Happy Friday the 13th ☺

Today under COVID-19 News is the announcement late yesterday to extend the EUA to include a booster dose for certain persons who are immunocompromised. After the FDA update I have tried to address the controversy over masks.

Under Journal Review I start with the prepublication Mayo Clinic study on comparative effectiveness of the two mRNA vaccines. Next is an update on Lambda infectivity and potential immune resistance. The next article is a CDC update on reported adverse events from the three authorized vaccines in the US. The last article is a Cochrane review on Ivermectin in preventing or treating Covid-19.

Have a wonderful weekend

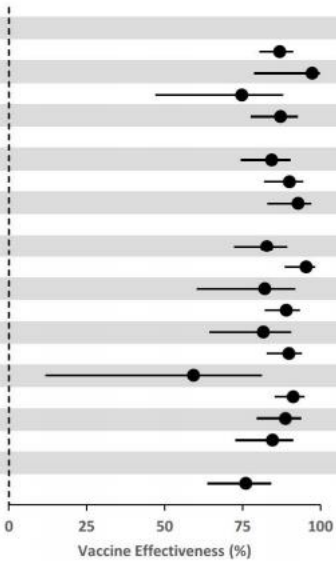
Ed

COVID-19 News

U.S. FDA Authorizes COVID-19 Vaccine Boosters for the Immunocompromised
August 12, 2021
The FDA on Thursday amended the emergency use authorizations for the vaccines to allow an additional dose in certain individuals, specifically for recipients of solid organ transplant or those diagnosed with conditions that are considered to have an equivalent level of immunocompromise. U.S. regulators must fully authorize the COVID-19 vaccines or amend their emergency use approvals before officials can recommend additional shots. A panel of advisers to the CDC will meet on Friday to discuss eligibility of immunocompromised individuals for booster doses. About 2.7% of American adults are immunocompromised, which also includes people who live with HIV or take cancer treatments and other drugs that suppress their immune systems.

VII Comment: The media and politicians have been obsessed with the mask debate, but the FDA is keeping the focus where I think it should be: vaccines. Yesterday the FDA approved Covid-19 booster shots for immuno-compromised patients, and more people will probably need them soon. A recent study (medRxiv doi.org/10.1101/2021.07.08.21259776) found that immuno-compromised patients who received an mRNA vaccine are only 59% protected against hospitalization. See figure below.

Subgroup	Vaccinated case patients / total case patients (%)	Vaccinated control patients / total control patients (%)	Vaccine effectiveness (95% confidence interval)
Full vaccination			
Overall	45/499 (9.0)	215/489 (44.0)	86.9 (80.4 to 91.2)
18 to 49 yr	1/186 (0.5)	25/140 (17.9)	97.3 (78.9 to 99.7)
50 to 64 yr	14/185 (7.6)	39/136 (28.7)	74.7 (47.2 to 87.9)
≥65 yr	30/128 (23.4)	151/213 (70.9)	87.2 (77.6 to 92.7)
Covid-19 vaccine product			
Pfizer-BioNTech	28/482 (5.8)	122/396 (30.8)	84.3 (74.6 to 90.3)
Moderna	17/471 (3.6)	93/367 (25.3)	90.0 (82.0 to 94.4)
B.1.1.7 variant lineage	7/116 (6.0)	215/489 (44.0)	92.8 (83.0 to 96.9)
Underlying medical condition			
Chronic cardiovascular disease	38/263 (14.5)	150/311 (48.2)	82.8 (72.3 to 89.3)
No chronic cardiovascular disease	7/236 (3.0)	65/178 (36.5)	95.4 (88.5 to 98.1)
Chronic lung disease	14/98 (14.3)	72/158 (45.6)	82.1 (60.3 to 91.9)
No chronic lung disease	31/398 (7.8)	143/331 (43.2)	89.0 (82.1 to 93.2)
Diabetes mellitus	19/151 (12.6)	73/162 (45.1)	81.6 (64.5 to 90.5)
No diabetes mellitus	26/347 (7.5)	142/327 (43.4)	89.8 (82.8 to 94.0)
Immunocompromising condition	20/79 (25.3)	56/116 (48.3)	59.2 (11.9 to 81.1)
No immunocompromising condition	25/417 (6.0)	159/373 (42.6)	91.3 (85.5 to 94.7)
Obesity	21/289 (7.3)	95/215 (44.2)	88.7 (79.7 to 93.8)
No obesity	24/203 (11.8)	120/273 (44.0)	84.6 (72.8 to 91.3)
Partial vaccination			
Overall	45/499 (9.0)	103/377 (27.3)	76.0 (63.7 to 84.1)



Studies have found that a third shot can substantially increase antibodies. A new Mayo Clinic study (see below) found that Moderna's vaccine was 76% protective against infection and Pfizer's 42% in July, versus the 94% to 95% against symptomatic illness in their clinical trials. While both remained 75% to 80% protective against hospitalizations, that still means some who get infected could become seriously ill.

The political media fight over masks is the wrong focus. However, unlike vaccinations which can take up to 6 weeks before becoming fully protective, masks work immediately. Wearing a mask also helps protect children who cannot be vaccinated yet, and others who are susceptible, like the elderly and those with compromised immune systems even if vaccinated, and the unvaccinated. Covid-19 is never going away, and the best way to manage the virus long term is vaccinations. I hope the next announcement from the FDA will be full authorization for mRNA vaccines. For now, however, mask up and if not vaccinated I urge everyone who is eligible to take the vaccine.

Journal Review

Comparison of Two Highly Effective mRNA Vaccines for COVID- 19 During Periods of Alpha and Delta Variant Prevalence

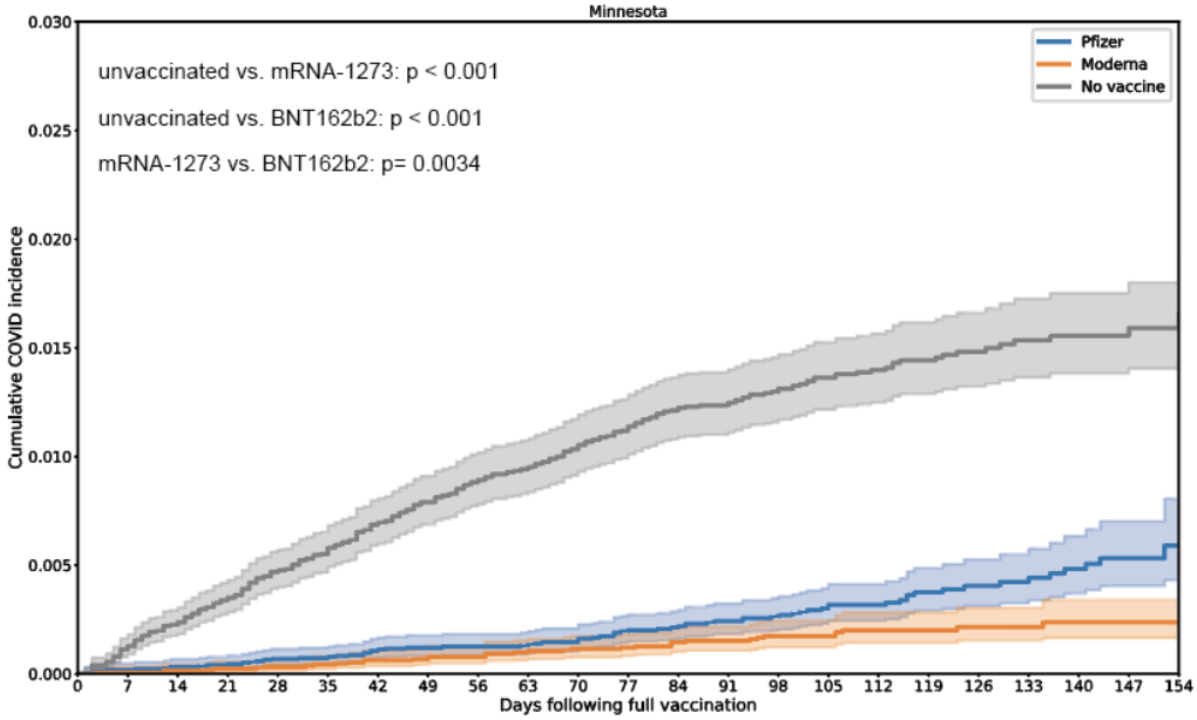
medRxiv published online August 6, 2021

doi.org/10.1101/2021

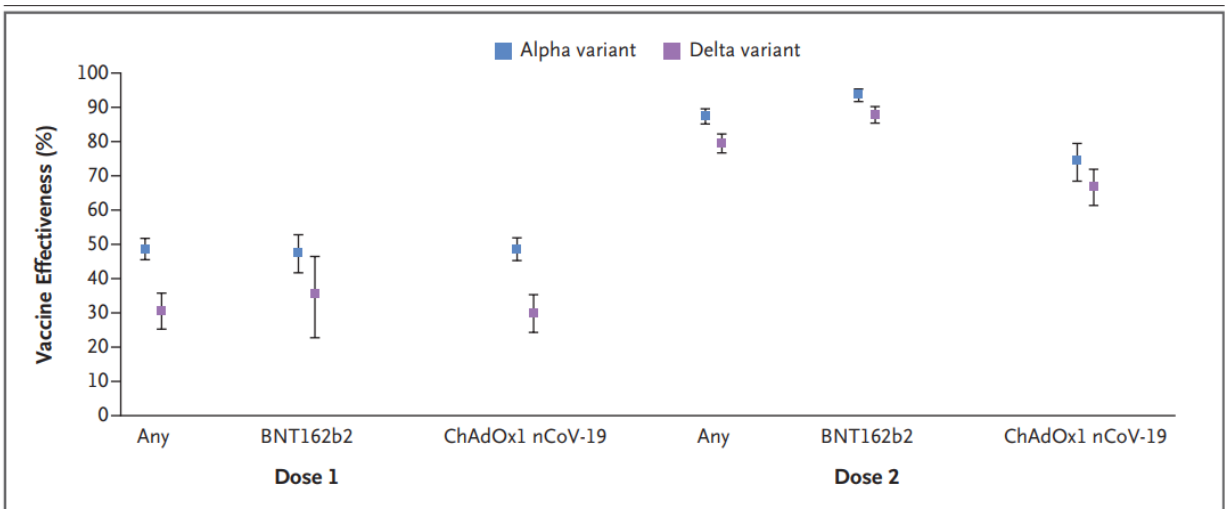
The investigators compare the effectiveness of the two mRNA vaccines from Moderna and Pfizer in the Mayo Clinic Health System over time from January to July 2021 during which either the Alpha or Delta variant was highly prevalent. They defined cohorts of vaccinated and unvaccinated individuals from Minnesota (n = 25,589 each) matched on age, sex, race, history of prior SARS-CoV-2 PCR testing, and date of full vaccination. Both vaccines were highly effective during this study period against SARS-CoV-2 infection (Moderna: 86%, 95%CI: 81-90.6%; Pfizer: 76%, 95%CI: 69-81%) and COVID-19-associated hospitalization (Moderna: 91.6%, 95% CI: 81-97%; Pfizer: 85%, 95% CI: 73-93%). In July, vaccine effectiveness against hospitalization has remained high (Moderna: 81%, 95% CI: 33-96.3%; Pfizer: 75%,

95% CI: 24-93.9%), but effectiveness against infection was lower for both vaccines (Moderna-1273: 76%, 95% CI: 58-87%; Pfizer: 42%, 95% CI: 13-62%), with a more pronounced reduction for Pfizer.

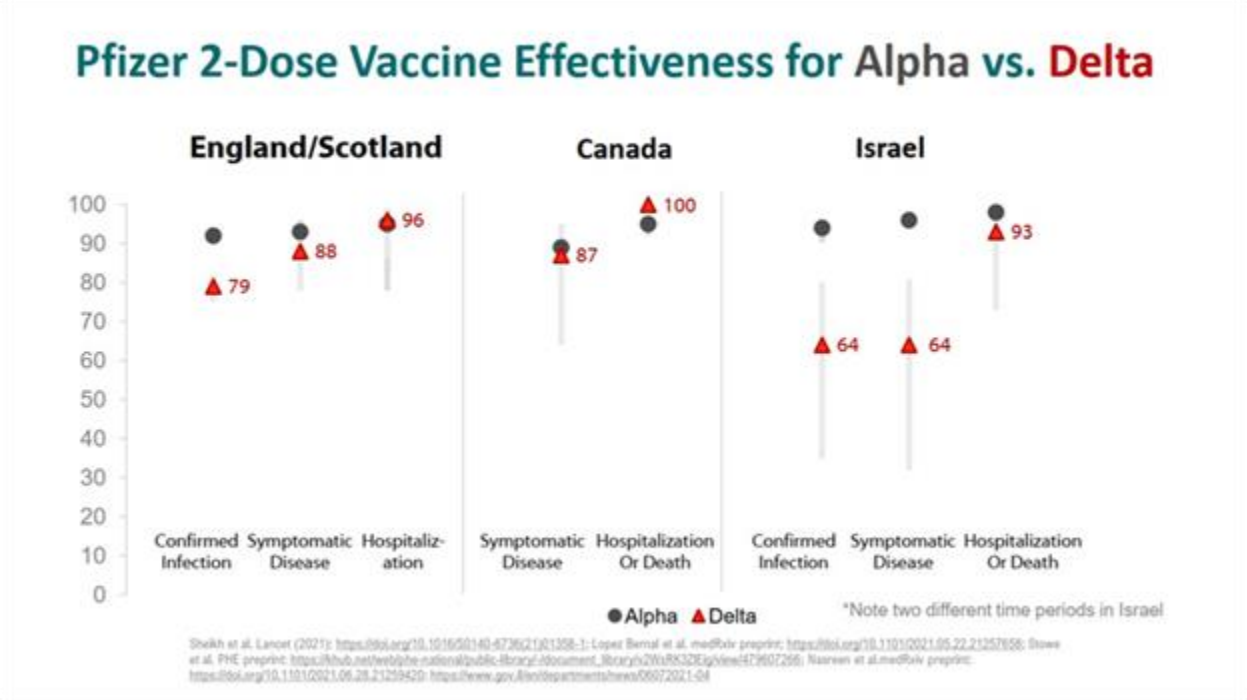
Delta variant prevalence in Minnesota increased from 0.7% in May to over 70% in July whereas the Alpha variant prevalence decreased from 85% to 13% over the same time period. Comparing rates of infection between matched individuals fully vaccinated with Moderna versus Pfizer across Mayo Clinic Health System sites in multiple states (Minnesota, Wisconsin, Arizona, Florida, and Iowa), Moderna conferred a two-fold risk reduction against breakthrough infection compared to Pfizer (IRR = 0.50, 95% CI: 0.39-0.64). In Florida, which is currently experiencing its largest COVID-19 surge to date, the risk of infection in July after full vaccination with Moderna was about 60% lower than after full vaccination with Pfizer (IRR: 0.39, 95% CI: 0.24-0.62).



Comment: This observational study suggests that while both mRNA COVID-19 vaccines strongly protect against infection and severe disease, there are differences in their real-world effectiveness relative to each other and relative to prior months of the pandemic. Despite differences in vaccines, this observational study highlights that both mRNA COVID-19 vaccines strongly protect against infection and severe disease with Moderna appearing to be more protective. This result is different from a study published in the NEJM last month from the UK. (See below – reviewed in Briefing July 23rd)



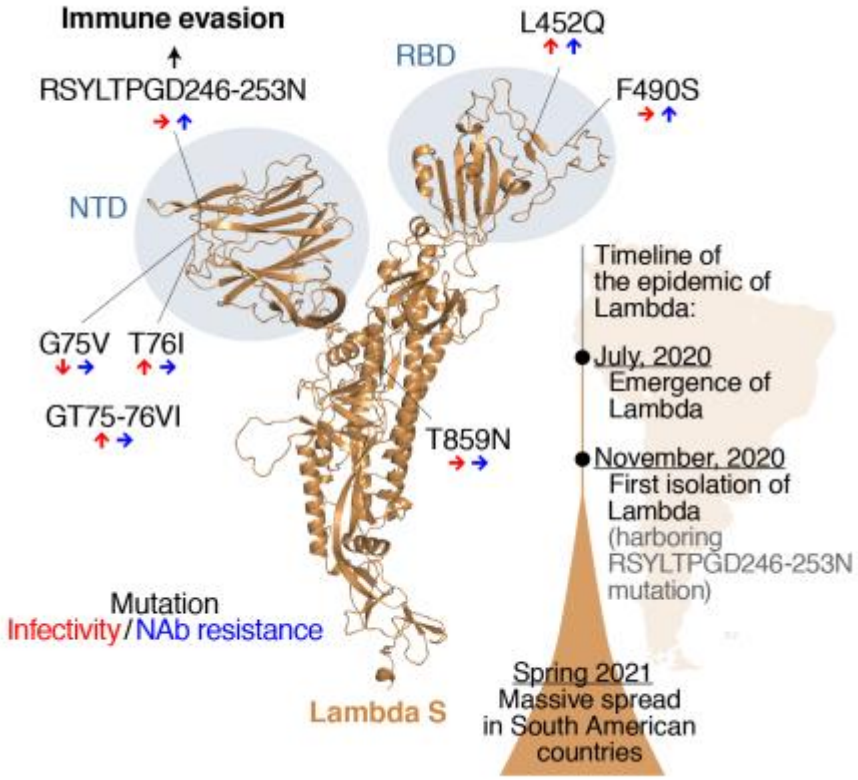
And the Israeli and Canadian studies – see slide below as well.



Larger studies with more diverse populations are warranted to guide critical pending public and global health decisions, such as the optimal timing for booster doses and which vaccines should be administered to individuals who have not yet received one dose.

SARS-CoV-2 Lambda Variant Exhibits Higher Infectivity and Immune Resistance
bioRxiv published online July 28, 2021
doi.org/10.1101/2021.07.28.454085
SARS-CoV-2 Lambda, a new variant of interest, is now spreading in some South American countries such as Peru, Chile, Argentina, and Ecuador; however, its virological features and evolutionary trait remain unknown.

There are at least two virological features on the Lambda variant: increasing viral infectivity (by the T76I and L452Q mutations) and exhibiting resistance to antiviral immunity (by the RSYLTPGD246-253N, L452Q and F490S mutations). The RSYLTPGD246-66 253N mutation, a unique 7-amino-acid deletion mutation in the N-terminal domain of the Lambda spike protein, is responsible for evasion from neutralizing antibodies. Virological experiments demonstrated that a large 7-amino-acid deletion, the RSYLTPGD246-253N mutation, does not affect viral infectivity but is responsible for the resistance to the vaccine-induced neutralization as well as an NTD-targeting NAb.



Comment: Their data suggest that the insertion of the RSYLTPGD246-253N mutation is closely associated with the infection spread of the Lambda variant in South America. Lambda is currently a VOI (variant of interest) not a VOC (variant of concern). To date Lambda represents <1% of variants in the US, however, this variant due to the RSYLTPGD246-253N mutation could evade protection from vaccination and natural immunity.

Use of COVID-19 Vaccines After Reports of Adverse Events Among Adult Recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 Vaccines (Pfizer-BioNTech and Moderna): Update from the Advisory Committee on Immunization Practices — United States, July 2021
MMWR published August 10, 2021
As of July 22, 2021, 187 million persons in the US had received at least 1 dose of COVID-19 vaccine.

Close monitoring of safety surveillance has demonstrated that serious adverse events after COVID-19 vaccination are rare. Three adverse conditions have been reported in temporal association with receipt

of COVID-19 vaccines. Two of these (thrombosis with thrombocytopenia syndrome [TTS], a rare syndrome characterized by venous or arterial thrombosis and thrombocytopenia, and Guillain-Barré syndrome [GBS]), have been reported after J&J COVID-19 vaccination. One (myocarditis, cardiac inflammation) has been reported after Pfizer COVID-19 vaccination or Moderna COVID-19 vaccination, particularly after the second dose. These were reviewed together and will be referred to as mRNA COVID-19 vaccination.

ACIP continues to review the data associated with these reports of serious adverse events and has comprehensively assessed the benefits and risks associated with receipt of these vaccines. During their last meeting in July 2021, ACIP determined that, overall, the benefits of COVID-19 vaccination in preventing COVID-19 morbidity and mortality far outweigh the risks for these rare serious adverse events in adults aged ≥18 years. To assess the benefit-risk balance of COVID-19 vaccination in adults, ACIP reviewed an assessment comparing the benefits of vaccination (numbers of COVID-19 cases and severe disease outcomes prevented) to the risks (numbers of cases of GBS, TTS, and myocarditis). Information regarding risks and how they vary by age, sex, and type of vaccine should be disseminated to providers, vaccine recipients, and the public.

Vaccine	Benefits: COVID-19 outcomes prevented				Harms: adverse events†	
Sex/Age group, yrs	Cases	Hospitalizations	ICU admissions	Deaths	GBS	TTS
Janssen (Johnson & Johnson) COVID-19 vaccine§						
Females						
18–29	8,900	700	50	5	1	4–5
30–49	10,100	900	140	20	6–7	8–10
50–64	12,100	1,600	350	120	7–8	3–4
≥65	29,000	5,900	1,250	840	8–10	0
Males						
18–29	6,600	300	60	3	2	2–3
30–49	7,600	650	150	25	7–8	1–2
50–64	10,100	1,800	480	140	14–17	1–2
≥65	36,600	11,800	3,300	2,300	7–8	0
mRNA (Pfizer-BioNTech or Moderna) COVID-19 vaccine¶					**Myocarditis**	
Females						
18–29	12,800	750	50	5	3–4	
30–49	14,600	950	140	20	1–2	
50–64	17,500	1,700	375	125	1	
≥65	32,000	6,200	1,300	900	<1	
Males						
18–29	9,600	300	60	3	22–27	
30–49	11,000	700	160	25	5–6	
50–64	14,700	1,900	500	150	1	
≥65	52,700	12,500	3,500	2,400	1	

Abbreviations: GBS = Guillain-Barré syndrome; ICU = intensive care unit; TTS = thrombosis with thrombocytopenia syndrome.
* Benefits and harms were calculated using case incidence and hospitalization data for the week ending June 19, 2021, and for harms using cases through June 30 (GBS and myocarditis) and through July 8 (TTS), projected for a 120-day period using methods described here: https://www.cdc.gov/vaccines/covid-19/info-by-product/janssen/risk-benefit-analysis.html
† Estimates for adverse events are based on an estimated risk of cases per million doses administered with a +/- 10% range.
§ Benefits and harms calculated per million doses of Janssen vaccine administered.
¶ Benefits and harms calculated per million second doses of mRNA (Pfizer-BioNTech and Moderna) vaccine administered.

Comment: CDC and FDA continue to closely monitor reports of serious adverse events and will present any additional data to ACIP for consideration. I think the table above makes a compelling case for vaccination.

Ivermectin for Preventing and Treating COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD015017
DOI: 10.1002/14651858.CD015017.pub2
The authors found 14 studies with 1678 participants investigating ivermectin compared to no treatment, placebo, or standard of care. No study compared ivermectin to an intervention with proven efficacy.

There were nine studies treating participants with moderate COVID-19 in inpatient settings and four treating mild COVID-19 cases in outpatient settings. One study investigated ivermectin for prevention of SARS-CoV-2 infection. Eight studies had an open-label design, six were double-blind and placebo-controlled. Of the 41 study results contributed by included studies, about one third were at overall high risk of bias. Ivermectin doses and treatment duration varied among included studies.

Ivermectin compared to placebo or standard of care for inpatient COVID-19 treatment
The authors were uncertain whether ivermectin compared to placebo or standard of care reduces or increases mortality.

Ivermectin compared to placebo or standard of care for outpatient COVID-19 treatment
They were uncertain whether ivermectin compared to placebo or standard of care reduces or increases mortality up to 28 days.

Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection
They found one study. Mortality up to 28 days was the only outcome eligible for primary analysis. They were uncertain whether ivermectin reduces or increases mortality compared to no treatment (0 participants died; 1 study, 304 participants; very low-certainty evidence). The study reported results for development of COVID-19 symptoms and adverse events up to 14 days that were included in a secondary analysis due to high risk of bias. No study reported SARS-CoV-2 infection, hospital admission, and quality of life up to 14 days.

Comment: Based on the current very low- to low-certainty evidence, the authors are uncertain about the efficacy and safety of ivermectin used to treat or prevent COVID-19. The completed studies are small, and few are considered high quality. Several studies are underway that may produce clearer answers in review updates. Overall, the reliable evidence available does not support the use ivermectin for treatment or prevention of COVID-19 outside of well-designed randomized trials.

NIH: There is insufficient evidence for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.