Dr. Leo's COVID Corner
April 2022

1. A 4th dose of mRNA vaccine leads to 9-10x increased titers against Omicron with minimal additional adverse reactions
2. Although sotrovimab does not appear to have efficacy against BA.2, Remdesivir, Molnupiravir, and nirmatrelvir appear to retain effectiveness.
3. 2 articles from Nature with regards to misinformation in the time of pandemic as well the importance of trust and uncertainty
4. During the omicron wave, 3 doses of mRNA vaccine were 94% effective against severe disease.
5. Humoral titers after vaccination maybe slightly reduced on people taking immunosuppressive therapy, however, neutralization capacity and recall responses may be unaffected.
6. The immunomodulator CD24Fc demonstrated to accelerates clinical improvement of hospitalized patients with COVID-19 who are receiving oxygen support
7. Effectiveness of prior infection, vaccination with 2 or 3 doses, and hybrid immunity is >74% against hospitalization and death.
8. Antiplatelet therapy has no impact in survival or clinical course when used in critically ill COVID patients - RCT
9. The incidence rate of CVT (cerebral Venous thrombosis) after SARS-CoV-2 infection was significantly higher compared with after mRNA-based SARS-CoV-2 vaccination
10. Intrinsic severity of Omicron BA.2 is higher in unvaccinated children than delta and influenza with higher rates of mortality, PICU admissions and neurologic complications

NEJM - 3/16/2022 - 4th dose of mRNA vaccine against Omicron	• After the fourth dose, both messenger RNA (mRNA) vaccines induced IgG antibodies against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor-binding domain (Figure 1A) and increased neutralizing antibody titers (Fig. S3); • each measure was increased by a factor of 9 to 10, to titers that were slightly higher than those achieved after the third dose, with no significant difference between the two vaccines. • Concurrently, antibody levels in the control group continued to wane (Table S5). • Both vaccines induced an increase in live neutralization of the B.1.1.529 (omicron) variant and other viral strains by a factor of approximately 10 (Figure 1B), similar to the response after the third dose.[3] • We found that the fourth dose did not lead to substantial adverse events despite triggering mild systemic and local symptoms in the majority of recipients (Fig. S2 and Table S4A and S4B

	• Our data provide evidence that a fourth dose of mRNA vaccine is immunogenic, safe, and somewhat efficacious (primarily against symptomatic disease) • https://www.nejm.org/doi/full/10.1056/NEJMc2202542?query=featured_coronavirus
NEJM - 3/9/2022 - efficacy of antiviral agents against omicron sub variant BA.2	• S309 (the precursor of sotrovimab), which has been shown to have lower neutralizing activity against omicron/BA.1 and omicron/BA.1.1 than against the ancestral strain and other variants of concern,[3,4] had even less neutralizing activity against omicron/BA.2 in our study • The susceptibilities of omicron/BA.2 (NCD1288) to Remdesivir, Molnupiravir, and nirmatrelvir were similar to those of the ancestral strain and other variants of concern (i.e., 50% inhibitory concentration values for these three agents that differed by factors of 2.5 to 4.5, 0.7 to 1.6, and 1.5 to 3.3, respectively) • https://www.nejm.org/doi/full/10.1056/NEJMc2201933?query=featured_coronavirus
Nature - 3/10/2022 - an epidemic of uncertainty.	• The COVID-19 'infodemic' continues to undermine trust in vaccination efforts aiming to bring an end to the pandemic. However, the challenge of vaccine hesitancy is not only a problem of the information ecosystem and it often has little to do with the vaccines themselves. In this Perspective, we argue that the • *epidemiological and social crises brought about by COVID-19 have magnified widely held social anxieties and trust issues that, in the unique circumstances of this global pandemic, have exacerbated skepticism toward vaccines*. We argue that **trust is key to overcoming vaccine hesitanc**y, especially in a context of widespread social uncertainty brought about by the pandemic, where public sentiment can be volatile. • Finally, we draw out some implications of our argument for strategies to build vaccine confidence • https://www.nature.com/articles/s41591-022-01728-z
Nature - 3/10/2022 - Misinformation: Susceptibility spread and interventions to	• The spread of misinformation poses a considerable threat to public health and the successful management of a global pandemic. For example, studies find that exposure to misinformation can undermine vaccination uptake and compliance with public-health guidelines. As research on the science of misinformation is rapidly emerging, this conceptual Review summarizes what we know along • three key dimensions of the infodemic: ○ susceptibility, spread, and immunization.

immunize the public.	• Extant research is evaluated on the questions of why (some) people are (more) susceptible to misinformation, how misinformation spreads in online social networks, and which interventions can help to boost psychological immunity to misinformation. Implications for managing the infodemic are discussed. • https://www.nature.com/articles/s41591-022-01713-6
CDC - 3/18/2022 - Effectiveness of 3rd dose of mRNA vaccine	• Receiving 2 or 3 doses of an mRNA COVID-19 vaccine was associated with a 90% reduction in risk for COVID-19–associated IMV or death. • Protection of **3 mRNA vaccine** doses during the period of Omicron predominance wa**s 94% against severe disease** • https://www.cdc.gov/mmwr/volumes/71/wr/mm7112e1.htm?s_cid=mm7112e1_x
Lancet - 3/17/2022 - humoral responses to 2nd and 3d doses of mRNA vaccine on people on immunosuppressant therapy.	• Between Feb 2 and Aug 1, 2021, we included 3222 participants in our cohort. Sera from 2339 participants, 1869 without and 470 participants with previous SARS-CoV-2 infection were analyzed (mean age 49·9 years [SD 13·7]; 1470 [62·8%] females and 869 [37·2%] males). • Humoral responses did not differ between disorders. • Anti-CD20 therapy, sphingosine 1-phosphate receptor (S1P) modulators, and mycophenolate mofetil combined with corticosteroids were associated with lower relative risks for reaching seroconversion following standard vaccination (0·32 [95% CI 0·19–0·49] for anti-CD20 therapy, 0·35 [0·21–0·55] for S1P modulators, and 0·61 [0·40–0·90] for mycophenolate mofetil combined with corticosteroids). • A third vaccination increased seroconversion for mycophenolate mofetil combination treatments (from 52·6% after the second vaccination to 89·5% after the third) but not significantly for anti-CD20 therapies (from 36·8% to 45·6%) and S1P modulators (from 35·5% to 48·4%). • **Most other immunosuppressant groups showed moderately reduced antibody titers after standard vaccination that did not increase after a third vaccination, although seroconversion rates and neutralization capacity were unaffected.** In participants with previous SARS-CoV-2 infection, SARS-CoV-2 antibodies were boosted after vaccination, regardless of immunosuppressive treatment. • Humoral responses following vaccination are impaired by specific immunosuppressants

	• After standard vaccination regimens, patients with immune-mediated inflammatory disorders taking most immunosuppressants show similar seroconversion to controls, although antibody titers might be moderately reduced. As neutralization capacity and recall responses are also preserved in these patients, this is not likely to translate to loss of (short-term) protection • https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(22)00034-0/fulltext
Lancet - 3/11/2022 - safety and efficacy of CD24Fc (immunomodulator) against moderate to severe COVID.	• CD24Fc is an immunomodulator with potential to reduce the exaggerated inflammatory response to tissue injuries • Between April 24 and Sept 22, 2020, 243 hospitalized patients were assessed for eligibility and 234 were enrolled and randomly assigned to receive CD24Fc (n=116) or placebo (n=118). The prespecified interim analysis was done when 146 participants reached the time to clinical improvement endpoint among 197 randomized participants. In the interim analysis, the • 28-day clinical improvement rate was 82% (81 of 99) for CD24Fc versus 66% (65 of 98) for placebo; • median time to clinical improvement was 6·0 days (95% CI 5·0–8·0) in the CD24Fc group versus 10·0 days (7·0–15·0) in the placebo group (hazard ratio [HR] 1·61, 95% CI 1·16–2·23; log-rank p=0·0028, which crossed the prespecified efficacy boundary [α=0·0147]). 37 participants were randomly assigned after the interim analysis data cutoff date; among the 234 randomized participants, median time to clinical improvement was 6·0 days (95% CI 5·0–9·0) in the CD24Fc group versus 10·5 days (7·0–15·0) in the placebo group (HR 1·40, 95% CI 1·02–1·92; log-rank p=0·037). • The proportion of participants with disease progression within 28 days was 19% (22 of 116) in the CD24Fc group versus 31% (36 of 118) in the placebo group (HR 0·56, 95% CI 0·33–0·95; unadjusted p=0·031). • The incidences of adverse events and serious adverse events were similar in both groups. No treatment-related adverse events were observed • https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00058-5/fulltext
MedRXiV - 3/22/2022 - Effect of prior infection,	• Effectiveness of only prior infection against symptomatic BA.2 infection was 46.1% (95% CI: 39.5-51.9%). ○ Effectiveness of only two-dose BNT162b2 vaccination was negligible at -1.1% (95% CI: -7.1-4.6), but nearly all

vaccination and hybrid immunity on BA.1 and BA.2	individuals had received their second dose several months earlier. ○ Effectiveness of only three-dose BNT162b2 vaccination was 52.2% (95% CI: 48.1-55.9%). ○ Effectiveness of hybrid immunity of prior infection and two-dose BNT162b2 vaccination was 55.1% (95% CI: 50.9-58.9%). ○ Effectiveness of hybrid immunity of prior infection and three-dose BNT162b2 vaccination was 77.3% (95% CI: 72.4-81.4%). • **Meanwhile, prior infection, BNT162b2 vaccination, and hybrid immunity all showed strong effectiveness >70% against any severe, critical, or fatal COVID-19 due to BA.2 infection**. Similar levels and patterns of effectiveness were observed for BA.1 and for the mRNA-1273 vaccine. CONCLUSIONS: There are no discernable differences in the effects of prior infection, vaccination, and hybrid immunity against BA.1 versus BA.2. Hybrid immunity resulting from prior infection and recent booster vaccination confers the strongest protection against either subvariant. Vaccination enhances protection of those with a prior infection • https://www.medrxiv.org/content/10.1101/2022.03.22.22272745v1
JAMA - 3/22/22 - effect of antiplatelet therapy on on survival and organ support free days in critically ill patients.	• Among critically ill patients with COVID-19, treatment with an antiplatelet agent, compared with no antiplatelet agent, had a low likelihood of providing improvement in the number of organ support–free days within 21 days • https://jamanetwork.com/journals/jama/fullarticle/2790488
JAMA - 3/17/2022 - Incidence of CVT (cerebral venous thrombosis) after COVID infection vs	• Among 62 447 individuals diagnosed with SARS-CoV-2 infections included in this study, 58 989 (94.5%) were male; the median (range) age was 34 (0-102) years; 6 CVT cases were identified (all were male; median [range] age was 33.5 [27-40] years). Among 3 006 662 individuals who received at least 1 dose of mRNA-based SARS-CoV-2 vaccine, 1 626 623 (54.1%) were male; the median (range) age was 50 (12-121) years; 9 CVT cases were identified (7 male individuals [77.8%]; median [range] age: 60 [46-76] years).

mRNA vaccination in Singapore	• The crude IR of CVT after SARS-CoV-2 infections was 83.3 per 100 000 person-years (95% CI, 30.6-181.2 per 100 000 person-years) • and 2.59 per 100 000 person-years (95% CI, 1.19-4.92 per 100 000 person-years) after mRNA-based SARS-CoV-2 vaccination. Six (66.7%) received BNT162b2 (Pfizer-BioNTech) vaccine and 3 (33.3%) received mRNA-1273 (Moderna) vaccine. • The crude IRR of CVT hospitalizations with SARS-CoV-2 infection compared with those who received mRNA SARS-CoV-2 vaccination was 32.1 (95% CI, 9.40-101; *P* < .001) • https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2790206
Lancet Preprint - 3/21/2022 - Omicron BA.2 severity in unvaccinated children	• Four deaths (0.35%) occurred during the Omicron wave, resulting in a higher in-hospital case fatality rate than other SARS-CoV-2 variants (0%), influenza (0.05%) and parainfluenza (0.04%). • PICU admission was higher for Omicron than other SARS-CoV-2 variants (OR=18.50, 95% CI 2.42-140.70, p=0.005) and influenza (OR=2.32, 95% CI 1.48-3.64, p<0.001). • The proportion with neurological complications was 14.91% (171 out of 1,147) for Omicron, which was higher than influenza and parainfluenza (OR=1.75 95% CI 1.48-2.08 and OR=2.06 95% CI 1.74-2.46, p<0.001 for both, respectively). Croup occurred for Omicron more than other SARS-CoV-2 variants (OR=11.47, 95% CI 2.77-47.46 p = 0.001) and influenza (OR= 2.08, 95% CI 1.58-2.74 p<0.001) but not parainfluenza • The intrinsic severity of Omicron BA.2 is not mild as evident by the fatality and severe complications of the uninfected and unvaccinated children • https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4063036