“Happy” Tax Day ☹️

I hope everyone had time to relax and recharge this past weekend after a topsy turvy week.

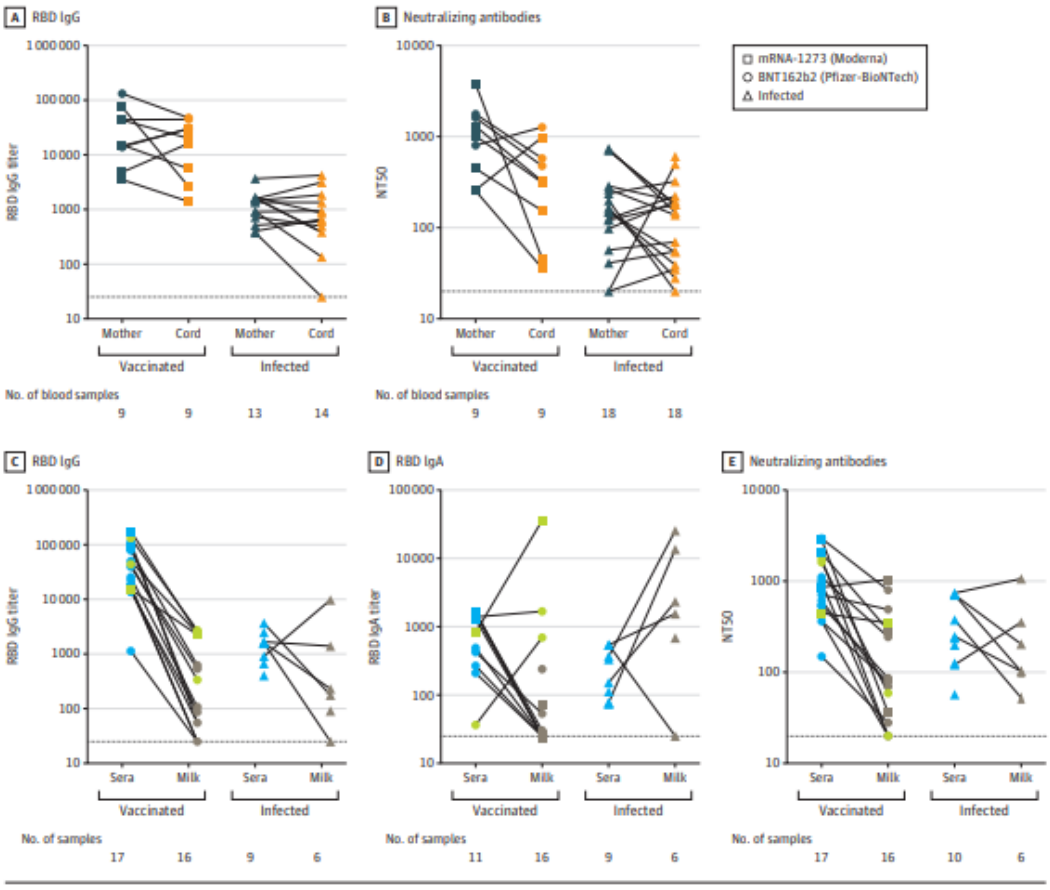
Today I have chosen 4 articles to review. The first is on the immunogenicity of mRNA vaccines in pregnancy and lactating women. The second article reports on delayed local hypersensitivity reactions to the Moderna vaccine. The third article looks at the vaccine neutralizing response against B.1.617.1 (India) variant. The last article is a very nice outline of how to study vaccine efficacy in cancer patients. This is very timely with the recent CDC update on masking. A key to moving forward is to counsel patients that if you are immunosuppressed, you may NOT be fully protected even if you are fully vaccinated. This is one of the important considerations as organization begin to open and eliminate mask wearing.

Have a productive week. I hope there will not be another CDC surprise!

Ed

Immunogenicity of COVID-19 mRNA Vaccines in Pregnant and Lactating Women
JAMA published online May 13, 2021
doi:10.1001/jama.2021.7563
This was a prospective cohort study which enrolled women who received a COVID-19 vaccine from December 2020 through March 2021 and 28 women who had confirmed SARS-CoV-2 infection from April 2020 through March 2021. This study enrolled 30 pregnant, 16 lactating, and 57 neither pregnant nor lactating women who received either the mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) COVID-19 vaccines and 22 pregnant and 6 nonpregnant unvaccinated women with SARS-CoV-2 infection. SARS-CoV-2 receptor binding domain binding, neutralizing, and functional nonneutralizing antibody responses from pregnant, lactating, and nonpregnant women were assessed following vaccination. Spike-specific T-cell responses were evaluated using IFN-γ enzyme-linked immunospot and multiparameter intracellular cytokine-staining assays. Humoral and cellular immune responses were determined against the original SARS-CoV-2 USA-WA1/2020 strain as well as against the B.1.1.7 and B.1.351 variants.

This study enrolled 103 women aged 18 to 45 years (66% non-Hispanic White) who received a COVID-19 mRNA vaccine. After the second vaccine dose, fever was reported in 4 pregnant women (14%; SD, 6%), 7 lactating women (44%; SD, 12%), and 27 nonpregnant women (52%; SD, 7%). Binding, neutralizing, and functional nonneutralizing antibody responses as well as CD4 and CD8 T-cell responses were present in pregnant, lactating, and nonpregnant women following vaccination. Binding and neutralizing antibodies were also observed in infant cord blood and breast milk. Binding and neutralizing antibody titers against the SARS-CoV-2 B.1.1.7 and B.1.351 variants of concern were reduced, but T-cell responses were preserved against viral variants.

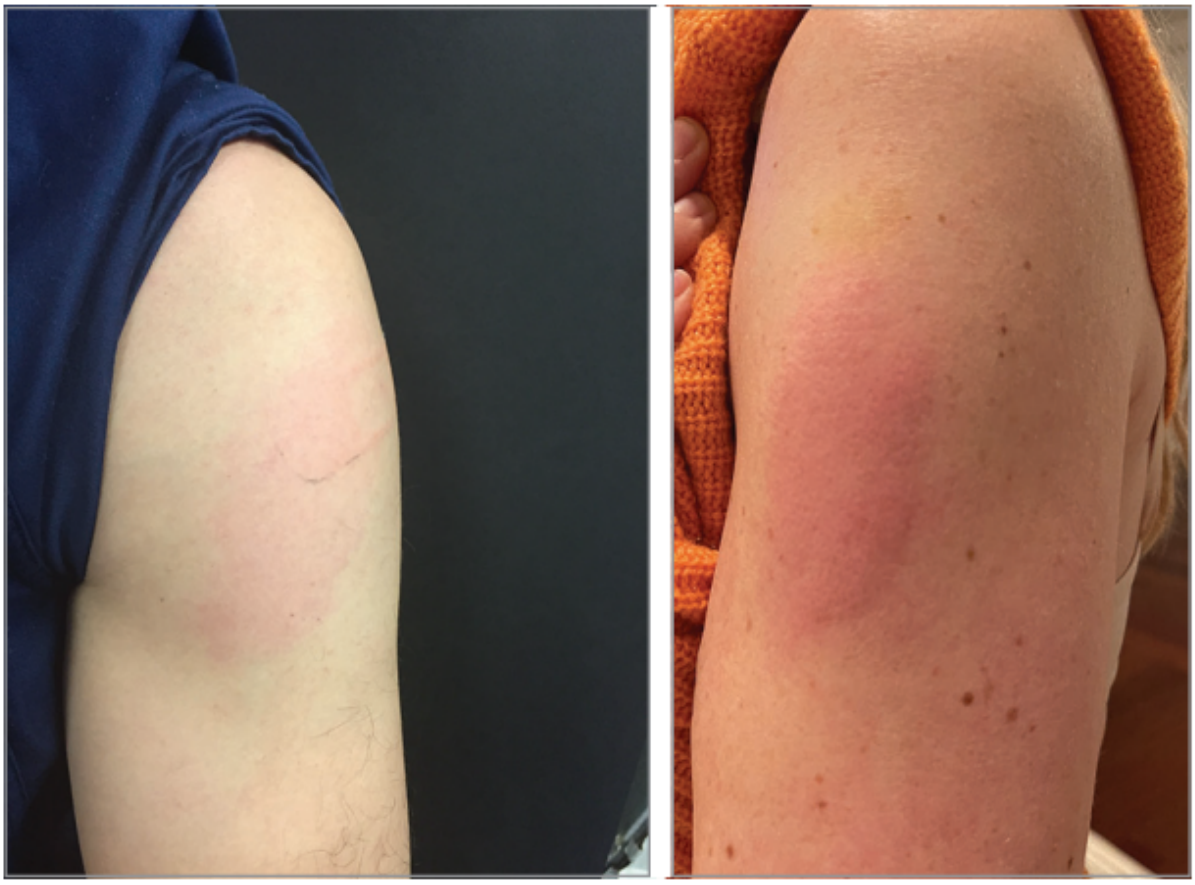


Comment: Receipt of a COVID-19 mRNA vaccine was immunogenic in pregnant women, and vaccine-elicited antibodies were transported to infant cord blood and breast milk. Pregnant and nonpregnant women who were vaccinated developed cross-reactive antibody responses and T-cell responses against SARS-CoV-2 variants of concern (B.1.1.7 UK and B.1.351 South Africa). The study size is small, and thus conclusions about vaccine safety and tolerability are limited. The correlates of immunogenicity and protection against COVID-19 infection has not yet been determined. Lastly this was a cohort study not a RCT.

Delayed Localized Hypersensitivity Reactions to the Moderna COVID-19 Vaccine A Case Series
JAMA Derm published online May 12, 2021
doi:10.1001/jamadermatol.2021.1214
This is a retrospective case series study performed at Yale with 16 patients referred with localized cutaneous injection-site reactions from January 20 through February 12, 2021. They collected each patient's demographic information, a brief relevant medical history, clinical course, and treatment (if any); and considered the findings of a histopathologic examination of on skin biopsy specimen.

Of 16 patients (median [range] age, 38 [25-89] years; 13 [81%] women), 14 patients self-identified as White and 2 as Asian. The delayed localized cutaneous reactions developed in a median (range) of 7 (2-12) days after receiving the Moderna vaccine. These reactions occurred at or near the injection site and were described as pruritic, painful, and edematous pink plaques. [see pictures below] None of the participants had received the Pfizer vaccine. Results of a skin biopsy specimen demonstrated a mild predominantly perivascular mixed infiltrate with lymphocytes and eosinophils, consistent with a dermal

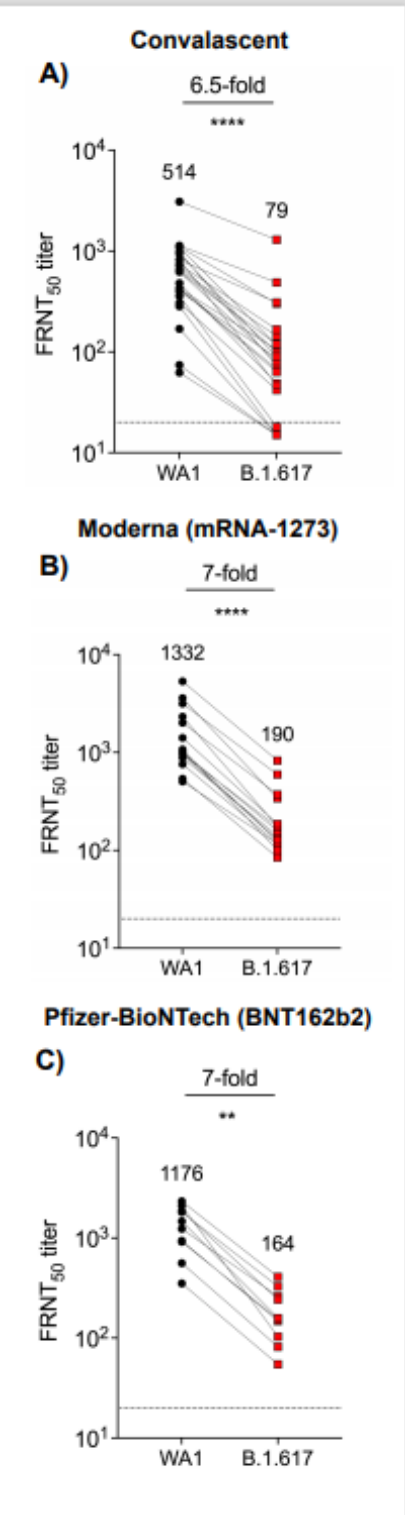
hypersensitivity reaction. Of participants who had a reaction to first vaccine dose (15 of 16 patients), most (11 patients) developed a similar localized injection-site reaction to the second vaccine dose; most (10 patients) also developed the second reaction sooner compared to the first-dose reaction.



Comment: The clinical and histopathologic findings of this case series study indicate the reactions to the Moderna vaccine are consistent with a delayed hypersensitivity reaction. These reactions may occur sooner after the second dose, but they are self-limited and not associated with serious vaccine adverse effects and are not a contraindication to receiving the second dose. Most of the patients were health care workers, which may limit generalizability. I think we have all seen this reaction and it does seem to be seen primarily with the Moderna vaccine. This reaction contrasts with immediate hypersensitivity reactions (e.g., anaphylaxis, urticaria).

Infection and Vaccine-Induced Neutralizing Antibody Responses to the SARS-CoV-2 B.1.617.1 Variant
bioRxiv published online May 9, 2021
doi.org/10.1101/2021.05.09.443299
The B.1.617.1 variant has rapidly spread throughout India and to several other countries. In this study, using a live virus assay, the investigators describe the neutralizing antibody response to the B.1.617.1 variant in serum from infected and vaccinated individuals. They used a live virus Focus Reduction Neutralization Test (FRNT) to compare the neutralizing antibody response in serum from 24 convalescent COVID-19 individuals (31-91 days after symptom onset).

They found that the B.1.617.1 variant is 6.8-fold more resistant to neutralization by sera from COVID-19 convalescent and Moderna and Pfizer vaccinated individuals. Despite this, a majority of the sera from convalescent individuals and all 37 sera from vaccinated individuals were still able to neutralize the B.1.617.1 variant.



Comment: This report suggests that protective immunity by the mRNA vaccines tested here are likely retained against the B.1.617.1 variant. This is encouraging and consistent with prior studies with other variants such as the B.1.1.7 (UK), P.1 (Brazil), and B.1.351 (So. African). As the B.1.617.1 variant and others continue to evolve, it is critical to monitor how additional mutations impact viral transmission and vaccine efficacy. Vaccine boosters will need to be modified to optimize vaccine efficacy in the future.

COVID-19 Vaccines in Patients with Cancer — A Welcome Addition, but There Is Need for Optimization
JAMA published online May 13, 2021
doi:10.1001/jamaoncol.2021.1218
Patients with cancer have high COVID-19-associated mortality rates, although there appears to be significant heterogeneity in risk among different cancer subgroups. Current vaccine studies were not powered to detect a signal for mortality benefit from fatal COVID-19 in high-risk subgroups, such as patients with cancer. Although mucosal surface antibodies, such as IgA and protective T-cell responses, might be similarly or even more important in protection following natural SARS-CoV-2 infection or vaccination, there are no comparable data for patients with cancer. Although many unknowns remain regarding the optimal schedule of COVID-19 vaccines in patients with cancer, it seems reasonable to administer COVID-19 vaccination before cytotoxic chemotherapy or chemoradiation and delay the second dose after the nadir of cytopenias and before the next cycle of chemotherapy to increase vaccine immunogenicity. The same principle should be applied, if feasible, for patients with cancer (e.g., patients with lymphoid malignancies or monoclonal gammopathies) who receive lympholytic agents, such as monoclonal antibodies (e.g., rituximab) or long-term corticosteroids. In addition to the urgency in vaccinating patients with cancer, COVID-19 vaccination of their caregivers is also critical, as households contacts are a substantial source transmission of SARS-CoV-2.

Box. Unanswered Research Questions for Future Clinical Trials

- What is the response to COVID-19 vaccines in patients with cancer who have suboptimal humoral responses (eg, myeloma, lymphoma, leukemia, stem cell transplant, and corticosteroids) with conventional vaccines?
- Does the mRNA approach make a difference?
- What should be the optimal timing of vaccines in patients who are receiving chemotherapy?
- Do we need more than 2 doses and more frequent boosting?
- What about immune adjuvants?
- What should be the vaccination strategy (timing and dosing) in patients with cancer with predominant T-cell immunosuppression or cytopenias?
- What is the benefit (COVID-19 has higher mortality in patients with cancer) vs any perceived risk or futility (poor responses)?
- Are there any concerns of toxic effects in mRNA vaccines for patients with cancer? Should we consider that the conventional vaccine approach (heat-killed virus, protein-based SARS-CoV-2 vaccines) might be safer and more or less immunogenic?
- As patients with cancer have prolonged shedding and are prone to reinfections and relapses of SARS-CoV-2, should we administer vaccines to patients with cancer with a history of COVID-19? If so, when?
- Are there any concerns regarding antibody-mediated enhancement in these patients who have dysregulated immune systems?
- Do checkpoint inhibitors boost vaccination responses in patients with cancer? What is the optimal timing of COVID-19 vaccination in patients who are taking checkpoint inhibitors?
- How does prior convalescent serum or IVIG affect vaccine decision-making?
- What is the best vaccination strategy for patients with regional radiation, chemoradiation, or TBI?
- When is the optimal time for vaccination for patients with cancer who are to undergo surgery or in postsurgical setting?

Abbreviations: IVIG, intravenous immunoglobulins; mRNA, messenger RNA; TBI, total body irradiation.

Comment: Prior studies in SOT and other immunosuppressed patients clearly support the importance of receiving the second dose of an mRNA vaccine in optimizing antibody response. The research questions above are a great roadmap for future trials. Now that the mask mandates are being lifted, what is the correct approach for patients vaccinated with cancer or patients who are immunosuppressed?