COVID-19 Literature Review

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1. 78% reduction in death for 4 shots (2nd booster) vs 3 shots (1 booster) after 4 or more months in people 60 year or older.
2. The Coping With COVID study, found that burnout approached 50% in 2020 among 9266 physicians across medical discipline... In the February 2022 survey, 62% of 847 clinicians had personal knowledge of other primary care clinicians who retired early or quit during the pandemic and 29% knew of practices that had closed up shop - "I think we have a platform that is collapsed, and we haven't recognized it yet," ...A quarter of clinicians said they planned to leave primary care within 3 years. in Etz's February survey in a mid-2021 survey by the nonprofit Physicians Foundation. About 20% of 2504 physicians said they knew a physician who had either considered, attempted, or died by suicide during the COVID-19 pandemic...frontline clinicians are experiencing high rates of depression, anxiety, sleep disturbance, and posttraumatic stress disorder
3. Vaccine effective against omicron :
    1. hospitalization 12-18 yo -> 40%
    2. critical illness 12-18 y -> 79%
    3. Hospitalization 5-12 yo ->69%
4. ZyCoV-D is a DNA-based vaccine developed in India with 66% Vaccine effectiveness.
5. COVID human challenge study done to study viral kinetics in native infection.
6. Mothers who received an mRNA COVID-19 vaccine during pregnancy delivered infants with no increased risk for morbidity or mortality
7. Cohort study demonstrates that incidence rate of COVID with Omicron was 6 to 8 times that of Delta in children younger than 5 years, but severe clinical outcomes were less frequent than with Delta variant
8. Pulse oximetry monitoring at home did not improve overall outcomes for COVID pts.
9. In patients with cancer undergoing treatment or s/p SCT, titers peaked at 1 month and remained stable over the next 6 months. There was a 20-fold increase in titers from a third dose compared to first.
10. durable cellular and humoral response were found in patients with cancer with solid tumors who were receiving active treatment.
11. During the omicron wave, unvaccinated children were 2x more likely to be hospitalized.
    1. 30% had no underlying condition
    2. 20% required ICU care.
12. New mAb (Tixagevimab-Cilgavimab) provided 76% relative risk reduction against COVID in this Ongoing trial

In Review Natureportfolio - 3/24/2022 - Second booster	• This retrospective cohort study included all members of Clalit Health Services, aged 60 to 100, eligible for the second-booster. • Mortality due to Covid-19 among participants who received the second-booster was compared with participants who received one booster dose. A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association between the

vaccine and CoVID-10 in adults 60 to 100	second-booster and death due to Covid-19 while adjusting for demographic factors and coexisting illnesses. • A total of 563,465 participants met the eligibility criteria. Of those, 328,597 (58%) received a second-booster dose during the 40-day study period. • Death due to Covid-19 occurred in 92 second-booster recipients and in 232 participants who received one booster dose (adjusted hazard ratio 0.22; 95% confidence interval 0.17 to 0.28). • This study demonstrates a substantial reduction in Covid-19 mortality by the second-booster in eligible subjects • 78% reduction of death for 4 shots vs 3 shots (post 4 or more months) • https://www.researchsquare.com/article/rs-1478439/v1
JAMA - 3/30/2022 - Pushed to their limits - 1 in 5 physicians intend to leave their practice	• The Coping With COVID study, found that burnout approached 50% in 2020 among 9266 physicians across medical disciplines • In the February 2022 survey, 62% of 847 clinicians had personal knowledge of other primary care clinicians who retired early or quit during the pandemic and 29% knew of practices that had closed up shop - "I think we have a platform that is collapsed, and we haven't recognized it yet," • A quarter of clinicians said they planned to leave primary care within 3 years in Etz's February survey • in a mid-2021 survey by the nonprofit Physicians Foundation. About 20% of 2504 physicians said they knew a physician who had either considered, attempted, or died by suicide during the COVID-19 pandemic • frontline clinicians are experiencing high rates of depression, anxiety, sleep disturbance, and posttraumatic stress disorder • https://jamanetwork.com/journals/jama/fullarticle/2790791
NEJM - 3/30/2022 - pfizer protection against Omicron in children and adolescents.	• We enrolled 1185 case patients (1043 [88%] of whom were unvaccinated, 291 [25%] of whom received life support, and 14 of whom died) and 1627 controls. • During the delta-predominant period, vaccine effectiveness against hospitalization for Covid-19 among adolescents 12 to 18 years of age was 93% (95% confidence interval [CI], 89 to 95) 2 to 22 weeks after vaccination and was 92% (95% CI, 80 to 97) at 23 to 44 weeks. • Among adolescents 12 to 18 years of age (median interval since vaccination, 162 days) during the omicron-predominant period, vaccine effectiveness was 40% (95% CI, 9 to 60) against hospitalization for Covid-19, 79% (95% CI, 51 to 91) against critical Covid-19, and 20% (95% CI, −25 to 49) against noncritical Covid-19.

	• During the omicron period, vaccine effectiveness against hospitalization among children 5 to 11 years of age was 68% (95% CI, 42 to 82; median interval since vaccination, 34 days) • https://www.nejm.org/doi/full/10.1056/NEJMoa2202826
Lancet - 3/25/2022 - SARS-CoV2 and influenza coinfection	• We examined clinical outcomes of co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses in 212 466 adults with SARS-CoV-2 infection who were admitted to hospital in the UK between Feb 6, 2020, and Dec 8, 2021, using the International Severe Acute Respiratory and Emerging Infection Consortium–WHO Clinical Characterization Protocol • Co-infection with influenza viruses was associated with increased odds of receiving invasive mechanical ventilation compared with SARS-CoV-2 monoinfection (table). SARS-CoV-2 co-infections with influenza (OR 4.14 {2.0 - 8.49}) viruses and adenoviruses were each significantly associated with increased odds of death • https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00383-X/fulltext
Lancet - 4/2/2022 - ZyCoV-D Efficacy and safety	• ZyCoV-D, a DNA-based vaccine • Between Jan 16, and June 23, 2021 (data cutoff), 33 194 individuals were screened, of whom 5241 did not meet screening criteria and 27 703 were enrolled and randomly assigned to receive ZyCoV-D (n=13 851) or placebo (n=13 852). Per-protocol, 81 cases were eligible and included in efficacy analysis (20 of 12 350 in the ZyCoV-D group and 61 of 12 320 in placebo group). • The ZyCoV-D vaccine efficacy was found to be 66·6% (95% CI 47·6–80·7). • The occurrence of solicited adverse events was similar between the treatment groups (623 [4·49%] in the ZyCoV-D group *vs* 620 [4·47%] in the placebo group). • There were two deaths (one in each group) reported at the data cutoff, neither of which was considered related to the study treatments • ZyCoV-D vaccine was found to be efficacious, safe, and immunogenic in a phase 3 trial • https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00151-9/fulltext
Nature - 3/31/2022 - Safety, tolerability and viral kinetics	• Since its emergence in 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused hundreds of millions of cases and continues to circulate globally. To establish a novel SARS-CoV-2 human challenge model that enables controlled investigation of pathogenesis, correlates of protection and efficacy testing of forthcoming interventions, 36 volunteers aged 18–29 years without

during COVID human challenge in young adults.	evidence of previous infection or vaccination were inoculated with 10 $TCID_{50}$ of a wild-type virus (SARS-CoV-2/human/GBR/484861/2020) intranasally in an open-label, non-randomized study (ClinicalTrials.gov identifier NCT04865237; funder, UK Vaccine Taskforce). • After inoculation, participants were housed in a high-containment quarantine unit, with 24-hour close medical monitoring and full access to higher-level clinical care. The study's primary objective was to identify an inoculum dose that induced well-tolerated infection in more than 50% of participants, with secondary objectives to assess virus and symptom kinetics during infection. All pre-specified primary and secondary objectives were met. Two participants were excluded from the per-protocol analysis owing to seroconversion between screening and inoculation, identified post hoc. • Eighteen (~53%) participants became infected, with viral load (VL) rising steeply and peaking at ~5 days after inoculation. • Virus was first detected in the throat but rose to significantly higher levels in the nose, peaking at ~8.87 log_{10} copies per milliliter (median, 95% confidence interval (8.41, 9.53)). • Viable virus was recoverable from the nose up to ~10 days after inoculation, on average. There were no serious adverse events. • Mild-to-moderate symptoms were reported by 16 (89%) infected participants, beginning 2–4 days after inoculation, whereas two (11%) participants remained asymptomatic (no reportable symptoms). • Anosmia or dysosmia developed more slowly in 15 (83%) participants. • No quantitative correlation was noted between VL and symptoms, with high VLs present even in asymptomatic infection. All infected individuals developed serum spike-specific IgG and neutralizing antibodies. Results from lateral flow tests were strongly associated with viable virus, and modeling showed that twice-weekly rapid antigen tests could diagnose infection before 70–80% of viable virus had been generated. Thus, with detailed characterization and safety analysis of this first SARS-CoV-2 human challenge study in young adults, viral kinetics over the course of primary infection with SARS-CoV-2 were established, with implications for public health recommendations and strategies to affect SARS-CoV-2 transmission. Future studies will identify the immune factors associated with protection in those participants who did not develop infection or symptoms and define the effect of prior immunity and viral variation on clinical outcome • https://www.nature.com/articles/s41591-022-01780-9
JAMA - 4/5/2022 - Maternal COVID	• A study in Israel found that **individuals who received an mRNA COVID-19 vaccine during pregnancy delivered infants with no increased risk for morbidity or mortality compared** with infants whose birthing parents weren't vaccinated

vaccine safe for infants	• The investigators analyzed 24 288 singleton live births from a health care organization in Israel from March 2021 through September 2021. • The study included 16 697 newborns exposed in the first and second trimesters to maternal vaccination with the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) • https://jamanetwork.com/journals/jama/article-abstract/2790650
JAMA - 4/1/2022 - incidence rates and clinical outcomes of Omicron in children younger than 5 compared to delta.	• This cohort study included a total of 651 640 children younger than 5 years: (1) Omicron cohort, 22 772 children; (2) Delta cohort, 66 692 children; and (3) Delta2 cohort, 10 496 children. • The monthly incidence rate of SARS-CoV-2 infections was mostly stable (1.0-1.5 cases per 1000 persons per day) between September and November 2021 (Delta-predominant period) but rapidly increased to 2.4 to 5.6 cases per 1000 persons per day in December 2021, coincident with the emergence of Omicron variant. • Monthly incidence rate of SARS-CoV-2 infections peaked at 8.6 cases per 1000 persons per day in the first half of January 2022 (Omicron-predominant period) and 8.2 in the second half of January 2022. • Incidence rate of Omicron infection was higher in children aged 0 to 2 years than in those aged 3 to 4 years. Omicron cohort was younger and with fewer comorbidities than Delta cohort, but differences were eliminated after matching (Table). • Risks for severe clinical outcomes in children infected with Omicron variant were significantly lower than those in the matched Delta cohort (Figure, A), whereas the risks for severe clinical outcomes in Delta2 cohort did not differ from those in Delta cohort (Figure, B). There were fewer than 10 deaths in all cohorts • https://jamanetwork.com/journals/jamapediatrics/fullarticle/2790793
NEJM - 4/6/2022 - Pulse Oximetry monitoring at home for COVID pts	• A total of 1041 patients (606 of whom had test-confirmed Covid-19) were assigned to the standard program group, and 1056 patients (611 of whom had test-confirmed Covid-19) were assigned to the pulse oximetry group • Among patients with Covid-19, the addition of home pulse oximetry to remote monitoring did not result in a greater number of days alive and out of the hospital than subjective assessments of dyspnea alone • https://www.nejm.org/doi/full/10.1056/NEJMc2201541?query=featured_coronavirus
JAMA - 4/21/2022 - Durability of immune humoral response to COVID	• This study enrolled 453 patients (mean [SD] age, 60.4 [13,1] years; 253 [56%] were female). Of 450 patients, 273 (61%) received the BNT162b2 vaccine (Pfizer), 160 (36%) received the mRNA-1273 vaccine (Moderna), and 17 (4%) received the JNJ-7846735 vaccine (Johnson & Johnson). • The GMTs (geometric means titer) of the anti-RBD for all patients were

vaccines in pts with cancer undergoing treatment or who received stem cell transplant	○ 1.70 (95% CI, 1.04-2.85) before vaccination, ○ 18.65 (95% CI, 10.19-34.11) after the first dose, ○ 470.38 (95% CI, 322.07-686.99) at 1 month after the second dose, ○ 425.80 (95% CI, 322.24-562.64) at 3 months after the second dose, ○ 447.23 (95% CI, 258.53-773.66) at 6 months after the second dose, and ○ 9224.85 (95% CI, 2423.92-35107.55) after the third dose. • The rate of threshold neutralization (≥30%) was observed in 203 of 252 patients (80%) 1 month after the second dose and in 135 of 166 patients (81%) 3 months after the second dose. Anti-RBD and nAb were highly correlated (Spearman correlation coefficient, 0.93 [0.92-0.94]; $P < .001$). Three months after the second dose, anti-RBD titers were lower in male vs female patients (ratio of GMTs, 0.52 [95% CI, 0.34-0.81]), patients older than 65 years vs patients 50 years or younger (ratio of GMTs, 0.38 [95% CI, 0.25-0.57]), and patients with hematologic malignant tumors vs solid tumors (ratio of GMTs, 0.40 [95% CI, 0.20-0.81]) • In this cross-sectional study, after 2 doses of an mRNA vaccine, anti-RBD titers peaked at 1 month and remained stable over the next 6 months. Patients older than 65 years of age, male patients, and patients with a hematologic malignant tumor had low antibody titers. Compared with the primary vaccine course, a 20-fold increase in titers from a third dose suggests a brisk B-cell anamnestic response in patients with cancer • https://jamanetwork.com/journals/jamaoncology/fullarticle/2791560
JAMA - 4/22/2022 - Long-term immunogenicity of mRNA vaccine in pts with solid tumors.	• Of the 169 patients, 97 (57%) were men; the mean (SD) age was 66 (11) years. Most patients (137 [81%]) had metastatic disease. Common cancers were gastrointestinal (55 [33%]), lung (38 [23%]), breast (28 [17%]), and genitourinary (21 [12%]). • Treatments consisted of chemotherapy (97 [57%]), biological agents (61 [36%]), immunotherapy (63 [37%]), or combined modalities. A total of 134 patients (79%) were evaluated for T-cell response because of a low viable cell count. Age, sex, and cancer type were not associated with cellular response. • Although treatment with chemotherapy was associated with humoral response, SFU was not associated with treatment type (Figure 1). We found a significant correlation between serological and cellular response (Figure 2), while 5 (22%) of the seronegative patients had SFU levels equal to or higher than the mean SFU of the seropositive patients. • Following receipt of a booster dose, 113 (67%) demonstrated a significant increase in cellular immune response (9.2 vs 31.3 SFU/10^6 peripheral blood mononuclear cells; $P = .02$), and 100% had

	an increase in antibody levels (117 vs 732 AU/mL; $P < .001$). At 12 months post vaccination, there were no documented COVID-19 cases • we found a durable cellular and humoral response in patients with cancer with solid tumors who were receiving active treatment. Humoral and cellular response were associated, although B-cell response was negatively associated with chemotherapy,[2] whereas T-cell response seemed to be unaffected, which may have been associated with a differential association of chemotherapy with B-cell counts. • https://jamanetwork.com/journals/jamaoncology/fullarticle/2791657
CDC - 4/22/2022 - Hospitalization of Children with COVID	• During the period of Omicron predominance (December 19, 2021–February 28, 2022), COVID-19–associated • hospitalization rates in children aged 5–11 years were approximately twice as high among unvaccinated as among vaccinated children. Non-Hispanic Black children represented the largest group of unvaccinated children. • Thirty percent of hospitalized children had no underlying medical conditions, and • 19% were admitted to an intensive care unit. Children with diabetes and obesity were more likely to experience severe COVID-19 • https://www.cdc.gov/mmwr/volumes/71/wr/mm7116e1.htm?s_cid=mm7116e1_x
NEJM - 4/20/2022 - mAb (Tixagevimab-Cilgavimab) for the prevention of COVID	• A total of 5197 participants underwent randomization and received one dose of AZD7442 or placebo (3460 in the AZD7442 group and 1737 in the placebo group). • The primary analysis was conducted after 30% of the participants had become aware of their randomized assignment. In total, 1221 of 3461 participants (35.3%) in the AZD7442 group and 593 of 1736 participants (34.2%) in the placebo group reported having at least one adverse event, most of which were mild or moderate in severity. • Symptomatic Covid-19 occurred in 8 of 3441 participants (0.2%) in the AZD7442 group and in 17 of 1731 participants (1.0%) in the placebo group (relative risk reduction, 76.7%; 95% confidence interval [CI], 46.0 to 90.0; P<0.001); extended follow-up at a median of 6 months showed a relative risk reduction of 82.8% (95% CI, 65.8 to 91.4). Five cases of severe or critical Covid-19 and two Covid-19–related deaths occurred, all in the placebo group • A single dose of AZD7442 had efficacy for the prevention of Covid-19, without evident safety concerns. • https://www.nejm.org/doi/full/10.1056/NEJMoa2116620?query=featured_coronavirus