-19 among unvaccinated adults with previous SARS-CoV-2 infection were 5.49-fold higher than the odds among fully vaccinated recipients of an mRNA COVID-19 vaccine who had no previous documented infection (95% confidence interval = 2.75–10.99) • https://www.cdc.gov/mmwr/volumes/70/wr/mm7044e1.htm?s_cid=mm7044e1_w
LANCET - 10/29/2021 - COVID community	• The SAR (Secondary Attack Rate) in household contacts exposed to the delta variant was 25% (95% CI 18–33) for fully vaccinated individuals compared with 38% (24–53) in unvaccinated individuals.

transmission and viral kinetics	• The median time between second vaccine dose and study recruitment in fully vaccinated contacts was longer for infected individuals (median 101 days [IQR 74–120]) than for uninfected individuals (64 days [32–97], p=0·001). • SAR among household contacts exposed to fully vaccinated index cases was similar to household contacts exposed to unvaccinated index cases (**25%** [95% CI 15–35] for vaccinated *vs* **23%** [15–31] for unvaccinated). 12 (39%) of 31 infections in fully vaccinated household contacts arose from fully vaccinated epidemiologically linked index cases, further confirmed by genomic and virological analysis in three index case–contact pairs. • Although peak viral load did not differ by vaccination status or variant type, it increased modestly with age (difference of 0·39 [95% credible interval –0·03 to 0·79] in peak $\log_{10}$ viral load per mL between those aged 10 years and 50 years). • Fully vaccinated individuals with delta variant infection had a faster (posterior probability >0·84) mean rate of viral load decline (0·95 $\log_{10}$ copies per mL per day) than did unvaccinated individuals with pre-alpha (0·69), alpha (0·82), or delta (0·79) variant infections. Within individuals, faster viral load growth was correlated with higher peak viral load (correlation 0·42 [95% credible interval 0·13 to 0·65]) and slower decline (–0·44 [–0·67 to –0·18]). • Vaccination reduces the risk of delta variant infection and accelerates viral clearance. Nonetheless, fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases and can efficiently transmit infection in household settings, including to fully vaccinated contacts. • https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00648-4/fulltext
JAMA - 11/1/2021 - Durability of Ab levels after vaccination in individuals with and without prior infection.	• Health care workers with prior SARS-CoV-2 infection followed by 2 doses of mRNA vaccine (3 independent exposures to spike antigen) developed higher spike antibody measurements than individuals with vaccination alone. Consistent with work comparing extended vaccine dosing intervals, the study showed that a longer interval between infection and first vaccine dose may enhance the antibody response.[6] • https://jamanetwork.com/journals/jama/fullarticle/2785919?guestAccessKey=d6d49995-b0f4-4849-bcb5-1a486171137a&utm_source=For_The_Media&utm_medium=referral&utm_campaign=ftm_links&utm_content=tfl&utm_term=110121 • Prior SARS-CoV-2 infection was associated with a statistically significantly lower risk for breakthrough infection among individuals receiving the BNT162b2 or mRNA-1273 vaccines in Qatar between December 21, 2020, and September 19, 2021 • https://jamanetwork.com/journals/jama/fullarticle/2785918?guestAccessKey=6ee768d4-0daf-47a1-8177-ab636e03c6d3&utm_source=For_The_Media&utm_medium=referral&utm_campaign=ftm_links&utm_content=tfl&utm_term=110121
JAMA - 11/5/2021 - Antibody titers before and after 3rd dose of mRNA vaccine	• Among the 97 study participants, the median age was 70 years (IQR, 67-74), and 61% were women (Table 1). • Before the third dose (median, 221 days [IQR, 218-225] after the first vaccination), 94 participants (97%) were seropositive. The median titer level increased significantly after the third dose, from a median of 440 AU/mL (IQR, 294-923) to 25 468 AU/mL (IQR, 14 203-36 618) ($P < .001$), and all participants became seropositive (Table 1). No significant correlation was observed between age and IgG titers ($R = -0.075$; $P = .47$). No variable was significantly associated with higher IgG titers, including age, sex, days after first vaccination, and comorbidities (Table 2).

	• No major adverse events were reported • A third dose of the SARS-CoV-2 mRNA-1273 vaccine (Moderna) induced seropositivity in 49% of kidney transplant recipients who did not respond after 2 vaccine doses,[3]although this observation cannot be generalized to older adults. In a study from Israel among 1 137 804 adults aged 60 years and older who had received 2 BNT162b2 doses 5 or more months earlier, a third dose was associated with lower rates of confirmed SARS-CoV-2 infections and severe illness • https://jamanetwork.com/journals/jama/fullarticle/2786096
JAMA - 11/3/2021 - Immune response of neonates born to mothers with COVID	• In total, 28 mother-infant dyads (mean [SD] maternal age, 31.8 [6.4] years; mean [SD] gestational age, 38.1 [2.3] weeks; 18 [60%] male infants) were enrolled at delivery, and 21 dyads completed the study at 2 months' follow-up. Because maternal infection was recent in all cases, transplacental transfer of virus spike-specific IgG antibodies occurred in only 1 infant. One case of potential vertical transmission and 1 case of horizontal infection were observed. • Virus spike protein–specific salivary IgA antibodies were significantly increased ($P = .01$) in infants fed breastmilk (0.99 arbitrary units [AU]; IQR, 0.39-1.68 AU) vs infants fed an exclusive formula diet (0.16 AU; IQR, 0.02-0.83 AU). • Maternal milk contained IgA spike immune complexes at 48 hours (0.53 AU; IQR, 0.25-0.39 AU) and at 2 months (0.09 AU; IQR, 0.03-0.17 AU) and may have functioned as specific stimuli for the infant mucosal immune response • SARS-CoV-2 spike–specific IgA antibodies were detected in infant saliva, which may partly explain why newborns are resistant to SARS-CoV-2 infection. Mothers infected in the peripartum period appear to not only passively protect the newborn via breastmilk secretory IgA but also actively stimulate and train the neonatal immune system via breastmilk immune complexes • https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2785791
NEJM - 11/9/2021 - evaluation of mRNA vaccines in children 5-11 years of age	• During the phase 1 study, a total of 48 children 5 to 11 years of age received 10 μg, 20 μg, or 30 μg of the BNT162b2 vaccine (16 children at each dose level). • On the basis of reactogenicity and immunogenicity, a dose level of 10 μg was selected for further study. • In the phase 2–3 trial, a total of 2268 children were randomly assigned to receive the BNT162b2 vaccine (1517 children) or placebo (751 children). At data cutoff, the median follow-up was 2.3 months. • In the 5-to-11-year-olds, as in other age groups, the BNT162b2 vaccine had a favorable safety profile. No vaccine-related serious adverse events were noted. • One month after the second dose, the geometric mean ratio of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neutralizing titers in 5-to-11-year-olds to those in 16-to-25-year-olds was 1.04 (95% confidence interval [CI], 0.93 to 1.18), a ratio meeting the prespecified immunogenicity success criterion (lower bound of two-sided 95% CI, >0.67; geometric mean ratio point estimate, ≥0.8). • Covid-19 with onset 7 days or more after the second dose was reported in three recipients of the BNT162b2 vaccine and in 16 placebo recipients (vaccine efficacy, 90.7%; 95% CI, 67.7 to 98.3) • https://www.nejm.org/doi/full/10.1056/NEJMoa2116298

CDC - 11/5/2021 - 2-dose mRNA vaccination effectiveness in immunosuppressed individuals	• Effectiveness of mRNA vaccination against laboratory-confirmed COVID-19–associated hospitalization was lower (77%) among immunocompromised adults than among immunocompetent adults (90%). Vaccine effectiveness varied considerably among immunocompromised patient subgroups • https://www.cdc.gov/mmwr/volumes/70/wr/mm7044e3.htm?s_cid=mm7044e3_x
JAMA - 11/10/2021 - Sleep-related hypoxia and COVID outcomes	• Of 350 710 individuals tested for SARS-CoV-2, 5402 (mean [SD] age, 56.4 [14.5] years; 3005 women [55.6%]) had a prior sleep study, of whom 1935 (35.8%) tested positive for SARS-CoV-2. Of the 5402 participants, 1696 were Black (31.4%), 3259 were White (60.3%), and 822 were of other race or ethnicity (15.2%). • Patients who were positive vs negative for SARS-CoV-2 had a higher AHI score (median, 16.2 events/h [IQR, 6.1-39.5 events/h] vs 13.6 events/h [IQR, 5.5-33.6 events/h]; $P < .001$) and increased TST <90 (median, 1.8% sleep time [IQR, 0.10%-12.8% sleep time] vs 1.4% sleep time [IQR, 0.10%-10.8% sleep time]; $P = .02$). • After overlap propensity score–weighted logistic regression, no SDB measures were associated with SARS-CoV-2 positivity. Median TST <90 was associated with the WHO-designated COVID-19 ordinal clinical outcome scale (adjusted odds ratio, 1.39; 95% CI, 1.10-1.74; $P = .005$). • Time-to-event analyses showed sleep-related hypoxia associated with a 31% higher rate of hospitalization and mortality (adjusted hazard ratio, 1.31; 95% CI, 1.08-1.57; $P = .005$ • sleep-related hypoxia were not associated with increased SARS-CoV-2 positivity; however, once patients were infected with SARS-CoV-2, sleep-related hypoxia was an associated risk factor for detrimental COVID-19 outcomes • https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2785921
LANCET - 11/15/2021 - Long-term immunosuppressive meds and in-hospital COVID outcomes.	• Among 231 830 potentially eligible adults in the N3C repository who were admitted to hospital with confirmed or suspected COVID-19 during the study period, 222 575 met the inclusion criteria (mean age 59 years [SD 19]; 111 269 [50%] male). • The most common comorbidities were diabetes (23%), pulmonary disease (17%), and renal disease (13%). • 16 494 (7%) patients had long-term immunosuppression with medications for diverse conditions, including rheumatological disease (33%), solid organ transplant (26%), or cancer (22%). In the propensity score matched cohort (including 12 841 immunosuppressed patients and 29 386 non-immunosuppressed patients), immunosuppression was associated with a reduced risk of invasive ventilation (HR 0·89, 95% CI 0·83–0·96) and there was no overall association between long-term immunosuppression and the risk of in-hospital death. None of the 15 medication classes examined were associated with an increased risk of invasive mechanical ventilation. Although there was no statistically significant association between most drugs and in-hospital death, increases were found with rituximab for rheumatological disease (1·72, 1·10–2·69) and for cancer (2·57, 1·86–3·56). Results were generally consistent across subgroup analyses that considered race and ethnicity or sex, as well as across sensitivity analyses that varied exposure, covariate, and outcome definitions

	• with the exception of rituximab, there was no increased risk of mechanical ventilation or in-hospital death for the rheumatological, antineoplastic, or antimetabolite therapies examined • https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00325-8/fulltext

Lancet - 11/11/2021 - Co-administration od COVID vaccine and Flu vaccine.	• Between April 1 and June 26, 2021, 679 participants were recruited to one of six cohorts, as follows:
	  o 129 ChAdOx1 plus cellular quadrivalent influenza vaccine,
	  o 139 BNT162b2 plus cellular quadrivalent influenza vaccine,
	  o 146 ChAdOx1 plus MF59C adjuvanted, trivalent influenza vaccine,
	  o 79 BNT162b2 plus MF59C adjuvanted, trivalent influenza vaccine,
	  o 128 ChAdOx1 plus recombinant quadrivalent influenza vaccine, and
	  o 58 BNT162b2 plus recombinant quadrivalent influenza vaccine.
	• 340 participants were assigned to concomitant administration of influenza and a second dose of COVID-19 vaccine at day 0 followed by placebo at day 21, and 339 participants were randomly assigned to concomitant administration of placebo and a second dose of COVID-19 vaccine at day 0 followed by influenza vaccine at day 21.
	• **Non-inferiority was indicated in four cohorts**, as follows: ChAdOx1 plus cellular quadrivalent influenza vaccine (risk difference for influenza vaccine minus placebos −1·29%, 95% CI −14·7 to 12·1), BNT162b2 plus cellular quadrivalent influenza vaccine (6·17%, −6·27 to 18·6), BNT162b2 plus MF59C adjuvanted, trivalent influenza vaccine (–12·9%, −34·2 to 8·37), and ChAdOx1 plus recombinant quadrivalent influenza vaccine (2·53%, −13·3 to 18·3).
	• In the other two cohorts, the upper limit of the 95% CI exceeded the 0·25 non-inferiority margin (ChAdOx1 plus MF59C adjuvanted, trivalent influenza vaccine 10·3%, −5·44 to 26·0; BNT162b2 plus recombinant quadrivalent influenza vaccine 6·75%, −11·8 to 25·3).
	• Most systemic reactions to vaccination were mild or moderate. Rates of local and unsolicited systemic reactions were similar between the randomly assigned groups. One serious adverse event, hospitalization with severe headache, was considered related to the trial intervention. Immune responses were not adversely affected
	• Concomitant vaccination with ChAdOx1 or BNT162b2 plus an age-appropriate influenza vaccine raises no safety concerns and preserves antibody responses to both vaccines
	• https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02329-1/fulltext

Lancet - 11/11/2021 - IVIG and COVID	• In patients with COVID-19 who received invasive mechanical ventilation for moderate-to-severe ARDS, IVIG did not improve clinical outcomes at day 28 and tended to be associated with an increased frequency of serious adverse events, although not significant. The effect of IVIGs on earlier disease stages of COVID-19 should be assessed in future trials • https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00440-9/fulltext
Lancet - 11/9/2021 - humoral and cellular immunogeni	• Between Jan 14 and April 4, 2021, 121 individuals were recruited, and data were available for 82 participants after the second vaccination. • The study population included patients with psoriasis receiving methotrexate (n=14), TNF inhibitors (n=19), IL-17 inhibitors (n=14), IL-23 inhibitors (n=20), and 15 healthy controls, who had received both vaccine doses. The median age of the study

city of mRNA vaccination in people receiving methotrexate and targeted immunosuppression	population was 44 years (IQR 33–52), with 43 (52%) males and 71 (87%) participants of White ethnicity. • All participants had detectable spike-specific antibodies following the second dose, and all groups (methotrexate, targeted biologics, and healthy controls) demonstrated similar neutralizing antibody titers against wild-type, alpha, and delta variants. • By contrast, a lower proportion of participants on methotrexate (eight [62%] of 13, 95% CI 32–86) and targeted biologics (37 [74%] of 50, 60–85; p=0·38) had detectable T-cell responses following the second vaccine dose, compared with controls (14 [100%] of 14, 77–100; p=0·022). There was no difference in the magnitude of T-cell responses between patients receiving methotrexate (median cytokine-secreting cells per 10^6 cells 160 [IQR 10–625]), targeted biologics (169 [25–503], p=0·56), and controls (185 [133–328], p=0·41). • Functional humoral immunity (i.e., neutralizing antibody responses) at 14 days following a second dose of BNT162b2 was not impaired by methotrexate or targeted biologics. A proportion of patients on immunosuppression did not have detectable T-cell responses following the second dose • https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00333-7/fulltext
OFID - 10/11/2021 - Longest persistence of viable SARS-CoV2 in Immunosuppressed pt	• In our patient, SARS-CoV-2 persisted with proven infectivity for >8 months. Viremia was associated with COVID-19 relapses, and Remdesivir treatment was effective in viremia clearance and symptom remission, although it was unable to clear the virus from the upper respiratory airways. During the viremic phase, we observed a low frequency of terminal effector CD8+ T lymphocytes in peripheral blood; these are probably recruited in inflammatory tissue for viral eradication. In addition, we found a high level of NK-cell repertoire perturbation with relevant involvement during SARS-CoV-2 viremia. • https://academic.oup.com/ofid/article/8/11/ofab217/6257145
OFID - 7/6/2021 - Meta-analysis of RCT for Ivermectin as therapy for COVID	• Ivermectin is an antiparasitic drug being investigated for repurposing against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). • Ivermectin showed in vitro activity against SARS-COV-2, but only at high concentrations. • This meta-analysis investigated Ivermectin in 23 randomized clinical trials (3349 patients) identified through systematic searches of PUBMED, EMBASE, MedRxiv, and trial registries. The primary meta-analysis was carried out by excluding studies at a high risk of bias. • Ivermectin did not show a statistically significant effect on survival (risk ratio [RR], 0.90; 95% CI, 0.57 to 1.42; *P* = .66) or hospitalizations (RR, 0.63; 95% CI, 0.36 to 1.11; *P* = .11). • Ivermectin displayed a borderline significant effect on duration of hospitalization in comparison with standard of care (mean difference, –1.14 days; 95% CI, –2.27 to –0.00; *P* = .05). • There was no significant effect of Ivermectin on time to clinical recovery (mean difference, –0.57 days; 95% CI, –1.31 to 0.17; *P* = .13) or binary clinical recovery (RR, 1.19; 95% CI, 0.94 to 1.50; *P* = .15). Currently, the World Health Organization recommends the use of Ivermectin only inside clinical trials. A network of large clinical trials is in progress to validate the results seen to date. • https://academic.oup.com/ofid/article/8/11/ofab358/6316214

In review - Nature - 11/2021 - Long-Covid after breakthrough infection	• The post-acute sequelae of COVID-19 have been described[1], but whether breakthrough COVID-19 (that is the disease that ensues following vaccine breakthrough SARS-CoV-2 infection) results in post-acute sequelae is not yet clear. Here we use the national healthcare databases of the US Department of Veterans Affairs to characterize 6-month risks of incident post-acute sequelae in people with breakthrough COVID-19 who survived for at least 30 days after diagnosis. • We show that compared to people with no evidence of COVID-19, beyond the first 30 days of illness, people with breakthrough COVID-19 exhibit a higher risk of death and broad array of incident post-acute sequelae in the pulmonary system, as well as extra pulmonary sequelae that include cardiovascular disorders, coagulation disorders, gastrointestinal disorders, general disorders (e.g., fatigue), kidney disorders, mental health disorders, metabolic disorders, musculoskeletal disorders, and neurologic disorders. Our analyses by care setting of the acute phase of the disease show that people who were not hospitalized during the first 30 days after diagnosis with breakthrough COVID-19 exhibit a small but not insignificant increase in risk of death and post-acute sequelae; the risks are further increased in people who were hospitalized during the acute phase of the disease. Our comparative approach shows that people with breakthrough COVID-19 exhibit lower risks of death and post-acute sequelae than people with COVID-19 who were not previously vaccinated for it; and in analyses among individuals who were hospitalized during the acute phase of the disease, people with breakthrough COVID-19 exhibit higher risks of death and post-acute sequelae than people with seasonal influenza. • Altogether, our findings show increased risks of death and post-acute sequalae in people with breakthrough COVID-19; the risks are evident among those who were not hospitalized during the acute phase of the disease. Our comparative approach provides context for understanding the risks in relation to COVID-19 without prior vaccination and seasonal influenza. The findings will inform the ongoing effort to optimize strategies for prevention of breakthrough SARS-CoV-2 infections and will guide development and optimization of post-acute care pathways for people with breakthrough COVID-19. • https://www.researchsquare.com/article/rs-1062160/v1