The Medical Letter®
on Drugs and Therapeutics

Treatments Considered for COVID-19 (Updated April 1, 2022)

The table below lists pertinent evidence on the clinical effectiveness and safety of some drugs and other therapies being considered for COVID-19. Most authorities recommend use of these drugs only in the setting of a clinical trial or when access via clinical trial is not available. **Inclusion in this table is not a recommendation for use for treatment of COVID-19.** The information on these drugs is evolving rapidly and The Medical Letter does not warrant that all the material in this publication is current, accurate, or complete in every respect.

RECENT TABLE UPDATES

March 30, 2022/April 1, 2022

Monoclonal Antibodies –

- FDA restricts use of sotrovimab in areas where the BA.2 variant causes >50% of COVID-19 cases

Ivermectin –

- Randomized, double-blind, placebo-controlled trial in high-risk outpatients found no benefit of ivermectin use

mRNA Vaccines –

- FDA authorizes second booster doses of the Pfizer/BioNTech and Moderna vaccines for persons ≥50 years old and certain immunocompromised persons

February 28, 2022

Monoclonal Antibodies –

- FDA amends EUA for tixagevimab and cilgavimab to increase the recommended dose of each drug from 150 mg to 300 mg

mRNA Vaccines –

- CDC issues new guidance allowing for an interval of up to 8 weeks between the 1st and 2nd primary doses of an mRNA vaccine in certain patients 12-64 years old, especially males 12-39 years old

February 17, 2022

Monoclonal Antibodies –

- FDA issues EUA for bebtelovimab for IV treatment of mild to moderate COVID-19 in patients ≥12 years old who weigh ≥40 kg and are at high risk of progressing to severe disease, including hospitalization and death, and for whom alternative treatment options are unavailable or inappropriate; bebtelovimab is active against the Omicron variant of SARS-CoV-2

Adenovirus-Vectored Vaccines –

- CDC recommends **immunocompromised** persons who received the J&J vaccine for their primary series should receive 1 dose of Pfizer/BioNTech or Moderna (100 mcg) vaccine ≥4 weeks after initial J&J vaccine dose; a booster dose with an mRNA vaccine (Pfizer/BioNTech or Moderna [50 mcg]) should be given ≥2 months after the additional mRNA dose

mRNA Vaccines –

- CDC recommends **immunocompromised** persons can receive a booster dose ≥3 months after completion of a 3-dose mRNA vaccine primary series

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INVESTIGATIONAL DRUGS

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Antivirals			
FAVIPIRAVIR – *AVIGAN* (FUJIFILM) *(updated 9/24/2020)* **Dosage:** ▪ 1600 mg PO bid on day 1, then 600 mg bid on days 2-7[1] ▪ Some suggest a dosage of 2400-3000 mg bid on day 1, then 1200-1800 mg bid[2]	**Q Cai et al. 2020**[1] **Population:** hospitalized, non-severe (n=80) **Design:** open-label, non-randomized **Results:** shorter viral clearance time (4 vs 11 days) and improvements in chest CT (91.4% vs 62.2%) with favipiravir vs lopinavir/ritonavir; results should be interpreted with caution[1] **Chen et al. 2020**[3] **Population:** hospitalized patients (n=236) **Design:** ▪ randomized, open-label ▪ favipiravir vs arbidol (an influenza drug not available in the US); both in addition to standard therapy **Results:** ▪ clinical recovery rate at day 7 was similar for favipiravir and arbidol (51.67% vs 61.21%; p=0.1396) ▪ in patients with moderate disease, clinical recovery rates were higher with favipiravir than arbidol (71.43% vs 55.86%; p=0.0199) **Limitations**: ▪ not peer-reviewed **Ivashchenko et al. Clin Infect Dis 2020**[5] *(added 8/9/2020)*	**Adverse Effects:** ▪ Elevated LFTs, diarrhea, nausea, vomiting, chest pain and elevated serum uric acid **Drug Interactions:** ▪ May increase serum concentrations of some drugs such as acetaminophen, penicillins, tazobactam, repaglinide, pioglitazone and rosiglitazone, oseltamivir, theophylline, and progestins	▪ Not FDA-approved and not available yet in the US ▪ Approved in other countries for treatment of influenza ▪ Russian Ministry of Health granted conditional marketing authorization for favipiravir (*Avifavir*) *(added 8/9/2020)* ▪ Viral RNA polymerase inhibitor ▪ Limited data available to date; may be less effective for patients with more severe disease ▪ Randomized controlled trial of favipiravir alone and in combination with tocilizumab ongoing in China **Pregnancy:** ▪ Contraindicated for use in pregnant women[4] ▪ Teratogenic effects in animal studies ▪ Men taking the drug should avoid intercourse with pregnant women during treatment and for at least 7 days after the last dose

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
FAVIPIRAVIR (continued)	**Population:** hospitalized patients with moderate COVID-19 pneumonia in Russia; 25% on supplemental oxygen and 75% on ambient air (n=60) **Design:** adaptive, multicenter, randomized, open-label trial; results from 60 patients in phase II trial presented ▪ Favipiravir 1600 mg BID on day 1, then 600 mg bid days 2-14, favipiravir 1800 mg BID on day 1, then 800 mg bid days 2-14, or standard of care (75% received hydroxychloroquine or chloroquine) ▪ Mean 6.7 days from start of symptoms **Results:** ▪ Viral clearance (2 negative PCR tests with at least a 24-hour interval) was achieved by day 5 in 62.5% of patients taking favipiravir vs 30.0% of those who received standard of care (p=0.018) ▪ Viral clearance by day 10 was achieved in 92.5% of favipiravir-treated patients vs 80.0% on standard of care (p=0.155) **Limitations:** interim results **Phase 3 Trial 2020**[6]*(added 9/24/2020)* **Population:** COVID-19 patients with non-severe pneumonia in Japan (n=156) **Design:** randomized, placebo-controlled, single-blind phase 3 trial		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	Results: recovery time was 11.9 days with favipiravir vs 14.7 days with placebo (p=0.0136) **Limitations:** preliminary data; trial not yet published		

1. Q Cai et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Available at : https://www.researchgate.net/pulication/340000976_experimental_treatment_with_favipiravir_for_covid-19_an_open-label_control_study**.** Accessed April 2, 2020.
2. JM Sanders et al. Pharmacologic treatment for coronavirus disease 2019 (COVID-19). A review. JAMA 2020 April 13 (epub).
3. C Chen et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. Available at: https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v2.article-info**.** Accessed April 1, 2020.
4. FG Hayden and N Shindo. Influenza virus polymerase inhibitors in clinical development. Curr Opin Infect Dis. 2019; 32:176.
5. AA Ivashchenko et al. Avifavir for treatment of patients with moderate COVID-19: interim results of a phase II/III multicenter randomized clinical trial. Clin Infect Dis 2020 August 9 (epub).
6. Press release. Anti-influenza drug Avigan Tablet meets primary endpoint in phase III clinical trial in Japan for COVID-19 patients. Fujifilm. Available at: https://www.fujifilm.com/jp/en/news/hq/5451. Accessed September 24, 2020.

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REMDESIVIR – *VEKLURY* (GILEAD) *(updated 1/24/2022)* **Dosage[1]:** *(updated 1/24/2022)* Hospitalized: ▪ Patients ≥12 years old or ≥40 kg: 200 mg IV on day 1, then 100 mg IV once/day for a total of 5 days (not on invasive mechanical ventilation or ECMO) or 10 days (on mechanical ventilation or ECMO)[2] ▪ Pediatric patients weighing 3.5 kg-<40 kg: 5 mg/kg on day 1, then 2.5 mg/kg once daily for 5 or 10 days Outpatient: ▪ Patients ≥12 years old or ≥40 kg: 200 mg IV on day 1, then 100 mg IV once/day for a total of 3 days ▪ Pediatric patients weighing 3.5 kg-<40 kg: 5 mg/kg on day 1, then 2.5 mg/kg once daily for 3 days ▪ Infuse over 30-120 minutes ▪ Not recommended if eGFR <30 ml/min or ALT >10x ULN; discontinue if signs and symptoms of liver inflammation are observed ▪ Monitor eGFR, hepatic function, and prothrombin time before starting and periodically during treatment	**Beigel et al. NEJM 2020[3]** *(added 5/4/20; updated 10/8/20)* **Population:** 1062 hospitalized patients with evidence of lower respiratory tract infection (85.0% had severe disease) **Design:** ▪ randomized, double-blind, placebo-controlled trial in US, Europe and Asia ▪ 200 mg on day 1, then 100 mg once/day days 2-10 or until discharge or death median time from symptom onset to randomization was 9 days **Results :** ▪ recovery time shorter with remdesivir (10 days vs 15 days with placebo; 95% CI 13 to 18) ▪ the median number of days between symptom onset and randomization was 9; the benefit of remdesivir was larger when given earlier in the illness ▪ Kaplan-Meier estimates of mortality by day 29 were 11.4% with remdesivir vs 15.2% with placebo (HR 0.73; 95% CI 0.52 to 1.03) ▪ Effect appeared to be greatest in hospitalized patients requiring oxygen (baseline ordinal score of 5; this category had largest sample size); mortality difference between remdesivir and placebo groups appeared smaller in patients who did not require oxygen (ordinal score of 4) and in those who required mechanical ventilation (ordinal score of 6)	**Adverse Effects:** *(updated 11/9/2020)* ▪ Elevated liver enzymes, increased prothrombin time, hypokalemia, headache, and infusion-related reactions, including hypotension, nausea, vomiting, sweating, and shivering ▪ European Medicine's Agency is evaluating cases of acute kidney injury in patients treated with remdesivir, but a causal relationship has not been established; COVID-19 itself can also cause kidney injury; the Pharmacovigilance Risk Assessment Committee (PRAC) safety review concluded there is no evidence to indicate remdesivir is associated with kidney injury *(updated 2/16/2021)* ▪ PRAC is investigating cases of sinus bradycardia in patients taking remdesivir after the Italian Medicines Agency raised a safety signal *(updated 2/16/2021)* **Drug Interactions:** *(updated 6/18/2020)* ▪ No human drug trial conducted ▪ Substrate for CYP2C8, CYP2D6, and CYP3A4, and for Organic Anion Transporting Polypeptides 1B1 (OAPT1B1) and P-glycoprotein (P-gp) transporters *in vitro*.[2] Strong inducers of these enzymes/transporters may decrease serum concentrations of remdesivir[5,6] and inhibitors of these	▪ Broad-spectrum nucleotide analog prodrug that inhibits viral RNA replication by blocking RNA-dependent RNA polymerase ▪ Has *in vivo* and *in vitro* activity against Ebola virus and coronaviruses (MERS and SARS) and *in vitro* activity against SARS- CoV-2 ▪ Remdesivir FDA approved for treatment of COVID-19 in hospitalized patients ≥12 years old weighing ≥40 kg[22] *(updated 10/22/2020)*; indication expanded to include patients with mild to moderate COVID-19 who are not hospitalized and are at high risk for progression to severe COVID-19, including hospitalization or death *(added 1/24/22)* ▪ To ensure continued availability of the drug for pediatric patients, FDA revised its Emergency Use Authorization (EUA) to allow use of remdesivir for treatment of COVID-19 in hospitalized pediatric patients weighing ≥3.5 kg-<40 kg or < 12 years of age weighing ≥3.5 kg[2,22] *(updated 10/22/2020);* indication expanded to include patients with mild to moderate COVID-19 who are not hospitalized and are at high risk for progression to severe COVID-19, including hospitalization or death *(added 1/24/22)* ▪ NIH guidelines state there are insufficient data to recommend for or

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REMDESIVIR (CONTINUED) ▪ NIH guidelines recommend a duration of 5 days or until hospital discharge[7]	**Limitations:** unclear if earlier use of remdesivir would improve outcomes; not powered to detect differences in subgroups **J Grein et al. NEJM 2020[4]** **Population:** 53 hospitalized patients in US, Canada, Europe and Japan with SaO_2 ≤94% on O_2 or room air (n=61) ▪ 57% on mechanical compassionate ventilation **Design:** ▪ report on use **Results:** ▪ median follow-up 18 days ▪ 68% had improvement in O_2 support class; 57% were extubated; 47% discharged; 18% died **JD Goldman et al. NEJM 2020[9]** **Population:** hospitalized patients w/oxygen saturation ≤94% on ambient air, radiologic evidence of pneumonia **Design:** ▪ randomized, open-label (n = 397) ▪ remdesivir x 5 days vs 10 days **Results:** ▪ baseline clinical status significantly worse in patients in the 10-day group ▪ no significant differences between 5 and 10 days of treatment were reported ▪ 64% in the 5-day group and 54% in the 10-day group achieved clinical improvement of ≥2 points on a 7-point ordinal scale by day 14	enzymes/transporters could potentially increase the risk of toxicity such as hepatotoxicity[14] ▪ Inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP ▪ Clinical relevance has not been established ▪ FDA warns that coadministration of remdesivir and chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; concurrent use is not recommended[12] *(added 6/18/2020)* **Pregnancy:** *(updated 11/9/2020)* ▪ In 86 pregnant and postpartum women with severe COVID-19 who were treated with compassionate-use remdesivir, the rate of serious adverse events was low[7] ▪ No adverse effects on embryo-fetal development were observed in animals	against routine use of remdesivir in hospitalized patients who do not require supplemental oxygen; use of remdesivir may be appropriate for patients who are at high risk for diseases progression[7] *(updated 7/12/2021)* ▪ NIH guidelines recommend use of remdesivir in hospitalized patients who require supplemental oxygen, but it is not routinely recommended in patients who require mechanical ventilation[7] *(updated 12/6/2020)* ▪ NIH guidelines recommend that patients recently hospitalized (i.e., within the previous 3 days) with COVID-19 who have rapidly increasing oxygen needs, require high-flow oxygen therapy or noninvasive ventilation and have increased markers of inflammation receive dexamethasone with or without remdesivir, plus either tocilizumab or baricitinib. For patients hospitalized who require invasive mechanical ventilation or ECMO, dexamethasone is recommended; for those who were admitted to the ICU ≤24 hours previously and require invasive mechanical ventilation or ECMO, dexamethasone plus tocilizumab is recommended[7] *(updated 7/12/2021)* ▪ IDSA guidelines suggest use of remdesivir in hospitalized patients with severe, but not critical, COVID-19 (SpO_2≤94% on room air); they suggest against routine initiation of remdesivir

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REMDESIVIR (CONTINUED)	▪ in a post-hoc analysis, among patients on mechanical ventilation or ECMO at day 5, 40% in the 5-day group died by day 14 vs 17% in the 10-day group **Limitations**: open-label, no placebo group[10] **Spinner et al. JAMA 2020[11,16]** *(updated 8/23/2020)* **Population:** hospitalized patients with moderate COVID-19 (pneumonia, but not reduced oxygen levels) (n = 584) **Design:** randomized, open-label; remdesivir x 5 days or 10 days in addition to standard care or standard care alone **Results:** ▪ median duration of symptoms before day 1 was 8 days in the remdesivir groups and 9 days in the standard care group ▪ median duration of treatment was 5 days in the 5-day group and 6 days in the 10-day group ▪ on day 11, the odds of a better clinical status distribution on a 7-point ordinal scale was significantly higher in those treated with remdesivir for 5 days than with standard care (OR 1.65; 95% CI 1.09-2.48; p=0.02); clinical importance unclear ▪ treatment with remdesivir x 10 days did not reach statistical significance **Limitations:** open-label; median symptom duration at start of trial was 8 days; only 38% of remdesivir		in patients on invasive ventilation and/or ECMO; suggested duration of treatment is 5 days in patients on supplemental oxygen, but not mechanical ventilation or ECMO and 10 days in patients on mechanical ventilation or ECMO; they recommend against routine use in hospitalized patients not on supplemental oxygen[19] *(updated 7/12/2021)* ▪ The manufacturer has initiated a phase 1a trial of an inhaled, nebulized solution of remdesivir in healthy volunteers; this trial is intended to form the basis for further clinical studies of this formulation in outpatients with COVID-19[13] *(added 7/9/2020)* ▪ In a case report, occurrence of a mutation in RdRP polymerase following failure of remdesivir in a patient with B-cell immunodeficiency was described[18] *(added 9/28/2020)* ▪ NIH starting a trial (ACTIV-5 Big Effect Trial) to evaluate use of remdesivir in combination with the monoclonal antibodies risankizumab or lenzilumab[21] *(added 10/19/2020)* ▪ European Society of Intensive Care Medicine expected to recommend against routine use of remdesivir in patients requiring critical care in upcoming recommendations *(added 11/13/2020)* ▪ FDA issued an Emergency Use Authorization (EUA) for use of

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REMDESIVIR (CONTINUED)	10-day group received the drug for 10 days **Olender et al. Clin Infect Dis 2020[15]** *(added 7/31/2020)* **Population:** hospitalized adults with severe COVID-19 (oxygen saturation ≤94% on room air or requiring supplemental oxygen and pulmonary infiltrates) (n=312 remdesivir; n=818 non-remdesivir) **Design:** comparative analysis of 2 ongoing studies ▪ a randomized, open-label phase 3 trial comparing 2 courses of remdesivir and a retrospective cohort study in patients receiving standard-of-care **Results:** ▪ 74.4% of remdesivir-treated patients recovered at day 14 vs 59.0% of non-remdesivir-treated patients (adjusted OR 2.03; p<0.001) ▪ 7.6% of remdesivir-treated patients died vs 12.5% in non-remdesivir-treated patients (adjusted OR 0.38; p=0.001) **Limitations:** comparative analysis of interim data sponsored by manufacturer **Wang et al. Lancet 2020[23]** *(added 11/9/2020)* **Population:** hospitalized patients with severe COVID-19 in China (n=237; 453 planned) **Design:** randomized, double-blind, placebo-controlled multicenter trial		baricitinib, in combination with remdesivir, for treatment of COVID-19 in hospitalized patients ≥2 years old who require supplemental oxygen, invasive mechanical ventilation or ECMO[24] *(added 11/20/2020)* ▪ American College of Physicians (ACP) practice points recommend remdesivir should not be started in patients on mechanical ventilation or ECMO (these patients likely past the viral stage of the illness); remdesivir for 5 days can be considered for treatment of hospitalized patients not on mechanical ventilation or ECMO; use of remdesivir for up to 10 days can be considered in patients who require mechanical ventilation or ECMO within the 5-day course[25] *(added 2/10/2021)* ▪ The manufacturer has stopped a trial of IV remdesivir in high-risk non-hospitalized patients; the trial was not stopped for efficacy or safety reasons, but because the manufacturer believes outpatient administration of a treatment that requires multiple days of an IV infusion addresses an unmet need *(added 4/13/2021)*

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REMDESIVIR (CONTINUED)	▪ Remdesivir vs placebo x 10 days ▪ Patients were also allowed to received corticosteroids, lopinavir/ritonavir, and interferon **Results:** ▪ Median time from symptom onset to randomization 9 days with remdesivir and 10 days with placebo ▪ Trial stopped before target enrollment reached ▪ No difference in time to clinical improvement between groups (18 vs 23 days; HR 1.23, 95% CI 0.87-1.75) ▪ The time to clinical improvement was numerically, but not statistically significantly, faster in patients who received remdesivir within 10 days of symptom onset (HR 1.52, 95% CI 0.95-2.43) **Limitations:** small sample size; trial stopped before enrollment reached **Inhaled Remdesivir** *(added 7/9/2020)* ▪ The manufacturer has initiated a phase 1a trial evaluating remdesivir in an inhaled, nebulized formulation in healthy volunteers[13] **NIH Adaptive COVID-19 Treatment Trial 3 (ACTT 3)** *(added 8/9/2020)* ▪ A randomized, double-blind trial comparing remdesivir plus interferon beta 1a to remdesivir alone has begun		

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REMDESIVIR (CONTINUED)	▪ Expected to enroll >1000 adults **<u>NIH Adaptive COVID-19 Treatment Trial 2 (ACTT-2) 2020</u>[17]** *(added 9/18/2020)* **Population:** hospitalized patients with COVID-19 (n>1000) **Design:** Phase 3 randomized, double-blind, placebo-controlled trial ▪ remdesivir plus baricitinib 4 mg vs remdesivir alone **Results:** ▪ mean recovery time was about 1 day shorter with the combination of remdesivir plus baricitinib compared to remdesivir alone, a statistically significant difference ▪ the combination improved outcomes at day 15 on an ordinal scale compared to remdesivir alone **Limitations:** limited data available; not yet published or peer reviewed **<u>WHO SOLIDARITY 2020</u>**[20] *(added 10/19/20; updated 12/2/2020)* **Population:** hospitalized patients with COVID-19 at 405 hospitals in 30 countries (n=11,330 patients randomized; n=2750 to remdesivir) **Design:** randomized, open-label trial evaluating remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon-beta 1a compared to local standard of care **Results:** ▪ Remdesivir did not reduce mortality, need for ventilation, or duration of hospitalization		

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REMDESIVIR (CONTINUED)	▪ death rate ratio with remdesivir was 0.95 (95% CI 0.81-1.11; 301/2743 active vs 303/2708 control; p=0.50**)** ▪ ventilation initiated after randomization in 295 patients in the remdesivir group vs 284 in the control group ▪ 69% of patients who received remdesivir were still hospitalized at day 7 vs 59% in the control group **Limitations:** interim analysis; open-label; conducted in many varied settings around the world; timing of treatment initiation not standardized **BT Garibaldi et al. JAMA Netw Open 2021**[28] *(added 3/29/2021)* **Population:** consecutive adults admitted with COVID-19 (n=2483) **Design:** retrospective comparative effectiveness study in a hospital system in Baltimore, MD and Washington, DC ▪ Patients who received remdesivir matched to individuals who did not receive the drug **Results:** ▪ 342 patients received remdesivir; 184 also received corticosteroids and 128 received remdesivir alone ▪ 80.7% of patients who received remdesivir self-identified as non-White race/ethnicity ▪ Time to clinical improvement was shorter in those treated with remdesivir compared to matched controls (5 days vs 7 days; adjusted hazard ratio 1.47, 95% CI 1.22-1.79) ▪ 28-day mortality rate was 7.7% (22 death) in remdesivir recipients and 14.0% (40 deaths) in matched controls, the difference was not		

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REMDESIVIR (CONTINUED)	statistically significant (adjusted hazard ratio 0.70, 95% CI 0.38-1.28) **Limitations:** retrospective data **Gilead 2021** *(added 6/29/2021)* **Population:** hospitalized patients with COVID-19 (n=~100,000) **Design:** data from 3 retrospective studies **Results:** ▪ Lower risk for mortality in patients given remdesivir compared to controls in all 3 studies ▪ Increased likelihood of hospital discharge in patients given remdesivir in 2 studies **Limitations:** retrospective data; not yet published **Barratt-Due et al. NOR-Solidarity Ann Intern Med 2021**[30] *(added 7/15/2021)* **Population:** hospitalized adults with confirmed SARS-CoV-2 at 23 hospitals in Norway (n=185) **Design:** independent, add-on, randomized controlled trial to WHO Solidarity trial ▪ Patients given remdesivir, hydroxychloroquine, or standard of care **Results:** ▪ No significant difference in mortality during hospitalization between groups ▪ There was a decrease in SARS-CoV-2 oropharyngeal viral load during the first week after randomization in all groups; the decreases in viral load and 10-day viral loads were similar		

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REMDESIVIR (CONTINUED)	among remdesivir, hydroxychloroquine, and standard of care groups **Limitations:** no placebo group, small sample size **<u>Ohl et al JAMA Netw Open 2021[31]</u>** *(added 7/23/2021)* **Population:** US veterans hospitalized with COVID-19 (n=2344) **Design**: cohort study ▪ Patients who initiated remdesivir vs controls who did not **Results:** ▪ 30-day mortality 12.2% in remdesivir recipients and 10.6% in controls (log rank p=.26) ▪ Median time to hospital discharge 6 days in remdesivir recipients and 3 days in controls (p<0.001) **Limitations :** retrospective data **<u>Ader et al. DisCoVeRy Lancet Infect Dis 2021[32]</u>** *(added 9/20/2021)* **Population:** hospitalized adults with COVID-19 illness of any duration and clinical evidence of hypoxemic pneumonia or required oxygen (n=857) **Design:** phase 3, open-label, adaptive, multicenter, randomized trial ▪ Remdesivir 200 mg infusion on day 1, then 100 mg infusions once daily x up to 9 days plus standard care vs standard care only **Results:** At day 15, distribution on WHO scale (remdesivir vs standard care alone): ▪ Not hospitalized, no limitations on activities (15% vs 17%)		

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	▪ Not hospitalized, no limitation on activities (31% vs 32%) ▪ Hospitalized, not requiring supplemental oxygen (12% vs 7%) ▪ Hospitalized, requiring supplemental oxygen (18% vs 16%) ▪ Hospitalized, non-invasive ventilation or high-flow oxygen (4% vs 3%) ▪ Hospitalized, on invasive mechanical ventilation or ECMO (15% vs 19%) ▪ Death (5% vs 6%) ▪ Difference between treatment groups not statistically significant (OR 0.98, 95% CI 0.77-1.25) **Limitations:** open-label, not placebo-controlled, variations in standard care		
REMDESIVIR (CONTINUED)	**RL Gottlieb et al. (PINETREE) NEJM 2021**[33,41] *(added 9/23/2021; updated 12/23/2021)* **Population:** non-hospitalized patients ≥12 years old with COVID-19 with symptom onset within the previous 7 days at high risk for disease progression (n=562) **Design:** phase 3, randomized, double-blind, placebo-controlled trial ▪ IV remdesivir x 3 days vs placebo **Results:** ▪ The primary endpoint of COVID-19 related hospitalization or death from any cause by day 28 occurred in 0.7% (2/279) of patients treated with remdesivir compared to 5.3% (15/283) of those who received placebo (hazard ratio 0.13, 95% CI 0.07-0.56; p=0.008) ▪ A COVID-19-related medically attended visit by day 28 occurred in 1.6% (4/246) of patients given		

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	remdesivir and 8.3% (21/252) of those given placebo (hazard ratio 0.19; 95% CI 0.07-0.56) ▪ No patients died by day 28 ▪ In a subgroup of 126 patients who completed the FLU-PRO Plus questionnaire at baseline, 34.8% of patients in the remdesivir group had alleviation of symptoms by day 14 compared to 25.0% of those in the placebo group ▪ There were no significant differences between the two groups in viral load reduction **Limitations:** limitations in representation of groups potentially at risk for severe COVID-19 in the trial population; excluded vaccinated patients; conducted before Delta or Omicron; trial stopped early		
MOLNUPIRAVIR (Ridgeback Biotherapeutics/Merck) *(updated 12/23/2021)* **Dosage:** ▪ 800 mg (4 200-mg capsules) PO twice daily x 5 days ▪ Should be started as soon as possible after diagnosis and within 5 days of symptom onset	▪ Phase 2/3 efficacy and safety trials underway in outpatients and hospitalized patients; manufacturer plans to continue to phase 3 trials in outpatients, but not inpatients *(updated 4/15/2021)* **Ridgeback/Merck 2021[26]** **Population:** 202 outpatient adults with confirmed COVID-19 with signs or symptoms within 7 days **Design:** phase 2a randomized, double-blind, placebo-controlled trial ▪ 200, 400, or 800 mg of molnupiravir or placebo **Results:** ▪ At day 5, infectious virus was recovered on nasopharyngeal swab from 0% of molnupiravir-treated patients and 24% of placebo-treated patients	▪ No serious adverse events considered related to the study drug were reported in the phase 2a trial ▪ Headache, nausea, diarrhea, and rash were among the adverse effects reported in a phase 1 trial[27] ▪ In the phase 3 trial (MOVe-OUT), the most common adverse effects (occurring in 6.3% of molnupiravir-treated patients and 9.6% of placebo-treated patients were COVID-19 pneumonia, diarrhea, bacterial pneumonia; the most common adverse effects deemed related to molnupiravir were diarrhea, nausea, and dizziness[37] *(updated 12/20/2021)* ▪ In the phase 3 MOVe-OUT trial, adverse events were reported in 30.4% of patients in the molnupiravir group and 33.0% of	▪ Ribonucleoside analog that inhibits replication of RNA viruses, including SARS-CoV-2 ▪ Prodrug of the synthetic nucleoside derivative β-D-N4-hydroxycytidine; targets viral RNA polymerase, introducing copying errors during viral RNA replication ▪ Merck/Ridgeback filed for FDA emergency use authorization (EUA) based on interim results of phase 3 trial (MOVe-OUT) *(added 10/11/2021)* ▪ UK Medicines and Healthcare products Regulatory Agency (MHRA) authorized molnupiravir for treatment of mild to moderate COVID-19 *(added 11/7/2021)*

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	Limitations: not yet published or peer reviewed, phase 2a; small sample size **AJ Bernal et al. (MOVe-OUT) NEJM 2021**[34,37] *(added 10/4/2021; updated 12/6/2021; updated 12/20/2021)* **Population:** non-hospitalized, unvaccinated adults with mild to moderate COVID-19 with symptom onset ≤5 days before randomization and ≥1 risk factor for poor disease outcome (obesity, age ≥60 years, diabetes, heart disease) (n=1433) **Design:** phase 3 randomized, double-blind, placebo-controlled trial ▪ Molnupiravir 800 mg PO bid x 5 days vs placebo **Results:** ▪ Trial stopped early based on interim results ▪ At the interim analysis, the risk of hospitalization for any cause or death through day 29 was 7.3% (28/385) with molnupiravir vs 14.1% (53/377) with placebo (difference -6.8 percentage points; 95% CI -11.3 to -2.4; p=0.001) ▪ At the final analysis the risk of hospitalization or death was 6.8% (48/709) with molnupiravir vs 9.7% (68/699) with placebo (difference -3.0 percentage points; 95% CI -5.9 to -0.1) ▪ 1 death was reported in the molnupiravir group and 9 deaths in the placebo group through day 29 ▪ Efficacy appears similar among Gamma, Delta, and Mu variants ▪ In subgroup analyses, patients with previous SARS-CoV-2 infection, low baseline viral load, or diabetes did	patients in the placebo group[37] *(updated 12/20/2021)*	▪ FDA issued an emergency use authorization (EUA) for molnupiravir for oral treatment of mild to moderate COVID-19 in patients ≥18 years old who are at high risk for progression to severe disease and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate[42-44] *(added 12/23/2021)* ▪ Not authorized for treatment in patients hospitalized due to COVID-19[42-44] *(added 12/23/2021)* ▪ Not authorized for use in patients <18 years old because it may affect bone and cartilage growth[42-44] *(added 12/23/2021)* **Pregnancy:** ▪ Molnupiravir may cause fetal harm and is not recommended for use during pregnancy ▪ Molnupiravir caused embryofetal lethality and teratogenicity in animal studies ▪ Females of childbearing potential should use a reliable method of birth control during treatment with molnupiravir and for 4 days after stopping the drug ▪ Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of birth control during treatment with molnupiravir and for at least 3 months after the last dose

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	not appear to have better outcomes with use of molnupiravir compared to placebo ▪ Pregnant patients were excluded from the trial **Limitations:** only unvaccinated persons included; enrollment stopped early based on interim results		▪ Breastfeeding is not recommended during treatment and for 4 days after the last dose
Nirmatrelvir (PF-07321332)/Ritonavir (*Paxlovid*; Pfizer) (Updated 12/22/2021) **Dosage:**[40] ▪ Nirmatrelvir 300 mg (2 150-mg tablets) plus ritonavir 100 mg PO twice daily x 5 days ▪ Should be started as soon as possible and within 5 days of symptom onset ▪ Available as daily blister cards containing 4 150-mg nirmatrelvir tablets copackaged with 2 100-mg ritonavir tablets ▪ Moderate renal impairment (eGFR ≥30 to <60 mL/min): reduce dose to 150 mg of nirmatrelvir and 100 mg of ritonavir bid	**Pfizer EPIC-HR Trial 2021**[35,36] *(added 11/7/2021; updated 12/14/2021)* **Population:** non-hospitalized adults with laboratory confirmed SARS-CoV-2 infection with mild to moderate symptoms and at least 1 condition associated with risk of severe illness (n=2246) **Design:** phase 2/3 randomized, double-blind trial ▪ *Paxlovid* or placebo bid x 5 days **Results:** Interim analysis (11/7) ▪ n=1219 ▪ Trial stopped early for efficacy ▪ In patients treated within 3 days of symptom onset: 0.8% of patients who received *Paxlovid* were hospitalized (3/389 hospitalizations; 0 deaths) compared to 7.0% of patients who received placebo and were hospitalized or died (27/385 hospitalizations; 7 deaths) (p<0.001)	**Adverse Effects:** ▪ In EPIC-HR trial, treatment emergent adverse effects reported in 19% of patients treated with *Paxlovid* and 21% of those given placebo[35] ▪ Impaired sense of taste, diarrhea, high blood pressure, muscle aches ▪ Hepatotoxicity; hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred with ritonavir ▪ Use in patients with uncontrolled or undiagnosed HIV infection may lead to HIV-1 drug resistance **Drug Interactions:** ▪ *Paxlovid* is a CYP3A inhibitor ▪ Contraindicated for use with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious or life-threatening	▪ SARS-CoV-2 protease inhibitor that blocks the activity of SARS-CoV-2-3CL protease, and enzyme needed for viral replication ▪ Coadministration with ritonavir slows metabolism of PF-07321332 ▪ Administered orally ▪ FDA issued an emergency use authorization (EUA) for nirmatrelvir copackaged with ritonavir *(Paxlovid)* for treatment of mild to moderate COVID-19 in patients ≥12 years old and ≥40 kg at high risk for progression to severe COVID-19[38,39] *(added 12/22/2021)* **Pregnancy:** ▪ No available human data on use of nirmatrelvir during pregnancy ▪ Reduced fetal body weights observed after oral administration of nirmatrelvir to pregnant rabbits at systemic

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
▪ Severe renal impairment (eGFR <30 mL/min): not recommended ▪ Severe hepatic impairment (Child-Pugh Class C): not recommended	▪ In patients treated within 5 days of symptom onset: 1.0% of patients who received *Paxlovid* were hospitalized (6/607 hospitalizations; 0 deaths) compared to 6.7% of patients who received placebo and were hospitalized or died (41/612 hospitalizations; 10 deaths) (p<0.001) Final Analysis (12/14) ▪ n=2246 ▪ In patients treated within 3 days of symptom onset, hospitalization or death occurred in 0.7% of patients given *Paxlovid* (5/697 hospitalized/0 deaths) vs 6.5% of those given placebo (44/682 hospitalized/9 deaths) (p<0.0001) ▪ In patients treated within 5 days of symptom onset, hospitalization or death occurred in 0.8% of patients given *Paxlovid* (8/1039 hospitalized/0 deaths) vs 6.3% of those given placebo (66/1046 hospitalized/12 deaths) (p<0.0001) ▪ In patients ≥65 years old, hospitalization or death occurred in 1.1% of patients given *Paxlovid* (1/94 hospitalized/0 deaths) vs 16.3% of those who received placebo (16/98 hospitalized/6 deaths) (p<0.0001) ▪ In a subgroup analysis of 499 patients, *Paxlovid* reduced viral load aout 10-fold relative to placebo **Limitations:** not yet published or peer-reviewed **Pfizer EPIC-SR Trial 2021[36]** *(added 12/14/2021)* **Population:** unvaccinated adults at standard risk and vaccinated adults	reactions (see fact sheet for table of drug interactions)[40] ▪ Nirmatrelvir and ritonavir are CYP3A substrates; *Paxlovid* is contraindicated for use with potent CYP3A inducers which may reduce plasma concentrations of nirmatrelvir or ritonavir and result in loss of virologic response or possible resistance (see fact sheet for table of drug interactions)[40]	exposures 10x higher than authorized human dose ▪ Ritonavir may reduce efficacy of combined hormonal contraceptives; an alternative contraceptive method or additional barrier method should be used

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	with ≥1 risk factor for progressing to severe disease (n=673) **Design:** phase 2/3 trial ▪ *Paxlovid* vs placebo **Results:** ▪ Did not meet the primary endpoint of self-reported, sustained alleviation of all symptoms for 4 consecutive days, compared to placebo ▪ *Paxlovid* reduced hospitalization by 70% compared to placebo, a secondary endpoint ▪ 10-fold decrease in viral load compared to placebo **Limitations:** not yet published or peer reviewed		

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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Convalescent Plasma			
CONVALESCENT PLASMA *(updated 12/22/2021)* **Dosage:** ▪ Only high titer convalescent plasma should be used ▪ One or two 200-ml infusions[1]	▪ **Case series** of 5 critically ill patients with COVID-19 and ARDS in China; administration of convalescent plasma improved clinical status (e.g., body temperature normalized, viral load decreased, antibody titers increased, ARDS resolved, weaning from mechanical ventilation).[2] ▪ **Case series** of 10 patients with severe COVID-19; clinical symptoms improved within 3 days and improvement in lung lesions reported within 7 days[3] **Li et al. JAMA 2020**[7] *(added 8/16/2020)* **Population:** hospitalized patients in China with severe or life-threatening COVID-19 (n=103) **Design:** open-label, multicenter, randomized trial ▪ Convalescent plasma plus standard treatment vs standard treatment alone ▪ Plasma units with an S-RBD–specific IgG titer of at least 1:640 were used ▪ Median time from symptom onset to randomization: 30 days **Results:** ▪ Trial stopped early ▪ Clinical improvement within 28 days occurred in 51.9% of patients treated with convalescent plasma vs 43.1% of those given standard	**Adverse Effects:** ▪ No severe adverse effects were reported in case series ▪ Risks expected to be similar to those of other transfusions ▪ Transfusion-transmissible infection risk is very low in the US ▪ Allergic transfusion reactions, transfusion associated circulatory overload (TACO), and transfusion related acute injury (TRALI) ▪ Theoretical risk of antibody-dependent enhancement (ADE) presumably due to antibodies from previous infection with other coronaviruses ▪ May lower natural immune response when given for prophylaxis ▪ In an evaluation of 20,000 hospitalized patients administered convalescent plasma under the US FDA expanded access program, serious adverse events included transfusion reactions (n=89, <1%), thromboembolic or thrombotic events (n=87, <1%), and cardiac events (n=680, ~3%); 37 TACO events, 20 TRALI events, and 26 severe allergic reactions occurred; mortality rate was higher in more critically ill patients[10] *(added 10/1/2020)*	▪ Passive antibody therapy by infusion of convalescent plasma may prevent infection or reduce severity of illness[1] ▪ Used previously for treatment of SARS-CoV-1, MERS, Ebola, and H1N1 influenza ▪ Most likely to be effective when given as prophylaxis or early in the course of disease ▪ Clinical trials underway in the US ▪ NIH guidelines recommend against use of low-titer COVID-19 convalescent plasma[4] *(updated 4/23/2021)* ▪ NIH guidelines recommend against use of convalescent plasma in mechanically ventilated patients[4] *(updated 4/23/2021)* ▪ NIH guidelines recommend against use of high-titer convalescent plasma for treatment of patients who do not require mechanical ventilation, except in a clinical trial[4] *(updated 4/23/2021)* ▪ NIH guidelines state there are insufficient clinical data to recommend either for or against use of high-titer convalescent plasma in hospitalized patients with COVID-19 who have impaired immunity[4,11] *(updated 4/23/2021)*

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CONVALESCENT PLASMA (continued)	treatment alone, not a statistically significant difference (p=0.26) ▪ In those with severe disease, clinical improvement occurred in 91.3% with convalescent plasma vs 68.2% with standard care alone (p-0.03) and in those with life-threatening disease in 20.7% vs 24.1% (p=0.83) ▪ 28-day mortality was 15.7% with convalescent plasma vs 24.0% with standard care (p=0.30) ▪ Negative conversion rate of viral PCR at 72 hours was 87.2% with convalescent plasma vs 37.5% with standard care (p<0.001) **Limitations:** trial stopped early before full enrollment reached; open label; time from symptom onset 30 days **A Gharbharan et al. ConCOVID, MedRxiv 2020**[13] *(added 10/14/2020)* **Population**: hospitalized patients in the Netherlands (n=86) **Design:** open-label, randomized trial ▪ convalescent plasma vs standard care **Results:** ▪ Trial stopped early; SARS-CoV-2 neutralizing antibody titers of participant and convalescent plasma were comparable ▪ 53/66 patients tested had SARS-CoV-2 antibodies at baseline; symptomatic for 10 days at the time of inclusion ▪ No difference in mortality, duration of hospitalization, or disease severity		▪ Surviving Sepsis Campaign guidelines suggest against routine use of convalescent plasma in critically ill adults[5] ▪ IDSA guidelines recommend use of convalescent plasma in ambulatory patients with mild-to-moderate COVID-19 only in the context of a clinical trial; they recommend against use in patients hospitalized with COVID-19[12] *(updated 4/15/2021)* ▪ FDA issued an Emergency Use Authorization for convalescent plasma[6,9] (*added 8/19/2020*) ▪ NIH released statement following FDA EUA (Sept 1, 2020) stating insufficient data to recommend for or against use of convalescent plasma for COVID-19, Serious adverse effects infrequent, but long-term risks, including whether use of convalescent plasma attenuates the immune response to SARS-Co-V-2 making patients more susceptible to reinfection, are unknown ▪ FDA EUA revised to limit use to only high titer convalescent plasma for treatment of hospitalized patients early in the disease course and to those hospitalized patients who have impaired humoral immunity and cannot produce and adequate antibody response[17] (*added 2/10/2021)* ▪ WHO recommends against use of convalescent plasma for treatment of non-severe COVID-19 patients; it should only be used in clinical trial for severe

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CONVALESCENT PLASMA (continued)	**Limitations:** trial stopped early; not peer reviewed **A Agarwal et al. PLACID, BMJ 2020**[14] *(updated 10/26/2020)* **Population**: hospitalized patients in India with moderate COVID-19 (PaO2/FiO2 ratio 200-300 mm Hg or respiratory rate > 24/min with oxygen saturation ≤93% in room air) (n=464) **Design:** open-label, multicenter, phase 2, randomized controlled trial ▪ convalescent plasma (2 doses of 200 mL each, transfused 24 hrs apart) plus standard care vs standard care alone ▪ administered within 3 days of symptom onset **Results:** ▪ Composite outcome (progression to severe disease or all-cause mortality at 28 days) was 19% with convalescent plasma vs 18% with standard care (risk difference 0.008, 95% CI -0.062-0.078; risk ratio 1.04, 95% CI 0.71-1.54) ▪ More patients treated with convalescent plasma had resolution of shortness of breath (76% vs 66%; 95%) and fatigue (73% vs 60%) at day 7 compared to standard care; differences in resolution of fever and cough were not significantly different between groups ▪ Negative conversion of SARS-CoV-2 RNA at day 7 was higher in patients given convalescent plasms		and critical COVID-19 patients; according to WHO, current evidence shows it does not improve survival or reduce the need for mechanical ventilation, but has significant costs[22] *(added 12/10/2021)* **Pregnancy:** ▪ Clinical trials ongoing evaluating use in pregnant women

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CONVALESCENT PLASMA (continued)	compared to those who were not (68% vs 55%; 95% CI 1.04-1.5) ▪ 83% had detectable neutralizing antibodies at enrollment **Limitations:** open-label; presence and level of neutralizing antibodies not measured before administration **MJ Joyner et al NEJM 2020[8]** *(added 8/17/2020; updated 1/18/2021)* **Population:** hospitalized patients ≥18 years old in the US who had or were at high risk of progressing to severe or life-threatening COVID-19 (n=3082) **Design:** open-label exploratory analysis of patients who received convalescent plasma through an Expanded Access Program in the US **Results:** ▪ 52.3% of patients in ICU; 27.5% on mechanical ventilation ▪ Death within 30 days after plasma transfusion occurred in 115 of 515 patients (22.3%) in the high-titer group, 549 of 2006 (27.4%) in the medium-titer group, and 166 of 561 (29.6%) in the low-titer group ▪ Transfusion with high-titer plasma was associated with a lower risk of death than low-titer plasma in patients not on mechanical ventilation (relative risk 0.66; 95% CI 0.48-0.91) ▪ There was no effect on the risk of death in patients who were on mechanical ventilation (relative risk 1.02; 95% CI 0.78-1.32)		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CONVALESCENT PLASMA (continued)	▪ 30-day mortality was lower in patients who received a transfusion within 3 days after diagnosis than in those who received a transfusion ≥4 days after diagnosis **Limitations:** retrospective, no control arm; only limited amount of total data available at the time of this analysis **VA Simonovich et al. PlasmAr. NEJM 2020**[15] *(added 11/28/2020)* **Population:** hospitalized adults in Argentina with severe COVID-19 pneumonia (SaO2<93% on ambient air, PaO2:FiO2 <300 mm Hg, SOFA or mSOFA score of ≥2 points above baseline) (n=334) **Design:** randomized, double-blind, placebo-controlled multicenter trial ▪ convalescent plasma or placebo in addition to usual therapy **Results:** ▪ Median time from onset of symptoms to enrollment was 8 days ▪ >95% of transfused convalescent plasma units had a total anti-SARS-CoV-2 antibody titer of at least 1:800 ▪ No significant difference in clinical status after 30 days between the two groups (p=0.46) ▪ Overall mortality was 10.96% and 11.43% in the convalescent plasma group and placebo group, respectively ▪ Infusion reactions occurred in 4.8% of patients given convalescent		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CONVALESCENT PLASMA (continued)	plasma vs 1.9% of those given placebo **Limitations:** only in patients with severe disease; usual therapy not standardized **P Janiaud et al. JAMA 2021[17]** *(added 2/27/2021)* **Population:** patients with COVID-19 in any treatment setting treated with convalescent plasma or control (n=1060) **Design:** meta-analysis of 4 peer-reviewed, published, randomized clinical trials **Results:** ▪ Risk ratio for mortality was 0.93 ▪ In a secondary analysis, with addition of 6 unpublished trials (n=10,772), risk ratio for mortality was 1.02 ▪ Convalescent plasma was not associated with improvement in length of hospitalization, mechanical ventilation use, clinical improvement, or clinical deterioration **Limitations:** meta-analysis; reporting of clinical outcomes inconsistent across trials; data too limited for analysis of high-titer plasma **R Libster et al. NEJM 2021[18]** *(added 2/28/2021)* **Population:** older adults with mild COVID-19 within 72 hours after symptom onset (n=160) **Design:** randomized, double-blind, placebo-controlled trial ▪ High-titer convalescent plasma vs placebo		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CONVALESCENT PLASMA (continued)	**Results:** ▪ Severe respiratory disease developed in 16% of patients who received convalescent plasma vs 31% who received placebo (RR 0.52; 95% CI 0.29-0.94, p=0.03) ▪ Trial stopped early at 76% of projected sample size due to lack of patient enrollment after local COVID-19 infection rates dropped **Limitations:** trial stopped early; only mild cases **RECOVERY Group Lancet 2021[19]** *(added 5/19/2021)* **Population:** hospitalized patients with COVID-19 in the UK (n=11558) **Design:** randomized, controlled, open-label, platform trial ▪ High-titer convalescent plasma plus usual care vs usual care alone **Results:** ▪ 28-day mortality rate ratio was not significantly different between the convalescent plasma and usual care groups (24% vs 24%; rate ratio 1.00, 95% CI 0.93-1.07 p=0.95) ▪ There was no significant difference between groups in the proportion of patients discharged from the hospital within 28 days (66% vs 66%; rate ratio 0.99, 95% CI 0.94-1.03; p=0.57) ▪ The proportion of patients who were not on invasive mechanical ventilation at baseline meeting a composite endpoint of progression to invasive mechanical ventilation or death was 29% in the convalescent plasma group and 29% in the usual care group (rate ratio 0.99, 95% CI 0.93-1.05; p=0.79)		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CONVALESCENT PLASMA (continued)	▪ There were no differences in mortality noted in any subgroup analyses including duration of symptoms before randomization **Limitations:** only hospitalized patients studied **<u>Korley et al. SIREN-C3PO NEJM 2021</u>[20]** *(added 9/8/2021)* **Population:** patients treated in the emergency department for COVID-19 symptoms (≤7 days after symptom onset) who were ≥50 years old or had ≥1 risk factor for disease progression (n=511) **Design:** randomized, multicenter, single-blind trial ▪ Patients received 1 unit of high-titer convalescent plasma or placebo **Results:** ▪ Disease progression within 15 days after randomization occurred in 77 patients (30.0%) treated with convalescent plasma and 81 patients (31.9%) given placebo (risk difference, 1.9 percentage points; 95% credible interval -6.0 to 9.8; posterior probability of superiority of convalescent plasma 0.68) **Limitations:** single-blind trial; failure could have resulted from conditions other than COVID-19; optimal timing, dose, patient population for convalescent plasma unknown **<u>REMAP-CAP JAMA 2021</u>[21]** *(added 10/12/2021)* **Population:** critically ill patients with COVID-19 (n=2011) **Design:** international, open-label, adaptive platform, randomized clinical trial		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CONVALESCENT PLASMA (continued)	▪ 2 units high-titer convalescent plasma vs no convalescent plasma **Results:** ▪ Median number of organ support-free days with convalescent plasma was 0 (IQR -1 to 16) and 3 (IQR -1 to 16) with no convalescent plasma ▪ In-hospital mortality rate was 37.3% with convalescent plasma and 38.4% without convalescent plasma ▪ Median-adjusted OR was 0.97 (95% credible interval 0.83-1.15) and the posterior probability of futility (OR <1.2) was 99.4% for convalescent plasma compared to no convalescent plasma ▪ Trial was stopped when prespecified criteria for futility was met **Limitations:** open-label; critically ill patients only; days from symptom onset unknown; 85.6% of patients in treatment group received treatment per protocol and 0.6% in no treatment group received treatment **DJ Sullivan et al. medRxiv 2021** *(added 12/22/2021)* **Population:** outpatient adults with COVID-19 with symptom onset ≤8 days before enrolment (n=1225 randomized patients; 1181 transfused patients pre-specified modified ITT analysis) **Design:** randomized, double-blind trial ▪ High-titer convalescent plasma (greater than 1:320 SARS-CoV-2 spike protein titers) vs placebo control plasma **Results:** ▪ In ITT analysis, COVID-19-related hospitalization within 28 days occurred in 2.9% (17/592) patients		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	infused with convalescent plasma and 6.3% (37/589) of those who received placebo control plasma (relative risk 0.46; one sided 95% upper bound confidence interval 0.733; p=0.004) **Limitations:** not yet published or peer reviewed; outcome only evaluated hospitalization not deaths; hospitalization rate in control group lower than US average		

ARDS = acute respiratory distress syndrome

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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Intravenous Immune Globulin (IVIG			
INTRAVENOUS IMMUNE GLOBULIN (IVIG) *(added 6/8/2020)* **Dosage:** ▪ Optimal dosage for COVID-19 unclear ▪ Phase 3 trial of *Octagam* will use a dosage of 0.5 g/kg IV infusion over 2 hours x 4 days	**W Cao et al. Open Forum Infect Dis 2020[1]** **Population:** Hospitalized patients in China with severe disease and deteriorating course (n = 3) **Design:** Case series; patients received IVIg at the start of respiratory distress **Results:** all 3 patients had clinical improvement; no fever within 1-2 days, alleviation of breathing difficulties in 3-5 days **Limitations:** small case series, 2 patients also received antivirals, 1 received steroids **Xie et al. J Infect 2020[2]** **Population**: ICU patients with severe or critical illness in Wuhan, China (n=58) **Design:** retrospective review of 58 cases **Results:** administration of IVIG within 48 hrs of hospital admission was associated with reduced 28-day mortality, shorter hospital stay, and reduced ventilator use compared to administration after 48 hours **Limitation:** small retrospective study **Shao et al. 2020[3]** **Population:** Hospitalized severely and critically ill patients (n=325) **Design:** multicenter retrospective cohort study **Results:**	**Adverse Effects:** rarely can case anaphylaxis, aseptic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury	▪ Used for treatment of immune disorders and as an adjunct for treatment of severe pneumonia in influenza patients; modulates immune inflammation, improves passive immunity ▪ Existing IVIG product unlikely to contain antibodies against SARS-CoV-2 ▪ FDA approved an investigational new drug application (IND) for a phase 3 trial with *Octagam* 10% in COVID-19 patients with severe disease progression (SpO2≤93%, requiring oxygen supplementation)[4] ▪ Surviving Sepsis Campaign guidelines suggest against routine use of standard IVIG in critically ill adults[5] ▪ NIH guidelines recommend against use of non-SARS-CoV-2-specific IVIG outside of the context of a clinical trial for treatment of COVID-19; they state this should not preclude use of IVIG when otherwise indicated for treatment of complications arising during the course of COVID-19 illess[6] ▪ NIH guidelines state there are insufficient data to recommend for or against use of SARS-CoV-2 immunoglobulins[6] *(added 7/22/2020)* ▪ Shortages have been an issue (even prior to COVID-19)

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
INTRAVENOUS IMMUNE GLOBULIN (IVIG) (CONTINUED)	▪ IVIG not associated with improved 28- or 60-day mortality compared to no IVIG in overall cohort ▪ Duration of hospitalization and disease were longer in patients treated with IVIG than in those who were not ▪ In a subgroup analysis, IVIG was associated with reduced 28-day mortality in critically ill patients **Limitation:** not peer reviewed, IVIG group more likely to have coronary heart disease and severe COVID-19		

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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Monoclonal Antibodies			
LY-CoV555 (bamlanivimab) and LY-CoV016 (etesevimab) **(Eli Lilly/AbCellera)** *(updated 1/25/2022)* **FDA has limited bamlanivimab and etesevimab for use only in patients likely to have been infected with or exposed to a variant susceptible to these treatments; bamlanivimab and etesevimab are highly unlikely to be effective against the Omicron variant and are not authorized for use in the US at this time *(updated 1/25/2022*) Bamlanivimab:[7] **(EUA for bamlanivimab alone revoked 4/16/2021)** *(added 11/23/2020)* ▪ Single 700 mg IV infusion given over at least 60 minutes ▪ Patients should be monitored for hypersensitivity reactions during infusion and for at least 1 hour after completion ▪ Should be given as soon as possible after a SARS-CoV-2 positive test result and within 10 days of COVID-19 symptom onset ▪ Patients should be treated in facility staffed and equipped to manage anaphylaxis	**NIH ACTIV-2[1]** ▪ Phase 2 trial ▪ Expected to enroll 200 outpatients with mild to moderate COVID-19 symptoms for < 10 days ▪ LY-CoV555 vs placebo **BLAZE-4 Trial[16]** *(added 1/29/2021)* ▪ Randomized, double-blind, phase 2 trial in patients with mild to moderate COVID-19 ▪ Trial expanded to evaluate bamlanivimab in combination with VIR-7831, a monoclonal antibody that binds to a different region of the spike protein than bamlanivimab ▪ VIR-7831 is being developed by GSK and Vir Biotechnology ▪ The manufacturer states VIR-7831 has a high barrier to resistance **ACTIV-3/TICO LY-CoV555 Study Group. NEJM 2020 (NIH ACTIV-3)[1]** *(updated 1/1/2021; updated 3/14/2021)* ▪ Trial stopped based on review of data that suggested the antibody is unlikely to improve clinical outcomes in hospitalized patients **Population:** hospitalized patients with COVID-19 without end-organ failure (n=314) **Design:** Randomized, platform trial of therapeutic agents ▪ LY-CoV555 7000 mg vs placebo; both groups received standard	▪ Infusion reactions (pruritis, flushing, rash, facial swelling) ▪ Hypersensitivity reactions including anaphylaxis have occurred ▪ Clinical worsening of COVID-19 has been reported after administration of bamlanivimab; it has not been established if these events were related to use of bamlanivimab use or COVID-19 *(added 2/10/2021)* ▪ Adverse effects reported with bamlanivimab and etesevimab given together include nausea, dizziness, pruritis, and rash *(added 2/10/2021)*	▪ LY-CoV555 and LY-CoV016 are investigational monoclonal antibodies for treatment of COVID-19 ▪ Discovered in a blood sample from a recovered COVID-19 patient ▪ LY-CoV555 and LY-CoV016 bind different regions of the SARS-CoV-2 spike protein ▪ FDA updated the emergency use authorization (EUA) for bamlanivimab (LY-CoV555) for treatment of mild to moderate COVID-19 in adults and pediatric patients, including newborns (previously authorized only in persons ≥12 years old), who test positive for SARS-CoV-2 and who are at high risk for progressing to severe COVID-19[7,18,45]; FDA revoked EUA for bamlanivimab when administered alone based on sustained increase of SARS-CoV-2 viral variants resistant to bamlanivimab alone[24] (*updated 12/5/2021)* ▪ FDA EUA updated to authorize use of bamlanivimab and etesevimab for post-exposure prophylaxis for COVID-19 in adults and pediatric patients, including newborns (previously authorized only in persons ≥12 years old), who are at high risk for progression to severe COVID-19, who are not fully vaccinated or who are not expected to mount an adequate immune response (e.g., people with immunocompromising conditions or taking

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Bamlanivimab and Etesevimab[19] *(added 12/5/2021)* ▪ 700 mg of bamlanivimab and 1400 mg of etesevimab given together as a single IV infusion (for adults ≥18 years old and <18 years old who weigh >40 kg) ▪ >20 mg to <40 kg: 350 mg bamlanivimab and 700 mg etesevimab ▪ >12 kg to 20 kg: 175 mg bamlanivimab and 350 mg etesevimab ▪ 1 kg to 12 kg: 12 mg/kg bamlanivimab and 24 mg/kg etesevimab ▪ Authorization of the 700/1400 mg dose was based on analysis of pre-clinical, clinical, and virologic data and pharmacokinetic/ pharmacodynamic modeling suggesting it would have similar clinical effects to a 2800/2800 mg dose of bamlanivimab and etesevimab ▪ Patients should be monitored for hypersensitivity reactions during infusion and for at least 1 hour after completion ▪ Should be given as soon as possible after a SARS-CoV-2 positive test result and within 10 days of COVID-19 symptom onset ▪ Patients should be treated in facility staffed and equipped to manage anaphylaxis	care including remdesivir, oxygen, steroids **Results:** ▪ Data safety and monitoring board recommended stopping enrollment for futility after 314 patients were randomized and received an infusion (163 to LY-CoV555 and 151 to placebo) ▪ Median interval since onset of symptoms was 7 days ▪ Distribution of patients across 7 categories of the pulmonary ordinal outcome were similar between groups at day 5 ▪ 50% (81/163) who received LY-CoV555 vs 54% (81/151) who received placebo were in 1 of the 2 most favorable categories ▪ The odds ratio of being in a more favorable category in the LY-CoV555 group than in the placebo group was 0.85 (95% CI 0.56-1.29; p=0.45) ▪ The percentage of patient with the primary safety outcome (composite of death, serious adverse events, or clinical grade 3 or 4 adverse events through day 5) was similar between the groups (19% LY-CoV555 group vs 14% placebo group; OR 1.56, 95% CI 0.78-3.10, p=0.20 **Limitations:** preliminary report; trial stopped early; wide CI for safety endpoint **BLAZE-2**[14] *(updated 1/24/2021)* **Population:** residents and staff of nursing homes who tested negative		immunosuppressants), and who have been in close contact with a person with SARS-CoV-2 or who are at high risk for exposure because of occurrence of SARS-CoV-2 in other persons in the same institutional setting (e.g., nursing homes, prisons)[41,45] *(updated 12/5/2021)* ▪ Bamlanivimab and etesevimab not authorized for use in patients who are hospitalized or require oxygen therapy for COVID-19; monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *(added 2/10/2021)* ▪ NIH guidelines recommend against use of bamlanivimab monotherapy [8] *(updated 4/12/2021)* ▪ NIH guidelines recommend against use of bamlanivimab plus etesevimab due to an increase in the proportion of Gamma (P.1) and Beta (B.1.351), which have reduced susceptibility to bamlanivimab and etesevimab[8] *(updated 7/12/2021)* ▪ NIH guidelines recommend use of casirivimab plus imdevimab or sotrovimab for treatment of patients with mild to moderate COVID-19 not requiring hospitalization or supplemental oxygen who are at high risk of clinical progression[8] *(updated 7/12/2021)*

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
LY-CoV555 (bamlanivimab) and LY-CoV016 (etesevimab) (continued)	for SARS-CoV-2 at baseline (n=965; 299 residents and 666 staff) **Design:** ongoing randomized, phase 3 trial evaluating bamlanivimab for COVID-19 prophylaxis ▪ Bamlanivimab 4200 mg vs placebo **Results:** ▪ Frequency of symptomatic COVID-19 at 8 weeks was significantly lower with bamlanivimab than placebo (odds ratio 0.43; p=0.00021); for the subgroup of nursing home residents OR was 0.20 (p=0.00026) ▪ 4 deaths occurred in the placebo group and 0 in the treatment group **Limitations:** interim results; not peer-reviewed or published **Chen et al. NEJM (BLAZE-1) 2020**[2,5] *(updated 10/29/2020)* **Population:** outpatients with mild to moderate COVID-19 (n=452) **Design:** phase 2 randomized, double-blind, placebo-controlled ▪ **Monotherapy cohort:** LY-CoV555 700 mg, 2800 mg, or 7000 mg vs placebo ▪ **Combination cohort:** LY-CoV555 plus LY-CoV016; 2800 mg of each antibody (n=112) vs placebo (n=156) **Results:** **Monotherapy Cohort (Chen et al NEJM 2020):** *(updated 10/29/2020)* ▪ Infusion given median of 4 days after onset of symptoms (>80% had mild symptoms)		▪ In situations where logistical constraints exist and eligible patients must be triaged, NIH guidelines suggest:[8] *(added 9/7/2021)* • Treatment of COVID-19 be prioritized over post-exposure prophylaxis • Prioritizing unvaccinated or incompletely vaccinated persons at high risk of progressing to severe COVID-19 and vaccinated persons not expected to mount an adequate immune response (e.g., immunocompromised persons) over vaccinated persons who are expected to mount an adequate immune response ▪ IDSA guidelines suggest bamlanivimab/etesevimab or casirivimab/imdevimab or sotrovimab among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease; local variant susceptibility should be considered in choosing an agent[10] *(updated 7/12/2021)* ▪ NIH ACTIV-3 trial of LY-CoV555 in hospitalized patients, which was previously paused because of a potential safety concern, has now been stopped because of insufficient evidence that the antibody improved clinical outcomes; no significant differences in safety outcomes were reported in updated dataset *(updated 10/27/2020)*

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
LY-CoV555 (bamlanivimab) and LY-CoV016 (etesevimab) (continued)	▪ Change from baseline in viral load at day 11 was statistically significant compared to placebo with the 2800 mg dose only (-0.53; 95%CI -0.98 to -0.08; p=0.02) ▪ Complete viral clearance by day 11 was achieved by most patients, including those in the placebo group ▪ In additional analysis, LY-CoV555 improved viral clearance at day 3 ▪ Hospitalization or ER visit occurred in 1.6% of patients taking LY-CoV555 vs 6.3% taking placebo ▪ Slightly lower severity of symptoms was reported in patients who received LY-CoV555 compared to those who received placebo on days 2-6 **Combination Cohort Results:** ▪ Reduced viral load at day 11 compared to placebo (p=0.011) ▪ Complete viral clearance by day 11 was achieved by most patients, including those in the placebo group ▪ Reduced viral levels at day 3 (p=0.016) and day 7 (p<0.001) ▪ Reduced symptoms vs placebo ▪ Lowered the rate of COVID-19-related hospitalization and ER visits vs placebo (0.9% vs 5.8%) **Limitations:** interim data; unclear if earlier evaluation of viral clearance would have shown a difference at lower dosages; unclear if RT-PCR is accurate measure of viral neutralization		▪ Department of Health and Human Services (HHS) will stop distribution of bamlanivimab alone because of sustained increase in SARS-CoV-2 viral variants in the US that are resistant to bamlanivimab; the FDA Fact Sheet has been updated to reflect resistance data *(updated 3/24/2021)*[18] ▪ FDA/DHHS has now re-authorized use of bamlanivimab and etesevimab nationwide; they state the combination is expected to retain activity against the Delta variant; its use was previously restricted because of a high frequency of variants expected to be resistant to the combination (e.g., Gamma, Beta, Lambda)[27,34,38,39] *(updated 9/5/2021)* ▪ Does not appear to maintain efficacy against **Omicron** variant[48-50] *(added 12/22/2021)* **Pregnancy:** *(updated 11/23/2020)* ▪ Insufficient data on the use of bamlanivimab during pregnancy ▪ Human IgG1 antibodies can cross the placenta; therefore, bamlanivimab has the potential to be transferred from the mother to the fetus ▪ NIH guidelines state bamlanivimab should not be withheld from pregnant women who have conditions that pose a high risk of progression to severe disease if the clinician thinks the potential benefit outweighs the risk

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
LY-CoV555 (bamlanivimab) and LY-CoV016 (etesevimab) (continued)	**RL Gottlieb et al. JAMA 2021 (BLAZE-1)**[13] *(added 1/24/2021)* **Population:** adult outpatients with mild to moderate COVID-19 presenting within 3 days of first positive test result (n=577) **Design:** phase 2 portion of a multicenter, randomized, double-blind phase 2/3 trial ▪ Patients randomized to receive bamlanivimab 700 mg, bamlanivimab 2800 mg, bamlanivimab 7000 mg, bamlanivimab 2800 mg plus etesevimab 2800 mg, or placebo **Results:** ▪ Change in viral load from baseline at day 11 was -3.72 with bamlanivimab 700 mg, -4.08 with 2800 mg, -3.49 with 7000 mg, -4.37 with bamlanivimab plus etesevimab, and -3.80 with placebo; only the reduction in viral load with bamlanivimab plus etesevimab was statistically significantly lower than with placebo ▪ The proportion of patients who required hospitalization or ED visit due to COVID-19 at day 29 was 1.0% with 700 mg, 1.9% with 2800 mg, 2.0% with 7000 mg, 0.9% with combination therapy, and 5.8% with placebo; the only difference that was statistically significant was with combination therapy **Limitations:** primary endpoint may have been too late to detect differences; only 1 combination dose		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
LY-CoV555 (bamlanivimab) and LY-CoV016 (etesevimab) (continued)	**Dougan et al. BLAZE-1 NEJM 2021**[17,35] *(added 2/5/2021; updated 7/23/2021)* **Population:** adult and adolescent outpatients with mild to moderate COVID-19 presenting within 3 days of first positive test result who were at high risk of progressing to severe COVID-19 and/or hospitalization (n=1035) **Design:** phase 3 portion of a randomized, double-blind, placebo-controlled phase 2/3 trial ▪ Bamlanivimab 2800 mg plus etesevimab 2800 mg vs placebo **Results:** ▪ The primary endpoint of COVID-19-related hospitalization or death occurred in 2.1% (11/518) of patients taking bamlanivimab plus etesevimab compared to 7.0% (36/517) of those taking placebo (relative risk difference 70%; p<0.001) ▪ 10 deaths (9 related to COVID-19)occurred in the placebo group and 0 in the treatment group (p<0.001) ▪ Reduction from baseline in viral load at day 7 was statistically significantly greater in the treatment group than in the placebo group **Limitations:** small percent of non-White patients; small percent of adolescent patients; small percent of patients with common coexisting		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
LY-CoV555 (bamlanivimab) and LY-CoV016 (etesevimab) (continued)	conditions or immunosuppressed; 5% of patients had symptoms for > 8 days **BLAZE-1 Phase 3 Lilly 2021[21]** *(added 3/15/2021)* **Population:** outpatients ≥12 years old with mild to moderate COVID-19 presenting within 3 days of first positive test result who were at high risk of progressing to severe COVID-19 and/or hospitalization (n=769) **Design:** new cohort of a phase 3, randomized, double-blind, placebo-controlled trial ▪ Bamlanivimab 700 mg mg plus etesevimab 1400 mg vs placebo **Results:** ▪ 4 events of COVID-19-related hospitalization or death occurred in patients taking bamlanivimab plus etesevimab compared to 15 events in those taking placebo; an 87% risk reduction (p<0.0001) ▪ 4 COVID-19-related deaths occurred in the placebo group and 0 in the treatment group **Limitations:** not published or peer reviewed **MS Cohen et al. BLAZE-2 JAMA 2021[30]***(added 6/5/2021)* **Population:** residents and staff at US skilled nursing and assisted living facilities with at least 1 confirmed SARS-CoV-2 index case and who were negative at baseline for SARS-CoV-2 infection and serology (n=966)		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
LY-CoV555 (bamlanivimab) and LY-CoV016 (etesevimab) (continued)	**Design:** randomized, double-blind phase 3 trial evaluating efficacy for post-exposure prophylaxis ▪ Single IV dose of bamlanivimab 4200 mg or placebo ▪ August-November 2020 **Results:** ▪ Incidence of COVID-19 was 8.5% among those treated with bamlanivimab and 15.2% with placebo (OR 0.43 95% CI 0.28-0.68; p<0.001) **Limitations:** trial conducted before widespread vaccination and before variants circulating **<u>BLAZE-1 <18 years old Package Insert 2021</u>** *(added 12/5/2021)* **Population:** pediatric patients with mild to moderate COVID-19 who were not hospitalized and at high risk of progressing to severe disease (n=125) **Design:** phase 2/3 randomized controlled trial ▪ Bamlanivimab plus etesevimab (700/1400 mg for patients >40 kg; weight-based dosing used for <40 kg) **Results:** ▪ No pediatric subjects died or required hospitalization due to COVID-19 ▪ Change in viral load by day 7 was -4.23 with 700 mg bamlanivimab/ 1400 mg etesevimab and -4.23 for subjects receiving weight-based dosing with bamlanivimab/ etesevimab		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	▪ Median time to complete symptom resolution was 7 days for subjects treated with bamlanivimab 700 mg/ etesevimab 1400 mg and 5 days for subjects treated with weight-based dosing of bamlanivimab/etesevimab **Limitations:** small pediatric population evaluated in trial		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
REGN-COV-2 (REGEN-COV) CASIRIVIMAB (REGN10933) and IMDEVIMAB (REGN10987) **(Regeneron)** *(updated 1/25/2022)* **FDA has limited casirivimab and imdevimab for use only in patients likely to have been infected with or exposed to a variant susceptible to these treatments; casirivimab and imdevimab are highly unlikely to be effective against the Omicron variant and are not authorized for use in the US at this time *(updated 1/25/2022*) **Dosage:**[9] *(updated 8/2/2021)* ▪ Dosage for treatment or prophylaxis: 1200 mg (casirivimab 600 mg and imdevimab 600 mg) administered together as a single IV infusion over at least 60 minutes or by SC injection ▪ For treatment, the FDA strongly recommends IV infusion; SC administration is an alternative when IV infusion is not possible or would delay treatment ▪ For post-exposure prophylaxis, the drug can be administered by IV infusion or SC injection	**Clinical trials ongoing** ▪ Two phase 2/3 trials in hospitalized and non-hospitalized patients ▪ Phase 3 RECOVERY trial ▪ Phase 3 prevention trial with NIAID and NIH **Regeneron 2020**[4,6,9] *(added 9/29/2020; updated 11/23/2020)* **Population:** outpatients with COVID-19 (n=799) **Design:** ongoing, randomized, double-blind phase 2/3 trial ▪ REGN-COV2 plus standard-of-care vs placebo plus standard-of-care **Results:** ▪ Significantly greater reduction in viral load though day 7 with REGN-COV-2 vs placebo ▪ Most benefit appears to be in seronegative patients and/or patients with higher baseline viral loads ▪ Reduced COVID-19 related medical visits (2.8% REGN-COV-2 vs 6.5% placebo; p=0.024) ▪ Also reduced COVID-19 related medical visits in patients with risk factors (>50 years of age, BMI>30, CV, metabolic, lung, liver or kidney disease, or immunocompromised) ▪ Post-hoc analysis: 2% of antibody-treated patients and 4% of placebo-treated patients were hospitalized or visited the emergency department within 28 days after treatment; percentages were 3% and 9% in patients at higher risk for hospitalization	▪ Infusion reactions and hypersensitivity reactions, including anaphylaxis, have been reported	▪ Investigational combination of 2 SARS-CoV-2 neutralizing antibodies that bind to the spike protein ▪ Partnered with Roche ▪ FDA issued an emergency use authorization (EUA) for casirivmab and imdevimab to be administered together for treatment of mild to moderate COVID-19 in adults and pediatric patients ≥12 years old who weigh ≥40 kg and are at high risk for progression to severe disease or hospitalization[9] (*added 11/23/2020)* ▪ Not authorized for use in patients who are hospitalized or require oxygen therapy for COVID-19; monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *(added 11/23/2020)* ▪ FDA EUA updated: dosage decreased from 2400 mg to 1200 mg and SC administration authorized when IV infusion not possible or would delay treatment *(added 6/5/2021)* ▪ FDA EUA updated to authorize use of REGEN-COV for post-exposure prophylaxis for COVID-19 in adults and children (≥12 years old weighing ≥40 kg) who are at high risk for progression to severe COVID-19, who are not fully vaccinated or who are not expected to mount an adequate immune response

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
REGN-COV2 (continued) ▪ Repeat doses for post-exposure prophylaxis: after an initial dose of 600 mg of casirivimab and 600 mg of imdevimab, repeat doses of 300 mg of casirivimab and 300 mg of imdevimab every 4 weeks can be given to persons who remain at risk of exposure for >4 weeks and who are not expected to mount an adequate immune response to full SARS-CoV-2 vaccination ▪ Available in separate vials or a co-formulated vial containing both casirivimab and imdevimab ▪ Patients should be monitored for hypersensitivity reactions during infusion and for at least 1 hour after completion ▪ Should be given as soon as possible after a SARS-CoV-2 positive test result and within 10 days of COVID-19 symptom onset ▪ Patients should be treated in facility staffed and equipped to manage anaphylaxis	▪ Median time to symptom improvement was 5 days with the antibody combination and 6 days with placebo. **Limitations:** preliminary data from an ongoing trial **Weinreich et al. NEJM 2020:**[11] *(added 12/18/2020)* **Population:** nonhospitalized patients with COVID-19 (n=275) **Design:** ongoing, randomized, double-blind, phase 1-3 trial ▪ data presented here are of first 275 patients in Regeneron trial described above ▪ Patients randomized to 2.4g REGN-COV2, 8.0 g REGN-COV2, or placebo **Results:** ▪ Least-squares mean difference (combined REGN-COV2 dose groups vs placebo group) in time-weighted average change in viral load from day 1-7 was -0.56 log_{10} copies/mL among serum antibody-negative patients and -0.41 log_{10} copies/mL in the overall trial population ▪ 3% of patients in the combined REGN-COV2 dose groups reported at least 1 medically attended visit, compared to 6% of those in the placebo group ▪ Among serum antibody-negative patients the percentages were 6% vs 15% (with placebo) ▪ Safety was similar between groups		(e.g., people with immunocompromising conditions or taking immunosuppressants), and who have been in close contact with a person with SARS-CoV-2 or who are at high risk for exposure because of occurrence of SARS-CoV-2 in other persons in the same institutional setting (e.g., nursing homes, prisons)[36] *(added 8/2/2021)* ▪ NIH guidelines recommend use of casirivimab plus imdevimab or sotrovimab for treatment of patients with mild to moderate COVID-19 not requiring hospitalization or supplemental oxygen who are at high risk of clinical progression[8] *(updated 7/12/2021)* ▪ NIH guidelines recommend against use of casirivimab plus imdevimab in patients hospitalized for COVID-19 outside of a clinical trial[8] *(added 12/2/2020)* ▪ NIH guidelines recommend use of casirivimab plus imdevimab SC or IV as post-exposure prophylaxis for people who are at high risk for progression to severe COVID-19 if infected with SARS-CoV-2 AND who are not fully vaccinated or not expected to mount an immune response to vaccination AND who had a recent exposure to someone with COVID-19 (within 6 feet of an infected person for a cumulative total of ≥15 minutes over 24 hours) or at high-risk of exposure due to recent

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
REGN-COV2 (continued)	**Limitations:** interim analysis; no formal hypothesis testing performed to control type I error **Regeneron 2020**[12] *(added 1/1/2021)* ▪ Initial data from ongoing phase 1/2/3 trial in hospitalized, seronegative patients on low-flow oxygen suggests treatment may be beneficial; lower risk of death or mechanical ventilation reported ▪ Trial to continue based on these preliminary data **MP O'Brien et al. NEJM 2021**[15,25,37] *(added 1/27/2020; updated 4/20/2021, 8/5/2021)* **Population:** individuals ≥12 years old enrolled within 96 hours after a household contact was diagnosed with SARS-CoV-2 (n= 1505) **Design:** randomized, double-blind, placebo-controlled phase 3 trial ▪ REGEN-COV (casirivimab and imdevimab) 1200 mg SC injection vs placebo **Results:** ▪ Symptomatic infection through day 28 occurred in 11/753 patients (1.5%) who received REGEN-COV and 59/752 patients (7.8%) who received placebo (relative risk reduction 81.4%; p<0.001) ▪ Among patients who developed symptomatic infection, median time to symptom resolution was 1.2 weeks with REGEN-COV and 3.2 weeks with placebo		SARS-CoV-2 infection in others in the same institutional setting (e.g., nursing homes, prisons); they state there is insufficient evidence to recommend for or against repeat dosing every 4 weeks for those who received post-exposure prophylaxis and continue to have high-risk eposures[8] (*added 8/19/2021*) ▪ In situations where logistical constraints exist and eligible patients must be triaged, NIH guidelines suggest:[8] *(added 9/7/2021)* ○ Treatment of COVID-19 be prioritized over post-exposure prophylaxis ○ Prioritizing unvaccinated or incompletely vaccinated persons at high risk of progressing to severe COVID-19 and vaccinated persons not expected to mount an adequate immune response (e.g., immunocompromised persons) over vaccinated persons who are expected to mount an adequate immune response ▪ IDSA guidelines suggest bamlanivimab/etesevimab or casirivimab/imdevimab or sotrovimab among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease; local

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
REGN-COV2 (continued)	▪ Duration of high viral load was 0.4 weeks with REGEN-COV and 1.3 weeks with placebo ▪ There were no hospitalizations or emergency department visits in the antibody group, compared to 4 in the placebo group **Limitations:** primary analysis in seronegative patients **Regeneron 2021[23]** *(added 3/29/2021)* **Population:** high-risk outpatients with COVID-19 (n=4567) **Design:** randomized, double-blind, placebo-controlled phase 3 trial ▪ REGN-COV2 1200 mg IV or 2400 mg IV vs placebo **Results:** ▪ Risk of hospitalization or death was reduced by 70% with the 1200 mg dose of REGN-COV2 and by 71% with the 2400 mg dose compared to placebo ▪ Median time to symptom resolution was 10 days with either dose of REGN-COV2 and 14 days with placebo, a statistically significant difference **Limitations:** data not yet published or peer reviewed **RECOVERY Trial 2021[32]** *(added 6/16/2021)* **Population:** hospitalized patients with severe COVID-19 (n=9785)		variant susceptibility should be considered in choosing an agent[10] *(updated 7/12/2021)* ▪ Enrollment of hospitalized patients who require high-flow oxygen or mechanical ventilation was suspended at the recommendation of an independent data monitoring committee due to a potential safety signal and unfavorable risk/benefit profile (added 11/2/2020); after review, it was recommended that the trial can continue enrollment in all arms *(updated 11/17/2020)* ▪ Intranasal delivery of the antibody therapy via adeno-associated virus vectors is being investigated *(added 12/6/2020)* ▪ Neutralizing titers against the India variant (B.1.617) were decreased about 5-fold in an *in vitro* study[26] *(added 5/20/2021)* ▪ Does not appear to maintain efficacy against **Omicron** variant[48-50] *(added 12/22/2021)* **Pregnancy:** *(updated 11/23/2020)* ▪ Insufficient data on use during pregnancy ▪ Human IgG1 antibodies can cross the placenta; therefore, casirivimab and imdevimab have the potential to be transferred from the mother to the fetus

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
REGN-COV2 (continued)	**Design:** phase 3 randomized, controlled trial ▪ REGEN-COV 8000 mg plus usual care vs usual care alone **Results:** ▪ All-cause mortality reduced by 20% in seronegative patients with addition of REGEN-COV to usual care vs usual care alone (24% of patients in REGEN-COV group died vs 30% in the usual care group by day 28; rate ratio 0.8 95% CI 0.70-0.91; p=0.001) ▪ When seropositive patients (and those with unknown status) were included, there was no significant difference in 28-day mortality between the groups (20% of patients in REGEN-COV group died vs 21% in the usual care group; rate ratio 0.96; 95% CI 0.86-1.03; p=0.17) **Limitations:** not yet published or peer-reviewed		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
AZD7442 **Tixagevimab (AZD8895) and Cilgavimab (AZD1061)** ***Evusheld* (AstraZeneca)** *(updated 2/28/2022)* **Dosage[47]:** *(updated 2/28/2022)* ▪ 300 mg of tixagevimab and 300 mg of cilgavimab given IM (as consecutive injections as separate sites) every 6 months while SARS-CoV-2 is in circulation • FDA authorized increased dosage from 150 mg to 300 mg • patients who have already received 150-mg doses of the two drugs should receive an additional 150 mg of each as soon as possible ▪ Preferred administration site is the gluteal muscle ▪ Monitor in a healthcare setting for at least 1 hour after injection ▪ Supplied in cartons containing one 150 mg/1.5 mL vial of tixagevimab and one 150 mg/1.5 mL vial of cilgavimab	▪ Phase 1 dose-escalation trial ongoing in the UK[3] ▪ Phase 3 trials underway: 1 trial for prevention of COVID-19 is expected to enroll ~5000 participants and another trial for post-exposure prophylaxis and pre-emptive treatment is expected to enroll ~1100 subjects; additional trials for treatment expected to enroll ~4000 subjects *(updated 11/29/2020)* **STORM CHASER 2021[33]** *(updated 6/16/2021)* **Population:** unvaccinated adults with confirmed exposure to a person with SARS-CoV-2 infection in the previous 8 days (n=1121) **Design:** phase 3 randomized, double-blind, placebo-controlled trial ▪ Single IM dose of AZD7442 vs placebo for post-exposure prevention of COVID-19 **Results:** ▪ Risk of developing SARS-CoV-2 infection was reduced 33% with AZD7442 compared to placebo, not a statistically significant difference (95% CI -26, 65) ▪ 23 cases (23/749) occurred in the treatment group vs 17 cases (17/372) in the placebo group ▪ In a planned subgroup analysis of PCR negative participants, the risk of developing SARS-CoV-2 was reduced 73% compared to placebo (95% CI 27, 90)	▪ The most common adverse effects in phase 3 trial were headache (6%) and fatigue (4%) ▪ Rates of overall and serious adverse events in antibody and placebo groups were similar ▪ In a post-hoc analysis there were more serious cardiac adverse events (e.g. myocardial infarction, cardiac failure, arrhythmia) in the antibody group than in the placebo group (0.6% vs 0.2%); 1 person in the antibody group died of myocardial infarction; no clear temporal relationship between drug administration and adverse cardiac events; causality not established	▪ Investigational combination of 2 SARS-CoV-2 neutralizing antibodies (AZD8895 [tixagevimab] and AZD1061 [cilgavimab]) that bind to distinct parts of the SARS-CoV-2 spike protein ▪ Discovered at Vanderbilt University Medical Center ▪ AstraZeneca proprietary technology being used to extend the half-life ▪ FDA issued Emergency Use Authorization (EUA) for tixagevimab and cilgavimab *(Evusheld)* administered together for pre-exposure prophylaxis (of COVID-19 in adults and children ≥12 years old and ≥40 kg who are moderately to severely immunocompromised and may not mount an adequate response to COVID-19 vaccination or have a history of severe adverse reactions to a COVID-19 vaccine and/or components of those vaccines; it is not authorized for use in persons with current SARS-CoV-2 infection or in persons recently exposed to an individual infected with SARS-CoV-2[46] *(added 12/10/2021)* ▪ Effective against Delta variant ▪ Does not appear to maintain efficacy against **Omicron** variant[48-50] *(added 12/22/2021)* ▪ *In vitro* data showed decreased neutralizing activity against Omicron variants BA.1 (by 12- to 30-fold vs the ancestral virus) and BA.1.1 (by 176-fold) and BA.2 (by 5.4-fold); FDA recommended increased dosage (to 300 mg) based on this data[47] *(added 2/27/2022)*

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
AZD7442 **Tixagevimab/cilgavimab (continued)**	▪ In a post-hoc analysis of PCR-negative subjects, the risk reduction was 51% up to 7 days following dosing and 92% more than 7 days after dosing **Limitations:** not yet published or peer reviewed **AstraZeneca/FDA Fact Sheet PROVENT 2021**[42,43,47] *(added 10/4/2021; updated 12/10/2021)* **Population:** adults at increased risk for inadequate response to immunization or increased risk for SARS-CoV-2 infection; at screening participants were unvaccinated and had a negative SARS-CoV-2 serology test (n=5197) **Design:** phase 3, randomized, double-blind, placebo-controlled ▪ Subjects randomized 2:1 to tixagevimab 150 mg plus cilgavimab 150 mg IM x 1 dose or placebo for prevention of COVID-19 **Results:** ▪ Median follow-up 83 days ▪ Symptomatic COVID-19 within 183 days of randomization occurred in 8 patients (0.2%) who received the antibodies and 17 (1.0% who received placebo (HR 0.23; 95% CI 0.10-0.54) ▪ Post-hoc analysis with median follow-up of 6.5 months (0.3% with antibodies vs 1.8% with placebo; HR 0.17; 95% CI 0.09-0.34)		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
AZD7442 **Tixagevimab/cilgavimab (continued)**	▪ No severe or critical COVID-19 events in antibody group vs 5 in placebo group **Limitations:** not peer reviewed or published **<u>AstraZeneca TACKLE 2021</u>[44]** *(added 10/11/2021)* **Population:** adult outpatients with mild to moderate COVID-19 who were symptomatic for ≤7 days (n=903) **Design:** phase 3, randomized, double-blind, placebo-controlled trial ▪ AZD7442 600 mg IM x 1 dose vs placebo **Results:** ▪ Risk of severe COVID-19 or death from any cause reduced 50% with AZD7442 vs placebo; 18 events reported in AZD7442 group and 37 events reported in placebo group ▪ In patients who were treated within 5 days of symptom onset risk was reduced by 67%; 9 events occurred in AZD7442 group and 27 events occurred in placebo group **Limitations:** not published or peer reviewed		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
VIR-7831 (Sotrovimab) (Vir Biotechnology/GSK) *(updated 3/29/2022)* **Dosage:** ▪ 500 mg IV infusion over 30 minutes ▪ Patients should be monitored for hypersensitivity reactions during infusion and for at least 1 hour after completion ▪ Should be given as soon as possible after a SARS-CoV-2 positive test result and within 10 days of COVID-19 symptom onset ▪ Patients should be treated in facility staffed and equipped to manage anaphylaxis	**COMET-ICE 2021**[20] *(added 3/14/2021; updated 3/26/2021; updated 10/30/2021)* **Population:** outpatient adults with symptomatic COVID-19 (≤5 days after the onset of symptoms) at high risk of hospitalization (n=583) **Design:** ongoing, randomized, double-blind, phase 3 trial ▪ VIR-7831 single 500 mg infusion vs placebo **Results:** ▪ Independent data monitoring committee recommend stopping early for efficacy ▪ Disease progression leading to hospitalization or death occurred in 3 patients (1%) in patients treated with sotrovimab and 21 patients (7%) given placebo (relative risk reduction 85%; 97.24% confidence interval 44-96; p=0.002) ▪ Death from any cause occurred in 1 patient in the placebo group and 0 patients in the sotrovimab group **Limitations:** interim analysis, not large enough to detect rare adverse events; only 3 hospitalizations in treatment group so not possible to determine reasons for treatment failure	▪ Infusion reactions and hypersensitivity reactions, including anaphylaxis, have been reported[29] ▪ Rash (2%) and diarrhea (1%) reported in COMET-ICE[28]	▪ Monoclonal antibody against SARS-CoV-2; may block viral entry into healthy cells and clear infected cells ▪ Binds to an epitope that is shared by SARS-CoV-1 and -2; may have a higher barrier to resistance ▪ Designed to achieve high lung concentrations ▪ Intramuscular formulation in development ▪ FDA has restricted sotrovimab use; it is not authorized for use in regions where the BA.2 (Omicron) variant of SARS-CoV-2 causes >50% of COVID-19 cases. As of 3/29/2022, this was the case in HHS Regions 1 (New England) and 2 (New York, New Jersey, Puerto Rico, US Virgin Islands)[54] *(added 3/29/2022)* ▪ FDA issued an emergency use authorization (EUA) for sotrovimab for treatment of mild to moderate COVID-19 in adults and pediatric patients ≥12 years old weighing ≥40 kg with results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death[28] (*added 5/27/2021)* ▪ Not authorized for use in patients who are hospitalized or require oxygen therapy for COVID-19; monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
VIR-7831 (Sotrovimab) (continued)			oxygen or mechanical ventilation[28] *(added 5/27/2021)* ▪ NIH guidelines recommend use of casirivimab plus imdevimab or sotrovimab for treatment of patients with mild to moderate COVID-19 not requiring hospitalization or supplemental oxygen who are at high risk of clinical progression[8] *(updated 7/12/2021)* ▪ In situations where logistical constraints exist and eligible patients must be triaged, NIH guidelines suggest:[8] *(added 9/7/2021)* • Treatment of COVID-19 be prioritized over post-exposure prophylaxis • Prioritizing unvaccinated or incompletely vaccinated persons at high risk of progressing to severe COVID-19 and vaccinated persons not expected to mount an adequate immune response (e.g., immunocompromised persons) over vaccinated persons who are expected to mount an adequate immune response ▪ IDSA guidelines suggest bamlanivimab/etesevimab or casirivimab/imdevimab or sotrovimab among ambulatory patients with mild to moderate CO VID-19 at high risk for progression to severe disease; local variant susceptibility should be considered in choosing an agent[10] *(updated 7/12/2021)* ▪ In vitro data suggest VIR-7831 may retain activity against UK, South Africa, and Brazil variants[22] *(added 3/26/2021)*

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
			▪ Neutralization potency of sotrovimab against Omicron variant decreased but preclinical findings suggest it may still maintain efficacy against **Omicron** variant[48-50] *(updated 12/22/2021)* ▪ *In vitro* 16-fold reduction in susceptibility to Omicron subvariant BA.2[29] *(added 2/29/2022)* **Pregnancy:** *(updated 5/27/2021)* ▪ Insufficient data on use during pregnancy ▪ Human IgG1 antibodies can cross the placenta; therefore, sotrovimab has the potential to be transferred from the mother to the fetus
LY-CoV1404 (Bebtelovimab) **(Eli Lilly)** *(updated 2/15/2022)* **Dosage:**[52] ▪ 175 mg IV injection over at least 30 seconds ▪ Administer as soon as possible after positive results of SARS-CoV-2 viral testing and within 7 days of symptom onset ▪ Patients should be observed for 1 hour after completion of injection	**BLAZE-4 2022**[53] **Population:** ▪ outpatients with COVID-19 symptoms who had undergone confirmatory testing for SARS-CoV-2 infection within the previous 3 days (n=706); 1 cohort included 380 unvaccinated, mostly low risk adults, another cohort had 150 mostly high-risk patients, and a single-arm cohort included 176 mostly high-risk patients **Design:** phase1/2, randomized, placebo-controlled, single-dose clinical trial ▪ Bebtelovimab alone, bebtelovimab plus bamlanivimab and etesevimab, or placebo (in low-risk cohort only) **Results:**	**Adverse Reactions**[53] ▪ Infusion reactions and hypersensitivity reactions, including anaphylaxis, could occur ▪ Most common were infusion-related reactions, pruritus, and rash	▪ Neutralizing IgG1 monoclonal antibody directed against spike protein of SARS-CoV-2 ▪ *In vitro* retained activity against Omicron and the Omicron subvariant BA.2 ▪ FDA issued an emergency use authorization (EUA) for bebtelovimab for treatment of mild to moderate COVID-19 in adults and pediatric patients ≥12 years old weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom other treatment options are not accessible or clinically appropriate[52]

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
▪ Administer only in healthcare settings equipped to treat severe infusion reactions, including anaphylaxis	▪ Most patients infected with Delta (49.8%) and Alpha (28.6%); trial conducted before emergence of Omicron ▪ In the low-risk cohort, persistently high viral load at day 7(the primary endpoint) was present in 14% who received bebtelovimab alone, 13% who received all three antibodies, and 21% who received placebo; these differences were not statistically significant; median time to symptom resolution shorter with bebtelovimab vs placebo (6 days [95% CI 5-7 days] vs 8 days [95% CI 7-9 days]); hospitalization due to COVID-19 occurred in <3% of patients in all three groups. ▪ In the high-risk cohort, the two groups had similar rates of hospitalization due to COVID-19 (3% with bebtelovimab alone vs 4% with combination therapy) and reductions in mean viral load; median time to symptom resolution after administration of bebtelovimab alone was 7 days ▪ In the single-arm cohort of high-risk patients, 3 patients (1.7%) required hospitalization due to COVID-19; median time to symptom resolution was 8 days **Limitations:** not yet published or peer-reviewed		▪ Not authorized for use in patients who are hospitalized or require oxygen therapy for COVID-19; monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation[52] **Pregnancy:** [53] ▪ Insufficient data on use during pregnancy ▪ Human IgG1 antibodies can cross the placenta; therefore, bebtelovimab has the potential to be transferred from the mother to the fetus

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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
GM-CSF Inhibitor			
Lenzilumab (Humanigen) *(added 7/12/2021)*	**Z Temesgen et al. medRxiv 2021**[1,3] **Population:** adults hospitalized with COVID-19 pneumonia (≤ 94% oxygen saturation on room air and/or requiring supplemental oxygen, but not invasive mechanical ventilation) (n=520) **Design:** phase 3 randomized, double-blind, placebo-controlled trial ▪ Lenzilumab 600 mg IV x 3 infusions 8 hours apart vs placebo **Results:** ▪ Likelihood of survival without need of invasive mechanical ventilation was 54% greater with lenzilumab compared to standard care alone ▪ Kaplan-Meier estimate for invasive mechanical ventilation and/or death was 15.6% in lenzilumab arm vs 22.1% in placebo arm ▪ Mortality 9.6% with lenzilumab and 13.9% with standard care (HR: 1.39; 05% CI 0.82-2.39; p=0.239) ▪ 94% of patients received, corticosteroids, 72% received remdesivir, and 69% received both (balanced in both study arms) **Limitations:** not peer reviewed or published; not powered for mortality		▪ Recombinant monoclonal antibody targeting human GM-CSF ▪ GM-CSF depletion may prevent cytokine release syndrome ▪ Humanigen plans to submit to FDA for EUA ▪ NIH guidelines state there is insufficient evidence to recommend either for or against use of GM-CSF inhibitors for treatment of patients hospitalized with COVID-19[2] *(added 7/12/2021)*

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2. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed July 12, 2021.
3. Z Temesgen et al. Lenlizumab efficacy and safety in newly hospitalized COVID-19 subjects: results from the Live-Air phase 3 randomized double-blind placebo-controlled trial. medRxiv 2021 (epub).

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Glutathione and N-acetylcysteine			
GLUTATHIONE **Dosage:** 2 g IV/PO used in case report[1] **N-ACETYLCYSTEINE (NAC; GLUTATHIONE PRECURSOR)** 6 g/day IV[2] *(Added 4/28/2020)*	No clinical trial results available Trial recruiting in the US using NAC in severely or critically ill patients[2] **R Horowitz et al. Resp Med Case Rep 2020[1] Case Report** **Population:** Two patients with COVID-19 pneumonia **Regimen:** 2 g IV/PO glutathione	**Adverse Effects:** ▪ Nausea, vomiting, other gastrointestinal symptoms, and rash, with or without fever ▪ Anaphylactoid reactions to IV acetylcysteine, including rash, pruritus, angioedema, bronchospasm, tachycardia, and hypotension have occurred. **Pregnancy:** ▪ Acetylcysteine crosses the placenta	▪ Intracellular anti-oxidant with possible antiviral properties ▪ One researcher has hypothesized that glutathione deficiency is risk factor for severe COVID-19 illness ▪ NAC has been proposed for treatment of multiple respiratory conditions and viral illnesses

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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Stem Cell Therapy			
MESENCHYMAL STEM CELL THERAPY *(updated 7/21/2020)*	**Remestemcel-L *(Ryoncil)*** ▪ 10 patients with ARDS treated with remestemcel-L under the FDA compassionate use program with encouraging results ▪ Randomized clinical trial to be conducted at Mount Sinai in NY ▪ **Results:** Dyspnea improved within 1 hour of administration **Leng et al. Aging Dis 2020[1]** *(updated 7/21/2020)* **Population:** hospitalized patients with COVID-19 pneumonia in China (n=10) **Design:** pilot trial; 7 patients (1 critical, 4 severe, 2 common-type illness) treated with mesenchymal stem cells and 3 (severe illness) treated with placebo **Results:** ▪ pulmonary function and symptoms improved within 2 days of transplantation ▪ All patients in the treatment group recovered **Limitation:** small pilot study **Shu et al. Stem Cell Res Ther 2020[6]** *(added 10/13/2020)* **Population:** hospitalized patients with severe COVID-19 who did not respond to 7-10 days of standard care in China (n=41) **Design:** single-center, open-label controlled trial	**Adverse Effects:** ▪ Risks in patients with COVID-19 not established ▪ Possible product contamination, infusion site reactions, thrombosis, infection, tumor growth ▪ Remestemcel-L well tolerated in trials reported by the manufacturer in children with GVHD	▪ May mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease by decreasing production of proinflammatory cytokines, increased production of anti-inflammatory cytokines, and recruitment of anti-inflammatory cells ▪ FDA granted an investigational new drug (IND) application for use of remestemcel-L (*Ryoncil* - Mesoblast), an allogenic mesenchymal stem cell therapy, to treat patients with ARDS caused by COVID-19[2] *(updated 7/21/2020)* ▪ FDA approved an expanded access protocol for compassionate use of remestemcel-L in children with multisystem inflammatory syndrome associated with COVID-19[3] *(updated 7/21/2020)* ▪ NIH guidelines recommend against use of mesenchymal stem cells, except in a clinical trial[4] *(updated 7/21/2020)* ▪ FDA has warned about safety concerns with use of unapproved or illegal stem cell therapies[5] *(updated 7/21/2020)* **Pregnancy:** ▪ There are inadequate data on the use of stem cell therapies in pregnant women

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
MESENCHYMAL STEM CELL THERAPY (continued)	▪ Human umbilical cord mesenchymal stem cells (n=12) vs standard care (n=29) **Results:** ▪ 0 patients in the stem cell group progressed to critical illness vs 4 patients in the control group ▪ 3 patients in the control group died **Limitation:** small study; due to lack of sufficient stem cells some patients were not randomized to the treatment arm		

1. Z Leng et al. Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 2020; 11:216.
2. Press Release. GlobeNewswire. FDA clears investigational new drug application for mesoblast to use remestemcel-L in patients with acute respiratory distress syndrome caused by COVID-19. Available at: https://www.globenewswire.com/news-release/2020/04/06/2011944/0/en/FDA-CLEARS-INVESTIGATIONAL-NEW-DRUG-APPLICATION-FOR-MESOBLAST-TO-USE-REMESTEMCEL-L-IN-PATIENTS-WITH-ACUTE-RESPIRATORY-DISTRESS-SYNDROME-CAUSED-BY-COVID-19.html. Accessed July 21, 2020.
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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Vasoactive Intestinal Peptide			
AVIPTADIL *(Zyesami)* *(added 6/8/2021)*	**NeuroRX 2021**[1] **Population:** critically ill adults with COVID-19 (n=196) **Design:** phase 2b/3 randomized, double-blind, placebo-controlled trial ▪ IV aviptadil vs placebo **Results:** ▪ In overall population: met primary endpoint of successful recovery from respiratory failure at day 28 (p=0.014) and day 60 (p=0.013) ▪ In patients treated with high flow nasal cannula (HFNC; n=127), chance of successful recovery was 71% with aviptadil vs 48% with placebo by day 28 (p=0.017) and 75% with aviptadil vs 55% with placebo by day 60 (p=0.036) ▪ 84% of HFNC patients given aviptadil were alive at day 60 compared to 60% of those given placebo (p=0.007) **Limitations:** company press release; not published or peer reviewed	**Adverse Effects:** ▪ In studies in healthy volunteers, alterations in blood pressure, heart rate, or ECG have been reported	▪ Anti-inflammatory and anti-cytokine activity in animal models of respiratory distress, acute lung injury and inflammation ▪ Binds to alveolar type II (ATII) cell in the lung and stimulations production of surfactant; ATII cells contain ACE2 receptors which are a route of entry for SARS-CoV-2; infection of ATII cells decreases surfactant production and increases production of inflammatory cytokines ▪ Clinical trial evaluating use of aviptadil for moderate and severe COVID-19 is ongoing ▪ The manufacturer has submitted to FDA for an EUA

1. News Release. NeuroRx announces Zyesami (aviptadil, RLF-100) met the primary endpoint of its phase 2b/3 clinical trial and also demonstrated a meaningful benefit in survival from COVID-19. March 29, 2021. Available at: https://www.prnewswire.com/news-releases/neurorx-announces-zyesami-aviptadil-rlf-100-met-the-primary-endpoint-of-its-phase-2b3-clinical-trial-and-also-demonstrated-a-meaningful-benefit-in-survival-from-critical-covid-19-301257291.html. Accessed June 8, 2021.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Oleandrin			
OLEANDRIN *(added 8/19/2020)*	▪ No published *in vivo* data on use of oleandrin for treatment or prevention of COVID-19 ▪ An *in vitro* study (not peer reviewed) suggested that oleandrin may inhibit SARS-CoV-2 replication[1]	**Adverse Effects:** ▪ Toxicity includes nausea, vomiting, abdominal pain, diarrhea (possibly bloody stools), anorexia, arrhythmias, drowsiness, tremors, seizures, coma, death ▪ Toxicity occurs several hours after ingestion	▪ There are no available data to support use of oleandrin for COVID-19 and it can have serious, life-threatening toxicity; avoid use ▪ Toxic cardiac glycoside from the *Nerium oleander* plant ▪ All parts of the oleander plant are toxic; it is responsible for cases of accidental poisoning worldwide

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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Corticosteroids (systemic)			
CORTICOSTEROIDS (DEXAMETHASONE, PREDNISONE, METHYLPREDNISOLONE, HYDROCORTISONE) *(updated 7/12/2021)* **Dexamethasone:** ▪ 6 mg PO or IV daily for up to 10 days or hospital discharge[3] ▪ If dexamethasone is not available, equivalent doses of other corticosteroids such as prednisone 40 mg (once daily or in two divided doses), methylprednisolone 32 mg (once daily or in two divided doses), or hydrocortisone 160 mg (in two to four divided doses) may be used[3,4]	**RECOVERY Trial 2020[1]** **Population:** hospitalized patients in the UK (n=6425) **Design:** ▪ Randomized, controlled, open-label, adaptive, platform trial designed to evaluate a range of treatments for COVID-19 including dexamethasone ▪ Dexamethasone 6 mg PO or IV once daily (n=2104) x 10 days vs usual care (n=4321) **Results:** 28-day mortality rates (dexamethasone vs usual care) ▪ Overall: 22.9% vs 25.7% (p<0.001) ▪ Patients on invasive mechanical ventilation: 29.3% vs 41.4% (rate ratio 0.64; 95% CI 0.51-0.81) ▪ Oxygen without invasive mechanical ventilation: 23.3% vs 26.2% (rate ratio 0.82; 95% CI 0.72-0.94) ▪ No respiratory support at randomization: 17.8% vs 14.0% (rate ratio 1.19; 95% CI 0.91-1.55) **Limitation:** preliminary results; open-label study	**Adverse Effects:** hyperglycemia, insomnia, adrenal suppression, delirium, depression, mania ▪ Prolonged use can increase the risk of reactivation of latent infections such as hepatitis B virus, herpesvirus infections, strongyloidiasis, tuberculosis **Drug Interactions:** ▪ Dexamethasone induces CYP3A4 and P-gp and may decrease concentrations of drugs that are substrates of CYP3A4 or P-gp ▪ Causes hyperglycemia; may decrease the efficacy of antihyperglycemic drugs	▪ Anti-inflammatory effects may modulate immune-mediated lung damage ▪ Authors of RECOVERY trial state that treating 8 ventilated patients or 25 patients requiring oxygen would prevent 1 death[2] ▪ NIH guidelines recommend that patients recently hospitalized (i.e., within the previous 3 days) with COVID-19 who have rapidly increasing oxygen needs, require high-flow oxygen therapy or noninvasive ventilation and have increased markers of inflammation receive dexamethasone with or without remdesivir, plus either tocilizumab or baricitinib. For patients hospitalized who require invasive mechanical ventilation or ECMO, dexamethasone is recommended; for those who were admitted to the ICU ≤24 hours previously and require invasive mechanical ventilation or ECMO, dexamethasone plus tocilizumab is recommended[3] *(updated 7/12/2021)* ▪ NIH guidelines recommend against use of dexamethasone in hospitalized patients who do not require supplemental oxygen[3] *(updated 7/12/2021)* ▪ NIH guidelines recommend use of oral dexamethasone in patients who are discharged from the ED despite new or

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CORTICOSTEROIDS (continued)	**Keller et al. J Hosp Med 2020[5]** *(added 7/27/2020)* **Population:** hospitalized patients in NYC (n=1806) **Design:** observational study ▪ patients treated with steroids within 48 hrs of admission (n=148) compared to those who did not receive steroid treatment **Results:** ▪ patients in the steroid group were more likely to have COPD, asthma, rheumatoid arthritis, or lupus, or to have taken steroids in the year before admission than those in the control group ▪ overall, early use of glucocorticoids was not associated with mortality or mechanical ventilation ▪ in patients with CRP ≥ 20 mg/dL, glucocorticoid treatment was associated with a significant reduction in risk of mortality or mechanical ventilation ▪ in those with CRP < 10 mg/dL, glucocorticoid use was associated with a significant increase in the risk of mortality or mechanical ventilation **Limitations:** observational data **Tomazini et al. JAMA 2020[6]** **The CoDEX Trial** *(added September 3, 2020)* **Population:** ICU patients w/ mod-severe ARDS (n=299) **Design:** ▪ randomized, open-label trial		increasing need for supplemental oxygen; dexamethasone should be continued for the duration of supplemental oxygen (or up to 10 days)[3] *(added 7/12/2021)* ▪ IDSA guidelines recommend use of dexamethasone for hospitalized patients with critical illness (mechanical ventilation, ECMO, ARDS)[4] *(updated 10/14/2020)* ▪ IDSA guidelines suggest use of dexamethasone for hospitalized patients with severe illness (patients with SpO_2≤94% on room air, including patients on supplemental oxygen)[4] *(updated 10/14/2020)* ▪ NIH and IDSA recommend against use of dexamethasone for treatment of COVID-19 in patients who do not require supplemental oxygen *(updated 10/14/2020)*[3,4] ▪ NIH recommends against use of dexamethasone or other systemic corticosteroids in outpatients in the absence of another indication[3] *(added 4/23/2021)* ▪ WHO recommends systemic corticosteroids (dexamethasone 6 mg PO or IV daily or hydrocortisone 50 mg IV q8h x 7-10 days) to treat patients with severe and critical COVID-19[10] *(added 9/3/2020)* ▪ WHO recommends against use of systemic corticosteroids in patients with non-severe disease[10] *(added 9/3/2020)*

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CORTICOSTEROIDS (continued)	▪ dexamethasone 20 mg IV daily x 5 days, then 10 mg daily x 5 days or until hospital discharge plus standard care vs standard care **Results:** ▪ patients in dexamethasone group had significantly more ventilator-free days (days alive and free of mechanical ventilation) compared to control group (6.6 vs 4.0) ▪ no significant difference in all-cause mortality at 28 days, ICU-free days durimg first 28 days, mechanical ventilation duration at 28 days **Limitations:** ▪ open-label ▪ 35% of patients in control group received steroids ▪ trial was underpowered to detect significant differences in secondary endpoints **PF Dequin et al. JAMA 2020[7]** *(added September 3, 2020)* **Population:** ICU patients w/ respiratory failure **Design:** ▪ randomized double-blind trial (n=149) ▪ low-dose hydrocortisone vs placebo **Results:** ▪ trial ended early ▪ no significant difference in rate of treatment failure (death or respiratory support) at day 21		**Pregnancy:** ▪ NIH recommends use of dexamethasone in pregnant women with COVID-19 who are mechanically ventilated or who require supplemental oxygen but are not mechanically ventilated[3] *(added 7/20/2020)* ▪ Monitor for hypoadrenalism in newborns of mothers who received substantial doses

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CORTICOSTEROIDS (continued)	(42.1% w/ low-dose hydrocortisone vs 50.7% w/ placebo **Limitations:** ▪ trial stopped early so underpowered to detect significant differences **REMAP-CAP JAMA 2020[8]** *(added September 3, 2020)* **Population:** ICU patients w/ respiratory or CV support (n=384) **Design:** ▪ open-label adaptive platform trial ▪ IV hydrocortisone 50 or 100 mg q6h x 7 days vs hydrocortisone 50 mg q6h when shock was clinically evident vs no hydrocortisone **Results :** ▪ No difference in median organ-support free days in patients treated with fixed-dose or shock-dependent hydrocortisone compared to no hydrocortisone (all 0 days) ▪ Bayseian model found both hydrocortisone regimens probably superior to no hydrocortisone **Limitations:** ▪ trial stopped early so underpowered to detect significant differences		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CORTICOSTEROIDS (continued)	**WHO JAMA 2020[9]** *(added September 3, 2020)* **Population:** critically ill patients (n=1703) **Design:** ▪ meta-analysis ▪ dexamethasone, hydrocortisone or methylprenisolone vs placebo or usual care **Results:** ▪ 28-day all-cause mortality was lower in those treated with a corticosteroid (OR 0.64 for dexamethasone; 0.69 0.69 for hydrocortisone; 0.91 for methylprednisolone) **L Pasin et al. J Cardiothorac Vasc Anesth 2021[11]** *(added 1/30/2021)* **Population:** hospitalized adult patients with COVID-19 with acute hypoxemic failure (n=7692) **Design:** meta-analysis of 5 randomized controlled trials of corticosteroids vs a comparator **Results:** ▪ Overall mortality was statistically significantly lower in patients treated with corticosteroids than with controls (26% vs 28%; RR=0.89, CI 0.82-0.96; p=0.003) ▪ In patients who required mechanical ventilation, mortality was lower than with controls (42% vs 48%; RR=0.85, 95% 0.72-1.00; p=0.05; NNT=19) ▪ In patients not requiring oxygen, mortality was increased (17% vs		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CORTICOSTEROIDS (continued)	13%; RR 1.23, 95% CI 1.00-1.62; p=0.05; NNH=29)) ▪ Risk of need for mechanical ventilation was lower in corticosteroid group than in control group (5% vs 7%; RR=0.74, CI 0.59-0.92; p=0.007) **Limitations:** meta-analysis; small number of trials, heterogeneity of studies **K Ranjbar et al. BMC Infect Dis 2021**[12] *(added 6/8/2021)* **Population**: hospitalized patients with COVID-19 in Iran (n=86) Design: randomized, triple-blinded trial ▪ Methylprednisolone 2 mg/kg/day vs dexamethasone 6 mg/day **Results:** ▪ Clinical status was statistically significantly better with methylprednisolone compared to dexamethasone at day 5 and day 10 ▪ Mean length of hospital stay was 7.43 days with methylprednisolone and 5.47 days with dexamethasone ▪ Mechanical ventilation was needed in 18.2% of patients given methylprednisolone and 38.1% of those given dexamethasone **Limitations:** small sample size, more potent methylprednisolone dose		

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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Inhaled Corticosteroids			
INHALED CORTICOSTEROIDS (ICSs) *(updated 8/23/2021)* ▪ **Ciclesonide *(Alvesco)*** ▪ **Budesonide *(Pulmicort Flexhaler)***	**Iwabuchi et al. J Infect Chemother 2020[1]** **Population:** hospitalized patients with poor oxygenation and CT findings in Japan (n=3) **Design:** case series: all given inhaled ciclesonide **Results:** favorable outcomes in all **Limitations:** cases series of 3 patients **Schultze et al. medRxiv 2020[2]** **Population:** asthma (n=817,973) and COPD (n=148,588) patients in the UK **Design:** cohort study using linked electronic health records (OpenSAFELY platform); compared patients using an ICS to those taking other drugs for COPD/asthma **Results:** ▪ COPD: risk of death higher in patients using ICSs than in those use a long-acting beta agonist and a long-acting muscarinic antagonist (adjusted HR = 1.38; 95% CI 1.08-1.75) ▪ Asthma: risk of death higher in patients using ICSs than in those using only a short-acting beta agonist (adjusted HR = 1.52; 95% CI 0.82-1.49) **Limitations:** observational; not peer reviewed; possible confounding **Covis Pharma 2021[6]** *(added 4/19/2021)* **Population:** outpatients ≥12 years old with symptomatic COVID-19 (n=400)	**Adverse Effects:** ▪ local adverse effects include oral candidiasis (thrush), dysphonia, and reflex cough and bronchospasm ▪ high doses may cause HPA axis suppression, changes in bone density, and development of cataracts or glaucoma ▪ increases the risk of pneumonia in patients with COPD ▪ rinse mouth after use to reduce the risk of local adverse effects **Drug Interactions:** ▪ Significant drug interactions less likely with inhaled corticosteroids than with systemic formulations ▪ Strong CYP3A4 inhibitors may increase serum concentrations of inhaled corticosteroids	▪ Hypothesized that inhaled corticosteroids delivered to the lungs may inhibit adhesion and inflammatory effects of cytokines released in response to the virus ▪ Ciclesonide may have anti-viral activity against SARS-CoV-2[3] ▪ NIH guidelines recommend that patients with COVID-19 who are using inhaled corticosteroids for treatment of asthma or COPD should not discontinue treatment[4] ▪ No data available on use of inhaled corticosteroids for treatment of COVID-19 from randomized controlled trials **Pregnancy:** ▪ Low-to-moderate doses appear to be safe for use during pregnancy[5]

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	Design: phase 3, randomized, double-blind, placebo-controlled trial ▪ Ciclesonide metered-dose inhaler (MDI) vs placebo **Results:** ▪ The primary endpoint of time to alleviation of COVID-19-related symptoms (defined as symptom-free for continuous period of ≥24 hours by day 30) was not statistically significantly different between the ciclesonide and placebo groups (p=0.5502) **Limitations:** not published or peer reviewed **Yu et al. Lancet 2021[7]** *(added 8/23/2021)* **Population:** outpatients in the UK with suspected COVID-19 at risk of an adverse outcome (≥65 years old or ≥50 years old with comorbidities) who were symptomatic for up to 14 days (n=4700) **Design:** randomized, controlled, open-label, adaptive platform trial ▪ Usual care plus inhaled budesonide (800 mcg bid x 14 days) vs usual care alone vs usual care plus other interventions **Results:** ▪ Time to self-reported recovery 11.8 days with budesonide and 14.7 days with usual care (hazard ratio 1.21, 95% Bayesian credible interval [BCI] 1.08-1.36); met prespecified superiority threshold ▪ Rate of hospital admission or death was 6.8% with budesonide and 8.8% with usual care (odds ratio		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	0.75, 95% BCI 0.55-1.03); did not meet prespecified superiority threshold **Limitations:** open label, usual care may vary, limited population		

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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
IL-6 Inhibitors			
SARILUMAB – *KEVZARA*[1] (SANOFI/REGENERON) *(updated 9/7/2021)* **Dosage:** ▪ No clinical trial data yet ▪ Optimal dosage not established ▪ High and low IV doses are expected to be studied	▪ US-based phase 2 and 3 clinical trials ongoing[2] ▪ Preliminary results have suggested that the drug may have negative or no effects in patients with severe illness (on oxygen therapy, not on ventilator/in ICU), but may be beneficial in critically ill patients (on a ventilator/requiring ICU) *(updated May 4, 2020)* ▪ Phase 3 trials will continue to enroll critical patients only ○ U.S. phase 3 trial in mechanically ventilated patients has been stopped because the trial did not meet primary or key secondary endpoints and negative trends were found in a subgroup of critically ill patients who were not mechanically ventilated at baseline[11] *(updated 7/6/2020)* **AC Gordon et al. REMAP-CAP Trial. NEJM 2021[19]** *(added 1/11/2021; updated 2/27/2021)* **Population:** adults in the ICU with COVID-19 within 24 hours of starting respiratory or cardiovascular organ support (n=803; 353 tocilizumab, 48 sarilumab, 402 control) **Design:** ongoing, randomized, open-label, multifactorial, adaptive platform trial	**Adverse Effects:** ▪ Neutropenia, thrombocytopenia, serious infections, hypersensitivity reactions including anaphylaxis **Drug Interactions:** ▪ May normalize CYP enzyme formation; could increase metabolism and decrease serum concentrations of drugs with narrow therapeutic indices that are metabolized by CYP isozymes ▪ Hematologic toxicity may be additive with other drugs such as linezolid, clozapine, or azathioprine	▪ Monoclonal antibody that inhibits IL-6 receptors; may mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease ▪ NIH guidelines state there are insufficient data to recommend for or against use of sarilumab for treatment of COVID-19 in patients who are within 24 hours of admission to the ICU and require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO2/30 L/min oxygen flow)[3] *(updated 4/26/2021)* ▪ NIH guidelines recommend IV sarilumab as an alternative to IV tocilizumab only when IV tocilizumab is not available or not feasible to use[3] *(added 9/7/2021)* ▪ NIH guidelines recommend against use of sarilumab, except in a clinical trial, for treatment of COVID-19 in patients who do not require ICU-level care or are admitted to the ICU but do not require mechanical ventilation or high-flow oxygen[3] *(updated 2/5/2021)* ▪ UK Medicines & Healthcare products Regulatory Agency (MHRA) recommends clinicians consider use of tocilizumab or sarilumab (alternative) in adult patients admitted to the ICU with COVID-19 pneumonia[20] *(added 1/11/2021)* **Pregnancy:** ▪ Crosses the placenta, especially in the third trimester, and may affect the immune response in an exposed infant

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	▪ Tocilizumab 8 mg/kg, sarilumab 400 mg, or standard care **Results:** ▪ 610/654 patients who were enrolled after announcement of RECOVERY trial results received corticosteroids ▪ Median organ support-free days: 10 with tocilizumab, 11 with sarilumab, 0 with standard care ▪ In-hospital mortality: 27% in pooled IL-6 group and 36% in standard care group **Limitations:** open-label; standard care varied; small number of patients received sarilumab **WHO REACT Working Group. JAMA 2021**[28] *(added 7/15/2021)* **Population:** trials that included patients hospitalized for COVID-19 who were randomly assigned to receive an IL-6 antagonist or no IL-6 antagonist or other immunomodulator (except corticosteroids) (n=27 trials; 10,930 patients) **Design:** meta-analysis of 27 trials **Results:** ▪ Lower 28-day all-cause mortality with IL-6 inhibitor vs no IL-6 inhibitor ▪ By 28 days, 1407 death were reported among 6449 patients who received and IL-6 inhibitor and 1158 deaths among 4481 subjects not receiving an IL-6 inhibitor (OR 0.86; 95% CI 0.79-0.95; p=0.003)		▪ Parturition is associated with IL-6 increases in the cervix and myometrium; inhibition of IL-6 may lead to possible delays of parturition ▪ Not associated with embryotoxic or teratogenic effects when given in high doses to pregnant monkeys

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	▪ OR for tocilizumab was 0.83 (95% CI 0.74-0.92, p<0.001) and 1.08 for sarilumab (95% CI 0.86-1.36, p=0.52) ▪ In those receiving corticosteroids, OR was 0.77 (95% CI 0.68-0.87) for tocilizumab and 0.92 (95% CI 0.61-1.38) for sarilumab; most trials of sarilumab patients not on corticosteroids **Limitations:** meta-analysis, some trials not peer-reviewed; some trials ongoing		
TOCILIZUMAB – *ACTEMRA*[4] (GENENTECH) *(updated 7/15/2021)* **Dosage:**[5] ▪ <30 kg: 12 mg/kg IV once ▪ ≥ 30 kg: 8 mg/kg IV once ▪ Max dose 800 mg/infusion ▪ Infuse over 1 hour ▪ Optimal timing of administration is unclear	**Zhou et al. Lancet 2020**[6] **Population:** hospitalized patients in China (n=191) **Design:** retrospective study **Results:** elevated levels of IL-6 were associated with severe illness and death **Xu et al 2020**[7] **Population:** hospitalized patients with severe or critical illness and elevated IL-6 levels; (n=20) **Design:** case series; tocilizumab added to standard care **Results:** ▪ improvement in fever (all patients), oxygen requirement (75% of patients), reduction in CRP levels (in 82.4% of patients), lung opacities on CT scan improved (90.5% of patients) **Limitations:**	**Adverse Effects:** ▪ Constipation, anxiety, diarrhea, insomnia, hypertension, nausea, neutropenia, thrombocytopenia, serious infections, GI perforation, hepatotoxicity, hypersensitivity reactions including anaphylaxis ▪ Increased risk of fungal infections in critically ill patients with COVID-19 **Drug Interactions:** ▪ May normalize CYP enzyme formation; could increase metabolism and decrease serum concentrations of drugs with narrow therapeutic indices that are metabolized by CYP isozymes ▪ Hematologic toxicity may be additive with other drugs such as linezolid, clozapine, or azathioprine	▪ Monoclonal antibody that inhibits IL-6 receptors; may mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease ▪ Surviving Sepsis Campaign guidelines state that there is insufficient evidence to make a recommendation on use of tocilizumab[8] ▪ Infectious Diseases Society of America (IDSA) recommends use of tocilizumab and a corticosteroid in all hospitalized patients with progressive severe (SpO2 ≤94% on room air) or critical (requiring mechanical ventilation or ECMO) COVID-19 and increased markers of inflammation[9] *(updated 7/12/2021)* ▪ NIH guidelines recommend that patients recently hospitalized (i.e., within the previous 3 days) with COVID-19 who have

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	▪ not peer-reviewed **<u>CORIMUNO-19</u>** *(added 5/4/2020)* **Population:** hospitalized patients in France with moderate to severe illness not requiring ICU care upon admission (n=129) **Design:** open-label; tocilizumab added to standard care vs standard care alone **Results:** ▪ significantly fewer patients who received tocilizumab died or required ventilation at day 14 **Limitations:** open-label; not yet published **<u>Somers et al. 2020</u>**[10] *(added 6/18/2020; updated 7/14/2020)* **Population:** hospitalized patients requiring mechanical ventilation (n=154) ▪ tocilizumab-treated patients were younger (55 yrs vs 60 yrs), less likely to have chronic pulmonary disease (10% vs 28%), and had lower D-dimer values at intubation (median 2.4 vs 6.5 mg/dL) **Design:** single-center cohort; patients treated with tocilizumab vs patients not treated with tocilizumab **Results:** median follow-up 47 days ▪ tocilizumab associated with a reduced risk of death (hazard ratio 0.55; 95% CI 0.33,0.90) ▪ tocilizumab associated with an increased risk of superinfections (54% vs 26%; p<0.001) ▪ no significant difference in 28-day case fatality rate in patients treated	▪ Avoid use of live vaccines in patients taking tocilizumab	rapidly increasing oxygen needs, require high-flow oxygen therapy or noninvasive ventilation and have increased markers of inflammation receive dexamethasone with or without remdesivir, plus either tocilizumab or baricitinib. For patients hospitalized who require invasive mechanical ventilation or ECMO, dexamethasone is recommended; for those who were admitted to the ICU ≤24 hours previously and require invasive mechanical ventilation or ECMO, dexamethasone plus tocilizumab is recommended[3] *(updated 7/12/2021)* ▪ NIH guidelines recommend against use of baricitinib in combination with tocilizumab because of the risk of additive immunosuppression[1] *(updated 7/12/2021)* ▪ The WHO recommends use of an IL-6 inhibitor such as tocilizumab and a corticosteroid in all patients with severe or critical COVID-19[27] *(added 7/12/2021)* ▪ Results of trials for tocilizumab have been mixed; some randomized controlled trials have not found the same benefits as those reported in observational trials *(added 10/26/2020)* ▪ UK Medicines & Healthcare products Regulatory Agency (MHRA) recommends clinicians consider use of tocilizumab or sarilumab (alternative) in adult patients admitted to the ICU with COVID-19 pneumonia[20] *(added 1/11/2021)*

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	with tocilizumab who had superinfections vs those who did not (22% vs15%; p=0.42) **Limitation:** observational data **I Rosas et al. (COVACTA) NEJM 2021[12]** *(added 8/16/2020; updated 2/5/2021; updated 2/27/2021)* **Population:** hospitalized patients with severe COVID-19 pneumonia (n=452) **Design:** randomized, double-blind, placebo-controlled ▪ IV tocilizumab plus standard of care vs placebo plus standard of care ▪ ~25% of patients received a 2nd tocilizumab or placebo dose 8-24 hrs after the 1st dose **Results:** ▪ No significant difference between tocilizumab and placebo in the primary endpoint of clinical status on a 7-point scale at week 4 (between group difference -1.0; 95% CI -2.5 to 0; p=0.31) ▪ No difference between groups in mortality at week 4 (19.7% tocilizumab vs 19.4% placebo) ▪ Median time to hospital discharge was 20 days with tocilizumab and 28 days with placebo (p=0.037) ▪ Duration of ICU stay was 9.8 days with tocilizumab and 15.5 days with placebo (p=0.045) ▪ Compared to the placebo group, fewer patients in tocilizumab group were given corticosteroids **Limitations:** other treatments not standardized; limitations of primary endpoint		▪ Results of REMAP-CAP trial in critically ill patients and RECOVERY trial in hospitalized patients reported improved outcomes with tocilizumab use, while the results of the COVACTA trial in hospitalized patients with severe pneumonia did not report improved outcomes with tocilizumab[23] *(added 2/27/2021)* ▪ Emergency use authorization (EUA) issued by FDA for use of tocilizumab in adults and children ≥2 years old who are hospitalized with COVID-19, receiving systemic corticosteroids, and who require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation[26] *(added 6/26/2021)* **Pregnancy:** ▪ Crosses the placenta, especially in the third trimester, and may affect the immune response in an exposed infant ▪ Parturition is associated with IL-6 increases in the cervix and myometrium; inhibition of IL-6 may lead to possible delays of parturition ▪ Increased incidence of abortion/ embryo-fetal death when given to pregnant monkeys during the period of organogenesis

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	**EMPACTA 2020**[13] *(added 9/18/2020; update below, See Salama et al.)* **Population:** hospitalized patients with COVID-19 pneumonia (SpO2 <94% on ambient air with no mechanical ventilation) (n=389) ▪ 85% of patients were from racial and ethnic minority groups **Design:** Phase 3 randomized, double-blind, placebo-controlled trial ▪ Tocilizumab plus standard care vs placebo plus standard care **Results:** ▪ Mechanical ventilation or death was less likely in patients treated with tocilizumab compared to those who were not (p=0.0348; HR 0.56) **Limitations:** not yet published or peer reviewed data **C Salvarani et al. JAMA Intern Med 2020**[14] *(added 10/22/2020)* **Population:** hospitalized patients in Italy with COVID-19 pneumonia and PaO2/FiO2 ratio of 200-300 mm Hg (n=126) **Design:** open-label, randomized trial ▪ tocilizumab (given within 8 hours of randomization) vs standard care **Results:** ▪ Composite outcome of clinical worsening (ICU admission with invasive mechanical ventilation, death from all causes, PaO2/FiO2 ratio <150 mm HG) occurred in 28.3% of patients who received tocilizumab vs 27.0% of patients who received standard care		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	▪ Trial was stopped early for futility **Limitations:** small open-label trial; tocilizumab allowed as rescue therapy in standard care group **S Gupta et al. JAMA Intern Med 2020**[15] *(added 10/22/2020)* **Population:** hospitalized patients in the ICU with COVID-19 (n=3924) **Design:** retrospective, multicenter cohort study ▪ patients who received tocilizumab within 2 days of ICU admission compared to those who did not **Results:** ▪ 1544 patients (39.3%) died; 125 (28.9%) who received tocilizumab and 1419 (40.6%) who did not receive tocilizumab ▪ During a median follow-up of 27 days, risk of death was lower in patients treated with tocilizumab compared to those who were not (HR 0.71; 95% CI 0.56-0.92) ▪ Estimated 30-day mortality was 27.5% in patients who were given tocilizumab and 37.1% in those who were not given tocilizumab (risk difference 9.6%; 95% CI 3.1%-16.0%) **Limitations:** retrospective data; differences in baseline characteristics between groups; possible unmeasured confounding **O Hermine et al. JAMA Intern Med 2020 – CORIMUNO-TOCI 1**[16] *(added 10/22/2020; updated 5/25/2021)* **Population:** hospitalized patients in France with moderate-to-severe		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	COVID-19 pneumonia (≥3 L of oxygen but not on ventilation or in the ICU) (n=131) **Design:** cohort-embedded, investigator-initiated, multicenter, open-label, bayesian randomized trial ▪ tocilizumab plus usual care vs usual care alone **Results:** ▪ At day 14, compared to the usual care group fewer patients in the tocilizumab group needed noninvasive ventilation or mechanical ventilation or died (24% vs 36% with usual care; median posterior HR 0.58; 90%CrI 0.33-1.00) ▪ Tocilizumab did not reduce scores on the WHO 10-point Clinical Progression Scale lower than 5 on day 4 ▪ No difference in 28-day mortality was found **90-Day Follow-up[25]** ▪ Death occurred in 7 of 63 (11%) patients in the tocilizumab group and in 11 of 67 (18%) patients in the usual care group by day 90 (HR 0.64; 95% CI 0.25-1.65) ▪ A post-hoc analysis stratified by CRP level found a benefit in patients given tocilizumab who had CRP levels >15.0 mg/dL ▪ 90-day mortality in patients with CRP >15 mg/dL was 9% with tocilizumab and 35% with usual care (HR 0.18; 95% CI 0.04-0.9; p=0.02)		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	**Limitations:** small sample, not blinded **J Stone et al. NEJM 2020**[17] *(added 10/22/2020)* **Population:** hospitalized patients with moderate COVID-19 not on mechanical ventilation (n=243) **Design:** randomized, double-blind, placebo-controlled trial ▪ Tocilizumab plus standard care vs placebo plus standard care **Results:** ▪ Tocilizumab not effective for preventing intubation or death (HR 0.83; 95% CI 0.38-1.81; p=0.64) ▪ Worsening of disease occurred in 18.0% of patients in the tocilizumab group vs 14.9% of those in the placebo group at 14 days ▪ Median time to oxygen discontinuation 5.0 days with tocilizumab and 4.9 days with placebo ▪ 24.6% of patients who received tocilizumab and 21.2% of those who received placebo were still receiving supplemental oxygen at 14 days ▪ There were fewer serious infections in patients who received tocilizumab **Limitations:** primary event rate lower than anticipated; higher number of patients >65 years old in tocilizumab group		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	**C Salama et al. NEJM 2020 (EMPACTA):**[18] *(added 12/17/2020)* **Population:** hospitalized patients with COVID-19 pneumonia not on mechanical ventilation (n=389) ▪ >25% were over 65 years of age, >75% had ≥1 coexisting condition, >80% were in a minority racial or ethnic group **Design:** randomized, double-blind, placebo-controlled trial ▪ Tocilizumab (1 or 2 doses of 8 mg/kg) plus standard care or standard care alone **Results:** ▪ Mechanical ventilation or death by day 28 was 12.0% with tocilizumab and 19.3% with standard care alone (hazard ratio 0.56; 95% CI 0.33-0.97; p=0.04) ▪ Outcome was similar to overall population when assessed according to race or ethnic group ▪ Mortality differences alone were not statistically significant **Limitations:** other treatments used not uniform; outcome by race or ethnic group was exploratory **AC Gordon et al. REMAP-CAP Trial. NEJM 2021**[19] *(added 1/11/2021; updated 2/27/2021)* **Population:** adults in the ICU with COVID-19 within 24 hours of starting respiratory or cardiovascular organ support (n=803; 353 tocilizumab, 48 sarilumab, 402 control)		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	**Design:** ongoing, randomized, open-label, multifactorial, adaptive platform trial ▪ Tocilizumab 8 mg/kg, sarilumab 400 mg, or standard care **Results:** ▪ 610/654 patients who were enrolled after announcement of RECOVERY trial results received corticosteroids ▪ Median organ support-free days: 10 with tocilizumab, 11 with sarilumab, 0 with standard care ▪ In-hospital mortality: 27% in pooled IL-6 group and 36% in standard care group **Limitations:** open-label; standard care varied; small number of patients received sarilumab **VC Veiga et al. BMJ 2021**[21] *(added 1/25/2021)* **Population:** hospitalized adults with severe or critical COVID-19 on supplemental oxygen or mechanical ventilation with abnormal levels of ≥2 serum biomarkers (C reactive protein, D dimer, lactate dehydrogenase, ferritin) (n=129) **Design:** randomized, open-label trial ▪ Tocilizumab 8 mg/kg IV single dose plus standard care vs standard care alone **Results:** ▪ A composite of mechanical ventilation or death at 15 days occurred in 28% of patients receiving tocilizumab compared to 20% of those receiving standard care alone		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	▪ Trial stopped early after enrollment of 129 patients because of an increased number of deaths in the tocilizumab group at day 15 **Limitations:** open-label; small sample; severe or critical illness only **RECOVERY Collaborative Group. Lancet 2021**[22] *(updated 5/5/2021)* **Population:** hospitalized adults with COVID-19 with evidence of hypoxia (oxygen saturation <92% on room air or requiring oxygen therapy) and systemic inflammation (C-reactive protein ≥75 mg/L) (n=4116) **Design:** randomized, open-label, platform trial ▪ Tocilizumab IV 400-800 mg (based on weight) added to standard care vs standard care alone **Results :** ▪ 28-day mortality was 31% (621/2022) with tocilizumab compared to 35% (729/2094) with standard care alone (rate ratio 0.85, 95% CI 0.76-0.94; p=0.0028) ▪ Results consistent in subgroups, including those on corticosteroids ▪ The percentage of patients discharged from the hospital alive within 28 days was 57% with tocilizumab and 50% with standard care (rate ratio 1.22, 95% CI 1.12-1.33; p<0.0001) ▪ In patients not on mechanical ventilation at baseline, the composite endpoint of invasive mechanical ventilation or death		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	occurred less often in patients who received tocilizumab compared to those on standard care (35% vs 42%; risk ratio 0.84, 95% CI 0.77-0.92; p<0.0001) **Limitations:** open-label trial; after randomization ~16% of patients did not receive treatment for unknown reasons; data past 28 days not yet available **REMDACTA 2021[24]** *(added 3/14/2021)* **Population:** patients with severe COVID-19 pneumonia **Design:** phase 3, randomized, double-blind, trial ▪ Tocilizumab + remdesivir vs placebo plus remdesivir **Results:** ▪ Primary endpoint of improvement in time to hospital discharge by day 28 was not met ▪ Secondary endpoints including death, likelihood of progression to mechanical ventilation or death, and clinical status were not met **Limitations:** not published **WHO REACT Working Group. JAMA 2021[28]** *(added 7/15/2021)* **Population:** trials that included patients hospitalized for COVID-19 who were randomly assigned to receive an IL-6 antagonist or no IL-6		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	antagonist or other immunomodulator (except corticosteroids) (n=27 trials; 10,930 patients) **Design:** meta-analysis of 27 trials **Results:** ▪ Lower 28-day all-cause mortality with IL-6 inhibitor vs no IL-6 inhibitor ▪ By 28 days, 1407 death were reported among 6449 patients who received and IL-6 inhibitor and 1158 deaths among 4481 subjects not receiving an IL-6 inhibitor (OR 0.86; 95% CI 0.79-0.95; p=0.003) ▪ OR for tocilizumab was 0.83 (95% CI 0.74-0.92, p<0.001) and 1.08 for sarilumab (95% CI 0.86-1.36, p=0.52) ▪ In those receiving corticosteroids, OR was 0.77 (95% CI 0.68-0.87) for tocilizumab and 0.92 (95% CI 0.61-1.38) for sarilumab; most trials of sarilumab patients not on corticosteroids **Limitations:** meta-analysis, some trials not peer-reviewed; some trials ongoing		

1. FDA-approved for treatment of rheumatoid arthritis.
2. Clinical trials information available at: https://clinicaltrials.gov/ct2/show/nct04315298?Term=sarilumab&draw=2&rank=4. Accessed March 31, 2020.
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4. FDA-approved for chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome, rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis.
5. Fact sheet for healthcare providers: emergency use authorization for Actemra (tocilizumab). Available at: https://www.fda.gov/media/150321/download. Accessed June 26, 2021.
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13. Press release. Roche's phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalized patients with COVID-19 associated pneumonia. Available at: https://www.roche.com/investors/updates/inv-update-2020-09-18.htm. Accessed 18 September 2020.
14. C Salvarani et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern Med 2020 October 20 (epub).
15. S Gupta et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. JAMA Intern Med 2020 October 20 (epub).
16. O Hermine et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. JAMA Intern Med 2020 October 20 (epub).
17. JH Stone et al. Efficacy of tociluzumab in patients hospitalized with COVID-19. N Engl J Med 2020; 383:2333.
18. C Salama et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2020 December 17 (epub).
19. The REMAP-CAP Investigators. AC Gordon et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med 2021 February 25 (epub).
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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
IL-1 Receptor Antagonists			
ANAKINRA – *KINERET* (BIOVITRUM AB) *(updated 7/27/2020)* **Dosage:** ▪ Optimal dosage for COVID-19 unknown[1,2,3] ▪ In a trial being conducted by the manufacturer, anakinra is being administered IV at a dosage of 100 mg q6h x 15 days. According to US *Kineret* labeling, the drug is indicated for SC administration.	**Cavalli et al. Lancet Rheum 2020[4]** **Population:** consecutive hospitalized patients with moderate-to-severe ARDS and serum C-reactive protein ≥100 mg/L, ferritin ≥900 ng/mL, or both; not on mechanical ventilation **Design:** retrospective cohort study; single hospital in Italy ▪ Addition of anakinra vs standard treatment (HCQ + LPV/RTV) **Results:** at 21 days ▪ Improved survival with high-dose (5 mg/kg IV bid) anakinra vs standard treatment (90% vs 56%; p=0.009) ▪ Mechanical ventilation-free survival similar between groups (72% vs 50%; p=0.15) ▪ Associated with reduced serum C-reactive protein and improved respiratory function **Limitations:** small, retrospective study **Cauchois et al. Proc Natl Acad Sci U S A 2020[5]** *(added 7/27/2020)* **Population:** hospitalized patients in France with hypoxemic pneumonia or ARDS (n=22) **Design:** retrospective ▪ anakinra plus standard care compared to standard care alone ▪ anakinra dosage: 300 mg IV x 5 days, then tapered to 200 mg/d x 2 days, then 100 mg x 1 day	**Adverse Effects:** ▪ Injection-site reactions, infections, neutropenia, thrombocytopenia, hepatic transaminase elevations **Drug Interactions:** ▪ Use with TNF inhibitors or other biologics may increase risk of serious infections and neutropenia and should be avoided	▪ Clinical trials are ongoing[1,2] ▪ IL-1 receptor antagonist; IL-1 mediates inflammatory and immune responses antagonist ▪ May mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease ▪ NIH guidelines state there are insufficient clinical data to recommend either for or against use of IL-1 inhibitors[3] *(updated 4/28/2020)* ▪ FDA-approved for treatment of rheumatoid arthritis and neonatal-onset multisystem inflammatory disease. **Pregnancy:** ▪ Not associated with adverse pregnancy outcomes in small retrospective studies in humans or in animal studies

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
ANAKINRA (continued)	**Results:** ▪ compared to standard care alone, all anakinra-treated patients had clinical improvement (p<0.01), decreases in oxygen requirements (p<0.05), and more days off invasive mechanical ventilation (p<0.06) ▪ there were no deaths in the anakinra group and 1 death in the standard care group ▪ significant reduction of fever and CRP by day 3 with anakinra **Limitations:** small retrospective study		
CANAKINUMAB – *ILARIS* (NOVARTIS) *(updated 7/21/2021)* **Dosage:** ▪ Optimal dosage for COVID-19 unknown ▪ Single IV infusion administered over 2 hours on day 1[6] Weight-based dosing: ▪ 40-<60 kg: 450 mg ▪ 60-80 kg: 600 mg ▪ >80 kg 750 mg	**CAN-COVID 2020[6]** *(updated 7/21/2021)* **Population:** hospitalized adult patients with severe COVID-19 (not on invasive mechanical ventilation) and with elevated C-reactive protein or ferritin levels (n=454) **Design:** phase 3, randomized, double-blind, placebo-controlled trial ▪ Canakinumab vs placebo ▪ Added to standard care **Results:** ▪ Survival without need for invasive mechanical ventilation at day 29 was achieved in 88.8% of patients who received canakinumab and 85.7% of those who received placebo (odds ratio 1.39, 95% CI 0.76-2.54; p=0.29) ▪ Mortality rates were 4.9% with canakinumab and 7.2% with	**Adverse Effects:** Injection-site reactions, infections, neutropenia, thrombocytopenia, and hepatic transaminase elevations **Drug Interactions:** Use with TNF inhibitors or other biologics may increase the risk of serious infections and neutropenia and should be avoided	▪ Selectively binds to IL-1β and inactivates its signaling, inhibiting the induction of intracellular mediators involved in inflammatory and immune responses ▪ May mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease ▪ NIH guidelines state there are insufficient clinical data to recommend either for or against use of IL-1 inhibitors[3] ▪ Interim analysis of one randomized controlled trial, sponsored by the manufacturer, did not meet primary or secondary endpoints for efficacy[6]

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CANAKINUMAB (CONTINUED)	placebo (odds ratio 0.67, 95% CI 0.30-1.50, p=0.33) **Limitations:** standard of care treatment and disease management changed over course of trial		▪ FDA-approved for treatment of cryopyrin-associated periodic syndromes (CAPS), tumor necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD), Familial Mediterranean Fever (FMF), adult onset Still's disease, and systemic juvenile idiopathic arthritis (SJIA) **Pregnancy:** ▪ Not adequately studied in pregnant women. Associated with delays in fetal skeletal development in animal studies. Monoclonal antibodies are unlikely to cross the placenta in the first trimester but may do so subsequently.

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3. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/**.** Accessed November 29, 2020.
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5. R Couchois et al. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. Proc Natl Acad Sci U S A 2020 July 22 (epub).
6. R Caricchio et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. JAMA 2021; 326:230.

ACALABRUTINIB – *CALQUENCE* (ASTRAZENECA)

(added 11/29/2020)

Dosage:

- Optimal dosage for COVID-19 unknown
- 100 mg PO q 12 h

CALAVI 2020[1]

Population: hospitalized adult patients with respiratory symptoms of COVID-19 (not on invasive mechanical ventilation or in ICU)
Design: phase 2, randomized, open-label trials (1 in US; 1 in other countries across the world)
- acalabrutinib vs placebo
- added to standard care

Results:
- Treatment with acalabrutinib did not meet the primary endpoint of reducing respiratory failure or death

Limitations: minimal information available

Adverse Effects:

- Neutropenia, anemia, pneumonia, thrombocytopenia, headache, diarrhea, musculoskeletal pain, hemorrhage, atrial fibrillation or flutter, serious and opportunistic infections

Drug Interactions:

- Avoid coadministration with strong CYP3A inhibitors and CYP3A inducers
- Avoid use with PPIs and stagger dosing with H2-receptor antagonists and antacids
- BTK inhibitors have broad immunosuppressive effects; can modulate signaling that promotes inflammation
- NIH guidelines recommend against use of BTK inhibitors[2]
- FDA-approved for treatment of mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL)

Pregnancy:

- May cause fetal harm and dystocia

1. News Release. AstraZeneca. Update on CALAVI phase II trials for Calquence in patients hospitalized with respiratory symptoms of COVID-19. Available at: https://www.astrazeneca.com/media-centre/press-releases/2020/update-on-calavi-phase-ii-trials-for-calquence-in-patients-hospitalised-with-respiratory-symptoms-of-covid-19.html. Accessed November 29, 2020.
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BARICITINIB –
***OLUMIANT* (LILLY)**

(updated 11/3/2021)

Dosage:

- **Adults and children ≥9 years old:** 4 mg PO once/daily x 14 days or until hospital discharge

- **Children 2-<9 years old:** 2 mg once daily x 14 days or until hospital discharge

- For patients unable to swallow, baricitinib tablets can be dispersed in water and given via G or NG tube

- **Renal Dosage Adjustments:**

eGFR 30-<60 mL/min/1.73m^2:
- 2 mg once daily in patients ≥9 years old
- 1 mg once daily in patients 2-<9 years old

eGFR 15-<30 mL/min/1.73m^2:
- 1 mg once daily in patients ≥9 years old
- Not recommended in patients 2-<9 years old

- Should not be used in patients with end-stage renal disease (eGFR <15 mL/min/1.73 m^2), or who are on dialysis

AC Kalil et al. NEJM 2020 (NIH Adaptive COVID-19 Treatment Trial 2 [ACTT-2])[6] *(added 9/18/2020; updated 12/11/2020)*
Population: hospitalized patients with moderate or severe COVID-19 (n=1033)
Design: Phase 3, randomized, double-blind, placebo-controlled trial
- remdesivir (≤10 days) plus either baricitinib (≤14 days) or placebo

Results:
- Mean recovery time was about 1 day shorter with the combination of remdesivir plus baricitinib compared to remdesivir alone (7 days vs 8 days; rate ratio for recovery 1.16; 95% CI 1.01-1.32; p=0.03)
- Recovery in patients on high-flow oxygen or noninvasive ventilation at enrollment was 10 days with combination treatment and 18 days with remdesivir alone (rate ratio for recovery 1.51; 95% CI 1.10-2.08)
- Odds of clinical improvement at day 15 was greater with the combination compared with remdesivir alone (OR 1.3; 95% CI 1.0 to 1.6)
- Number of patients who progressed to death or ventilation at day 29 was lower with the combination (23%) than with remdesivir alone (28%)
- Morality rate at day 28 after randomization was 5.1% with the combination and 7.8% with

Adverse Effects:
- Nausea is common

- Serious, sometimes fatal, infections, including multi-dermatomal herpes zoster and tuberculosis (TB)

- Serious, sometimes fatal, thromboembolic events

- Malignancy, GI perforation, neutropenia, lymphopenia, anemia, thrombocytosis, and elevations in liver enzymes, creatine phosphokinase levels, and lipid levels have also been reported

Drug Interactions:
- The strong organic anion transporter 3 (OAT3) inhibitor probenecid doubled baricitinib exposure

- Avoid use of live vaccines

- FDA-approved for treatment of rheumatoid arthritis

- Inhibits JAK enzymes, which mediate signaling of proinflammatory cytokines including IL-6; may mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease

- The NIH recommends that patients recently hospitalized (i.e., within the previous 3 days) with COVID-19 who have rapidly increasing oxygen needs, require high-flow oxygen therapy or noninvasive ventilation and have or increased markers of inflammation receive the corticosteroid dexamethasone with or without remdesivir, plus either tocilizumab or baricitinib[1] *(updated 7/12/2021)*

- NIH guidelines recommend against use of baricitinib in combination with tocilizumab because of the risk of additive immunosuppression[1] *(updated 7/12/2021)*

- FDA Emergency Use Authorization (EUA) allows use of baricitinib for treatment of COVID-19 in hospitalized patients ≥2 years old who require supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO[7] *(added 11/20/2020; updated 11/3/2021)*

Pregnancy:
- Administration to pregnant animals resulted in reduced fetal weights, embryolethality, and skeletal malformations

BARICITINIB (continued)

- Should not be used in patients with severe hepatic impairment (Child-Pugh C)

- Dosage reductions are recommended for patients taking strong OAT3 inhibitors with baricitinib: reduce daily dose to 2 mg if recommended dose is 4 mg; reduce daily dose to 1 mg if recommended dose is 2 mg; consider stopping OAT3 inhibitor if recommended dose is 1 mg

- Treatment should be interrupted for an absolute lymphocyte count <200 cells/mm^3 or absolute neutrophil count <500 cells/mm^3, or drug-induced liver injury is suspected

- Should not be used in patients with known active tuberculosis

- FDA requires boxed warning in the labeling about an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death *(added 9/7/2021)*

remdesivir alone (hazard ratio for death 0.65; 95% CI 0.39-1.09)
- Greatest mortality benefit appeared to be in patients receiving oxygen

Limitations: not powered to detect differences in mortality

V Marconi et al. COV-BARRIER Lancet Respir Med 2021[9,10]
(added 4/12/2021; updated 11/3/2021)

Population: patients hospitalized with COVID-19 who required supplemental oxygen (ordinal scale [OS] 5) or high-flow oxygen/non-invasive mechanical ventilation (OS 6) and ≥1 increased marker of inflammation (n=1525)

Design: phase 3 randomized, double-blind, placebo-controlled trial
- Baricitinib 4 mg vs placebo x 14 days or until discharge; both groups received standard care

Results:
- 79% of patients received corticosteroids (mostly dexamethasone) and 19% received remdesivir
- 27.8% of patients who received baricitinib progressed to non-invasive ventilation or death by day 28 compared to 30.5% of those who received standard care alone (OR 0.85; 95% CI 0.67-1.08; p=0.18)
- Death from any cause by day 28 occurred in 8% of patients who received baricitinib and 13% of those who received standard care alone (HR 0.57; 95% CI 0.57; 95% CI 0.41-0.78; nominal p=0.0018)
- 60-day all-cause mortality was 10% with baricitinib and 15% for standard

	care alone (HR 0.62; 95% CI 0.47-0.83; p=0.0050) ▪ **Limitations:** primary endpoint for disease progression measured by clinical status including oxygen support levels		
RUXOLITINIB – *JAKAFI* (INCYTE/NOVARTIS) *(updated 12/16/2020)* **Dosage:** ▪ Optimal dosage not established ▪ 10 mg PO bid x 14 days[2] ▪ Taper dosage when stopping: 5 mg bid x 2 days, then 5 mg once daily x 1 day	▪ Manufacturer is initiating phase III clinical trials in patients with severe COVID-19 to compare ruxolitinib to standard care[3,4] **<u>Novartis. RUXCOVID Trial 2020[8]</u>** *(added 12/16/2020)* **Population:** ▪ Patients ≥12 years old hospitalized for COVID-19 (not intubated or in ICU) (n=432) **Design:** ▪ Phase 3, randomized, double-blind, placebo-controlled trial ▪ Ruxolitinib plus standard care vs standard care alone **Results:** ▪ Did not meet primary endpoint of reducing the number of patients with severe complications (death, mechanical ventilation, or ICU admission) ▪ Proportion of patients with severe complications by day 29 was 12% with ruxolitinib and 11.8% with standard care	**Adverse Effects:** ▪ Most common adverse effects include thrombocytopenia, anemia, fatigue, diarrhea, bruising, dizziness, dyspnea, and headache ▪ Severe withdrawal symptoms including a systemic inflammatory response syndrome have been reported when ruxolitinib was stopped **Drug Interactions:** ▪ Strong CYP3A4 inhibitors can increase serum concentrations of ruxolitinib (ketoconazole increased ruxolitinib AUC by 91%) ▪ Concurrent use of ruxolitinib with a strong CYP3A4 inhibitor[5] should be avoided in patients with platelet counts less than 100 X 10^9/L; dosage reductions may be needed for patients with a platelet count ≥100 X 10^9 /L **Pregnancy:** ▪ No adequate studies in pregnant women ▪ Administration to pregnant animals resulted in an increase in late resorptions and reduced fetal weights	▪ NIH guidelines recommend against JAK inhibitors other than baricitinib except in a clinical trial[1] *(updated 8/5/2021)* ▪ *Jakavi* outside the US ▪ FDA-approved for treatment of myelofibrosis ▪ Inhibits JAK1 and 2, which mediate signaling of proinflammatory cytokines including IL-6; may mitigate the effects of cytokines release in response to the virus and limit lung damage in patients with severe disease ▪ Manufacturer initiating an open-label emergency Expanded Access Plan (EAP) in the US ▪ Should be avoided in patients with end stage renal disease (CrCl <15 mL/min) not requiring dialysis and in patients with moderate or severe renal impairment or hepatic impairment and a platelet count 100 X 10^9/L

TOFACITINIB –
***XELJANZ* (PFIZER)**

(updated 9/7/2021)

Dosage:

- Optimal dosage not established
- 10 mg PO bid x 14 days or until hospital discharge[2]
- Dosage adjustments needed for moderate to severe renal impairment
- Not recommended in patients with severe hepatic impairment
- Drug should be stopped if lymphocyte count or ANC is <500 cells/mm^3
- Dosing should be interrupted if ANC is 500-1000 cells/mm^3 or hemoglobin is <8 mg/dL or decreases by more than 2 g/dL
- FDA requires boxed warning in the labeling about an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death *(added 9/7/2021)*

Guimaraes et al NEJM 2021[9] *(added 8/5/2021)*

Population:

- Adults hospitalized for <72 hours with COVID-19 pneumonia in Brazil (n=289)

Design:

- Randomized, double-blind, placebo-controlled trial
- Tofacitinib 10 mg bid x 14 days or until hospital discharge vs placebo

Results:

-
- 75.4% of patients were receiving supplemental oxygen at baseline
- 89.3% of patients were treated with glucocorticoids
- Death or respiratory failure through day 28 (the primary endpoint) occurred in 18.1% of patients who received tofacitinib and 29.0% of those who received placebo (risk ration 0.63; 95% CI 0.41-0.97; p=0.04)

Limitations: did not include patients on mechanical ventilation

Adverse Effects:

- Most common adverse effects include upper respiratory tract infection, nasopharyngitis, diarrhea, headache, elevated cholesterol levels, increased blood creatine phosphokinase, rash, and herpes zoster
- Serious infections, thrombosis, and malignancies, and gastrointestinal perforation have been reported

Drug Interactions:

- Concurrent use of CYP3A4 inhibitors or CYP2C19 inhibitors can increase tofacitinib serum concentrations; tofacitinib dosage reductions are needed for patients taking concomitant strong CYP3A4 inhibitors or a moderate CYP3A4 inhibitor with a strong CYP2C19 inhibitor
- CYP3A4 inducers can decrease serum concentrations of tofacitinib and concurrent use is not recommended
- Concurrent use of other immunosuppressants can increase the risk of immunosuppression and is not recommended

Pregnancy:

- No adequate studies in pregnant women
- Administration to pregnant animals resulted in fetocidal and teratogenic effects

- NIH guidelines recommend tofacitinib as an alternative to baricitinib only when baricitinib is not available or not feasible to use[1] *(updated 9/7/2021)*
- FDA-approved for treatment of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis
- Selective inhibitor of JAK1 and 3, functional selectivity for JAK2; also modulates action of interferons and IL-6; these actions may mitigate the effects of inflammatory cytokines released in response to the virus and limit lung damage in patients with severe disease

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2. Dosage used in clinical trials for COVID-19.
3. Study of the efficacy and safety of ruxolitinib to treat COVID-19 pneumonia. Available at: https://clinicaltrials.gov/ct2/show/nct04331665?term=covid&cond=ruxolitinib&draw=2&rank=1. Accessed April 6, 2020.
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5. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2019 November 6 (epub). Available at: medicalletter.org/downloads/cyp_pgp_tables.pdf.
6. AC Kalil et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med 2021; 384:795.
7. FDA News Release. Coronavirus (COVID-19) update: FDA authorizes drug combination for treatment of COVID-19. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-combination-treatment-covid-19?utm_medium=email&utm_source=govdelivery. Accessed November 20, 2020.
8. Novartis. News Release. Novartis provides update on RUXCOVID study of ruxolitinib for hospitalized patients with COVID-19. Available at: https://www.novartis.com/news/media-releases/novartis-provides-update-ruxcovid-study-ruxolitinib-hospitalized-patients-covid-19. Accessed December 16, 2020.
9. PO Guimaraes et al. Tofacitinib in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2021; 385: 406.
10. VC Marconi et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021 September 1 (epub).
11. FDA. Baricitinib letter of authorization. Revised July 28, 2021. Available at: https://www.fda.gov/media/143822/download. Accessed November 3, 2021.

TNF INHIBITORS

(added 7/29/2020)

- Optimal dosage for treatment of COVID-19 not established

- Adalimumab *(Humira)*
- Certolizumab pegol *(Cimzia)*
- Infliximab (*Remicade*, and biosimilars)
- Etanercept *(Enbrel)*
- Golimumab *(Simponi)*

Brenner et al. Gastroenterology 2020[1]

Population: patients with inflammatory bowel disease (IBD) and COVID-19 (525 cases)
Design: international (33 countries) registry to monitor outcomes of IBD patients with COVID-19 (Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD)
Results:
- 31% hospitalized and 3% died
- Risk factors for severe COVID-19 included corticosteroid and sulfasalazine or 5-aminosalicylate use, but not TNF-inhibitor use

Limitations: observational data

Gianfrancesco et al. Ann Rheum Dis 2020[2]

Population: patients with rheumatic disease and COVID-19 (600 cases)
Design: international (40 countries) case series from the C19-GRA registry
Results:
- 46% hospitalized and 9% died
- Risk factors for hospitalization included corticosteroid use (prednisone dose ≥ 10 mg/day); TNF-inhibitor use was associated with reduced odds of hospitalization

Limitations: observational data

Adverse Effects:
- Injection-site reactions or infusion reactions (fever, urticaria, dyspnea, hypotension)
- Cytopenias; malignancies, especially lymphomas, have been reported, but a cause-and-effect relationship has not been established
- Increased risk of infections, including reactivated and disseminated tuberculosis, invasive or disseminated fungal infection, and other opportunistic infections; reactivation of HBV
- Rarely induces or exacerbates heart failure or induces a reversible lupus-like syndrome
- Demyelinating conditions, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome have been reported

Drug Interactions:
- Concomitant administration of a TNF inhibitor with another biologic agent may increase the risk of serious infections and neutropenia
- Patients being treated with TNF inhibitors should not receive live vaccines

- Patients with COVID-19 have been found to have increased levels of inflammatory cytokines including TNF

- TNF-inhibitors may mitigate the effects of cytokines released in response to the virus

- No clinical trial data yet available on efficacy of TNF inhibitors in patients with COVID-19

Pregnancy:
- Generally considered safe for use during pregnancy
- Placental transfer of anti-TNF antibodies is higher in the late second and third trimesters, especially with infliximab, adalimumab, and golimumab

1. EJ Brenner et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. Gastroenterology 2020 July 8 (epub).
2. M Gianfrancesco et al. Characteristics associated with hospitalization for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020; 79:859.

Anti-CD6 Monoclonal Antibody

ITOLIZUMAB

(added 7/16/2020)

- Optimal dosage for treatment of COVID-19 not established
- Formulation: 25 mg/5 mL vials for injection were approved for emergency use in India

Biocon Trial – 2020[1]

Population: hospitalized patients with moderate to severe ARDS in 4 hospitals in India (n=30)

Design: Randomized, controlled, open-label trial

- 20 patients randomized to itolizumab plus best supportive care and 10 patients randomized to best supportive care

Results:

- at one month, no deaths occurred in patients treated with itolizumab and 3 deaths occurred in patients treated with supportive care alone
- reductions in IL-6 and TNF-α were reported in itolizumab-treated patients

Limitation: trial results not yet published

Adverse Effects:

- Infusion reactions including nausea, rash, urticaria, flushing, cough, wheezing, dyspnea, dizziness, headache; diarrhea
- Increased risk of infections

Drug Interactions:

- Live vaccines should be avoided

- Approved in India for emergency use in COVID-19 patients; also approved in India for psoriasis
- Not available in the US
- Anti-CD6 IgG1 monoclonal antibody that binds to the CD6 receptor and blocks activation of T lymphocytes; may mitigate the effects of cytokines released in response to the virus

Pregnancy:

- No adequate data on use in pregnant women
- Crosses the placenta

1. Equillium. Press Release. Clinical trial shows itolizumab reduced mortality in patients hospitalized with COVID-19. Available at: https://www.globenewswire.com/news-release/2020/07/13/2060993/0/en/Clinical-Trial-Shows-Itolizumab-Reduces-Mortality-in-Patients-Hospitalized-with-COVID-19.html. Accessed July 16, 2020.

RAVULIZUMAB
Ultomiris (Alexion)

(added 1/21/2021)

- Weight-based dosing
- Administered IV on days 1, 5, 10, and 15

Phase 3 Trial – 2021[1]
Population: adults with severe COVID-19 requiring mechanical ventilation (trial was expected to enroll 270 patients; interim analysis conducted after 122 patients completed 29 days)
Design: phase 3 randomized, open-label trial
- Ravulizumab plus standard care vs standard care alone

Results:
- Enrollment in study paused because an independent data monitoring committee reported a lack of efficacy with addition of ravulizumab to standard care compared to standard care alone after an interim review of data
- Patients currently enrolled will continue the trial
- Primary endpoint: survival at day 29

Adverse Effects:
- Upper respiratory tract infection, headache, diarrhea, nausea, vomiting, hypertension, pyrexia
- Infusion reactions, life-threatening meningococcal infections

- FDA-approved for paroxysmal nocturnal hemoglobinuria in adults and for atypical hemolytic uremic syndrome in adults and children >1 month old

- C5 complement inhibitor thought to decrease levels of cytokines and chemokines and reduce lung inflammation

Pregnancy:
- No available data on use of ravulizumab in pregnant women
- In animal studies, developmental abnormalities and an increased rate of death in the offspring was reported

1. News Release. Alexion provides update on phase 3 study of Ultomiris (ravulizumab-cwvz) in hospitalized patients with severe COVID-19. January 13, 2021. Available at: https://ir.alexion.com/news-releases/news-release-details/alexion-provides-update-phase-3-study-ultomirisr-ravulizumab. Accessed January 21, 2021.

CHLOROQUINE[1]

(updated 4/23/2021)

Dosage:

- Optimal dosage not established
- Dosages used in COVID-19 clinical trials have varied

500 mg chloroquine phosphate (300 mg chloroquine base) bid x 7-10 days

OR

500 mg bid x 2 days, then 500 mg once/day x 12 days[2,3]

OR

1 g on day 1, then 500 mg once daily x 4-7 days

- Based on *in vitro* data (M Wang et al, Cell Res 2020)[4]
- Unpublished clinical data from China[3] in approximately 100 patients suggest more rapid decline in fever, improvement on lung CT scan, shorter time to recovery vs control group

ChloroCovid-19[5] *(updated 4/30/2020)*

Population: hospitalized patients with severe illness in Brazil (n=81)

Design:

- parallel, double-blind, randomized, phase IIb
- chloroquine high dose (600 mg bid x 10 days) vs low dose (450 mg bid x 1 day, then once/day x 4 days); all patients received azithromycin

Results:

- Trial stopped early because of a higher rate of death and QT interval prolongation in the high-dose chloroquine group
- Lethality was 39.0% (16 of 41) in the high-dosage group and 15.0% (6 of 40) in the low-dosage group at day 13
- QTc interval >500 milliseconds occurred in 18.9% (7 of 37) in the high-dose group compared to 11.1% (4 of 36) in the low-dosage group
- Respiratory secretion negative in 22.2% (6 of 27) at day 4

Adverse Effects:

- Retinopathy and other ocular disorders (generally associated with longer use), urticaria, angioedema, tinnitus, reduced hearing, myopathy, muscle atrophy, suppressed tendon reflexes, liver enzyme elevations, hepatitis, GI disturbances, skin reactions, cytopenias, hemolytic anemia (in G6PD-deficient patients), neuropathy, convulsions, extrapyramidal disorders, neuropsychiatric changes, hypotension, cardiomyopathy, hypoglycemia
- QT interval prolongation and arrhythmias, including torsades de pointes can occur. Risk is higher in patients with cardiac disease, electrolyte abnormalities, or concurrent use of other QT interval prolonging drugs such as azithromycin.[6-8] The AHA/ACC/HRS recommend the drug be withheld in patients with baseline QT prolongation or if QT interval exceeds 500 msec during treatment. Potassium and magnesium levels should be corrected and other QTc prolonging drugs should be avoided.[7]
- Cases (some fatal) of QT interval prolongation, ventricular tachycardia, and ventricular fibrillation have been reported in patients being treated with chloroquine or hydroxychloroquine, alone or in combination with azithromycin or other QTc prolonging drugs, for treatment of COVID-19[9]
- *In vitro* activity against SARS-CoV-2, SARS-CoV, and MERS-CoV
- FDA issued a Drug Safety Communication warning against use of chloroquine outside of a clinical trial because of the risk of serious cardiac arrhythmias, including QT prolongation; it is not recommended for treatment of outpatients[9] (updated 4/28/2020)
- Infectious Diseases Society of America recommends against use with or without azithromycin in the hospital setting[12] *(updated 8/23/2020)*
- NIH guidelines recommend against use of chloroquine (with or without azithromycin) in hospitalized patients and outpatients[19] *(updated 4/23/2021)*
- Clinical trials evaluating the efficacy and safety of chloroquine for pre-exposure and post-exposure prophylaxis and treatment of mild, moderate, or severe COVID-19 are underway in the US
- FDA revoked Emergency Use Authorization that allowed use in some hospitalized patients for whom a clinical trial was not feasible; ongoing analysis indicated that chloroquine and hydroxychloroquine are unlikely to be effective for treatment of COVID-19 and are associated with serious cardiac adverse events; FDA concluded benefit no longer outweighs risk[13] *(updated 6/16/2020)*

CHLOROQUINE[1] (CONTINUED)	**Mehra et al. 2020[22]** *(added 5/26/20) (updated 6/4/2020)* *****Study Retracted[24]***** ▪ *Retracted because of concerns about the accuracy of the data and analysis; an independent audit was not possible because the full dataset was not made available* **Population:** hospitalized patients with COVID-19 who received chloroquine or HCQ with or without a macrolide within 48 hrs of diagnosis; control patients did not receive treatment with these drugs (n = 96,032) **Design:** observational analysis of multinational registry **Results:** ▪ treatment was associated with an increased risk of in-hospital mortality and ventricular arrhythmia compared to control group **Limitation:** observational	**Drug Interactions:** ▪ Avoid use with QTc prolonging drugs[6-8] ▪ Substrate of CYP2C8, 2D6, and 3A4, and inhibitor of CYP2D6[10,11] ▪ Use with antihyperglycemic drugs can increase risk of hypoglycemia ▪ Separate from antacids/kaolin by 4 hours ▪ Use with tamoxifen can increase risk of ocular toxicity and should be avoided ▪ FDA warns that coadministration of remdesivir and chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; concurrent use is not recommended[26] *(added 6/18/2020)*	**Pregnancy:** ▪ Accumulates in fetal ocular tissues and is retained there for months after elimination from remainder of body ▪ Chloroquine has been used safely in pregnant women for treatment and prophylaxis of malaria
HYDROXYCHLOROQUINE (HCQ)[1] – GENERICS *PLAQUENIL* (CONCORDIA) *(updated 7/15/2021)* **Dosage:** ▪ Optimal dosage not established ▪ Dosages used in COVID-19 clinical trials have varied	**P Gautret et al. Int J Antimicrob Agents 2020[14]** **Population:** hospitalized patients; varying severity of illness (n=42) **Design:** ▪ open-label, observational ▪ HCQ + azithromycin vs HCQ vs standard care **Results:** ▪ HCQ-treated patients had more rapid viral clearance vs controls	**Adverse Effects:** ▪ Better tolerated than chloroquine ▪ Retinopathy and other ocular disorders (sometimes irreversible, but generally associated with longer use), serious cardiomyopathy, worsening of psoriasis and porphyria, proximal myopathy, neuropathy, suicidality, hypoglycemia ▪ QT interval prolongation and arrhythmias, including torsades de pointes can occur.	▪ *In vitro* activity against SARS-CoV-2 ▪ The FDA issued a Drug Safety Communication warning against use of hydroxychloroquine outside of a clinical trial because of the risk of serious arrythmias, including QT prolongation it; is not recommended for treatment of outpatients[9] *(updated 4/28/2020)*

HYDROXYCHLOROQUINE (CONTINUED)

- Most frequently used dosage in the US has been 400 mg PO bid on day 1, then 200 mg PO bid x 4 days[2]

- addition of azithromycin to HCQ (n=6) resulted in a more rapid decrease in viral load compared to treatment w/ HCQ alone

Limitations:

- not randomized or double-blind, some dropouts not included in trial results
- International Society of Antimicrobial Chemotherapy states concerns about the paper

Z Chen et al. 2020[15]

Population: hospitalized patients w/ pneumonia; mild illness (n=62)

Design:

- randomized, parallel-group
- hydroxychloroquine 200 mg bid vs standard care

Results:

- shortened duration of fever and cough
- pneumonia improvement on chest CT in 80.6% of patients w/ HCQ vs 54.8% w/ standard care
- 4 patients in control group progressed to severe illness vs none with HCQ

Limitations: published online ahead w/o peer review

M Mahevas et al. 2020[16]

Population: hospitalized patients with pneumonia requiring oxygen ≥2 L (n=181)

Design:

- Retrospective; HCQ 600 mg/day within 48 hrs of admission vs no HCQ

Results:

Risk is higher in patients with pre-existing cardiac disease, electrolyte abnormalities or concurrent use of other QT interval prolonging drugs such as azithromycin. EKG monitoring recommended.[6-8] The

AHA/ACC/HRS recommend use be avoided in patients with baseline QT prolongation or if QT interval exceeds

500 msec during treatment. Potassium and magnesium levels should be corrected and other QTc prolonging drugs should be avoided.[7]

- Cases (some fatal) of QT interval prolongation, ventricular tachycardia, and ventricular fibrillation have been reported in patients being treated with chloroquine or hydroxychloroquine, alone or in combination with azithromycin or other QTc prolonging drugs, for treatment of COVID-19[8]

- In a cohort of 84 patients with COVID-19 who were treated with hydroxychloroquine/azithromycin, QTc was significantly prolonged; in 9 (11%) patients, QTc was prolonged to >500 ms[18]

- In a cohort 649 COVID-19 patients, HCQ use was associated with a significant QT and QTc interval prolongation (median +13 ms); ventricular arrythmia rate was 1.1%[38] *(added 10/1/2020)*

- In a cohort of 90 COVID-19 patients, 19% of patients on HCQ monotherapy developed prolonged QTc ≥500 ms; concurrent azithromycin use was associated with a greater risk of QT

- Infectious Diseases Society of America recommends against use with or without azithromycin in the hospital setting[12] *(updated 8/23/2020)*

- NIH guidelines recommend against use of hydroxychloroquine (with or without azithromycin) in hospitalized patients or outpatients[19] *(updated 4/23/2021)*

- NIH guidelines recommend against use of hydroxychloroquine for SARS-CoV-2 post-exposure prophylaxis[19] *(added 2/14/2021)*

- Some clinicians claim the combination of HCQ plus azithromycin is effective for early outpatient treatment of COVID-19, but randomized, controlled trials are lacking *(added 9/10/2020)*

- FDA revoked Emergency Use Authorization that allowed use in some hospitalized patients for whom a clinical trial was not feasible; ongoing analysis indicated that chloroquine and hydroxychloroquine are unlikely to be effective for treatment of COVID-19 and are associated with serious cardiac adverse events; FDA concluded benefit no longer outweighs risk[13] *(updated 6/16/2020)*

- WHO guidelines strongly recommend against use of hydroxychloroquine for prevention of COVID-10[47] *(added 3/6/2021)*

Pregnancy:

- No evidence of increased rate of birth defects in pregnant women

HYDROXYCHLOROQUINE (CONTINUED)

- Transferred to ICU or died w/in 7 days: 20.2% HCQ vs 22.1% w/o HCQ (no significant difference)

Limitations: not randomized or peer reviewed

J Magagnoli et al 2020[17] *(updated 4/28/2020)*

Population: hospitalized male patients in VA medical centers across the US (n=368)

Design:

- Retrospective; HCQ vs HCQ plus azithromycin vs no HCQ

Results:

- No significant difference in the rate of mechanical ventilation between groups (13.3% HCQ, 6.9% HCQ + azithromycin, and 14.1% no HCQ)
- Compared to no HCQ, rates of death higher in the HCQ group, but not the HCQ + azithromycin group (11.4% no HCQ vs 27.8% with HCQ and 22.1% with HCQ + azithromycin)

Limitations: retrospective, not peer reviewed

J Geleris et al. NEJM 2020[20] *(added 5/9/2020)*

Population: consecutive hospitalized patients (n=1376 patients in analysis)

Design: observational; single medical center in New York City; median follow-up 22.5 days

Results:

- 811 (58.9%) patients treated with HCQ

interval changes than HCQ alone *(added 10/14/2020)*

Drug Interactions:

- Avoid use with other QT interval-prolonging drugs. Concurrent use with azithromycin can cause additive effects on the QT interval; avoid coadministration in patients at high risk of QT interval prolongation; ECG monitoring, correction of electrolyte abnormalities, and avoidance of other QT prolonging agents is recommended if coadministered[6-8]
- May inhibit CYP2D6 and may be metabolized by CYP2C8, 2D6, and 3A4 to some extent; less likely to cause CYP-related interactions than chloroquine
- Separate from antacids/kaolin by 4 hours
- May increase digoxin levels
- May impair activity of antiepileptic drugs
- FDA warns that coadministration of remdesivir and chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; concurrent use is not recommended[26] *(added 6/18/2020)*

Embryotoxicity:

- Embryonic deaths and ocular malformations have occurred in pregnant rats

HYDROXYCHLOROQUINE (CONTINUED)	▪ HCQ-treated patients had more severe illness than those who were not treated with the drug ▪ No significant association between HCQ use and intubation or death (HR 1.04; 95% CI 0.82-1.32) **Limitations:** observational data **W Tang et al. BMJ 2020**[21] *(added 5/18/20)* **Population:** hospitalized patients, mostly mild to moderate disease (n=150) **Design:** open-label HCQ 1200mg x 3 days, then 800 mg/day x2-3 weeks vs standard care **Results:** ▪ No significant difference in probability of negative conversion ▪ Adverse effects more common with HCQ (mainly diarrhea) **Limitations:** open label, tx initiated late, confounding tx allowed **Mehra et al. Lancet 2020**[22] *(added 5/26/20)* *(updated 6/4/2020)* ***Study Retracted[24]*** ▪ *Retracted because of concerns about the accuracy of the data and analysis; an independent audit was not possible because the full dataset was not made available* **Population:** hospitalized patients with COVID-19 who received chloroquine or HCQ with or without a macrolide within 48 hrs of diagnosis; control patients did not

HYDROXYCHLOROQUINE (CONTINUED)	receive treatment with these drugs (n = 96,032) **Design:** observational analysis of multinational registry **Results:** ▪ treatment was associated with an increased risk of in-hospital mortality and ventricular arrhythmia compared to control group **Limitation:** observational **<u>WHO Solidarity Trial 2020</u>[23,42]** *(updated 6/20/2020;)* ▪ HCQ arm stopped on June 18, 2020 based on data from the Solidarity trial, the RECOVERY trial, and a Cochrane review of other HCQ evidence *(update 10/19/2020; 12/2/2020)*[42] **Population:** hospitalized patients with COVID-19 at 405 hosptials in 30 countries (n=11,330 patients randomized; n=954 to HCQ) **Design:** randomized, open-label trial evaluating remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon-beta 1a **Results:** ▪ HCQ did not reduce mortality, need for ventilation, or duration of hospitalization ▪ death rate ratio with remdesivir was 1.19 (95% CI 0.89-1.59; 104/947 HCQ vs 84/906 control; p=0.23) ▪ ventilation initiated after randomization in 75 patients in the HCQ group vs 66 in the control group ▪ 64% of patients who received HCQ were still hospitalized at day 7 vs 54% in the control group

HYDROXYCHLOROQUINE (CONTINUED)	**Limitations:** interim results; open-label; conducted in many varied settings around the world; timing of treatment initiation not standardized **RECOVERY Trial 2020[41]** *(updated 10/14/2020)* **Population:** hospitalized adults in the UK (n=4716) **Design:** open-label, randomized controlled trial; HCQ vs usual care **Results**: ▪ 28-day mortality was not significantly different between patients treated with HCQ and those who received usual care (27.0% vs 25.0%; p=0.15) ▪ Consistent results reported in all subgroups ▪ Results suggested HCQ-treated patients less likely to be discharged alive within 18 days vs patients given standard care ▪ Among patients not on mechanical ventilation at baseline, HCQ group had higher frequency of invasive mechanical ventilation or death (30.7% vs 26.9%) ▪ No difference in incidence of new major cardiac arrhythmia **Limitations**: enrollment stopped early when interim analysis showed lack of efficacy **S Arshad et al. Int J Infect Dis 2020[28]** *(added July 7, 2020)* **Population:** Consecutive hospitalized patients in a hospital system in Michigan (n=2541)

HYDROXYCHLOROQUINE (CONTINUED)	**Design:** Multi-center, retrospective observational study comparing hydroxychloroquine alone or with azithromycin, azithromycin alone or neither **Results:** ▪ in-hospital mortality was 20.1% with hydroxychloroquine + azithromycin, 13.5% with hydroxychloroquine, 22.4% with azithromycin, and 26.4% with neither drug (p<0.001) ▪ 82% of patients received hydroxychloroquine within 24 hours of admission **Limitations:** retrospective, observational data **CP Skipper et al. Ann Intern Med 2020[29]** *(added 7/17/2020)* **Population:** symptomatic outpatients with COVID-19 or probable COVID-19 within 4 days of symptom onset (n=423) **Design:** randomized, double-blind, placebo-controlled trial ▪ HCQ (800 mg once, 600 mg 6-8 hrs later, then 600 mg once/day x 4 days) vs placebo **Results:** ▪ 81% had confirmed COVID-19 or exposure to a person with confirmed infection ▪ 56% enrolled within 1 day of symptom onset ▪ no significant difference in **symptom severity** over 14 days between HCQ and placebo groups (relative difference in symptom severity 12%; p=0.117) ▪ no significant difference in percentage of patients who had

HYDROXYCHLOROQUINE (CONTINUED)

symptoms at 14 days (24% vs 30% with placebo; p=0.21)
- significantly more patients treated with HCQ had **adverse effects** (43% vs 22%; p<0.001)
- 4 hospitalizations and 1 nonhospitalized death in the HCQ group vs 10 hospitalizations and 1 hospitalized death in the placebo group (p=0.29)

Limitations: only 58% of patients received COVID-19 testing

Rosenberg et al. JAMA 2020[30]
(added 7/22/2020)
Population: hospitalized patients
Design: retrospective multicenter cohort study
- HCQ plus azithromycin, HCQ alone, azithromycin alone, or neither

Results:
- Patients in the treatment groups had more severe disease at baseline than those not treated
- Compared with patients receiving neither drug, there was no difference in the in-hospital mortality rate in patients who received any of the 3 treatments
- Patients who received HCQ plus azithromycin had a higher risk of cardiac arrest compared to those who received neither drug

Limitations: observational data

Cavalcanti et al. NEJM 2020[31] *(added 7/23/2020; updated 11/28/2020)*
Population: hospitalized patients with suspected or confirmed COVID-19 receiving no supplemental oxygen or a max of 4 L/min (n=667

HYDROXYCHLOROQUINE (CONTINUED)	randomized; n=504 with confirmed COVID-19 in the modified intention-to-treat) **Design:** open-label, multicenter randomized controlled trial ▪ HCQ 400 mg bid vs HCQ 400 mg bid plus azithromycin 500 mg once/day x 7 days vs standard care alone **Results:** ▪ Treatment started a median of 7 days after symptom onset; patients who started treatment up to 14 days after symptom onset were included ▪ HCQ alone or with azithromycin did not improve clinical status at 15 days on an ordinal scale compared to standard care alone (primary endpoint in the modified intention-to-treat population, which included only those with confirmed COVID-19) ▪ QT interval prolongation and liver enzyme elevations occurred more frequently with HCQ with or without azithromycin than with standard care alone **Limitations:** open-label trial, some patients previously received treatment
	Mitja et al. Clin Infect Dis 2020[33] *(added 9/9/2020)* **Population:** non-hospitalized adults in Spain with COVID-19 and <5 days of symptoms (n=293) **Design:** open-label, randomized trial

HYDROXYCHLOROQUINE (CONTINUED)	▪ HCQ 800 mg x 1 day, then 400 mg once/day x 6 days vs no antiviral treatment (not placebo controlled) **Results:** ▪ Median time from symptom onset to randomization: 3 days ▪ No significant difference in mean reduction of viral load at day 3 or at day 7 ▪ Risk of hospitalization was not significantly different between the groups (5.9% HCQ vs 7.1% control) ▪ Time to resolution of symptoms was similar (10 days HCQ vs 12 days control; p=0.38) (study not powered for this endpoint) ▪ No cardiovascular events reported **Limitations:** open-label trail, did not evaluate HCQ with azithromycin; 7-day evaluations not included in original protocol **Million et al. Travel Med Infect Dis 2020**[34] *(added 9/9/2020)* **Population:** patients with mild (95% of patients) to severe COVID-19 in France (n=1061) **Design:** retrospective analysis of outcomes of patients who were given early treatment with HCQ + azithromycin for ≥3 days **Results:** ▪ Mean time from onset of symptoms to treatment was 6.4 days ▪ Good clinical outcome and virologic cure occurred in 973 patients (91.7%) within 10 days ▪ Poor clinical outcome (death, transfer to ICU, or hospitalization for >10 days) occurred in 46

HYDROXYCHLOROQUINE (CONTINUED)

patients (4.3%) and 10 patients (0.9%) died
- Poor clinical outcomes were associated with older age, illness severity, and low HCQ serum concentrations
- 9 patients had QTc prolongation ≥ 60 ms from baseline; none were > 500 ms

Limitations: retrospective data, no control group; data incomplete for some patients

Scholz, Derwand, Zelenko. 2020[35] *(added 9/10/2020; updated 1/1/2020)*

Population: outpatients with COVID-19 (n=141)

Design: retrospective case series
- **Cases** received treatment with HCQ + azithromycin + zinc x 5 days after risk stratification criteria were met
- **Untreated controls**: independent public reference data from 337 patients with COVID-19 from the same community

Results:
- Treatment started after 4 days of symptom onset
- 4 of 141 (2.8%) treated patients were hospitalized; 58 of 377 (15.4%) controls were hospitalized (p<0.001)
- 1 of 141 (0.7%) treated patients died vs 13 of 377 (3.5%) controls (p=0.16)

Limitations: not peer reviewed; retrospective case series; risk criteria unclear; control group characteristics unclear

HYDROXYCHLOROQUINE (CONTINUED)	**Barbosa Esper et al. 2020[36]** *(added 9/11/2020)* **Population:** symptomatic outpatients with suspected COVID-19 evaluated by telemedicine in Brazil (n=636) **Design:** Prospective, observational ▪ patients given hydroxychloroquine plus azithromycin (n=412) were compared to those who refused medication (n=224) **Results:** ▪ mean time from symptom onset to treatment was 5 days ▪ 1.9% of treatment group required hospitalization compared to 5.4% of control group (p<0.001) ▪ 1.17% of patients treated before day 7 of symptoms needed hospitalization compared to 3.2% of patients treated after day 7 **Limitations:** not peer reviewed, observational data **WH Self et al. JAMA 2020[44]** *(updated 11/9/2020)* **Population:** hospitalized adults with COVID-19 with respiratory symptoms (n=479) **Design:** multicenter, blinded, randomized trial ▪ Hydroxychloroquine 400 mg bid x 1 day, then 200 mg bid x 4 days vs placebo **Results:** ▪ At day 14, there was no significant difference in the COVID Outcomes Scale score between the hydroxychloroquine and placebo groups

HYDROXYCHLOROQUINE (CONTINUED)	▪ Trial enrollment stopped for futility **Limitations:** long duration of symptoms before randomization for treatment (up to 10 days), only monotherapy evaluated, drug concentrations not evaluated **FH Annie et al. Pharmacotherapy 2020[45]** *(added 11/30/2020)* **Population:** patients receiving HCQ within 48 hours of hospital admission (n=3012) **Design:** retrospective cohort study **Results:** ▪ No difference in overall 30-day mortality between the HCQ and no-HCQ groups ▪ No difference between groups in outcome combining mortality and an arrhythmogenic diagnosis ▪ Results remained statistically insignificant with HCQ+azithromycin **Limitations:** restrospective data **Barratt-Due et al. NOR-Solidarity Ann Intern Med 2021[48]** *(added 7/15/2021)* **Population:** hospitalized adults with confirmed SARS-CoV-2 at 23 hospitals in Norway (n=185) **Design:** independent, add-on, randomized controlled trial to WHO Solidarity trial ▪ Patients given remdesivir, hydroxychloroquine, or standard of care **Results:** ▪ No significant difference in mortality during hospitalization between groups

HYDROXYCHLOROQUINE (CONTINUED)

- There was a decrease in SARS-CoV-2 oropharyngeal viral load during the first week after randomization in all groups; the decreases in viral load and 10-day viral loads were similar among remdesivir, hydroxychloroquine, and standard of care groups

Limitations: no placebo group, small sample size

PROPHYLAXIS TRIALS:

DR Boulware et al NEJM 2020[25] (prophylaxis)

(added 6/4/2020)

Population: adults with household or occupational exposure to an individual with confirmed COVID-19 at a distance <6 feet for >10 mins with no mask or eye shield (high-risk) or with a mask but no eye shield (moderate-risk) (n = 821)

Design: randomized, double-blind, placebo-controlled trial in the US and Canada

Prophylaxis given within 4 days after exposure

- HCQ (800 mg x 1, then 600 mg in 6 to 8 hrs, then 600 mg daily x 4 days) vs placebo

Results:

- 87.6% had a high-risk exposure
- New illness compatible with COVID-19 within 14 days was similar between the 2 groups (11.8% HCQ vs 14.3% placebo; p=0.35)
- Patient-reported adherence to study drug regimen was lower in HCQ group (75.4% with HCQ vs 82.6% with placebo; p=0.01)

HYDROXYCHLOROQUINE (CONTINUED)

- Adverse effects occurred more often with HCQ (GI effects most common)
- No arrhythmias or deaths reported

Limitations: endpoint did not require laboratory-confirmed COVID-19; study population generally younger and healthier than those at most risk for COVID-19

N White and W Schilling et al (COPCOV trial)[27] *(added July 1, 2020)* **(prophylaxis)**

Population: Healthcare workers and staff who have close contact with COVID-19 patients (anticipated enrollment is 40,000+ subjects)

Design:

- Randomized, double-blind, placebo-controlled, multi-center prophylaxis trial
- Chloroquine/hydroxychloroquine vs placebo

Results: trial enrolling as of July 2020

Mitja et al. NEJM 2021[32]
(added 7/31/2020; updated 11/28/2020; updated ref 2/5/2021)

Population: asymptomatic contacts exposed to a PCR-positive COVID-19 case in Spain (n=2314)

Design: open-label, cluster-randomized trial

- HCQ 800 mg once, then 400 mg/day x 6 days vs usual care (no specific therapy)

Results:

- PCR-confirmed symptomatic COVID-19 within 14 days was not statistically significant between the two groups (5.7% with HCQ vs 6.2% with usual care)

HYDROXYCHLOROQUINE (CONTINUED)

- HCQ not associated with a lower incidence of SARS-CoV-2 transmission than usual care (18.7% vs 17.8%)
- Incidence of adverse effects higher in HCQ group (56.1% vs 5.9% with usual care) (mostly GI; 0.3% were cardiac events)

Limitations: open-label, no placebo group

Abella et al. JAMA Intern Med 2020 (PATCH trial)[37] *(added 10/1/2020)*

Population: healthcare workers exposed to patients with COVID-19 (n=132); all patients had negative results for SARS-CoV-2 at baseline

Design: randomized, double-blind, placebo-controlled pre-exposure prophylaxis trial

- HCQ 600 mg daily vs placebo x 8 weeks

Results:

- No significant difference in infection rates (determined by SARS-CoV-2 nasopharyngeal swab) in patients given HCQ vs placebo (6.3 vs 6.6%; p>0.99)
- 8 infections occurred during the study; none required hospitalization
- Mild adverse events more common in patients taking HCQ
- Median change in QTc was similar between groups

Limitations: trial stopped early for futility and may have insufficient power; most participants were young and healthy

Gentry et al. Lancet Rheumatol 2020[38]

Population: patients in the VA health system with rheumatoid arthritis,

systemic lupus erythematosus, or associated rheumatological conditions (n=32,109)
Design: retrospective cohort study
- Patients receiving chronic HCQ vs those not on HCQ

Results:
- Incidence of active SARS-CoV-2 infections not significantly different between patients receiving HCQ vs those who were not

Limitations: retrospective data

Rajasingham et al. Clin Infect Dis 2020[43] *(added 10/28/2020)*
Population: adult healthcare workers with ongoing exposure to persons with SARS-CoV-2 in the US and Canada (n=1483)
Design: randomized, double-blind, placebo-controlled
- HCQ 400 mg once/week or twice/week or placebo x 12 weeks

Results:
Incidence of COVID-19:
- 0.27 events per person-year with HCQ once/wk
- 0.28 events per person-year with HCQ twice/wk
- 0.38 events per person-year with placebo

Hazard Ratio (compared to placebo):
- HCQ once/wk: 0.72 (95% CI 0.44-1.16; p=0.18)
- HCQ twice/wk: 0.74 (95% CI 0.46-1.19; p=0.22)

Limitations: challenges with availability and sensitivity of PCR testing in early COVID illness; HCQ dosing; underpowered

RV Barnabas et al. Ann Intern Med 2020[46] *(added 12/10/2020)*

	Population: close contacts recently exposed (<96 hours) to persons with diagnosed SARS-CoV-2 infection (n=671 households) **Design**: Household-randomized, double-blind, controlled trial ▪ HCQ 400 mg/day x 3 days, then 200 mg/day x 11 days or ascorbic acid 500 mg/day, then 250 mg/day **Results:** ▪ SARS-CoV-2 acquisition at day 14 was not significantly different between HCQ (53 events) and control (45 events) among 689 participants who had a negative SARS-CoV-2 test result at baseline ▪ More patients in HCQ group experienced adverse effects ▪ **Limitations:** median delay of 2 days between exposure, testing, and treatment

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AZITHROMYCIN – GENERICS
***ZITHROMAX* (PFIZER)[1]**

(updated 7/23/2021)

Dosage:
- Optimal dosage not established

500 mg on day 1, then 250 mg once/day on days 2-5[2]

- In addition to hydroxychloroquine

P Gautret et al. Int J Antimicrob Agents 2020[3]

- Addition of azithromycin to hydroxychloroquine (n=6) resulted in a more rapid decrease in viral load compared to hydroxychloroquine treatment alone in one open-label trial in France (see hydroxychloroquine above)

Rosenberg et al. JAMA 2020[10]
(added 7/22/2020)
Population: hospitalized patients
Design: retrospective multicenter cohort study
- HCQ plus azithromycin, HCQ alone, azithromycin alone, or neither

Results:
- Patients in the treatment groups had more severe disease at baseline than those not treated
- Compared with patients receiving neither drug, there was no difference in the in-hospital mortality rate in patients who received any of the 3 treatments
- Patients who received HCQ plus azithromycin had a higher risk of cardiac arrest compared to those who received neither drug

Limitations: observational data

S Arshad et al. Int J Infect Dis 2020[11]
(added July 7, 2020)
Population: Consecutive hospitalized patients in a hospital system in Michigan (n=2541)

Adverse Effects:
- GI disturbances, headache, dizziness, hepatotoxicity, QT prolongation[4]

Drug Interactions:
- Use with other drugs that prolong the QT interval (such as chloroquine and hydroxychloroquine) can result in additive effects; avoid coadministration in patients at high risk of QT interval prolongation; ECG monitoring, correction of electrolyte abnormalities, and avoidance of other QT prolonging agents is recommended if coadministered[4-6]

- In a cohort of 84 patients with COVID-19 who were treated with hydroxychloroquine/azithromycin, QTc was significantly prolonged; in 9 (11%) patients, QTc was prolonged to >500 ms[7]

- May increase the risk of toxicity with digoxin, cyclosporine, tacrolimus

- *In vitro* activity against some viruses (influenza A H1N1 and Zika); no data on its activity against SARS-CoV-2

- Minimal data supporting efficacy in COVID-19 in humans and cardiac toxicity can occur when used with chloroquine/hydroxychloroquine

- Infectious Diseases Society of America recommends against use with chloroquine or hydroxychloroquine in the hospital setting [8]

- NIH guidelines recommend against use of hydroxychloroquine or chloroquine with or without azithromycin[9] *(updated 4/23/2021)*

- NIH guidelines recommend against use of antibacterial therapy, including azithromycin, in the absence of another indication[9] *(added 4/23/2021)*

- Some evidence of immunomodulatory and anti-inflammatory activity; it has been used as adjunctive treatment for other respiratory conditions (such as COPD)

Pregnancy:
- No evidence of fetal harm

AZITHROMYCIN (continued)	**Design:** Multi-center, retrospective observational study comparing hydroxychloroquine alone or with azithromycin, azithromycin alone or neither **Results:** ▪ in-hospital mortality was 20.1% with hydroxychloroquine + azithromycin, 13.5% with hydroxychloroquine, 22.4% with azithromycin, and 26.4% with neither drug (p<0.001) ▪ 82% of patients received hydroxychloroquine within 24 hours of admission **Limitations:** retrospective, observational data **Mehra et al. Lancet 2020**[12] *(added 5/26/20)* *(updated 6/4/2020)* *****Study Retracted**[13]******* ▪ *Retracted because of concerns about the accuracy of the data and analysis; an independent audit was not possible because the full dataset was not made available* **Population:** hospitalized patients with COVID-19 who received chloroquine or HCQ with or without a macrolide within 48 hrs of diagnosis; control patients did not receive treatment with these drugs (n = 96,032) **Design:** observational analysis of multinational registry **Results:** ▪ treatment was associated with an increased risk of in-hospital mortality and ventricular

AZITHROMYCIN (continued)

arrhythmia compared to control group

Limitation: observational

J Magagnoli et al 2020[14] *(updated 4/28/2020)*

Population: hospitalized male patients in VA medical centers across the US (n=368)

Design:

- Retrospective; HCQ vs HCQ plus azithromycin vs no HCQ

Results:

- No significant difference in the rate of mechanical ventilation between groups (13.3% HCQ, 6.9% HCQ + azithromycin, and 14.1% no HCQ)
- Compared to no HCQ, rates of death higher in the HCQ group, but not the HCQ + azithromycin group (11.4% no HCQ vs 27.8% with HCQ and 22.1% with HCQ + azithromycin)

Limitations: retrospective, not peer reviewed

Cavalcanti et al. NEJM 2020[15] *(added 7/23/2020)*

Population: hospitalized patients with suspected or confirmed COVID-19 receiving no supplemental oxygen or a max of 4 L/min (n=667 randomized; n=504 with confirmed COVID-19 in the modified intention-to-treat)

Design: open-label, multicenter randomized controlled trial

- HCQ 400 mg bid vs HCQ 400 mg bid plus azithromycin 500 mg once/day x 7 days vs standard care alone

AZITHROMYCIN (continued)	**Results:** ▪ Treatment started a median of 7 days after symptom onset; patients who started treatment up to 14 days after symptom onset were included ▪ HCQ alone or with azithromycin did not improve clinical status at 15 days on an ordinal scale compared to standard care alone (primary endpoint in the modified intention-to-treat population, which included only those with confirmed COVID-19) ▪ QT interval prolongation and liver enzyme elevations occurred more frequently with HCQ with or without azithromycin than with standard care alone **Limitations:** open-label trial, some patients previously received treatment **Barbosa Esper et al. 2020**[16] *(added 9/11/2020)* **Population:** symptomatic outpatients with suspected COVID-19 evaluated by telemedicine in Brazil (n=636) **Design:** Prospective, observational ▪ patients given hydroxychloroquine plus azithromycin (n=412) were compared to those who refused medication (n=224) **Results:** ▪ mean time from symptom onset to treatment was 5 days ▪ 1.9% of treatment group required hospitalization compared to 5.4% of control group (p<0.001) ▪ 1.17% of patients treated before day 7 of symptoms needed

AZITHROMYCIN (continued)	hospitalization compared to 3.2% of patients treated after day 7 **Limitations:** not peer reviewed, observational data **RHM Furtado et al Lancet 2020[17]** *(added 9/18/2020)* **Population:** hospitalized patients in Brazil with severe disease (requiring >4 L/min supplemental oxygen, high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation) (n=447; n=397 in mITT with confirmed COVID) **Design:** open-label, randomized trial ▪ azithromycin plus standard care (which included HCQ) vs standard care alone **Results:** ▪ clinical status measured on an ordinal scale at day 15 was similar between the two groups ▪ adverse events, including cardiac arrhythmias, were not significantly different between groups **Limitations:** open-label; high-risk population; some patients in control group received macrolide during trial **RECOVERY TRIAL Lancet 2021[18]** *(updated 2/15/2021)* **Population:** hospitalized adults with COVID-19 in the UK (n=7763) **Design:** randomized, open-label, adaptive platform ▪ Azithromycin 500 mg QD x 10 days vs standard care alone **Results:** ▪ 28-day mortality rate was 22% (561/2582) with azithromycin and

AZITHROMYCIN (continued)

22% (1162/5181) with standard care alone
- Duration of hospitalization or risk of requiring ventilation was also not significantly reduced with azithromycin

Limitations: open-label, hospitalized patients only

PRINCIPLE Trial Lancet 2021[19]
(added 3/7/2021)
Population: outpatient adults in the UK with suspected COVID-19 who were at risk of an adverse clinical outcome (≥65 years old or ≥50 years old with 1 or more comorbidities) (n=2265)
Design: primary care, randomized, open-label, multi-arm, adaptive platform trial
- Azithromycin 500 mg/day x 3 days, usual care plus other interventions, or usual care alone

Results:
- 80% of patients treated with azithromycin and 77% of patients treated with usual care reported feeling recovered within 28 days (HR 1.08; 95% Bayesian credibility interval 0.95-1.23)
- 3% of patients in the azithromycin group and 3% in the usual care group were hospitalized

Limitation: open-label; included patients without SARS-CoV-2 PCR test results

AZITHROMYCIN (continued)

Hinks et al. ATOMIC2 Lancet Respir Med 2021[20]

(added 7/15/2021)

Population: adults who presented to hospitals in the UK with highly probable or confirmed COVID-19 who were symptomatic <14 days and were considered suitable for ambulatory management (n=298)

Design: randomized, open-label trial

- azithromycin 500 mg PO once/day x 14 days plus standard care vs standard care alone

Results:

- 10% of patients who received azithromycin and 12% of those who received standard care alone were hospitalized or died during the study (adjusted odd ratio 0.91; 95% CI 0.43-1.92; p=0.80)

Limitations: small open-label trial; PCR confirmation not required for enrollment

Oldenburg et al. JAMA 2021[21]

(added 7/23/2021)

Population: adult outpatients in the US with a positive SARS-CoV-2 test result within 7 days prior to enrollment (n=263)

Design: remote, randomized trial

- Azithromycin 1.2g PO x 1 dose vs placebo

Results:

- Trial terminated early for futility
- At day 14, 50% of azithromycin-treated patients were symptom free and 50% of placebo-treated patients were symptom free
- By day 21, 5 patients treated with azithromycin were hospitalized

AZITHROMYCIN (continued)	compared to 0 of those given placebo (p=0.16) **Limitations:** terminated early, primary outcome changed, nonadherence

1. FDA-approved for other indications.
2. Experimental dosage used for treatment of COVID-19 in trials, but optimal dosage not yet established.
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HIV Protease Inhibitors

ATAZANAVIR[1] (ATV) – *REYATAZ* (BMS) AND GENERICS

Dosage:
- Optimal dosage/duration not established
- 300-400 mg PO once/day[2]

- Predicted to inhibit SARS-CoV-2 replication[3,4]
- No clinical trial data available

Adverse Effects:
- Nausea, diarrhea, asymptomatic indirect hyperbilirubinemia, rash, nephrolithiasis, cholelithiasis, PR interval prolongation

Drug Interactions:
- Substrate of CYP3A4 and inhibitor of CYP3A4 and CYP2C8[5]
- Use of drugs that increase gastric pH, such as PPIs, H2-antihistamines, and antacids may decrease absorption of atazanavir; administer atazanavir 2 hours before or 10 hours after an H2-antihistimine; consider avoiding use of PPIs

- No clinical trials available evaluating use of atazanavir for COVID-19
- Available in powder form or capsules can be opened for administration via enteral tube
- NIH recommends against use of HIV protease inhibitors, except in the context of a clinical trial, because of unfavorable pharmacodynamics and negative clinical trial data[6]

Pregnancy:
- Does not appear to increase the risk of major birth defects

DARUNAVIR/COBICISTAT[1] - *PREZCOBIX* (JOHNSON & JOHNSON)

Dosage:
800/150 mg
PO once/day x 5 days[7]

Shanghai Public Health Clinical Center (SPHCC)[8,9]
Population: hospitalized patients (n=30)
Design:
- randomized, open label
- darunavir/cobicistat 800/150 mg once/day x 5 days vs standard care

Results:
- darunavir/cobicistat was **not** effective

Adverse Effects:
- Nausea, diarrhea, increased transaminases, headache, rash, severe skin reactions (including Stevens-Johnson syndrome)

Drug Interactions:
- Substrate and inhibitor of CYP3A4 and CYP2D6[5]

- An initial laboratory study had suggested darunavir (at exposures higher than those achieved in humans) may be effective against SARS-CoV-2
- No evidence that darunavir is effective for treatment of COVID-19
- NIH recommends against use of HIV protease inhibitors, except in the context of a clinical trial, because of unfavorable pharmacodynamics and negative clinical trial data[6]

Pregnancy:
- Not recommended for use in pregnant women

LOPINAVIR/RITONAVIR[1] (LPV/RTV) – *KALETRA* (ABBVIE)

(updated 10/19/2020)

Dosage:

- Optimal dosage/duration not established
- Dosages/duration/ concomitant drugs used in COVID-19 clinical trials have varied
- 400/100 mg PO bid[2]
- With or without food
- Tablets should not be crushed (decrease exposure)

B Cao et al. NEJM 2020[10]

Population:

- hospitalized patients w/ pneumonia, SaO_2 ≤94% or PaO_2:FiO_2 ≤300 mm Hg (n=199)
- median time from symptom onset to randomization was 13 days

Design:

- randomized, open-label vs standard care

Results:

- no statistically significant difference in time to clinical improvement (median of 16 days in both groups), time to discharge (median 12 days with LPV/RTV vs 14 days with standard care), mortality (19.2% vs 25.0%), or viral load reduction

Limitations:

- not blinded
- treatment started long after symptom onset

Schoergenhofer et al. Ann Intern Med 2020[15] *(added 7/22/2020)*

Population: hospitalized patients admitted to "normal care" ward (n=8)

Design: case series; pharmacokinetic analysis

Results:

- median trough lopinavir concentrations 13.6 mcg/mL
- to achieve half-maximal effective concentration (EC_{50}) for SARS-CoV-2, lopinavir trough concentrations would need to be 60- to 120-fold higher

Adverse Effects:

- Diarrhea, nausea, vomiting, headache, asthenia, hepatoxicity, pancreatitis, PR and QT interval prolongation, bradycardia[14]

Drug Interactions:

- Substrate and inhibitor of CYP3A4[5]
- Avoid use with other PR or QT interval-prolonging drugs[11]
- *In vitro* activity against SARS-CoV, and MERS-CoV; data in SARS-CoV-2 limited
- Society of Critical Care Medicine recommends against use of LPV/RTV in critically ill patients[12]
- Infectious Diseases Society of America recommends use only in the context of a clinical trial[13]
- NIH recommends against use of HIV protease inhibitors, except in the context of a clinical trial, because of unfavorable pharmacodynamics and negative clinical trial data[6]

Pregnancy:

- No association with teratogenic effects; may be associated with preterm delivery

LOPINAVIR/RITONAVIR (continued)	**Limitations:** small case series; only trough concentration evaluated; no *in vivo* data on EC_{50} dose of lopinavir for SARS-CoV-2 **RECOVERY Group. Lancet 2020[16]** *(added 10/6/2020)* **Population:** hospitalized patients in the UK (n=5040) **Design:** randomized, open-label, platform trial ▪ LPV/RTV 400/100 mg or standard care x 10 days **Results:** ▪ Mortality at 28 days was 23% with LPV/RTV and 22% with standard care (p=0.60) ▪ Time until discharge was a median of 11 days in both groups ▪ In patients not on baseline invasive mechanical ventilation, no significant difference in number of patients who met a composite endpoint of invasive mechanical ventilation or death ▪ Results consistent across subgroups **Limitations:** open-label, very few intubated patients, unclear if dose achieved adequate lung concentrations **WHO SOLIDARITY 2020[17]** *(update 10/19/2020; 12/2/2020)* ▪ LPV/RTV arm stopped on July 4, 2020 **Population:** hospitalized patients with COVID-19 at 405 hospitals in 30 countries (n=11,330 patients randomized; n=1411 to LPV/RTV) **Design:** randomized, open-label trial evaluating remdesivir, HCQ, LPV/RTV,

LOPINAVIR/RITONAVIR (continued)	and interferon-beta 1a compared to local standard of care **Results:** ▪ LPV/RTV did not reduce mortality, need for ventilation, or duration of hospitalization ▪ death rate ratio with LPV/RTV was 1.00 (95% CI 0.79-1.25; 148/1399 vs 146/1372 control; p=0.97) ▪ ventilation initiated after randomization in 124 patients in the LPV group vs 119 in the control group ▪ 68% of patients who received LPV were still hospitalized at day 7 vs 59% in the control group **Limitations:** interim results; open-label; conducted in many varied settings around the world; timing of treatment initiation not standardized

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INTERFERON BETA-1B –
BETASERON
EXTAVIA

RIBAVIRIN –
***REBETOL*, AND GENERICS**

(added 5/14/2020; updated 10/19/2020)

Dosage:
- Optimal dosage unknown

- Dosage used in clinical trial: **Interferon beta-1b**: 1 mL on alternate days x 1-3 doses depending on day of initiation

Ribavirin: 400 mg q12h x 14 days

Hung et al. Lancet 2020[1]
Population: hospitalized patients with symptom duration ≤14 days (n=127)
Design:
- prospective, randomized, open-label, multi-center
- LPV/RTV + ribavirin + interferon beta-1b vs LPV/RTV x 14 days
- Treatment started within 48 hrs of admission

Results:
- Time to negative nasopharyngeal swab shorter with triple combination vs LPV/RTV (7 vs 12 days; p=0.0010)
- Time to alleviation of symptoms: 4 days with combination vs 8 days with LPV/RTV (p<0.0001)

Limitations: patients presenting ≥7 days from symptom onset did not receive interferon due to concerns about proinflammatory effects; no critically ill patients included

Adverse Effects:
- Hung et al trial found no difference in adverse events between 2 groups

- **Interferon:** injection- depression site reactions, flu-like symptoms, transaminase elevations, possible cardiac toxicity, autoimmune disorders, allergic reactions, hepatotoxicity, seizures, suicidal ideation, lymphopenia

- **Ribavirin:** hemolytic anemia, leukopenia, cough, dyspnea, bronchospasm, rash, conjunctival irritation, neuropsychologic symptoms

Drug Interactions:
- **Ribavirin:** may decrease anticoagulant effect of warfarin, increase concentrations of azathioprine, increased risk of hepatic decompensation and lactic acidosis with NRTIs, additive myelosuppression with interferons, linezolid, clozapine, adalimumab

- Interferons modulate immune response and may have antiviral properties

- *In vitro* activity against SARS-CoV and MERS-CoV, but did not appear to improve disease outcomes in human studies[2]

- Society of Critical Care Medicine recommends against use of LPV/RTV in critically ill patients and states the evidence is insufficient to recommend interferons or ribavirin[3]

- NIH guidelines recommend against use of interferons in patients with severe or critical illness, except in a clinical trial; they state there are insufficient data to recommend for or against use in patients with early (<7 days from symptom onset) mild and moderate illness[4]

- If administered, should be given early in course of disease

- Peginterferon lambda (not available in the US) accelerated viral decline in outpatients with COVID-19 in a phase 2 trial[7] *(added 2/10/2021)*

Pregnancy:
Interferon:
- may cause fetal harm, based on data from animal studies
- data from pregnancy registries have not found an association between interferon exposure and major birth defects

Ribavirin:
- contraindicated in pregnant women and in men whose partners are pregnant

			▪ pregnancy should be avoided for 6 months after treatment in women who received the drug and in women whose partners received the drug
INTERFERON BETA-1A – INHALED (SNG001) *(updated 1/13/2021)* **Dosage:** ▪ 6 MIU by inhalation via a mouthpiece once daily x 14 days[5]	**PD Monk et al. Lancet Respir Med – Inhaled Interferon[5]** *(added 7/20/2020; updated 11/13/2020)* **Population:** hospitalized patients in UK (n=101) **Design:** phase 2 randomized, double-blind, placebo-controlled trial ▪ Inhaled nebulized interferon beta-1a (SNG001) vs placebo **Results:** ▪ Mean symptom duration before starting treatment (9.6 days interferon vs 9.8 days placebo) ▪ Odds of improvement on the WHO Ordinal Scale for Clinical Improvement (OSCI) scale was more likely with interferon (HR 2.32; 95% CI 1.07-5.04; p=0.033) ▪ Development of severe disease (requiring ventilation or death) was nonsignificantly less likely in the ITT population with interferon than with placebo (OR 0.28; 95% CI 0.07-1.08; p=0.064) ▪ Breathlessness reduced in patients receiving interferon compared to placebo (p=0.007) ▪ 0 deaths with interferon; 3 deaths with placebo ▪ In patients with more severe disease on admission (requiring supplemental oxygen), interferon nonsignificantly increased the likelihood of hospital discharge (p=0.096)	▪ The most common adverse effect in the clinical trial was headache (15% vs 10% with placebo) ▪ Cough, decreased oxygen saturation, diarrhea, dry throat, oral pain, night sweats, tremor were also reported	▪ Interferons modulate immune response and may have antiviral properties ▪ *In vitro* activity against SARS-CoV and MERS-CoV, but did not appear to improve disease outcomes in human studies[2] ▪ SARS-CoV-2 suppresses interferon beta ▪ Patients with COVID-19 who develop more severe disease may have decreased interferon activity ▪ If administered, should be given early in course of disease ▪ NIH guidelines recommend against use of interferons in patients with severe or critical illness, except in a clinical trial; they state there are insufficient data to recommend for or against use in patients with early (<7 days from symptom onset) mild and moderate illness[4] ▪ Nebulized interferon not available in the US *(added 7/20/2020)* ▪ WHO SOLIDARITY trial arm of interferon beta-1a was stopped on October 16, 2020; no effects of IV interferon beta-1a compared to control on mortality (rate ratio, 1.16; 95% CI 0.96-1.39; p=0.11), ventilation, or duration of hospital stay were found[6] *(added 10/19/2020; updated 12/2/2020)*

INTERFERON BETA-1A – INHALED (SNG001) (continued)	▪ Median time to discharge was 6 days with interferon and 9 days with placebo **Limitations:** phase 2 trial; only in hospitalized, non-critically ill patients; limited sample size		▪ Synairgen initiating a phase 3 trial in the UK to evaluate use of an inhaled interferon beta 1a formulation (SNG001) for treatment of COVID-19 in hospitalized patients who require supplemental oxygen *(added 1/13/2021)* **Pregnancy:** ▪ data from pregnancy registries have not found an association between interferon exposure and major birth defects
INTERFERON ALPHA-2b (inhaled) *(added 5/25/2021)*	**J Yu et al. Br J Clin Pharmacol 2021[8]** *(added 5/25/2021)* **Population:** hospitalized adult patients with COVID-19 in China (n=1401) **Design:** retrospective study ▪ 852 (60.8%) patients received treatment with inhaled interferon alpha-2b 5 000 000 U twice daily **Results:** ▪ After adjusting for confounders, use of interferon alpha-2a was associated with a lower risk of the composite outcome of mechanical ventilation, ICU admission and death (hazard ratio 0.36; 95% CI 0.21-0.62) **Limitations:** retrospective study	▪ Adverse effects associated with interferons include depression, flu-like symptoms, transaminase elevations, possible cardiac toxicity, autoimmune disorders, allergic reactions, hepatotoxicity, seizures, suicidal ideation, lymphopenia	▪ Interferons modulate immune response and may have antiviral properties ▪ *In vitro* activity against SARS-CoV and MERS-CoV, but did not appear to improve disease outcomes in human studies[2] ▪ NIH guidelines recommend against use of interferons in patients with severe or critical illness, except in a clinical trial; they state there are insufficient data to recommend for or against use of interferon beta in patients with early (<7 days from symptom onset) mild and moderate illness[4] ▪ If administered, should be given early in course of disease ▪ Inhaled interferon alpha-2b not available in the US **Pregnancy:** ▪ Interferons may cause fetal harm, based on data from animal studies ▪ Data from pregnancy registries have not found an association between interferon exposure and major birth defects

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IVERMECTIN – *STROMECTOL* (MSD)

(updated 4/1/2022)

Dosage:
- Dosage for COVID-19 not established

200-400 mcg/kg/dose PO[1]

- Inhibits SARS-CoV-2 *in vitro*; ~5000-fold reduction in viral RNA in cell culture 48 hours after a single treatment[2]

Rajter et al. Chest 2020[5] *(updated 10/26/2020)*
Population: hospitalized patients (n=280)
Design: retrospective cohort; ivermectin compared to usual care
- 200 mcg/kg x 1 dose, 2nd dose given after 7 days if still hospitalized

Results:
- Most patients in both groups also received hydroxychloroquine and/or azithromycin
- Ivermectin associated with lower all-cause mortality compared to usual care (15.0% vs 25.2%; p=0.03)
- In the propensity-matched cohort, mortality remained lower with ivermectin (13.3% vs 24.5%; OR 0.47, CI 0.22-0.99; p<0.05)
- In 75 patients with severe pulmonary disease, mortality was lower with ivermectin (38.8% vs 80.7%, p=0.001)
- No significant difference in extubation rates (36.1% vs 15.4%, p=0.07)

Limitations: retrospective data; intervention timing not standardized

Adverse Effects:
- Generally well tolerated when used for treatment of lice; diarrhea has occurred
- Diarrhea, nausea, dizziness, pruritis, dermatologic reactions, lymphadenitis, arthralgia, and fever have been reported when used for treatment of onchocerciasis
- Overdose: symptoms include nausea, vomiting, diarrhea, hypotension, and neurologic effects (decreased consciousness, confusion, hallucinations, seizures, coma, and death) *(added 9/7/2021)*

Drug Interactions:
- Azithromycin may increase serum concentrations of ivermectin
- May potentiate effects of CNS depressants such as benzodiazepines

- FDA-approved for treatment of intestinal strongyloidiasis and onchocerciasis; used off-label for a variety of other parasitic infections including lice and scabies
- Inhibited SARS-CoV-2 *in vitro*; may inhibit nuclear transport activity
- NIH guidelines state there are insufficient data to recommend for or against use of ivermectin[3] *(updated 1/18/2021)*
- IDSA guidelines recommend against use of ivermectin outside the context of a clinical trial in outpatients or hospitalized patients with COVID-19[16] *(added 3/29/2021)*
- FDA warns against human use of ivermectin intended for use in animals[4]
- The American Medical Association (AMA), American Pharmacists Association (APhA), and American Society of Health-System Pharmacists (ASHP) issued a joint statement opposing use of ivermectin for treatment or prevention of COVID-19 outside of a clinical trial; they state there is insufficient evidence to support use of ivermectin for this indication and it has been demonstrated to be harmful to patients (calls to poison control centers due to ivermectin ingestion have increased 5-fold from pre-pandemic baseline)[20] *(added 9/7/2021)*
- CDC issued a health advisory regarding a rapid increase in ivermectin prescriptions and severe illness associated with use of the drug for prevention or treatment of COVID-19[21] *(added 9/7/2021)*

IVERMECTIN (continued)

R Mahmud et al. 2020[7] *(added 10/26/2020)*
Population: patients with mild to moderate COVID-19 in Bangladesh (n=400)
Design: randomized, double-blind, placebo-controlled
- Ivermectin + doxycycline added to standard care vs placebo plus standard care
- Ivermectin 6 mg stat; doxycycline 100 mg bid x 5 days

Results:
- More patients receiving ivermectin + doxycycline had early clinical improvement (60.7% vs 44.4%: p<0.03)
- Fewer patients receiving ivermectin + doxycycline had late clinical recovery (23.0% vs 37.2%; p<0.004)

Limitations: limited information available; has not been published or become available on a pre-print server; not peer reviewed

HA Hashim et al. MedRxiv 2020[8] *(added 11/4/2020)*
Population: outpatients or inpatients in Baghdad with COVID-19 with severity ranging from mild to critical (most patients had mild to moderate disease) (n=140)
Design: randomized controlled trial
Ivermectin (200 mcg/kg/day x 2 days; some patients received a 3rd dose 7 days after the 1st) plus doxycycline (100 mg bid x 5-10 days) added to standard care vs standard care alone
Results:
- Patients with critical disease were not included in the control group
- Results of an *in vitro* study suggest that ivermectin concentrations needed to inhibit SARS-CoV-2 in humans may not be achievable without toxic dosages of the drug[6] *(updated 10/26/2020)*

Pregnancy:
- Limited data available in pregnant women

IVERMECTIN (continued)	▪ 3/70 patients (4.28%) treated with ivermectin/doxycycline and 7/70 patients (10%) given standard care alone progressed to more advanced COVID-19 (p>0.05) ▪ Among patients with severe disease at randomization, 9% (1/11) given the active treatment and 31.81% (7/22) given standard care progressed to more advanced disease (p>0.05) ▪ Mortality rate in patients with severe disease was 0% (0/11) in patients treated with ivermectin/doxycycline and 27.27% (6/22) in those given standard care (p=0.14) ▪ Mean time to recovery was 10.61 days with ivermectin/doxycycline vs 17.9 days with standard care (p<0.05) **Limitations:** not peer reviewed, small sample size, single-blind **S Ahmed et al. Int J Infect Dis 2021**[9] *(added 1/19/2021)* **Population:** hospitalized patients with COVID-19 in Bangladesh (n=72) **Design:** randomized, double-blind, placebo-controlled trial ▪ Ivermectin alone (12 mg once/day x 5 days), ivermectin (12 mg single dose) + doxycycline (200 mg day 1, then 100 mg q12h x 4 days), or placebo **Results:** ▪ Virologic clearance occurred at 9.7 days in 5-day ivermectin vs 12.7 days with placebo (p=0.02); ivermectin + doxycycline not significantly different than placebo (11.5 days; p=0.27)

IVERMECTIN (continued)	**Limitations:** most patients mild disease; small study, if improves clinical outcomes unclear **AZK Chachar et al. Int J of Sci 2020**[10] *(added 1/19/2021)* **Population:** patients with mild COVID-19 in Pakistan (n=50) **Design:** open-label, randomized trial **Results:** no significant difference in percentage of patients who were asymptomatic at 7 days between ivermectin and placebo groups **Limitations:** small, open-label trial **ATMM Chowdhury et al. Research Square 2020**[11] *(added 1/19/2021)* **Population:** non-hospitalized patients with mild to moderate COVID-19 in Bangladesh (n=116) **Design:** randomized trial ▪ ivermectin + doxycycline or hydroxychloroquine + azithromycin **Results:** ▪ Difference in time to negative PCR and time to resolution of symptoms was not statistically significant between the two groups **Limitations:** small study, methods not clear, many patients excluded **P Soto-Becerra et al. medRxiv 2020**[12] *(added 1/19/2021)* **Population:** adults hospitalized with COVID-19 (without life-threatening illness) in mid- and high-level complexity hospitals in Peru (n=5683) **Design:** retrospective cohort emulating a target trial; data from electronic records from the Peruvian Social Security Health System

IVERMECTIN (continued)

- Hydroxychloroquine, ivermectin, azithromycin, hydroxychloroquine + azithromycin, or ivermectin + azithromycin within 48 hours of admission compared to standard care

Results:

- Ivermectin was not associated with improvements in mortality, death and/or oxygen requirement, or death and/or ICU admission

Limitations: observational data; not peer reviewed

A Elgazzar et al. Research Square 2020[13] *(added 1/19/2021; updated 7/21/2021)*

*****Study Retracted*****

- *Retracted because of discrepancies with the data and concerns about plagiarism.*

Population: treatment of patients with mild/moderate and severe COVID-19 (n=400) and prophylaxis of healthcare and/or household contacts (n=200) in Egypt

Design: randomized, controlled trial Ivermectin plus standard care vs hydroxychloroquine plus standard care

Results:

- Ivermectin reduced mortality compared to hydroxychloroquine and incidence of infection in contacts

Limitations: preprint; not peer reviewed

IVERMECTIN (continued)	**M Niaee et al. Research Square 2020[14]** *(added 1/19/2021)* **Population:** hospitalized patients with mild to severe COVID-19 (n=180) **Design:** randomized, double-blind, placebo-controlled phase 2 trial **Results:** ▪ Ivermectin reduced mortality rate, duration of low O2, and duration of hospitalization **Limitations:** preprint; not peer reviewed **E Lopez-Medina et al. JAMA 2021[15]** *(added 3/7/2021)* **Population:** outpatient or hospitalized adults in Colombia with mild COVID-19 who were symptomatic for ≤7 days (n=476) **Design:** randomized, double-blind trial ▪ Ivermectin 300 mcg/kg x 5 days vs placebo **Results:** ▪ Median time to resolution of symptoms was not significantly different between patients who received ivermectin (10 days) compared those who received placebo (12 days) (HR 1.07, 95% CI 0.87-1.32, p=0.53) **Limitations:** primary outcome changed after start of trial; labeling error occurred during trial; may have been underpowered; no virological assessments

IVERMECTIN (continued)	**YM Roman et al. medRxiv 2021[17]** **Population:** randomized controlled trials in adults with COVID-19 who were treated with ivermectin or a control (n=1173; 10 trials) **Design:** meta-analysis **Results:** ▪ Most trials evaluated patients with mild COVID-19 ▪ All cause mortality was not decreased with ivermectin compared to controls (RR 1.11; 95% CI 0.16-7.65, very low quality of evidence) ▪ Length of hospitalization was not reduced with ivermectin compared to controls (mean difference 0.72 days; 95% CI -0.86-2.29, very low quality of evidence) **Limitations:** meta-analysis; quality of evidence low or very low; not published or peer reviewed **Hill et al. Open Forum Infectious Diseases 2021[18,22]** *(added 7/15/2021; updated 7/21/2021; updated 11/7/2021)* *** **Includes data from A Elgazzar et al. trial, which was retracted** **Population:** included randomized controlled trials that compared and ivermectin-based regimen with a comparator or standard of care for treatment of COVID-19 (n=3328 participants) **Design:** meta-analysis of 24 randomized clinical trials **Results:** ▪ Ivermectin associated with reduced inflammatory markers such as C-reactive protein, d-dimer, and ferritin

- Ivermectin associated with faster viral clearance
- Total number of deaths was 128
- In 11 trials in patients with moderate to severe COVID-19, ivermectin was associated with a 56% reduction in mortality (relative risk 0.44; 95% CI 0.25-0.77; p=0.004); death occurred in 3% of patients on ivermectin and 9% of controls
- In mild to moderate disease, 70% improvement in survival with ivermectin (relative risk 0.44; 95% CI 0.25-0.77; p=0.0004)
- No significant difference in mortality between ivermectin and control in severe subgroup (relative risk 0.58; 95% CI 0.25-1.32; p=0.19)
- Ivermectin associated with shorter duration of hospitalization (-4.27 days; 95% CI -8.6 to -0.06; p=0.05)
- Ivermectin associated with shorter time to clinical recovery (-1.58 days; 95% CI -2.80 to-0.35; p=0.01)
- Ivermectin not associated with lower risk of hospitalization (RR 0.40; 95% CI 0.14-1.08; p=0.07)

Re-Analysis Update 11/7/2021[22]:

- When retracted Elgazzar study excluded, increase in survival reduced to 38% (p=0.05)
- When high risk of bias studies excluded, increase in survival was 10% (p=0.66)
- When studies with some concerns of bias excluded, 4% increase in survival (p=0.90)

Limitations: meta-analysis, many trials not peer-reviewed; dosing and

duration of ivermectin not standardized, comparators varied

J Vallejos et al. BMC Infec Dis 2021[19]
(added 7/21/2021)
Population: non-hospitalized adults in Argentina with a positive PCR test for COVID-19 within the previous 48 hours (n=501)
Design: randomized, double-blind, placebo-controlled
- Ivermectin (weight-based dosing) x 2 doses vs placebo

Results:
- Median time from symptom onset to inclusion was 4 days
- Hospitalization (the primary endpoint) occurred in 5.6% of patients in the ivermectin group and 8.4% of patients in the placebo group (odds ratio 0.65, 95% CI 0.32-1.31; p=0.227)
- Time to hospitalization was not statistically significantly different between the groups
- Time to invasive mechanical ventilatory support was 5.25 days with ivermectin and 10 days with placebo (p=0.019)

Limitations: low number of hospitalizations; dose of ivermectin lower than dose expected to be effective; unclear if study population was at high risk for the primary endpoint

G Reis et al. TOGETHER Trial NEJM 2022[23]*(added April 2, 2022)*
Population: adult outpatients in Brazil with COVID-19 who were symptomatic for ≤ 7 days and had at

least 1 risk factor for disease progression (n=3515)
Design: randomized, double-blind, placebo-controlled, adaptive platform trial
- Ivermectin 400 mcg/kg once daily x 3 days vs. placebo

Results:
- Primary composite outcome was hospitalization due to COVID-19 or an emergency department visit (resulting in observation for >6 hours) due to clinical worsening of COVID-19 within 28 days after randomization
- A primary outcome event occurred in 100 patients (14.7%) treated with ivermectin and 111 patients (16.3%) given placebo (relative risk 0.90; 95% Bayesian credible interval 0.70-1.16)
- 81.0% (171/211) were hospital admissions
- There were no significant effects of ivermectin use on secondary endpoints (such as SARS-CoV-2 viral clearance, hospitalization for any cause, time to hospitalization, duration of hospitalization, time to clinical recovery)
- Emergency department visit with observation for >6 hours was used a proxy for hospitalization because many patients who normally would have been hospitalized were not because of limited hospital capacity during peak COVID-19 waves

1. Dosage for other indications. For some indications only a single dose is required, but for others the dose may need to be repeated 2-3 times.
2. L Caly et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 2020 April 3 (epub).
3. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed January 18, 2021.

4. FDA letter to stakeholders: do not use ivermectin intended for animals as treatment for COVID-19 in humans. Available at: https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-covid-19-humans. Accessed August 29, 2020.
5. JC Rajter et al. Use of ivermectin is associated with lower mortality in hospitalized patients with COVID-19 (ICON study). Chest 2020 October 12 (epub; in press).
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9. S Ahmed et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis 2021; 103:214.
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12. P Soto-Becerra et al. Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru. medRxiv 2020 October 14 (epub).
13. A Elgazzar et al. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. Research Square 2020 December 28 (epub).
14. MS Niaee et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized multi-center clinical trial. Research Square 2020 November 24 (epub).
15. E Lopez-Medina et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. JAMA 2021; 325:1426.
16. A Bhimraj et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed March 29, 2021.
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22. A Hill et al. Ivermectin for COVID-19: addressing potential bias and medical fraud. Research Square 2021 October 25 (epub).
23. G Reis et al. Effect of early treatment with ivermectin among patients with Covid-19. N Engl J Med 2022 March 30 (epub).

ICATIBANT – *FIRAZYR,* and generics

Dosage:
- Dosage for COVID-19 not established
- 30 mg SC x 3 doses given 6 hours apart[1]

van de Veerdonk et al. JAMA Netw Open 2020[1]

Population: hospitalized patients with confirmed COVID-19 in the Netherlands (n=27; 9 cases/18 controls)
- oxygen saturation <90% without supplemental oxygen, requiring ≥3 L/min supplemental oxygen, and with computed tomography severity score ≥7

Design: case-control study

Results:
- icatibant-treated patients required less oxygen supplementation vs controls
- 4 of 9 patients given icatibant were no longer oxygen dependent within 10-35 hours
- 8 of 9 had a reduction of oxygen requirements ≥3 L/min after 24 hrs with icatibant vs 3 of 18 controls
- 3 patients had a resurgence in need for oxygen supplementation; possibly due to short half-life of icatibant

Limitations: retrospective data; 9 cases

Adverse Effects:
- Injection site reactions, pyrexia, transaminase increases, dizziness, rash

Drug Interactions:
- May attenuate antihypertensive effect of ACE inhibitors

- FDA-approved for treatment of acute attacks of hereditary angioedema (HAE)

- SARS-CoV-2 enters cells via ACE2, which breaks down bradykinin; loss of ACE2 may result in stimulation of the bradykinin 2 receptor, which could be a contributing factor in pulmonary edema in patients with COVID-19

- Icatibant is a competitive antagonist selective for the bradykinin B2 receptor

Pregnancy:
- Icatibant use has not been associated with a risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes based on available data from published literature and the pharmacovigilance database

- Adverse maternal and fetal outcomes have been reported in animal studies

1. FL van de Veerdonk et al. Outcomes associated with use of a kinin B2 receptor antagonist among patients with COVID-19. JAMA Netw Open 2020; 3:e2017708.

COLCHICINE
(updated 7/15/2021)

Dosage:
- Optimal dosage in patients with COVID-19 is unclear

GRECCO-19 trial[1]
Population: Hospitalized patients (n=105)
Design:
- Randomized, open-label trial in Greece
- Colchicine plus standard of care vs standard of care alone x 3 weeks

Results:
- Differences in inflammatory biomarkers (high sensitivity cardiac troponin, C-reactive protein) were not statistically significant between groups
- The clinical primary endpoint (time from baseline to clinical deterioration, defined as a 2-grade increase on a 7 point scale) occurred in 7 patients (14.0%) in the control group and in 1 patient (1.8%) in the colchicine group (p = 0.02)

Limitations:
- Small, open-label trial
- Almost all patients also received treatment with hydroxychloroquine and azithromycin or lopinavir/ritonavir

ColCORONA Trial 2021[4,6]
(added 1/26/2021; updated 4/23/2021)
Population: outpatients ≥ 40 years old with COVID-19 diagnosed within 24 hours of study entry who also had ≥1 risk factor for severe COVID-19 complications (>70 years old, BMI ≥ 30 kg/m^2, diabetes, uncontrolled hypertension, respiratory disease,

Adverse Effects:[2]
- Diarrhea, nausea, and vomiting are common
- Blood dyscrasias have been reported
- Neuromyopathy is rare; it typically occurs in elderly patients or in those with hepatic or renal impairment
- Overdosage of colchicine can be fatal

Drug Interactions:
- Substrate of CYP3A4 and the efflux transporter P-glycoprotein (P-gp); fatalities have been reported rarely in patients taking colchicine with a strong CYP3A4 inhibitor such as clarithromycin or a strong P-gp inhibitor such as cyclosporine
- Dosage should be reduced when colchicine is taken concurrently with or within 2 weeks after a CYP3A4 or P-gp inhibitor
- Myopathy and rhabdomyolysis have occurred in patients taking colchicine with a statin or a fibrate

- Colchicine has anti-inflammatory properties
- More trials are ongoing to evaluate the efficacy of colchicine for treatment of COVID-19
- The colchicine arm of the RECOVERY trial has been stopped because an independent data monitoring committee found lack of efficacy in hospitalized patients with COVID-19 *(added 3/6/2021)*
- NIH guidelines state there are insufficient data to recommend for or against use of colchicine in nonhospitalized patients with COVID-19[5] *(added 4/23/2021)*
- NIH guidelines recommend against use of colchicine in hospitalized patients for treatment of COVID-19[5] *(updated 7/15/2021)*

Pregnancy:
- No adequate studies in pregnant women
- Embryofetal toxicity and teratogenicity and altered postnatal development reported in animal studies

heart failure, coronary disease, fever ≥38.4°C in last 48 hours, dyspnea at presentation, bicytopenia, pancytopenia, or high neutrophil count + low lymphocyte count) (n=4488)

Design: contactless, randomized, double-blind, placebo-controlled trial

- Colchicine 0.5 mg bid x 3 days, then once/day x 27 days vs placebo

Results:

- Composite of death or hospitalization occurred in 4.7% of patients given colchicine and 5.8% of those given placebo (odds ratio 0.79, 95.1% CI 0.61-1.03; p=0.08)
- In 4159 patients with COVID-19 diagnosis confirmed by PCR, dealth or hospitalization occurred in 4.6% of patients given colchicine and 6.0% of those given placebo (odds ratio 0.75, 95% CI 0.57-0.99; p=0.04)
- Odds ratio for hospitalization 0.75 (95% CI 0.57-0.99), for mechanical ventilation 0.50 (95% CI 0.23-1.07) and for death 0.56 (95% CI 0.19-1.66)
- Diarrhea occurred more often with colchicine than with placebo (13.7% vs 7.3%)

Limitations: not peer reviewed or published yet; trial stopped before full enrollment reached; uncertainty about accuracy of diagnosis of cases; patient-reported outcomes potentially misclassified

1. SG Deftereos et al. Cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with Coronavirus Disease 2019. The GRECCO-19 randomized clinical trial. JAMA Netw Open 2020; 3:e2013136.
2. Drugs for gout. Med Lett Drugs Ther 2019; 61:33.
3. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2019 November 6 (epub). Available at: medicalletter.org/downloads/cyp_pgp_tables.pdf.
4. News Release. Institut de Cardiologie de Montreal. Colchicine reduces the risk of COVID-19-related complications. January 23, 2021. Available at: https://www.icm-mhi.org/en/pressroom/news/colchicine-reduces-risk-covid-19-related-complications. Accessed January 26, 2021.
5. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed July 15, 2021.
6. JC Tardif et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. MedRxiv 2021 January 27 (epub). Available at: https://www.medrxiv.org/content/10.1101/2021.01.26.21250494v1. Accessed April 26, 2021.

ALOGLIPTIN – *NESINA*
LINAGLIPTIN – *TRADJENTA*
SAXAGLIPTIN – *ONGLYZA*
SITAGLIPTIN – *JANUVIA*
(Updated 10/1/2020)

Dosage:
- Optimal dosage in patients with COVID-19 is unclear
- Dosage adjustments are needed for reduced renal function

Usual dosage for treatment of type 2 diabetes:
- Alogliptin: 25 mg PO once/day
- Linagliptin: 5 mg PO once/day
- Saxagliptin: 2.5-5 mg PO once/day
- Sitagliptin: 100 mg PO once/day

- Clinical trials with linaglipatin in patients with type 2 diabetes and mild or moderate COVID-19 are expected to begin to determine if use of the drug can improve glucose control and reduce the severity of COVID-19[1,2]

Solerte et al. Diabetes Care 2020[6] *(added 10/1/2020)*
Population: patients with type 2 diabetes hospitalized with COVID-19 (pneumonia, oxygen saturation <95% on ambient air or with oxygen support) (n=388)
Design: multicenter, case-control, retrospective, observational study
- Sitagliptin added to standard care (e.g., insulin) vs untreated controls

Results:
- Compared to controls, sitagliptin use associated with reduced mortality (18% vs 37% with controls; p=0.0001), improved clinical outcomes (60% vs 38% with controls; p=0.0001), and more hospital discharges (120 vs 89 with controls; p=0.008)

Limitations: retrospective data; increased inflammatory markers at baseline in sitagliptin group

Adverse Effects:
- Acute pancreatitis, fatal hepatic failure, possible worsening of heart failure, possible severe and disabling joint pain

Drug Interactions:
- Strong P-glycoprotein or CYP3A4 inducers[5] can decrease serum concentrations of linagliptin; concurrent use should be avoided if possible
- Strong CYP3A4/5 inhibitors[5] can increase saxagliptin concentrations; the dose of saxagliptin should not exceed 2.5 mg when used in combination with a CYP3A4/5 inhibitor
- Sitagliptin may increase digoxin concentrations; monitor patients taking digoxin

- Hypothesized that inhibition of DPP-4 may prevent infection with or progression of COVID-19

- Mechanism not established, but it has been suggested that DPP-4 may be involved in SARS-CoV-2 cell adhesion and DPP-4 inhibitors may have effects on inflammation[3,4]

Pregnancy:
- Limited data on use during pregnancy; insulin is generally preferred in pregnant women

1. G Iacobellis et al. Effects of DPP4 Inhibition on COVID-19. Available at: https://clinicaltrials.gov/ct2/show/NCT04341935?term=dpp&cond=COVID&draw=2&rank=1. Accessed May 12, 2020.
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5. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2019 November 6 (epub). Available at: medicalletter.org/downloads/cyp_pgp_tables.pdf.
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DAPAGLIFLOZIN – *FARXIGA* (ASTRAZENECA)

(Updated 6/6/2021)

Dosage:

- 10 mg once/day[1]

DARE-19 2021[1,4]

(updated 6/6/2021)

Population: hospitalized patients with COVID-19 who had risk factors for developing serious complications (hypertension, type 2 diabetes, atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease stage 3 or 4) (n=1250)

Design: phase 3 randomized, double-blind, placebo-controlled trial

- Addition of dapagliflozin 10 mg once daily to standard care vs standard care alone

Results:

- Addition of dapagliflozin did not result in statistically significant improvements in primary endpoints including organ dysfunction, all-cause mortality, or clinical status
- Organ failure or death (primary endpoint) occurred in 11.2% of patients treated with dapagliflozin and 13.8% of those given placebo (p=0.17)
- Primary outcome of recovery: Win ratio 1.09 (95% CI 0.97-1.22; p=0.14)
- Composite kidney endpoint occurred in 7.7% of dapagliflozin-treated patients and 10.4% of placebo-treated patients
- All cause mortality: 6.6% with dapagliflozin vs 8.6% with placebo (p>0.05)

Limitations: primary analysis; not yet published or peer reviewed

Adverse Effects:

- Genital mycotic and urinary tract infections, acute kidney injury, volume depletion, hypotension, and ketoacidosis

Drug Interactions:

- Metabolized primarily by UGT1A9; mefenamic acid *(Ponstel)*, a UGT1A9 inhibitor, increased dapagliflozin AUC by about 50%, but dapagliflozin dosage reduction not needed
- Taking dapagliflozin with insulin or a sulfonylurea increases the risk of hypoglycemia

- Some experts have advised that SGLT2 inhibitors be stopped in hospitalized COVID-19 patients because of in increased risk of DKA and have concerns with the conduction of the DARE-19 trial[2]
- SGLT2 inhibitors have been shown to have beneficial effects in patients with cardiovascular and renal comorbidities not infected with COVID-19; hypothesized that they may also have protective effects in patients with COVID-19[1]
- Mechanism not established, but SGLT2 inhibitors may have favorable effects on mechanisms involved in respiratory failure, sepsis, and multi-organ failure/cytokine storm[1]

Pregnancy:

- Not recommended during the second and third trimester; adverse renal effects have been reported in animal studies

	RJ Vitale et al. AACE Clinical Case Reports 2020[3] *(added 1/13/2021)* **Population:** patients with type 2 diabetes using SGLT2 inhibitors who developed SARS-CoV-2 infection (n=5) **Design:** case series **Results:** ▪ 5 cases of euglycemic diabetic ketoacidosis in patients with SARS-CoV-2 infection ▪ All patients were taking an SGLT2 inhibitor before hospital admission **Limitations:** case reports

1. Dapagliflozin in respiratory failure in patients with COVID-19 (DARE-19). Available at: https://clinicaltrials.gov/ct2/show/nct04350593?term=farxiga&cond=covid&draw=2&rank=1. Accessed April 29, 2020.
2. ME Tucker et al. New study of diabetes drug for COVID-19 raises eyebrows. Medscape. Available at: https://www.medscape.com/viewarticle/929716#vp_2. Accessed April 28, 2020.
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4. News Release. AstraZeneca. Update on the DARE-19 phase III trial for Farxiga in COVID-19. April 12, 2021. Available at: https://www.astrazeneca.com/media-centre/press-releases/2021/update-on-farxiga-covid-19-dare-19-phase-iii-trial.html. Accessed April 13, 2021.
5. DJ Kumbhani et al. Dapagliflozin in respiratory failure in patients with COVID-19 – DARE-19. Presented by M. Kosiborod at the American College of Caridology Virtual Annual Scientific Session (ACC 2021), May 16, 2021. Available at: https://www.acc.org/Latest-in-Cardiology/Clinical-Trials/2021/05/14/02/40/DARE-19. Accessed June 6, 2021.

FAMOTIDINE –
***PEPCID* (VALEANT)**
(Updated 11/4/2020)

Dosage:
- Clinical trial administering high-dose IV treatment (120 mg IV q8h)

- Ongoing trial in New York

- Review of patient records from China suggested that use of famotidine was associated with a lower death rate compared to those not taking the drug (Science April 26, 2020)

DE Freedberg et al. Gastroenterology 2020[1] *(updated 6/5/2020)*
Population: hospitalized, non-intubated, non-ICU (n=1620)
Design: Retrospective cohort, famotidine vs no famotidine
Results:
- Reduced risk for death or intubation (adjusted HR 0.42)
- PPI use not associated with lower risk
- 5.1% of patients were given famotidine within 24 hours of admission

Limitations: observational, retrospective, single center, not peer reviewed

T Janowitz et al. Gut 2020[2] *(added 6/5/2020)*
Population: non-hospitalized patients (n=10)
Design: case series; self-administered famotidine (80 mg tid x 11 days most commonly used)

Adverse Effects:
- Hepatitis, hematologic toxicity, and CNS effects such as headache, lethargy, depression, and cognitive impairment have occurred

Drug Interactions:
- May decrease serum concentrations of drugs that require gastric acidity for absorption

- Mechanism not established; computer simulation suggested famotidine may inhibit an enzyme required for replication of the virus

- Concerns about use in patients with renal impairment (especially at high doses)

Pregnancy:
- No adequate data in pregnant women; no evidence of risk in animal studies

FAMOTIDINE (continued)	**Results:** ▪ combined symptom score improved significantly within 24 hrs of famotidine ▪ symptoms (cough, shortness of breath, fatigue, headache, anosmia) were scored on a 4-point ordinal scale ▪ no patients were hospitalized ▪ time from onset of symptoms to start of treatment ranged from 2 to 26 days **Limitations:** case series (small number of patients, no placebo group) **Mather et al. Am J Gastroenterol 2020**[3] *(added 8/19/2020)* **Population:** hospitalized patients with COVID-19 at a single center in Connecticut (n=878; 83 received famotidine) **Design:** retrospective, propensity-matched observational study ▪ compared patients receiving famotidine (PO or IV at any dose within 7 days of COVID screening or hospital admission) to those not receiving the drug **Results:** ▪ patients treated with famotidine were younger than those who were not ▪ famotidine use associated with decreased risk of in-hospital mortality (OR 0.37; 95% CI 0.16-0.86; p=0.021) ▪ famotidine also associated with decreased risk of combined death or intubation and lower levels of serum markers for severe disease (CRP, procalcitonin, ferritin)

FAMOTIDINE (continued)	**Limitations:** observational data **Hogan et al. Pulm Pharmacol Ther 2020**[4] *(added 9/21/2020)* **Population**: hospitalized patients with COVID-19 treated with famotidine 20 mg bid and cimetidine 10 mg bid plus standard care (n=110) **Design:** retrospective cohort study **Results:** combination appeared to reduce symptom progression when compared to published reports of COVID-19 inpatients **Limitations:** retrospective data; not enough patients in control group for comparison **S Yeramaneni et al. Gastroenterology 2020**[5] *(added 11/4/2020)* **Population:** hospitalized adults with COVID-19 (n=7158) **Design:** multicenter, retrospective ▪ famotidine use within 24 hrs of admission vs no famotidine **Results:** ▪ 30-day mortality was higher in famotidine users than nonusers **Limitations:** observational; low to medium famotidine doses used

1. DE Freedberg et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: a propensity score matched retrospective cohort study. Gastroenterology 2020 (journal pre-proof).
2. T Janowtiz et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalized patients: a case series. Gut 2020 (epub).
3. JF Mather et al. Impact of famotidine use on clinical outcomes of hospitalized COVID-19 patients. Am J Gastroenterol 2020 (preprint). Available at: https://journals.lww.com/ajg/Documents/AJG-20-2074_R1.pdf. Accessed August 19, 2020.
4. RB Hogan et al. Dual-histamine receptor blockade with cetirizine-famotidine reduces pulmonary symptoms in COVID-19 patients. Pulm Pharmacol Ther 2020; 63:101942.
5. S Yeramaneni et al. Famotidine use is not associated with 30-day mortality: a coarsened exact match study in 7158 hospitalized COVID-19 patients from a large healthcare system. Gastroenterology 2020 October 6 (pre-proof).

FLUVOXAMINE

(updated 10/28/2021)

Dosage:
- 100 mg tid x 15 days

EJ Lenze et al. 2020[1]
(updated 11/12/2020)
Population: outpatient adults with mild COVID-19 with symptom onset within 7 days and oxygen saturation ≥ 92% (n=152)
Design: randomized, placebo-controlled, contactless trial
- Fluvoxamine 100 mg tid or placebo x 15 days

Results:
- After 15 days, 0 of 80 patients who received fluvoxamine had clinical deterioration vs 6 of 72 who took placebo (absolute difference 8.7%; 95% CI 1.8%-16.4%; p=0.009)

Limitations: small, preliminary study, short duration of follow-up, 20% of participants stopped responding to surveys during the trial

Seftel and Boulware Open Forum Infect Dis 2021[2]*(added 3/29/2021)*
Population: mostly Latino employees at a horse racing track in California during a mass outbreak of COVID-19 in Nov and Dec 2020 (n=113)
Design: prospective cohort
- Fluvoxamine (50-100 mg loading dose, then 50 mg bid x 14 days) offered to persons with documented disease

Results:
- 65 persons accepted treatment; 48 declined
- At 14 days, residual symptoms were present in 29 of 48 untreated patients (6 hospitalized, 2 intubated, and 1 died) and 0 of 65 treated patients

Adverse Effects:
- Restlessness, agitation, insomnia, nausea, diarrhea, headache, dizziness, fatigue, sexual dysfunction, hyponatremia
- SSRIs can increase the risk of bleeding by inhibiting serotonin uptake by platelets
- QT interval prolongation has been reported with all SSRIs; the risk appears to be greatest with citalopram and escitalopram

Drug Interactions:
- Increased risk of serotonin syndrome when used with other serotonergic drugs
- Use of SSRIs and monoamine oxidase inhibitors (MAOIs) concurrently or within 2 weeks of each other is contraindicated
- Use with antiplatelet or anticoagulant drugs may increase the risk of bleeding
- Use with other QT-interval prolonging drugs could result in additive effects and an increased risk of torsades de pointes
- Fluvoxamine is a strong inhibitor of CYP1A2 and moderate inhibitor of CYP2C19 and can increase serum concentrations of drugs metabolized by these pathways
- SSRI often used for treatment of OCD
- Effects on the sigma-1 receptor may down-regulate cytokine release
- A multicenter, phase 3, randomized, controlled trial for early treatment of COVID-19 is underway
- NIH guidelines state there are insufficient evidence to recommend for or against use of fluvoxamine for treatment of COVID-19[3] *(added 4/23/2021)*

Pregnancy:
- Limited data are available on use of fluvoxamine in pregnancy compared to other SSRIs
- Risk of congenital malformations after taking an SSRI during pregnancy appears to be very low, and no increase in perinatal mortality has been demonstrated
- Increased risk of cardiovascular and other malformations has been reported in infants born to mothers who took paroxetine in the first trimester

FLUVOXAMINE (continued)	**Limitations:** small sample, prospective cohort trial **G Reis et al. TOGETHER Lancet 2021[5]** *(updated 11/19/2021)* **Population:** symptomatic adults with COVID-19 with a risk factor for progression to severe disease in Brazil (n=1497) **Design:** randomized, placebo-controlled, adaptive platform trial ▪ Fluvoxamine 100 mg bid x 10 days vs placebo **Results:** ▪ The primary endpoint (composite of emergency room observation for >6 hours or hospitalization due to COVID-19 up to day 28 after randomization) occurred in 79/741 (11%) patients treated with fluvoxamine and 119/756 (16%) patients given placebo (RR 0.68; 95% Bayesian Credible Interval 0.52-0.88); probability of superiority surpassed the prespecified superiority threshold ▪ 87% of the composite primary outcome events were hospitalizations ▪ No significant relative effects between the groups in viral clearance at day 7, mortality, time to death, or duration of hospitalization or ventilation were reported ▪ 17 deaths occurred in fluvoxamine group vs 25 deaths in the placebo group **Limitations:** no standard of care; unknown who is at greatest risk of disease progression; higher rate of hospitalization than most trials;

1. EJ Lenze et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA 2020; 324:2292.
2. D Seftel and DR Boulware. Prospective cohort of fluxovamine for early treatment of coronavirus disease 19. Open Forum Infect Dis 2021 February 1 (epub).
3. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed April 23, 2021.
4. G Reis et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalization among patients with COVID-19: the TOGETHER randomized platform clinical trial. medRxiv 2021 August 26. Available at: https://www.medrxiv.org/content/10.1101/2021.08.19.21262323v2. Accessed August 31, 2021.
5. G Reis et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalization among patients with COVID-19: the TOGETHER randomised, platform clinical trial. Lancet 2021 October 27.

Progesterone

Progesterone *(added 3/29/2021)*	**S Ghandehari et al. 2021[1]** *(added 3/29/2021)* **Population:** men hospitalized with moderate to severe COVID-19 (n=42) **Design: pilot,** randomized, open-label trial ▪ Progesterone 100 mg SC bid x up to 5 days plus standard care vs standard care alone **Results:** ▪ Compared to standard care alone, on there was an improvement in clinical status with progesterone (1.5-point improvement on a 7-point ordinal scale; 95% CI 0.0-2.0; p=0.024) ▪ Duration of supplemental oxygen use was 4.5 days with progesterone and 7.5 days with standard care ▪ Duration of hospitalization was 7.0 days with progesterone and 9.5 days with standard care **Limitations:** small, open-label, pilot study	**Adverse Effects:** ▪ No serious adverse events were reported in the trial	▪ Severity of COVID-19 illness is lower in women ▪ Progesterone receptors are expressed on innate and adaptive immune cells, regulating local and systemic inflammation

1. S Ghandehari et al. Progesterone in addition to standard of care vs standard of care alone in the treatment of men hospitalized with moderate to severe COVID-19. Chest 2021 February 20 (epub)

Statins

Atorvastatin
(*Lipitor*, and generics)

(added 6/8/2021)

B Bikdeli et al. INSPIRATION-S ACC 2021[1]
(added 6/8/2021)
Population: ICU patients with COVID-19 (n=605)
Design: randomized, double-blind trial
- Atorvastatin 20 mg once/day vs placebo

Results:
- All-cause death, venous or arterial thrombosis, or ECMO occurred in 32.7% of patients treated with atorvastatin and 36.3% of those given placebo (p=0.35)
- Major bleeding occurred in 3.7% of atorvastatin-treated patients and 1.6% of placebo-treated patients (p-0.12)

Limitations: only available as abstract

Adverse Effects:
- Adverse effects of statins include muscle pain and weakness with or without increased creatinine kinase levels; rhabdomyolysis and myoglobinemia leading to renal failure, elevated serum aminotransferase levels, new-onset diabetes, peripheral neuropathy, memory loss, sleep disturbances, erectile dysfunction, gynecomastia, lupus-like syndrome, acute pancreatitis

Drug Interactions:
- Multiple drug interactions
- Concurrent use of CYP3A4 inhibitors can increase atorvastatin serum concentrations and the risk of rhabdomyolysis
- Use with caution in combination with inhibitors of organic anion transporter polypepties (OATP), P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP)
- Concurrent use with dabigatran etexilate can increase the risk of hemorrhage
- Statins are thought to have anti-inflammatory and antithrombotic effects

Pregnancy:
- Contraindicated

1. B Bikdeli et al. Intermediate versus standard-dose prophylactic anticoagulation in critically ill patients with COVID-19 – INSPRIATION-S. American College of Cariology Virtual Annual Scientific Session (ACC 2021). May 16, 2021. Available at: https://www.acc.org/latest-in-cardiology/clinical-trials/2021/05/14/03/14/inspiration-s. Accessed June 8, 2021.

ASCORBIC ACID – GENERICS

(updated 4/26/2021)

Dosage:

- Optimal dosage not established

12 g IV q12h x 7 days (infused at a rate of 12 ml/hr)[1]

Patients without COVID-19

- In the CITRIS-ALI trials, a 50 mg/kg dose q6h x 4 days did not significantly improve organ dysfunction or inflammation markers in patients with sepsis and ARDS[2]

- In clinical trials in patients with septic shock, treatment with vitamin C plus thiamine (+/- hydrocortisone) did not improve survival, but reductions in organ dysfunction and duration of shock were reported[4-6] *(added 11/9/2020)*

Patients with COVID-19

- Trials in China and Italy of high-dose ascorbic acid in patients with severe COVID-19-associated pneumonia are ongoing

- The results of these trials have not been published to date

S Thomas et al. JAMA Netw Open 2021[7] *(added 4/26/2021)*

Population: outpatient adults with PCR-confirmed SARS-CoV-2 infection (n=214)

Design: randomized, open-label trial

- Zinc gluconate 50 mg, ascorbic acid 8000 mg, both, or standard care x 10 days

Results:

- No significant difference between groups in the primary endpoint of number of days required to reach 50% reduction in symptoms (mean

Adverse effects:

- Large doses can acidify the urine, causing cysteine, urate, or oxalate stones; prolonged administration of high IV doses can cause oxalate nephropathy

- Nausea, vomiting, diarrhea, dizziness, and flushing can occur

Drug Interactions:

- May decrease serum concentrations of amphetamines

- May decrease the efficacy of bortezomib (*Velcade*, and generics) and cyclosporine

- May cause deferoxamine (*Desferal*) toxicity and left ventricular dysfunction; avoid oral doses >200 mg/day

- Accuracy of point-of-care glucometers may be affected by high circulating vitamin C levels *(added 11/9/2020)*

- Antioxidant properties may protect host cells against infection-induced oxidative stress; may boost host defenses against infection

- Infection may reduce vitamin C concentrations

- NIH guidelines state there are insufficient data to recommend for or against use of vitamin C in non-critically ill patients or in critically ill patients[3] *(added 7/21/2020)*

Pregnancy:

- No data are available in pregnant women

5.9 days with zinc, 5.5 days with ascorbic acid, 5.5 days for zinc +ascorbic acid and 6.7 days with usual care; overall p=0.45)
Limitations: small sample size, open-label

1. Randomized, controlled trial beginning. Https://clinicaltrials.gov/ct2/show/nct04264533.
2. AA Fowler et al. The CITRIS-ALI randomized clinical trial. JAMA 2019; 322:1261.
3. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed November 9, 2020.
4. T Fujii et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. JAMA 2020; 323:423.
5. P Chang et al. Combined treatment with hydrocortisone, vitamin c, and thiamine for sepsis and septic shock: a randomized controlled trial. Chest 2020; 158:174.
6. J Iglesias et al. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis: the ORANGES trial. Chest 2020; 158:164.
7. S Thomas et al. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. JAMA Netw Open 2021 Feb 1 (epub).

ZINC –
ZINC SULFATE

(updated 4/26/2021)

Dosage:
- Optimal dosage not established
- 220 mg daily x 5 days[1]
- Recommended dietary allowance: 11 mg/day for men and 8 mg/day for nonpregnant women

Carlucci et al. 2020[2] *(added 7/21/2020)*
Population: patients (n=932)
Design: retrospective observational study hospitalized
- Zinc plus hydroxychloroquine and azithromycin compared to hydroxychloroquine and azithromycin alone

Results:
- no difference in duration of hospitalization or mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, or average FiO_2 (in univariate analysis)
- zinc associated with increased frequency of discharge and reduced mortality or transfer to hospice (in bivariate logistic regression analysis)
- association with decreased mortality no longer significant when non-ICU patients were excluded

Limitations: observational data, only in combination with

Adverse Effects:
- Bad taste and nausea
- Irreversible anosmia when administered intranasally
- GI symptoms have occurred with high doses
- Long-term use: copper deficiency leading to reversible hematologic (anemia, leukopenia) and neurologic adverse effects (myelopathy, paresthesia, ataxia, spasticity)

Drug Interactions:
- Zinc can interfere with absorption of many drugs including fluoroquinolones

- Impairs replication of some RNA viruses including SARS-CoV *in vitro*[4]; no data on the activity of zinc against SARS-CoV-2
- Chloroquine/hydroxychloroquine may increase cellular uptake of zinc by SARS-CoV-2[5]
- NIH guidelines state there is insufficient data to recommend for or against use of zinc; they recommend against use of doses above the recommended dietary allowance for prevention of COVID-19, except in a clinical trial[6] *(added 7/21/2020)*
- Several trials are ongoing assessing the efficacy of zinc, some in combination with other vitamins, such as ascorbic acid, and/or drugs, such as hydroxychloroquine[3]

Pregnancy:
- Limited data on the safety of doses higher than the recommended daily allowance in pregnant women

ZINC (continued)

hydroxychloroquine and azithromycin, not peer-reviewed or published

S Abd-Elsalam et al Biol Trace Elem Res 2020[7] *(added 4/26/2021)*
Population: hospitalized patients with COVID-19 in Egypt (n=191)
Design: randomized clinical trial
- HCQ plus zinc vs HCQ alone

Results:
- No significant differences between the two groups for the endpoints of recovery within 28 days, the need for mechanical ventilation, and death

Limitations: small sample size

S Thomas et al. JAMA Netw Open 2021[8] *(added 4/26/2021)*
Population: outpatient adults with PCR-confirmed SARS-CoV-2 infection (n=214)
Design: randomized, open-label trial
- Zinc gluconate 50 mg, ascorbic acid 8000 mg, both, or standard care x 10 days

Results:
- No significant difference between groups in the primary endpoint of number of days required to reach 50% reduction in symptoms (mean 5.9 days with zinc, 5.5 days with ascorbic acid, 5.5 days for zinc +ascorbic acid and 6.7 days with usual care; overall p=0.45)

Limitations: small sample size, open-label

ZINC (continued)	**JS Yao et al. Chest 2021[9]** *(added 4/26/2021)* **Population:** patients with COVID-19 admitted to Hoboken University Medical Center (n=242) **Design:** retrospective, observational study ▪ 196 patients received zinc sulfate 440 mg (of those, 191 also received HCQ) ▪ 46 patients did not receive zinc (of those, 32 received HCQ) **Results:** ▪ Use of zinc was not significantly associated with a change in risk of in-hospital mortality **Limitations:** retrospective data; small sample size **JA Frontera et al. Res Sq 2020[10]** (*added 4/26/2021*) **Population:** hospitalized patients with PCR positive SARS-CoV-2 infection in New York City (n=3473) **Design:** multicenter cohort study ▪ Compared patients who received zinc plus HCQ to those who received HCQ without zinc **Results:** ▪ 12% of those who received zinc plus HCQ died compared to 17% who did not (adjusted hazard ratio 0.76, 95% CI 0.60-0.96; p=0.023) ▪ Treatment with HCQ alone appeared to be harmful **Limitations:** retrospective, observational data; not peer reviewed

1. Dosage regimen tried for treatment of covid-19; effective dosage has not been established in clinical trials.
2. PM Carlucci et al. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. medRxiv May 8, 2020.
3. Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/results?cond=Covid19&term=zinc&cntry=&state=&city=&dist=. Accessed July 22, 2020.
4. Aj te velthuis et al. Zn2+ inhibits coronavirus and arterivirus rna polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. Plos pathog 2010; 6: e1001176.
5. X xue j et al. Chloroquine is a zinc ionophore. Plos one 2014; 9:e109180.
6. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed July 21, 2020.
7. S Abd-Elsalam et al. Do zinc supplements enhance the clinical efficacy of hydroxychloroquine?: a randomized, multicenter trial. Biol Trace Elem Res 2020 Nov 27 (epub).
8. S Thomas et al. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. JAMA Netw Open 2021 Feb 1 (epub).
9. JS Yao et al. The minimal effect of zinc on the survival of hospitalized patients with COVID-19: an observational study. Chest 2021; 159:108.
10. JA Frontera et al. Treatment with zinc is associated with reduced in-hospital mortality among COVID-19 patients: a multi-center cohort study. Res Sq 2020 Oct 26 (preprint).

VITAMIN D

(updated 5/26/2021)

Dosage:

- Dosage in patients with COVID-19 not established
- 400-800 IU/day (recommended daily allowance for most people)
- Serum 25(OH)D 20 to 30 ng/mL: 800-2000 IU/day
- Serum 25(OH)D <20 ng/mL: may need 50,000 IU/week

- Observational studies have suggested there is an association between vitamin D levels and severity of COVID-19 illness; people with vitamin D deficiency may be at higher risk of more severe disease[1,2,8,9,10,11] *(updated 1/11/2020)*
- Earlier meta-analysis of randomized trials in patients with respiratory tract infections (non-COVID-19) found vitamin D supplementation associated with reduced risk of respiratory tract infections[3]
- Earlier randomized, double-blind trial of critically ill (non-COVID-19) patients found no significant effect of vitamin D administration on 90-day mortality vs placebo[4]

Adverse Effects:

- Excessive doses could cause toxicity (hypercalciuria, hypercalcemia, nausea, vomiting, anorexia, constipation, dehydration, fatigue, irritability, confusion, weakness)
- Metabolism of vitamin D altered in patients with chronic kidney disease

- Vitamin D plays an important role in immune function
- Limited data in COVID-19 and other serious illness
- NIH guidelines state there are insufficient data to recommend for or against use of vitamin D for prevention or treatment of COVID-19[7] *(added 7/22/2020)*
- NICE guidance states that there is no evidence to support use of vitamin D supplements to prevent or treat COVID-19[5] *(added 6/30/2020)*
- An expert consensus paper states that vitamin D supplements have not been shown to prevent or treat COVID-19 and strongly cautions against use of high doses of vitamin D; avoidance of vitamin D deficiency is recommended[6] *(added 6/17/2020)*

VITAMIN D (continued)	**A Rastogi et al. Postgrad Med J 2020[12]** *(added 1/11/2021)* **Population:** asymptomatic or mildly symptomatic patients with positive SARS-CoV-2 RNA test results who were vitamin D deficient (25(OH)D <20 ng/mL) (n=40) **Design:** randomized, placebo-controlled trial ▪ 60,000 IU cholecalciferol x 7 days (target 25(OH)D > 50 ng/mL) vs placebo **Results:** ▪ Baseline 25(OH)D was 8.6 in vitamin D group and 9.54 in placebo group ▪ 10 (62.5%) patients in the vitamin D group and 5 (20.8%) patients in the control group became SARS-CoV-2 RNA negative before day 21 (p<0.018) ▪ Statistically significant decrease in fibrinogen levels with vitamin D compared to placebo (p<0.01) **Limitations:** small sample size; only asymptomatic or mild cases included; high-dose treatment that could be associated with toxicity; clinical role of inflammatory markers unknown; long time frame of primary endpoint **M Castillo et al. J Steroid Biochem Mol Biol 2020[13]** *(added 1/11/2021)* **Population:** hospitalized patients with COVID-19 in Spain (n=76) **Design:** randomized, open-label trial Oral calcifediol vs standard care (hydroxychloroquine, azithromycin) **Results:** ▪ 1 of 50 patients in the calcifediol group required ICU admission	▪ Some sources of vitamin D include exposure to sunlight, fortified cereals and dairy products, fatty fish

VITAMIN D (continued)	compared to 13 of 26 patients in the standard care group ▪ 0 patients in the calcifediol group died and 2 patients in the standard care group died **Limitations:** small sample size; open-label; vitamin D status not evaluated at study entry **I Murai et al. JAMA 2021**[14] *(added 1/11/2021; updated 2/28/2021)* **Population:** hospitalized patients with severe COVID-19 in Brazil (n=240) **Design:** multicenter, randomized, double-blind, placebo-controlled trial Single oral dose of 200,000 IU vitamin D_3 vs placebo **Results:** ▪ Hospital length of stay was 7 days in both groups ▪ Mortality rate was 7.6% in the vitamin D group and 5.1% in the placebo group (p=0.43) ▪ Mechanical ventilation rate was 7.0% in the vitamin D group and 14.4% in the placebo group (p=0.09) ▪ ICU admission rate was 16.0% with vitamin D and 21.2% with placebo (p=0.30) **Limitations:** only in patients with severe disease; long time from symptom onset to randomization; percentage of patients with vitamin D deficiency low

VITAMIN D (continued)	**DO Meltzer et al. JAMA Netw Open 2020[15]** *(added 1/18/2021)* **Population:** patients with a vitamin D level measured in the year before being tested for COVID-19 (n=489) **Design:** retrospective cohort study **Results:** ▪ Relative risk of testing positive for COVID-19 was 1.77 times greater in patients with a vitamin D status of likely deficient compared to those with a status of likely sufficient (p=0.02) **Limitations:** retrospective data; limited sample size **DO Meltzer et al. JAMA Netw Open 2020[16]** *(added 3/20/2021)* **Population:** patients with a vitamin D level measured in the year before being tested for COVID-19 (n=4638) **Design:** retrospective cohort study **Results:** ▪ Risk of testing positive for COVID-19 in Black individuals was 2.64 times greater in patients with a vitamin D level of 30-39.9 ng/mL compared to those with a level ≥40 ng/mL ▪ There were no statistically significant associations observed in White individuals **Limitations:** retrospective data; limited sample size **Y Li et al. JAMA Netw Open 2021** **Population:** individuals that were part of an employer-sponsored health screening program who chose to be tested for SARS-CoV-2 IgG and who had vitamin D levels measured

VITAMIN D (continued)	before the COVID-19 pandemic (n=18148) **Design:** population-based cohort study **Results:** ▪ After adjusting for confounders, low vitamin D level (< 20 or 30 ng/mL) was not associated with seropositivity for SARS-CoV-2 (OR 1.04; 95% CI 0.88-1.22 for vitamin D level < 20 ng/mL and OR 1.09; 95% CI 0.93-1.27 for vitamin D level <30 ng/mL) **Limitations:** retrospective data

1. M Alipio. Vitamin D supplementation could possibly improve clinical outcomes of patients infected with Coronavirus-2019 (COVID-19). SSRN 2020 April 9. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3571484. Accessed May 12, 2020.
2. A Daneshkhah et al. The possible role of vitamin D in suppressing cytokine storm associated mortality in COVID-19 patients. MedRxiv 2020 April 30. Available at: https://www.medrxiv.org/content/10.1101/2020.04.08.20058578v3. Accessed May 12, 2020.
3. AR Martineau et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. Br Med J 2017; 356:i6583.
4. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early high-dose vitamin D3 for critically ill, vitamin D-deficient patients. N Engl J Med 2019; 381:2529.
5. NICE Guidance. COVID-19 rapid evidence summary: vitamin D for COVID-19. Available at: https://www.nice.org.uk/advice/es28/chapter/Key-messages. Accessed June 30, 2020.
6. SA Lanham-New et al. Vitamin D and SARS-CoV-2 virus/COVID-19 disease. BMJ Nutrition, Prevention & Health 2020 April 30 (epub).
7. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed July 22, 2020.
8. Abstract presented at American Society of Bone and Mineral Research (ASBMR) 2020 annual meeting. September 11-15, 2020. Virtual.
9. Z Maghbooli et al. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. PloS One 2020 September 25.
10. HW Kaufman et al. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. PloS One 2020 September 17.
11. M Pereira et al. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. Crit Rev Food Sci Nutr 2020 November 4 (epub).
12. A Rastogi et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled study (SHADE study). Postgrad Med J 2020 November 12 (epub).
13. ME Castillo et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. J Steroid Biochem Mol Biol 2020; 203:105751.
14. IH Murai et al. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. JAMA 2021; 325:1053.
15. DO Meltzer et al. Association of vitamin D status and other clinical characteristics with COVID-19 test results. JAMA Netw Open 2020; 3:e2019722.
16. DO Meltzer et al. Association of vitamin D levels, race/ethnicity, and clinical characteristics with COVID-19 test results. JAMA Netw Open 2021; 4:e214117.
17. Y Li et al. Assessment of the association of vitamin D level with SARS-CoV-2 seropositivity among working-age adults. JAMA Netw Open 2021; 4:e2111634.

THIAMINE

(added 7/29/2020)

Dosage:

- Dosage in patients with COVID-19 not established
- 200 mg IV q12h[1]

- There are no published trials evaluating use of thiamine for treatment or prevention of COVID-19
- One protocol that has not yet been evaluated in randomized controlled trials includes thiamine in addition to methylprednisolone, ascorbic acid, and heparin for treatment of hospitalized patients with COVID-19[1]
- In a retrospective study in (non-COVID) patients with septic shock, thiamine was associated with improved lactate clearance and reduced 28-day mortality compared to controls[2]
- In a randomized clinical trial of ICU patients (non-COVID), administration of an intervention consisting of IV vitamin C, hydrocortisone, and thiamine did not increase time alive or vasopressor free compared to hydrocortisone alone[3]

Adverse Effects:

- Thiamine is water-soluble and toxic levels are not expected

- Thiamine deficiency has been reported to occur commonly in critically ill patients; evidence on whether thiamine use can improve mortality in critically ill (non-COVID) patients has been conflicting[2,3]
- There are no controlled trials evaluating use of thiamine in critically ill patients with COVID-19

1. Dosage used in MATH+ protocol. Available at https://covid19criticalcare.com/treatment-protocol/. Accessed July 29, 2020.
2. JA Woolum et al. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. Crit Care Med 2018; 46:1747.
3. T Fujii et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. JAMA 2020 323:423.

ASPIRIN
(updated 3/29/2021)

Dosage:
- 81 mg once daily

JH Chow et al. Anesth Analg 2020[1]
(added 11/4/2020; updated 3/29/2021)
Population: hospitalized patients with COVID-19 (n=412)
Design: retrospective, observational cohort
- no aspirin vs low-dose aspirin within 24 hrs of admission or 7 days prior to admission

Results:
- Patients taking aspirin had significantly higher rates of hypertension, diabetes, coronary artery disease, and renal disease
- Aspirin use had a crude association with less mechanical ventilation (35.7% vs 48.4% no aspirin; p=0.030) and ICU admissions (38.8% vs 51.0% no aspirin; p=0.04), but not in-hospital mortality (26.5% aspirin vs 23.2% no aspirin; p=0.51)
- After adjustment for confounding, aspirin use was associated with decreased risk of mechanical ventilation (HR 0.56, 95% CI 0.37-0.85, p=0.007), ICU admission (HR 0.57, 95% CI 0.38-0.85, p=0.005), and in-hospital mortality (HR 0.53, 95% CI 0.31-0.90, p=0.02)
- No differences in major bleeding or thrombosis between groups

Limitations: observational; modest sample size; comorbidities in aspirin patients

Adverse Effects:
- Increased risk of bleeding
- Single doses can precipitate asthma symptoms in aspirin-sensitive patients
- High doses can cause GI ulceration and salicylate intoxication
- Risk of Reye's syndrome; should not be used to treat viral syndromes in children and teenagers

Drug Interactions:
- Concurrent use with other antiplatelet drugs or with anticoagulant drugs can increase the risk of bleeding
- Increased risk of GI, renal, and bleeding adverse effects with NSAIDs
- NSAIDs may decrease cardioprotective effects of aspirin; routine use should be avoided; separate doses if intermittent use of both drugs is needed
- Increased risk of metabolic acidosis and CNS toxicity if used in combination with carbonic anhydrase inhibitor

- Mainly used in low doses as platelet inhibitor; irreversibly inhibits platelet function for 8- to 10-day life of platelet

- Evidence of a hypercoagulability has been observed in patients with COVID-19; aspirin has antiplatelet and anti-inflammatory properties

- NIH guidelines recommend patients with COVID-19 who are taking anticoagulant or antiplatelet therapy for underlying medical conditions should continue their treatment unless significant bleeding develops or other contraindications are present

Pregnancy:
- Low-dose aspirin is generally considered safe for use during pregnancy

1. JH Chow et al. Aspirin use is associated with decreased mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized patients with COVID-19. Anesth Analg 2021; 132:930.
2. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed November 4, 2020.

Nasal Saline Irrigation

NASAL SALINE IRRIGATION – (NETI POT OR SINUS RINSE SQUEEZE BOTTLE) **Dosage:** Multiple times per day	▪ No data for treatment or prevention of COVID-19 ▪ Open-label, randomized trial in 61 patients with viral upper respiratory tract infections (including rhinovirus and coronavirus), hypertonic nasal saline irrigation shortened the duration of illness, lowered transmission to household contacts, and reduced viral shedding[1]	**Adverse Effects:** ▪ Minor nasal discomfort or irritation ▪ Sterile, distilled, or boiled (and cooled) tap water should be used to prevent bacterial or protozoal infection[2]	▪ No evidence that regular nasal saline irrigation can prevent or treat COVID-19 infection ▪ Some limited evidence that nasal irrigation with hypertonic saline can shorten the duration of the common cold ▪ Hypothesized mechanism is cellular use of chloride ions to produce hypochlorous acid (HOCL), which has antiviral effects[1]

1. S Ramalingam et al. A pilot, open labelled, randomised controlled trial of hypertonic saline nasal irrigation and gargling for the common cold. Sci Rep 2019; 9:1015.
2. FDA. Is rinsing your sinuses with Neti Pots safe? Available at: https://www.fda.gov/consumers/consumer-updates/rinsing-your-sinuses-neti-pots-safe. Accessed March 31, 2020.

Melatonin

MELATONIN – GENERICS

(updated 11/17/2020)

Dosage:

- Optimal dosage not established

5-10 mg/day PO[1]

- No data available on use of melatonin for treatment of COVID-19

- Based on data suggesting melatonin may be helpful in acute lung injury/acute respiratory distress syndrome caused by other pathogens[2]

- In a combined network-based prediction and propensity score matching observational study including 26,779 patients from a COVID-19 registry, melatonin use was significantly associated with a reduced chance of having a positive SARS-CoV-2 test result (OR 0.72; 95% CI 0.56-0.91)[4] *(added 11/17/2020)*

Adverse effects:

- Well tolerated; dizziness, headache, nausea, and sleepiness can occur

Drug Interactions:

- May decrease the antihypertensive effects of calcium channel blockers

- Melatonin is a substrate of CYP1A2; inducers of CYP1A2 may decrease melatonin concentrations and inhibitors of CYP1A2 may increase melatonin concentrations[3]

- May have anti-viral and anti-inflammatory effects; could decrease serum levels of inflammatory cytokines

- Has been used in critical care patients (not COVID-19) to reduce vessel permeability, anxiety, sedation use, and improving sleeping quality[2]

Pregnancy:

- Limited data on the safety of melatonin use during pregnancy

1. Dosage used for reduction of pro-inflammatory cytokines in studies for other indications. Optimal dosage for use in patients with COVID-19 unknown.
2. R Zhang et al. COVID-19: melatonin as a potential adjuvant treatment. Life Sci 2020; 250:117583.
3. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2019 November 6 (epub). Available at: medicalletter.org/downloads/cyp_pgp_tables.pdf.
4. Y Zhou et al. A network medicine approach to investigation and population-based validation of disease manifestations and drug repurposing for COVID-19. PLoS Biol 18:e3000970.

BENZALKONIUM CHLORIDE
(added 5/9/2020)

Dosage:

- Topical use

- Available OTC in hand sanitizer formulations and an intranasal formulation

- The manufacturer of a nasal formulation of 0.13% benzalkonium chloride *(NanoBio Protect)* states the product has been shown to kill SARS-CoV-2 in *in vitro* studies conducted by Public Health England; published data are not yet available[1]

Previous studies have reported that 0.05-0.2% benzalkonium chloride formulations were less effective than alcohol-based disinfectants against other coronaviruses

Adverse Effects:

- Irritation, burning or stinging, hypersensitivity reactions

- No clinical data demonstrating efficacy of a nasal formulation of benzalkonium chloride for prevention of COVID-19 infection

- The CDC recommends alcohol-based hand sanitizers containing 80% ethanol or 75% isopropanol[3]

1. Press Release. Available at: https://www.bluewillow.com/%ef%bb%bf%ef%bb%bfnanobio-protect-over-the-counter-nasal-antiseptic-kills-covid-19-virus-in-lab-tests/. Accessed May 6, 2020.
2. G Kampf et al. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect 2020; 104:246.
3. CDC. Hand hygiene recommendations. Guidance for healthcare providers about hand hygiene and COVID-19. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/hand-hygiene.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Fhand-hygiene-faq.html#references. Accessed May 6, 2020.

POVIDONE-IODINE
(updated 2/10/2021)

Dosage:

- Intranasal solution 0.5%
- OTC topical formulations are not safe for intranasal use

- In an *in vitro* study, a 15 second treatment with a 0.5% intranasal povidone-iodine solution appeared to inactivate SARS-CoV-2[1]
- In a small trial evaluating nasopharyngeal application of povidone-iodine 1% solution and 10% ointment, the mean relative difference in viral titers between baseline and day 1 was 75% in the povidone-iodine group and 32% in the control group, but the there was no influence on changes of viral RNA quantification over time and 42% of patients treated with povidone-iodine had thyroid disfunction[2] *(added 2/10/2021)*

Adverse Effects:

- Risk of iodine absorption expected to be minimal
- Avoid use in patients with thyroid disease or those undergoing radioactive iodine therapy
- Administration of topical povidone iodine formulations intranasally could be toxic and should not be used
- Povidone-iodine is a broad-spectrum antiseptic with antiviral activity
- A trial evaluating intranasal povidone-iodine for prophylaxis in health care workers and hospital patients is ongoing

Pregnancy:

- Avoid use in pregnant women

1. S Frank et al. In vitro efficacy of a povidone-iodine nasal antiseptic for rapid inactivation of SARS-CoV-2. JAMA Otolaryngol Head Neck Surg 2020 September 17 (epub).
2. J Guenezan et al. Povidone iodine mouthwash, gargle, and nasal spray to reduce nasopharyngeal viral load in patients with COVID-19: a randomized clinical trial. JAMA Otolaryngol Head Neck Surg 2021 February 4 (epub).

VENOUS THROMBOEMBOLISM (VTE) PROPHYLAXIS

DRUG	DOSAGE
Unfractionated Heparin (UFH)	
Heparin	Usual adult dosage for VTE prophylaxis: ▪ 5000 units SC q8-12h
Low Molecular Weight Heparin (LMWH)	
Enoxaparin (*Lovenox*, and generics)	Usual adult dosage for VTE prophylaxis: ▪ 40 mg SC once/day ▪ CrCl<30 ml/min: 30 mg SC once/day ISTH recommends consideration of higher prophylactic doses (40-60 mg SC once/day) or half-therapeutic-doses (0.5 mg/kg bid) in critically ill patients at high risk, and consideration of higher doses for obese patients
Dalteparin (*Fragmin*)	Usual adult dosage for VTE prophylaxis: ▪ 2500-5000 IU SC once/day
Factor Xa Inhibitor	
Fondaparinux (*Arixtra*, and generics)	Usual adult dosage for VTE prophylaxis: ▪ ≥50 kg: 2.5 mg SC once/day ▪ <50 kg: contraindicated ▪ CrCl <30 mL/min: contraindicated

RECOMMENDATIONS/COMMENTS

- SARS-CoV-2 infection is associated with arterial and venous thrombotic complications including MI, ischemic stroke, and VTE[1]
- Thrombosis may contribute to multisystem organ dysfunction in patients with severe COVID-19
- Use of direct oral anticoagulants (DOACs) is not recommended due to bleeding risk and drug-drug interactions with DOACs
- LMWH or fondaparinux are recommended over UFH to limit staff exposure (once-daily dosing) and because of the lower risk of heparin-induced thrombocytopenia
- Optimal dosages of anticoagulant drugs for VTE prophylaxis in patients with COVID-19 are not established
- In a large clinical trial, compared to thromboprophylaxis, therapeutic-dose anticoagulation increased the probability of survival to hospital discharge and reduced the need for vital organ support, such as mechanical ventilation, in moderately ill patients hospitalized for COVID-19, but not in critically ill patients (REMAP-CAP, ACTIV-4a, ATTACC)[4,8] *(updated 8/5/2021)*
- In an observational cohort study in 4297 hospitalized patients with COVID-19, early initiation of prophylactic anticoagulation was associated with a 27% decreased risk for 30-day mortality[5] *(added 2/16/2021)*
- In a randomized trial in 600 patients in the ICU with COVID-19, there was no significant difference in the primary endpoint of a composite of adjudicated venous or arterial thrombosis, treatment with ECMO, or mortality within 30 days between patients given intermediate-dose (enoxaparin 1 mg/kg daily) or prophylactic-dose (enoxaparin 40 mg daily) anticoagulation[6] *(added 3/20/2021)*

ACCP[2] AND ISTH[3] RECOMMENDATIONS

(in patients without contraindications)

Critically ill patients with COVID-19:

- ACCP and ISTH recommend LMWH

Acutely (non-critically ill) hospitalized patients with COVID-19:

- ACCP recommends LMWH or fondaparinux
- ISTH recommends LMWH

DRUG	DOSAGE	RECOMMENDATIONS/COMMENTS
		After Discharge: ▪ Extended prophylaxis not recommended by ACCP ▪ ISTH recommends considering LMWH (or a DOAC) for up to 30 days in patients at high thrombosis risk and low bleeding risk **Nonhospitalized patients with COVID-19:** ▪ Routine prophylaxis not recommended by ACCP, ISTH, or NIH[7]

ACCP = American College of Chest Physicians; ISTH = International Society on Thrombosis and Haemostasis

1. G Piazza and DA Morrow. Diagnosis, management, and pathophysiology of arterial and venous thrombosis in COVID-19. JAMA 2020 November 23 (epub).
2. LK Moores et al. Prevention, diagnosis, and treatment of VTE in patients with Coronavirus Disease 2019. CHEST Guideline and Expert Panel Report. Chest 2020; 158:1143.
3. AC Spyropoulos et al. Scientific and Standardization Committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020; 18:1859.
4. The ATACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. N Engl J Med 2021 August 4 (epub).
5. CT Rentsch et al. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. BMJ 2021; 372:n311.
6. INSPIRATION Investigators. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. JAMA 2021; 325:1620.
7. NIH. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/ Accessed April 23, 2021.
8. The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med 2021 August 4 (epub).

CONCOMITANT DRUGS

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
Renin-Angiotensin System (RAS) Inhibitors			
ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS *(updated 2/28/2021)* ▪ Benazepril (*Lotensin*, and generics) ▪ Captopril (generic) ▪ Enalapril (*Vasotec*, and others) ▪ Fosinopril (generic) ▪ Lisinopril (*Zestril*, *Prinivil*, and others) ▪ Moexipril (generic) ▪ Perindopril (generic) ▪ Quinapril (*Accupril*, and generics) ▪ Ramipril (*Altace*, and generics) ▪ Trandolapril (generic) **ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)** ▪ Azilsartan (*Edarbi*) ▪ Candesartan (*Atacand*, and generics) ▪ Eprosartan (*Teveten* and generics) ▪ Irbesartan (*Avapro*, and generics) ▪ Losartan (*Cozaar*, and generics) ▪ Olmesartan (*Benicar*, and generics) ▪ Telmisartan (*Micardis*, and generics)	▪ Increased risk of severe COVID-19 in patients with cardiovascular disease ▪ ACE inhibitors and ARBs increase expression of ACE2 by epithelial cells in the lung, and pathogenic coronaviruses such as SARS-CoV-2 enter these cells via ACE2 receptors[1] ▪ Some researchers have suggested that this increase in risk may be due to use of ACE inhibitors or ARBs in patients with diabetes, hypertension, or heart failure ▪ Others have suggested, however, that ACE2 may protect against lung injury in coronavirus infection and that taking an ACE inhibitor or an ARB might be beneficial[2,3]	**P Zhang et al. Circ Res 2020[4]** **Population:** ▪ hospitalized patients w/ hypertension (n=1128) ▪ 188 taking an ACE inhibitor or ARB **Design:** ▪ retrospective, multi-center **Results:** ▪ all-cause mortality was lower in patients taking an ACE inhibitor or ARB compared to those not taking an ACE inhibitor or ARB (3.7% vs 9.8%) ▪ adjusted HR 0.37 (95% CI, 0.15-0.89; P = 0.03) in a propensity score-matched analysis **Limitations:** retrospective **J Li et al. JAMA Cardiol 2020[5]** **Population:** hospitalized patients (n = 1178); 362 patients with hypertension, 115 taking an ACE inhibitor or ARB **Design:** retrospective, single-center **Results:** percentage of patients taking an ACE inhibitor or ARB was similar between patients with (32.9%) and without (30.7%) severe infection and between survivors (33.0%) and non-survivors (27.3%) **Limitations:** no adjustment for confounding factors	▪ Multiple medical organizations, including the NIH, have advised against stopping or starting these drugs to prevent or treat COVID-19 infection[3,10,11] ▪ Patients who are taking an ACE inhibitor or an ARB and subsequently develop COVID-19 should continue to take the drug[3,10,23] ▪ Some evidence from retrospective trials suggesting that use of an ACE inhibitor or an ARB in patients with hypertension who were hospitalized for COVID-19 was associated with similar or lower mortality rates compared to patients who were not taking a drug from either class prior to infection.[4,5,6] ▪ Prospective randomized-controlled trials evaluating these drugs in patients hospitalized for COVID-19 are in progress[16]

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
▪ Valsartan (*Diovan*, and generics)		**DM Bean et al. 2020[6]** **Population:** hospitalized patients (n=205) **Design:** retrospective, single-center **Results:** Lower rate of death or transfer to the ICU within 7 days of symptom onset in patients on an ACE inhibitor (OR 0.29) **Limitations:** small sample size, not peer reviewed **Mancia et al. NEJM 2020[7]** **Population:** 6272 case patients with COVID-19; 30,759 controls **Design:** population-based case-control study in Italy **Results:** ▪ use of ACE inhibitors or ARBs was not associated with COVID-19 among case patients (adjusted OR for ACE inhibitors 0.96 [CI 0.87-1.07] and for ARBs 0.95 [CI 0.86-1.05]) ▪ no association between use of ACE inhibitors or ARBs and severe or fatal disease (adjusted OR for ACE inhibitors 0.91 [CI 0.69-1.21] and for ARBs 0.83 [CI 0.63-1.10]) **Limitations:** observational data **Mehra et al. NEJM 2020[8]** *(updated 6/4/2020)* *****Study Retracted[12]***** ▪ *Retracted because of concerns about the accuracy of the data and analysis; an independent audit was not possible because the full dataset was not made available* **Population:** 8910 hospitalized patients in Asia, Europe, and North America **Design:** observational; data collected from an international registry	▪ A review of multiple trials of ACEI or ARB use in patients with COVID-19 concluded there is high-certainty evidence that use of these drugs is not associated with more severe disease[17] *(added 7/28/2020)*

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
ACE INHIBITORS AND ARBS (CONTINUED)		**Results:** Use of ACE inhibitors or ARBs was not found to be associated with an increased risk of in-hospital death **Limitations:** observational data **Reynolds et al. NEJM 2020**[9] **Population:** 12,954 patients tested for COVID-19 in a New York City health system **Design:** observational; data obtained from electronic medical records **Results:** ▪ 5894 (46.8%) were positive; 1002 of them (17.0%) had severe illness ▪ ACE inhibitors, ARBs, or other antihypertensive drug classes (beta-blockers, calcium channel blockers, thiazide diuretics) were not associated with an increased risk of COVID-19 infection or of severe illness **Limitations:** observational data **Flacco et al. Heart 2020**[13] *(added 7/15/2020)* **Population:** 9890 hypertensive patients treated with ACE inhibitors, ARBs, or both vs untreated patients **Design:** meta-analysis of observational data from 10 cohort or case-control studies comparing risk of severe/fatal COVID-19 in patients treated with ACE inhibitors/ARBs vs untreated patients **Results:** The risk of severe/fatal COVID-19 was similar between patients treated with ACE inhibitors/ARBs and untreated patients (OR 0.90, 95% CI 0.65 to 1.26 for ACE inhibitors; OR 0.92, 95% CI 0.75 to 1.12 for ARBs) **Limitations:** meta-analysis of observational data; intermediate-to-high level of heterogeneity	

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
ACE INHIBITORS AND ARBS (CONTINUED)		**Fosbøl et al. JAMA 2020[14]** *(added 7/28/2020)* **Population: Retrospective Cohort Study:** ▪ hypertensive patients with COVID-19 (n=4480) **Nested, Case-Control:** ▪ Cases (COVID-19, prior hypertension; n=571); controls (no COVID-19, prior hypertension; n=5710) **Design:** retrospective cohort study examining outcomes in patients with COVID-19; nested, case-control design for susceptibility analysis; from Danish registry **Results:** **Retrospective Cohort Study: ACEI/ARB use vs no use** ▪ Mortality within 30 days was 18.1% in the ACEI/ARB group compared to 7.3% in the nonuser group (significant difference in unadjusted analysis; not statistically significant after adjustment for age, sex, and medical history) ▪ Death or severe COVID-19 occurred in 31.9% of ACEI/ARB users and 14.2% of nonusers by 30 days (significant difference in unadjusted analysis; not statistically significant after adjustment) **Nested Case-Control Susceptibility Analysis: ACEI/ARB use vs other hypertensive drugs** ▪ ACEI/ARB use was not associated with a higher incidence of COVID-19, compared with use of other antihypertensives **Limitations:** retrospective data	

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
ACE INHIBITORS AND ARBS (CONTINUED)		**Felice et al. Am J Hypertens 2020[15]** *(added 7/28/2020)* **Population:** consecutive hypertensive patients presenting to ER in Italy with acute respiratory symptoms and/or fever or diagnosis of COVID-19 (n=133) **Design:** single center, retrospective study **Results:** rate of admission to semi-intensive/intensive care units was lower patients treated with ACEIs or ARBs, compared to patients not treated with ACEIs or ARBs **Limitations:** small retrospective study **Selçuk et al. Clin Exp Hypertens 2020[18]** *(added 7/28/2020)* **Population:** consecutive hypertensive patients hospitalized for COVID-19 in Turkey (n=113) **Design:** retrospective study **Results:** ▪ Patients in the ACEI/ARB group were older and were more likely to have coronary artery disease than those taking other antihypertensives ▪ Use of an ACEI or ARB was associated with a higher frequency of admission to the ICU, endotracheal intubation, and death compared with other antihypertensives **Limitations:** small retrospective study; patients on ACEIs/ARBs more likely to have coronary artery disease and were older **Lopes et al. BRACE CORONA Trial, JAMA 2021[21]** *(added September 2020; updated 1/19/2021)* **Population:** patients hospitalized with mild to moderate COVID-19 who were taking an ACEI or ARB before admission (n=659)	

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
ACE INHIBITORS AND ARBS (CONTINUED)		**Design:** multicenter, registry-based, open-label randomized clinical trial with blinded endpoint assessment ▪ Patients randomized to discontinue or continue taking ACEI or ARB therapy for 30 days **Results:** ▪ No significant differences between those who stopped taking the ACEI or ARB and those who continued taking it ▪ Number of days alive and out of hospital 21.9 in those who stopped their ACEI or ARB vs 22.9 in those who continued taking it ▪ Death occurred in 2.7% of patients in the discontinuation group and in 2.8% of those in the continuation group ▪ Cardiovascular death (0.6% vs 0.3%) ▪ COVID-19 progression (38.3% vs 32.3%) **Limitations:** open-label, results limited to trial population; few patients with heart failure; effect of ACEI/ARB on susceptibility to COVID not evaluated **Chu et al. Br J Clin Pharmacol 2020**[19] *(added 12/21/2020)* **Population:** **Non-COVID-19:** 25 studies (330,780 patients) **COVID-19**: risk of infection (11 studies; 8.4 million patients); mortality risk (34 studies; 67,644 patients) **Design:** meta-analysis ▪ **Non-COVID-19 patients:** meta-analysis of effects of ACEIs and ARBs on risk of pneumonia and pneumonia-related death ▪ **COVID-19 studies:** meta-analysis of risk of infection with SARS-CoV-2, risk of severe adverse clinical outcomes, and risk of all-cause mortality in patients treated with ACEIs or ARBs **Results:**	

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
ACE INHIBITORS AND ARBS (CONTINUED)		**Non-COVID-19:** ▪ ACEI (but not ARB) associated with a 26% reduction in pneumonia risk (OR 0.74; p<0.001) ▪ ACEI associated with reduction in pneumonia-related death (OR 0.73; p=0.004) **COVID-19:** ▪ ACEI (but not ARB) associated with a 13% reduction in risk of SARS-CoV-2 infection (OR 0.87; p=0.014) ▪ RAAS blockade associated with 24% reduced all-cause mortality (OR 0.76; p=0.04) **Limitations:** meta-analyses; high heterogeneity **JB Cohen et al. REPLACE COVID, Lancet Respir Med 2021**[20] *(added 1/11/2021)* **Population:** hospitalized patients with COVID-19 who were receiving an ACE inhibitor or ARB before admission (n=152) **Design:** multicenter (7 countries), prospective, randomized, open-label trial ▪ Patients were randomized to continue their ACE inhibitor/ARB or to discontinue treatment **Results:** ▪ No significant different in the global rank score between groups ▪ ICU admission or invasive mechanical ventilation occurred in 21% of patients in the continuation group and 18% of patients in the discontinuation group (p=0.61) ▪ Death occurred in 15% of patients in the continuation group and 13% in the discontinuation group (p=0.99) **Limitations:** small sample size; open-label; no control for dosing or other therapies given	

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
		RSG Sablerolles et al. COMET Study, Br J Clin Pharmacol 2021[22] *(added 2/28/2021)* **Population:** hospitalized patients with COVID-19 who were receiving an ACE inhibitor or ARB before admission (n=4870) **Design:** observational, multinational study **Results:** ▪ No significant association with use of ACE inhibitors or ARBs and the composite endpoint of hospital mortality and ICU admission (ACE inhibitors: adjusted OR 0.94; 95% CI 0.79-1.12; ARBs: adjusted OR 1.09 95% CI 0.90-1.30) **Limitations:** observational data	

1. L Fang et al. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020 March 11 (epub).
2. MA Sparks et al. The coronavirus conundrum: ACE2 and hypertension edition. Available at: http://www.nephjc.com/news/covidace2. Accessed April 30, 2020.
3. M Vaduganathan et al. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. N Engl J Med 2020 March 30 (epub).
4. P Zhang et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res 2020 April 17 (epub).
5. J Li et al. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. JAMA Cardiol 2020 April 23 (epub).
6. DM Bean et al. Treatment with ACE-inhibitors is associated with less severe disease with SARS-COVID-19 infection in a multisite UK acute hospital trust. Medrxiv 2020 April 11 (preprint).
7. G Mancia et al. Renin-angiotensin-aldosterone system blockers and the risk of COVID-19. N Engl J Med 2020 May 1 (epub).
8. MR Mehra et al. Cardiovascular disease, drug therapy, and mortality in COVID-19. N Engl J Med 2020 May 1 (epub).
9. HR Reynolds et al. Renin–angiotensin–aldosterone system inhibitors and risk of COVID-19. N Engl J Med 2020 May 1 (epub).
10. ACC. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. Available at: https://bit.ly/2uimyt6. Accessed May 4, 2020.
11. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed May 4, 2020.
12. MR Mehra et al. Retraction: cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med 2020 June 4 (epub).
13. ME Flacco et al. Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. Heart 2020 July 1 (epub).
14. EL Fosbøl et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. JAMA 2020; 324:168.
15. C Felice et al. Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: results from an Italian cohort of 133 hypertensives. Am J Hypertens 2020 June 8 (epub).
16. DHF Gommans et al. Rationale and design of the PRAETORIAN-COVID trial: a double-blind, placebo-controlled randomized clinical trial with valsartan for prevention of acute respiratory distress syndrome in patients with SARS-COV-2 infection disease. Am Heart J 2020; 226:60.
17. K Mackey et al. Update Alert 2: Risks and impact of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers on SARS-CoV-2 infection in adults. Ann Intern Med 2020 July 23 (epub).
18. M Selçuk et al. Is the use of ACE inb/ARBs associated with higher in-hospital mortality in Covid-19 pneumonia patients? Clin Exp Hypertens 2020; 42:738.
19. C Chu et al. Comparison of infection risks and clinical outcomes in patients with and without SARS-CoV-2 lung infection under renin-angiotensin-aldosterone system blockade: systemic review and meta-analysis. Br J Clin Pharmacol 2020 December 18; 1-18.
20. JB Cohen et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. Lancet Respir Med 2021 January 7 (epub).

21. RD Lopes et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. JAMA 2021; 325: 254.
22. RSG Sablerolles et al. No association between use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers prior to hospital admission and clinical course of COVID-19 in the COvid MEdicaTion (COMET) study. Br J Clin Pharmacol 2021 January 28 (epub).
23. NIH. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/ Accessed April 23, 2021.

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)			
NSAIDS (E.G., IBUPROFEN, NAPROXEN)	▪ The Health Minister of France has warned that use of NSAIDs such as ibuprofen (*Advil*, *Motrin*, and others) to reduce fever in patients with COVID-19 increases the risk of severe adverse events and recommended use of acetaminophen (*Tylenol*, and others) instead[1]	▪ No convincing evidence that NSAIDs are especially dangerous for patients with COVID-19,[2] but they can cause GI bleeding, fluid retention, and renal dysfunction in any patient, which can be dangerous for the critically ill ▪ Acetaminophen is an effective antipyretic alternative to an NSAID and in recommended doses is less likely than an NSAID to cause serious adverse effects in most patients ▪ In a cohort study in the UK, NSAID use was not associated with higher mortality or increased disease severity in hospitalized patients with COVID-19[4] (*added 5/8/2021*)	▪ Use of an NSAID or acetaminophen for continual fever suppression may reduce the immune response and prolong viral shedding ▪ NIH guidelines recommend that antipyretic strategies (e.g., with acetaminophen or NSAIDs) should not differ between patients with or without COVID-19[3] ▪ Patients who are taking NSAIDs for other indications should not stop taking them[3]

1. M Day. COVID-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ 2020; 368:m1086.
2. FDA. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. Available at: https://bit.ly/3dnggwx. Accessed May 4, 2020.
3. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed May 4, 2020.
4. TM Drake et al. Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC clinical characterisation protocol UK cohort: a matched, prospective cohort study. Lancet Rheumatol 2021 May 7 (epub).

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
Proton Pump Inhibitors (PPIs)			
PROTON PUMP INHIBITORS (PPIs) *(updated 6/8/2021)* ▪ Dexlansoprazole *(Dexilant)* ▪ Esomeprazole magnesium (*Nexium*, *Nexium 24HR*, and generics) ▪ Lansoprazole (*Prevacid*, *Prevacid 24HR*, and generics) ▪ Omeprazole (*Prilosec*, *Prilosec OTC*, and generics) ▪ Omeprazole/sodium bicarbonate (*Zegerid*, *Zegerid OTC*, and generics) ▪ Pantoprazole (*Protonix*, and generics) ▪ Rabeprazole (*Aciphex*, and generics)	▪ PPI use may increase the risk of COVID-19 ▪ PPIs increase gastric pH and have been associated with an increased risk of enteric infections[1] ▪ SARS-CoV-1 is impaired at a pH of 3 or below; it is possible that pH has a similar effect on SARS-CoV-2 ▪ Theoretically, higher gastric pH may allow viral replication in the gut; SARS-CoV-2 enters cells via ACE-2 receptors, which are widely expressed in the GI tract[1]	**Almario Gastroenterology 2020[2]** **Population:** English-speaking adults in the US (n=53,130) **Design:** online population-based survey ▪ Survey included questions about PPI and/or H2-receptor antagonist use and positive test results for COVID-19 **Results:** ▪ Twice-daily PPI use was associated with a 3.7-fold increased odds of COVID-19 and once-daily PPI use was associated with a 2.2-fold increase, compared to no PPI use ▪ Use of H2-receptor antagonists was not associated with an increased risk of COVID-19 **Limitations:** observational data, patients taking PPIs may have more underlying risk factors than those not on PPIs **Lee et al. Gut 2020[3]** *(added 10/14/2020)* **Population:** adults tested for SARS-CoV-2 in South Korea (n=132,316) **Design:** nationwide cohort study with propensity score matching ▪ 111,911 PPI non-users, 14,163 current PPI users, 6242 past PPI users **Results:** ▪ SARS-CoV-2 test positivity rate was not associated with current or past PPI use ▪ Current PPI use was associated with higher risk of severe clinical outcomes in patients positive for COVID-19 **Limitations:** observational data; potential confounders	▪ No randomized controlled trials ▪ Twice-daily PPI use was associated with higher risk than once-daily use in an observational trial[2] ▪ American College of Gastroenterology (ACG) recommends use of the lowest effective dose of PPIs in patients with a clinical indication for their use[1] ▪ Some meta-analyses have reported associations between PPI use and severe outcomes such as severe COVID-19, increased risk of secondary infection, and mortality[4,5,6]; other meta-analyses have reported no significant difference in severe events with or without PPI use[7] *(updated 6/8/2021)*

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DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
Biguanide			
METFORMIN *(updated 1/25/2021)* ▪ *Glucophage*, *Glucophage XR,* and generics ▪ *Riomet, Riomet ER* ▪ *Glumetza* ▪ Also available in multiple combinations with other antihyperglycemic agents	▪ Metformin associated with reduced risk of death from COVID-19 in patients with type 2 diabetes in observational studies[1] ▪ Mechanism not established, but may be associated with effects of metformin on glucose control, body weight, and insulin resistance, anti-inflammatory effects of metformin, and decreased viral entry due to effects of metformin on ACE2[1] ▪ Potential risk of lactic acidosis in hospitalized COVID-19 patients with multiple organ failure	**Crouse et al MedRxiv 2020[2]** **Population:** hospitalized patients tested for COVID-19 at a single hospital in the Southern US (n=25,326) **Design:** retrospective review of electronic health records **Results:** in patients with diabetes and COVID-19, metformin was associated with a significant reduction in mortality (OR 0.33; 95% CI 0.13-0.84; p=0.0210) **Limitations:** not peer reviewed, observational data, possible confounders **Bramante et al. Lancet Healthy Longevity 2020[3]** **Population:** hospitalized patients with COVID-19 (n=6,256) **Design:** retrospective review of records from a large health insurance organization **Results:** ▪ Metformin use was associated with a decreased risk of mortality in women by COX proportional hazards (HR 0.785; 95% CI 0.650-0.951) and propensity matching (OR 0.759; 95% CI 0.601-0.960, p=0.021) ▪ Metformin use was not associated with a reduction in mortality in men **Limitations:** retrospective, observational trial; possible confounders; selection bias **AB Crouse et al. Front Endocrinol 2021[4]** *(added 1/25/2021)* **Population:** consecutive patients tested for COVID-19 (n=24,722 COVID-19 negative and 604 COVID-19 positive) **Design:** retrospective observational study ▪ analysis of electronic health record data	▪ No randomized controlled trials ▪ Diabetes is a risk factor for severe COVID-19 illness and death

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
METFORMIN (continued)		**Results:** ▪ In patients with diabetes and COVID-19, metformin use before diagnosis was associated with a reduction in mortality (OR 0.33, 95% CI 0.13-0.84; p=0.0210) **Limitations:** retrospective trial	

1. AJ Scheen. Metformin and COVID-19: from cellular mechanisms to reduced mortality. Diabetes Metab 2020 August 1 (epub). Available at:
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VACCINE	EFFICACY	SAFETY	COMMENTS
Adenovirus-Vectored Vaccines			
CHIMPANZEE ADENOVIRUS-VECTORED COVID-19 (ChAdOx1 nCoV-19) VACCINE (AZD1222) (AstraZeneca/Oxford) *(updated 11/7/2021)* ▪ Two-dose vaccine (4-12 weeks apart)	**Folegatti et al. Lancet 2020[1]** **Population:** healthy adults 18-55 years old in the UK (n=1077) **Design:** phase 1/2, single-blind, multicenter, randomized controlled trial ▪ participants randomized to 1 dose of ChAdOx1 nCoV-19 vaccine or a comparator meningococcal conjugate vaccine (MenACWY) **Results:** ▪ >90% of participants developed neutralizing antibodies; in 10 patients who received a booster dose, 100% had neutralizing antibodies ▪ Increases in SARS-CoV-2 spike-specific effector T-cell responses occurred by day 7, peaked at day 14, and were maintained up to day 56 ▪ Local and systemic adverse effects were common **Limitations:** preliminary results of phase 1/2 trial **M Voysey et al. (COV002 and COV003) Lancet 2020[5]** *(added 11/23/2020; updated 12/10/2020)* **Population:** healthy adults ≥18 years old (23,848 enrolled; 11,636 included in interim efficacy analysis) ▪ 12.2% of subjects ≥56 years old **Design: ongoing,** phase 2/3, randomized, controlled trials in the UK and Brazil ▪ Half-dose/full-dose regimen (n=2741; subset in UK received this dose) ▪ 2 full-dose regimen (n=8895) ▪ Meningococcal conjugate vaccine (MenACWY) or saline as control	▪ Common adverse effects in the phase 1/2 trial included injection-site pain (67%) and tenderness (83%), fatigue (70%), headache (68%), muscle ache (60%), malaise (61%), chills (56%), feeling feverish (51%), fever (18%) ▪ Use of acetaminophen reduced adverse effects ▪ Transient neutropenia was reported in 46% ▪ A participant in one of the ongoing phase 3 trials in the UK experienced a serious neurologic adverse reaction, which has been reported to possibly be transverse myelitis; whether the adverse reaction was caused by the vaccine is under investigation *(added 9/18/2020)* ▪ Two additional cases of transverse myelitis were reported, but determined to be unlikely to be related to the vaccine *(12/10/2020)* ▪ A safety investigation is ongoing after a trial volunteer in Brazil died; it has been reported that the volunteer may have received placebo *(added 10/22/2020)*	▪ Replication-deficient chimpanzee adenovirus-vectored vaccine expressing the SARS-CoV-2 spike protein ▪ Demonstrated immunogenicity in a phase 1/2 trial ▪ Phase 2/3 trials ongoing in several countries including the US ▪ Phase 3 trials were temporarily halted due to a serious neurologic adverse reaction in a participant in the UK who received the vaccine; the UK trial was restarted in September after review by the Medicines Health Regulatory Authority (MHRA); the US trial was cleared by the FDA to restart on October 23, 2020 *(added 9/18/2020; updated 10/26/2020)* ▪ Manufacturer reported the vaccine has produced immune responses in older adults that were similar to those seen in younger adults and vaccine-related adverse events were lower in older subjects *(added 10/28/2020)* ▪ AstraZeneca to conduct more clinical trials to clarify vaccine efficacy data after it was reported that some patients in the current phase 2/3 trial received a half dose of the vaccine *(added 11/30/2020)*

VACCINE	EFFICACY	SAFETY	COMMENTS
AZD1222 (continued)	**Results:** ▪ Vaccine efficacy 90.0% when given as a half dose, followed by a full dose at least 1 month apart ▪ Vaccine efficacy 62.1% when given as 2 full doses at least 1 month apart ▪ Average vaccine efficacy from combined analysis 70.4%; 30 cases of COVID-19 among 5807 vaccine recipients and 101 cases among 5829 subjects in the control group ▪ All results statistically significant ▪ 10 patients hospitalized, 2 of these had severe COVID-19 and 1 case was fatal; all cases were in control group **Limitations:** interim analysis; half-dose regimen due to manufacturing error; efficacy data from combined analysis includes 2 different vaccine dosages that were used; duration of protection unknown **MN Ramasamy et al. Lancet 2020 (COV002)[6]** *(added 12/21/2020)* **Population:** adults enrolled in an age-escalation manner: 18-55 years (n=160), 56-69 years (n=160), and ≥70 years old (n=240) without severe or uncontrolled medical comorbidities or a high frailty score in (those ≥65 years old) **Design:** ongoing phase 2 component of a single-blind, randomized phase 2/3 trial ▪ ChAdOx1 nCoV-19 vaccine (1 or 2 doses) vs control MenACWY vaccine (1 or 2 doses) ▪ Some patients received low-dose ChAdOx1 vaccine **Results:** ▪ Local and systemic adverse reactions (injection-side pain, feverish, muscle ache, headache) more frequent with ChAdOx1 nCoV-19 vaccine compared to control vaccine; adverse effects were	*Thromboembolic Events: (updated 4/19/2021)* ▪ Cases of thrombotic events and thrombocytopenia have been reported with the Oxford/AstraZeneca vaccine (cases have included cerebral venous sinus thrombosis [CVST], splanchnic-vein thrombosis, pulmonary embolism, disseminated intravascular coagulation [DIC]) ▪ Reported cases were almost all in women < 55 years old and most occurred within 14 days after vaccination ▪ In a population-based cohort study in Denmark and Norway, increased rates of venous thromboembolism were observed within 28 days of vaccination; 11 excess events/100,000 vaccinations, including 2.5 excess cerebral venous thrombosis events/100,000 vaccinations; absolute risks of events were small[20] *(added 5/10/2021)* ▪ Incidence of CVST with thrombocytopenia has been associated with high serum levels of antibodies against platelet factor 4 (PF4)-polyanion complexes similar to those that occur in heparin-induced thrombocytopenia (HIT); treatment with platelet transfusions or heparin is not recommended; use of a non-heparin anticoagulant and intravenous immune globulin should be considered instead[15-18]	▪ Approved for use in the UK by the Medicines & Healthcare products Regulatory Agency; vaccination is expected to begin 1/4/2021 *(added 1/1/2021)* ▪ WHO has listed the AstraZeneca/Oxford COVID-19 vaccine for emergency use; this listing allows the vaccine to be available through the COVID-19 Vaccines Global Access (COVAX) Facility[9] *(added 2/16/2021)* ▪ Phase 2 trial has been initiated in children and adolescents 6-17 years old; expected to enroll 300 participants; trial has been paused due to concerns about blood clots that have been reported in adults given the vaccine (added 2/16/2021; updated 4/7/2021) ▪ Com-COV study in the UK will evaluate efficacy of using one vaccine for the 1st dose and a different vaccine for the 2nd dose (Oxford/AstraZeneca and Pfizer-BioNTech vaccines will be used) *(added 2/28/2021)* ▪ Use of the vaccine suspended in some countries in Europe because of several reports of serious adverse effects, including blood clots; on March 18th the EMA safety committee review concluded that the benefit of the vaccine continues to outweigh the risk and the vaccine is not associated with an increase in the overall risk of thromboembolic events, however,

VACCINE	EFFICACY	SAFETY	COMMENTS
AZD1222 (continued)	less common in adults ≥56 years old compared to younger subjects ▪ Median anti-spike SARS-CoV-2 IgG responses and neutralizing antibody titers after the boost doses were similar across all age groups ▪ By 14 days after the boost dose, >99% of participants had neutralizing antibody responses **Limitation:** preliminary data; ongoing trial; single-blind; half-dose regimen **M Voysey et al. Lancet 2021**[7] *(added 2/4/2021)* **Population:** healthy adults ≥ 18 years old (n=17,177) **Design:** primary analysis of phase 3 trials in UK and Brazil and data from phase 1/2 trials in UK and South Africa ▪ 2 doses of vaccine vs a control vaccine/saline placebo ▪ A subset of patients in the UK received a low dose (LD) of vaccine for the first dose and a standard dose (SD) for the second **Results:** ▪ Overall vaccine efficacy >14 days after the second dose (including LD/SD and SD/SD dose groups) was 66.7% ▪ Vaccine efficacy after a single SD vaccine from day 22 to day 90 post-vaccination was 76% ▪ After a second SD vaccine, efficacy was 82.4% when the 2nd dose was given 12 weeks or more after the 1st, compared to 54.9% with an interval <6 weeks ▪ From the day of vaccination, 2 hospitalizations were reported in the vaccine group and 22 in the control group, 3 were severe ▪ In subjects who performed weekly nasal swabs, regardless of symptoms, PCR positive readings were reduced by 67%	▪ In a prospective cohort study that identified 170 definite and 50 probable cases of vaccine induced thrombocytopenia and thrombosis, overall mortality was 22% and was highest in among patients with a low platelet count and intracranial hemorrhage[28] *(added 8/11/2021)* EMA evaluating reports of Guillain-Barre syndrome (*added 5/8/2021)* ▪ In a trial evaluating vaccine mixing, greater systemic reactogenicity (feverishness, chills, fatigue, headache, joint pain, malaise, and muscle ache) was reported following heterologous vaccine schedules compared to their homologous counterparts[21] (see RH Shaw et al in Efficacy column; *added 5/19/2021*) ▪ In a self-controlled case series in England, there was an increased risk of some adverse thrombotic events leading to hospital admission or death within 28 days after a first vaccine dose (Oxford/AstraZeneca or Pfizer/BioNTech); the risks of most of these events after vaccination were lower than with SARS-CoV-2 infection[30] *(added 9/7/2021)* ▪ In a multicenter cohort study, vaccine-induced immune thrombotic thrombocytopenia, was associated with more intracranial veins thrombosed, more frequent extracranial thrombosis, and more frequent outcome of death or dependency than non-vaccine induced immune thrombotic thrombocytopenia;	the vaccine may be associated with very rare cases of blood clots with thrombocytopenia (7 cases of disseminated intravascular coagulation [DIC] and 18 cases of cerebral venous sinus thrombosis [CVST] reported after vaccination of ~20 million people); reported cases were almost all in women < 55 years old and most occurred within 14 days after vaccination; the number of thromboembolic events reported after vaccination was lower than the expected number in the general population[14-17] *(added 3/13/2021; updated 3/20/2021)(see safety column)* ▪ The National Advisory Committee on Immunization in Canada has recommended use of the AstraZeneca vaccine be paused in people <55 years of age because of reports of blood clots; no blood clots have been reported in Canada after administration of 300,000 vaccinations *(added 3/30/2021)* ▪ Oxford has started a phase 1 trial of a nasal spray vaccine formulation *(added 3/27/2021)* **Variants:** ▪ B.1.1.7 Variant: Vaccine efficacy after 2 doses was 74.6% (95% CI 41.6-88.9) against symptomatic infection from the B.1.1.7 variant based on data from the phase 2/3 trials; efficacy against non-B.1.1.7 lineages was 84% (95% CI 70.7-91.4)[8] *(added 2/10/2021)*; in an exploratory analysis of a randomized controlled trial,

VACCINE	EFFICACY	SAFETY	COMMENTS
AZD1222 (continued)	after a single vaccine dose and 50% after 2 doses; the authors suggest these data may indicate an impact of the vaccine on virus transmission, but the trials were not designed to evaluate this outcome **Limitations:** primary analysis of data from multiple trials; studies not designed to determine differences in efficacy by dose interval; LD/SD group; variable duration of follow-up after 2nd dose **J Lopez Bernal et al. BMJ 2021[10]** *(added 3/8/2021; updated 5/20/2021)* **Population:** older adults in the UK who received the Pfizer/BioNTech or AstraZeneca COVID-19 vaccine **Design:** test negative case control **Results:** ▪ The B.1.117 variant was prominent in the UK during the period of this study ▪ After 1 dose of either vaccine, protection against symptomatic COVID-19 was 60-70% and protection against hospitalization was ~80% ▪ Pfizer/BioNTech vaccine efficacy ~60-70% after 1 dose and ~85-90% after 2 doses; ~85% effective at preventing death ▪ AstraZeneca vaccine was ~60-75% effective after 1 dose ▪ Patients who were infected after 1 dose of the Pfizer/BioNTech vaccine were 43% less likely to be hospitalized and 51% less likely to die compared to those who were not vaccinated; patients who received 1 dose of the AstraZeneca vaccine were 37% less likely to be hospitalized **Limitations:** observational; not peer reviewed	outcomes of death or dependency less frequent in patients who received non-heparin anticoagulants and in those who received IV immunoglobulin[31] *(added 9/7/2021)*	reduced neutralization activity against B.1.1.7 variant was reduced, but clinical efficacy against symptomatic infection with the B.1.1.7 variant was 70.4% and against non-B.1.1.7 lineages was 81.5%[19] *(updated 4/26/2021)* ▪ B.1.351 Variant: vaccine efficacy 10.4% against South Africa variant[11] *(added 3/23/2021)* ▪ AstraZeneca vaccine (2 doses) was 92% effective for preventing hospitalization in patients infected with the Delta variant; based on observational data from England *(added 6/15/2021)*[23] ▪ In observational data from Scotland, the AstraZeneca vaccine was 60% effective against infection with Delta variant (2 weeks after the 2nd dose)[24] *(added 6/29/2021)* ▪ In a study in Canada, vaccine efficacy against **Alpha** was 89% after 2 doses of Pfizer/BioNTech, 92% after 2 doses of Moderna, and 64% after 1 dose of AstraZeneca; against **Beta/Gamma** 84% after 2 doses of Pfizer/BioNTech, 77% after 1 dose of Moderna, and 48% after 1 dose of AstraZeneca; against **Delta** 87% after 2 doses of Pfizer/BioNTech, 72% after 1 dose of Moderna, and 67% after 1 dose of AstraZeneca[26] *(added 7/15/2021)* ▪ In a test-negative case-control design in England, effectiveness of 1 dose of the BNT162b2 or

VACCINE	EFFICACY	SAFETY	COMMENTS
AZD1222 (continued)	**<u>SA Madhi et al. NEJM 2021[11]</u>** *(added 3/23/2021)* **Population:** HIV-negative persons 18-<65 years old in South Africa (n=2026) **Design:** randomized, double-blind trial ▪ 2 doses of AZD1222 vaccine or placebo 21-35 days apart **Results:** ▪ Mild-to-moderate COVID-19 reported in 23 of 717 placebo recipients (3.2%) and 19 of 750 vaccine recipients (2.5%); efficacy of 21.9% (95% CI -49.9-59.8) ▪ Among the 42 COVID-19 cases, 39 (92.9%) were caused by the B.1.351 variant; efficacy against this variant was 10.4% (95% CI -76.8-54.8) **Limitations:** not enough data to determine efficacy against severe COVID-19; efficacy against variant a secondary analysis **<u>AstraZeneca 2021[12]</u>** *(added 3/26/2021)* **Population:** healthy adults ≥18 years old (n=32,449) **Design:** randomized, double-blind, placebo-controlled phase 3 trial ▪ Two doses of AZD1222 or placebo 4 weeks apart **Results:** **Primary efficacy analysis in US** ▪ 76% overall efficacy (15 days after 2nd dose) ▪ 100% efficacy against severe/critical disease and hospitalization ▪ 85% efficacy against symptomatic infection in those ≥65 years old **Limitations:** AstraZeneca criticized for initially releasing interim results reporting 79% overall efficacy when additional data from the primary analysis were available, but not included *(3/23/2021)*[13]		ChAdOx1 nCoV-19 vaccine against the Delta variant was 30.7% and against the Alpha variant was 48.7%; after 2 doses of BNT162b2 effectiveness against Delta was 88% and against Alpha was 93.7%; after 2 doses of ChAdOx1 nCoV-19 effectiveness against Delta was 67.0% and 74.5% against Alpha[22] *(added 7/22/2021)* ▪ In an analysis that evaluated neutralizing antibodies induced by AZD1222 in 106 Legacy study participants in the UK, neutralizing antibody titers were about 2.5-fold lower with AZD1222 vs BNT162b2 (Pfizer/BioNTech) against variants Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2)[27] *(added 7/22/2021)* ▪ In a prospective, longitudinal, cohort study, the secondary attack rate in household contacts exposed to the delta variant was 25% (95% CI 18-33) in fully vaccinated persons and 38% in unvaccinated persons (95%CI 24-53); peak viral load was similar between unvaccinated and vaccinated persons; rate of viral load decline was faster in vaccinated persons[32] *(added 11/7/2021)* **Vaccine Storage:** ▪ Refrigeration required for vaccine storage

VACCINE	EFFICACY	SAFETY	COMMENTS
AZD1222 (continued)	**RH Shaw Lancet 2021[21]** *(added 5/19/2021)* **Population:** subjects ≥50 years old with no or mild-to-moderate, well controlled comorbidity in the UK (n=830) **Design:** multicenter, participant-masked, randomized heterologous prime-boost COVID-19 vaccination study Subjects randomized to 1 of 4 vaccine schedules administered 28 or 84 days apart: ▪ AstraZeneca/AstraZeneca ▪ AstraZeneca/Pfizer-BioNTech ▪ Pfizer-BioNTech/Pfizer-BioNTech ▪ Pfizer-BioNTech/AstraZeneca **Results:** ▪ Reactogenicity results reported for 436 subjects who received vaccines at 28-day intervals ▪ Greater systemic reactogenicity was reported following heterologous vaccine schedules compared to their homologous counterparts ▪ Adverse effects that were reported in more subjects who received a heterologous vaccine schedule included feverishness, chills, fatigue, headache, joint pain, malaise, and muscle ache ▪ There were no hospitalizations due to these adverse reactions ▪ No thrombocytopenia was reported in any group at 7 days post-boost ▪ Efficacy results expected in June 2021 **Limitations:** interim results; only subjects ≥ 50 years old **AM Borobia et al. Lancet 2021[25]** *(added 6/29/2021)* **Population:** adults 18-60 years old in Spain who were vaccinated with a single dose of		

VACCINE	EFFICACY	SAFETY	COMMENTS
AZD1222 (continued)	ChAdOx1-S 8-12 weeks before screening (n=676) **Design:** phase 2, open-label, randomized trial ▪ Subjects randomized 2:1 to BNT162b2 or maintain observation (control group) **Results:** ▪ At day 14, geometric mean titres of receptor binding domain antibodies, and IgG against trimeric spike protein were significantly increased from baseline ▪ Injection-site pain and induration, headache, and myalgia were the most common adverse events **Limitations:** ongoing trial; not compared to a control group that received a 2nd dose of ChAdOx1-S **Antonelli et al. Lancet Infect Dis 2021[29]** *(added 9/5/2021)* **Population:** adult users of a COVID Symptom Study mobile phone app in the UK **Design:** prospective, community-based, nested, case-control study ▪ Subjects included persons vaccinated with BNT162b2, mRNA-1273, or ChAdOx1 nCoV-19 **Results**: ▪ Breakthrough COVID-19 cases were reported in 0.5% of people who had received 1 vaccine dose and 0.2% of people who received 2 vaccine doses ▪ Vaccination was associated with reduced odds of hospitalization or having >5 symptoms in the first week of illness compared with no vaccination ▪ Vaccination was associated with reduced odds of long duration symptoms (≥28 days) compared with no vaccination ▪ Vaccinated participants were more likely to be asymptomatic		

VACCINE	EFFICACY	SAFETY	COMMENTS
	▪ In older adults (≥60 years old), frailty was associated with breakthrough infection after the 1st vaccine dose **Limitations:** observational study; patient-reported data; some disproportionate demographic characteristics; may not apply to all timepoints post-vaccination or different proportions of variants		
RECOMBINANT ADENOVIRUS TYPE-5 (Ad5)-VECTORED COVID-19 VACCINE (CanSino Biologics) *(updated 9/23/2020)*	**Zhu et al. Lancet 2020[2]** **Population:** healthy adults >18 years old (n=508) **Design:** phase 2, randomized, double-blind, placebo-controlled trial ▪ Participants randomized to 1 dose of vaccine with $1x10^{11}$ viral particles/mL or $5x10^{10}$ viral particles/mL or to placebo **Results:** ▪ Seroconversion rates were >96% ▪ >90% had T-cell responses ▪ antibody responses were lower in participants >55 years old and in those with previous vector immunity ▪ local and systemic adverse reactions were common **Limitations:** phase 2 data; possible lack of power to show a difference between dose groups	▪ The most common adverse effects in the phase 2 trial were injection-site pain (56-57%), fatigue (34-42%), fever (16-32%), and headache (28-29%) ▪ No serious adverse events were reported	▪ Non-replicating adenovirus type-5 (Ad5)-vectored COVID-19 vaccine ▪ Contained replication-defective Ad5 vectors expressing the full-length spike gene based on Wuhan-Hu-1 ▪ Possibly lower responses in people with pre-existing immunity to the vector and in those >55 years old ▪ In earlier trials, Ad5-vectored vaccines were not effective for prevention of HIV; in one trial, the incidence of HIV was higher in the vaccinated group than the placebo group *(added 9/23/2020)* ▪ Approved for military use in China

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VACCINE	EFFICACY	SAFETY	COMMENTS
ADENOVIRUS SEROTYPE 26 (Ad26) VECTOR-BASED COVID-19 VACCINE (Ad26.COV2.S)(JNJ-78436735) (Janssen/Johnson & Johnson) *(updated 2/16/2022)* **Dosage:**[9] ▪ ≥18 years old: a single 0.5 mL dose ▪ Suspension for IM injection ▪ Available in multiple-dose vials; each vial contains 5 doses ▪ CDC recommends preferential use of an mRNA vaccine (Pfizer/BioNTech or Moderna) over J&J vaccine because of the risk of thrombosis with thrombocytopenia syndrome (TTS) associated with the J&J vaccine *(added 12/16/2021)* ▪ Immunocompromised: CDC recommends 1 dose of Pfizer/BioNTech or Moderna (100 mcg) vaccine ≥4 weeks after initial J&J vaccine Booster: ▪ FDA EUA and CDC recommend a booster dose (mRNA vaccine preferred for booster dose) ≥2 months after the primary dose for all persons who received a primary J&J vaccine dose; for immunocompromised persons, the booster dose can be given ≥2 months after the additional mRNA vaccine dose[45,46] *(updated 2/16/2022)* ▪ FDA and CDC authorize use of each of the available COVID-19 vaccines as a	▪ A single dose induced neutralizing antibody responses in primates (Mercado et al. Nature 2020)[1] ▪ Antibodies detected in vaccine recipients by day 8 and in all recipients by day 57 after a single dose in a phase 1 trial[13] *(added 3/14/2021)* **J Sadoff et al. NEJM 2020**[4] *(added 10/1/2020; updated 1/18/2021)* **Population:** adults 18-55 years old (n=405; cohort 1a) or ≥65 years old (n=405; cohort 3) in Belgium and the US **Design**: ongoing, phase 1/2a randomized, double-blind, placebo-controlled trial ▪ Vaccine given at a dose of $5x10^{10}$ (low dose) or $1x10^{11}$ (high dose) viral particles per vaccination, either as a single dose or 2 doses (separated by 56 days) ▪ Subjects randomized to 1 of 5 groups: low dose followed by low dose, low dose followed by placebo, high dose followed by high dose, high dose followed by placebo, or placebo followed by placebo **Results:** ▪ Data reported are after the 2nd dose in patients 18-55 years old and after the 1st dose in those ≥65 years old ▪ On day 29 after the first vaccine dose, >90% of all participants had neutralizing antibody titers against wild-type virus detected; 100% by day 57 ▪ A 2nd vaccine dose increased the titer by a factor of 2.6 to 2.9 ▪ Titers remained stable for at least 71 days **Limitations:** interim analysis of phase 1/2a data **ENSEMBLE Trial 2021**[7] *(added 1/30/2021; updated 6/9/2021)*	▪ Adverse effects in the clinical trials included injection-site pain, fatigue, headache, myalgia, fever, nausea, injection-site erythema and swelling ▪ Systemic adverse effects were less common in subjects ≥65 years old than in those 18-55 years old ▪ Reactogenicity was lower after the 2nd dose ▪ Urticaria was reported in 5 subjects who received vaccine and 1 who received placebo within 7 days of vaccination; 1 case of hypersensitivity with urticaria and angioedema was reported in a vaccinated subject ▪ Thromboembolic events, such as deep vein thrombosis (6 events vs 2 events with placebo), pulmonary embolism (4 events vs 1 event with placebo), and transverse sinus thrombosis (1 event vs 0 with placebo), seizures (4 events vs 1 events with placebo), and tinnitus (6 events vs 0 with placebo) were reported in numerically more vaccine recipients than placebo recipients, but a causal relationship has not been established ▪ Fever occurred in 9% of patients who received the vaccine in the ENSEMBLE trial; 0.2% had grade 3 fever *(updated 2/28/2021)* ▪ Serious adverse events were more common in placebo group than among those who received the vaccine in the ENSEMBLE trial *(updated 2/28/2021)*	▪ Adenovirus serotype 26 (Ad26) vector-based vaccine expressing the SARS-CoV-2 spike (S) protein ▪ Ad26 technology used in the manufacturer's Ebola vaccine recently approved by the European Commission ▪ Phase 3 trial (ENSEMBLE) has started; expected to enroll up to 60,000 participants[2,3] *(updated 9/23/2020)* ▪ After being paused for safety review due to an unexplained illness in a study participant, the phase 3 trial (ENSEMBLE) has restarted in the US; no clear cause of the adverse event was identified[5] *(updated 10/26/2020)* Adolescents 12-17 years old are now being enrolled in clinical trials *(added 11/2/2020)* ▪ Phase 3 study to investigate a 2-dose regimen (given 57 days apart) initiated (ENSEMBLE 2); expected to enroll up to 30,000 participants *(11/17/2020)* ▪ FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) scheduled to review EUA for Janssen's COVID-19 vaccine on February 26, 2021 *(added 2/10/2021)* ▪ FDA issued an Emergency Use Authorization (EUA) to allow administration of the Janssen COVID-19 vaccine for prevention of COVID-19 caused by SARS-CoV-

VACCINE	EFFICACY	SAFETY	COMMENTS
heterologous (or "mix and match") booster dose in eligible individuals following completion of primary vaccination with a different available COVID-19 vaccine[45,46] *(updated 10/22/2021)* **ADENOVIRUS SEROTYPE 26 (Ad26) VECTOR-BASED COVID-19 VACCINE (Ad26.COV2.S)(JNJ-78436735) (continued)** ▪ J&J announced data that booster given 2 months after initial dose increased antibodies and protection against moderate to severe disease in the US was 94% (see efficacy column) *(added 9/23/2021)* ▪ According to CDC, booster shots are likely to be needed for people who received the J&J vaccine, but evaluation of data is ongoing[38] *(added 8/18/2021)* Immunocompromised: According to the FDA and CDC, there are not data at this time to support use of an additional COVID-19 vaccine dose after primary vaccination with the J&J/Janssen vaccine[35-37] (added 8/14/2021) ▪ COVID-19 vaccines should generally not be given within 14 days of other vaccines[11] *(added 3/6/2021)*	**Population:** adult participants ≥18 years old (n=43,783) **Design:** phase 3, multinational, randomized, double-blind, placebo-controlled trial ▪ Single dose of vaccine vs placebo **Results:** ▪ In the overall study population, the vaccine was 66% effective in preventing moderate to severe COVID-19 at 28 days after vaccination (468 symptomatic cases in 43,783 participants); 67% effective 14 days after vaccination ▪ In the US, the vaccine was 72% effective at 28 days after vaccination ▪ Efficacy was 66% in Latin America and 57% in South Africa (95% of cases were due to infection with the variant from the B.1.351 lineage) ▪ 85% effective in preventing severe disease 28 days after vaccination ▪ 100% effective against hospitalization and death ▪ 74% effective against asymptomatic infection at 71 days after vaccination[10] **Limitations:** long-term data not available **CDC report (data based on persons vaccinated with any 1 of the 3 vaccines authorized in the US)[23]** *(updated 10/4/2021)* **MMWR Report[25]:** *(added 5/26/2021)* ▪ As of April 30, 2021 10,262 vaccine breakthrough cases reported in the US out of ~101 million vaccinated persons ▪ 6446 (63%) were in women ▪ Median patient age: 58 years ▪ 2725 (27%) were asymptomatic ▪ 995 (10%) were hospitalized; of these 289 (29%) were asymptomatic or unrelated to COVID-19 ▪ 160 (2%) died; of these, 28 (18%) were asymptomatic or unrelated to COVID-19	▪ Severe hypersensitivity reactions, including anaphylaxis, have been reported with use of the Johnson & Johnson vaccine[10] *(added 3/6/2021)* ▪ Allergy to polysorbate (a vaccine ingredient) is a contraindication to vaccination with the Janssen vaccine[11] *(added 3/6/2021)* ▪ Case report of Guillain-Barre syndrome (GBS) within 2 weeks of vaccination in a patient in the clinical trial (GBS was also reported in a patient in the placebo group); a causal association was not established[14] *(added 4/7/2021)* ▪ Warning added to labeling about increased risk of Guillain-Barré syndrome (GBS) *(added 7/12/2021)* • 100 cases reported after 12.8 million doses • 95 required hospitalization; 1 death • Persons >50 years old and men appear to be at greatest risk • Most cases occurred within 42 days after vaccination *Thromboembolic Events:* ▪ FDA and EUA are evaluating rare reports of thromboembolic events in people who received the J&J COVID-19 vaccine; >6.8 million doses of the Johnson & Johnson vaccine have been administered in the US[15-18] ▪ FDA and CDC are investigating 6 cases of cerebral venous sinus thrombosis in combination with thrombocytopenia; all cases occurred in women 18-4 years	2 in persons ≥18 years old; this is the third EUA for a COVID-19 vaccine issued by the FDA[8] *(added 2/27/2021)* ▪ Endorsed for use by the European Commission *(added 3/14/2021)* ▪ WHO recommends J&J vaccine for use in adults *(added 3/20/2021)* ▪ FDA and CDC recommend lifting the pause and resuming use of the Johnson & Johnson (Janssen) vaccine in the US; they state that available data suggest the chance of thrombosis-thrombocytopenia syndrome (TTS) occurring is very low; the vaccine labeling now contains information about the risks of TT [15-18,24] *(updated 4/26/2021)* **Variants:** ▪ In a small *in vitro* study, neutralizing antibody titers against the Delta variant were reduced 1.6-fold[28] *(added 7/15/2021)* ▪ In a small *in vitro* study, neutralizing antibody titers were decreased by 5.4-fold for Delta and 6.7-fold for Beta; the authors state, according to mathematical modeling, that these decreases could result in decreased protection against infection[29] *(added 7/22/2021)*

VACCINE	EFFICACY	SAFETY	COMMENTS
ADENOVIRUS SEROTYPE 26 (Ad26) VECTOR-BASED COVID-19 VACCINE (Ad26.COV2.S)(JNJ-78436735) (continued)	▪ Median age of patients who died: 82 years ▪ Sequence data was available for 555 (5%); of these 356 (64%) were variants of concern (B1.1.7 in 199 [56%], B.1.429 in 88 [25%], B1.427 in 28 [8%], P.1 in 28 [8%], and B.1.351 in 13 [4%]) **October 4th Report** (CDC now monitoring only hospitalized or fatal cases instead of all cases) ▪ 30,177 hospitalized or fatal vaccine breakthrough cases out of >185 million fully vaccinated ▪ 5660 (86%) deaths and 15,792 hospitalizations (67%) were ≥65 years old ▪ 2902 (44%) deaths and 11,474 (49%) hospitalizations in women ▪ 968 (15%) deaths and 3483 (15%) hospitalizations asymptomatic or not COVID-related **DH Barouch et al. NEJM 2021[30]** *(added 7/22/2021)* ▪ Description of 20 participants who received the Ad26.CoV2.S vaccine (10 participants received 1 dose and 10 received 2 doses) ▪ Antibody and T-cell responses assessed on day 239 (8 months after single dose or 6 months after 2 dose series) ▪ humoral and cellular immune responses with minimal decrease reported for at least 8 months after vaccination ▪ authors report expansion of neutralizing antibody breadth against variants including Delta, Beta, and Gamma **AM Cavanaugh et al. MMWR 2021[32]** *(added 8/10/2021)*	old and symptoms occurred 6-13 days after vaccination; in addition to CVST, three of the women had extracranial thromboses; 4 women developed intraparenchymal brain hemorrhage, and one died; comorbid conditions included obesity (n=3), hypertension (n=1), hypothyroidism (n=1), and asthma (n=1); one woman was taking estrogen/progesterone [15-18,21](*added 4/12/2021; updated 4/16/2021*) ▪ CDC Update: 28 cases of TTS reported to VAERS as of May 7, 2021 out of ~9 million vaccinations; median age 40 years (range 18-59 years), median time to onset 9 days (range 3-15 days); 22 cases were in women; 19 of 28 cases were CVST[27] *(added 6/8/2021)* ▪ Incidence of CVST with thrombocytopenia has been associated with high serum levels of antibodies against platelet factor 4 (PF4)-polyanion complexes similar to those that occur in heparin-induced thrombocytopenia (HIT)[19,20,22]*(added 4/16/2021)* ▪ The CDC recommends that persons who experience a thrombotic event and thrombocytopenia after administration of the Johnson & Johnson vaccine be screened with a PF4 HIT enzyme-linked immunosorbent assay (ELISA) and referred to a hematologist; if the assay is positive or cannot be completed, heparin should not be used for thrombosis management; other anticoagulants and intravenous immune globulin should be considered instead *(added 4/16/2021)*[17]	▪ 469 COVID-19 cases were identified following large public gatherings in a Massachusetts town, of these 469 cases, 346 (74%) were in fully vaccinated persons; testing of specimens from 133 patients identified the Delta variant in 90%; among breakthrough cases, 4 (1.2%) were hospitalized and 0 deaths were reported[31] *(added 8/3/2021)* ▪ CDC evaluation of data from the HEROES-RECOVER trial that included all available COVID-19 vaccines in the US reported vaccine efficacy of 66% during a period when Delta variant was predominant[129] *(8/24/2021)* **Pregnancy:** ▪ American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM) recommend all pregnant and breastfeeding individuals be vaccinated against COVID-19[11]*(updated 8/12/2021)* ▪ CDC recommends COVID-19 vaccination for all pregnant people (and people who are trying get pregnant or plan to become pregnant in the future) and breastfeeding people; pregnant people are at increased risk for severe illness from COVID-19 compared to non-pregnant people and pregnant people with COVID-19 are at risk for preterm birth[12] *(updated 8/12/2021)*

VACCINE	EFFICACY	SAFETY	COMMENTS
ADENOVIRUS SEROTYPE 26 (Ad26) VECTOR-BASED COVID-19 VACCINE (Ad26.COV2.S)(JNJ-78436735) (continued)	**Population:** Kentucky residents ≥18 years old infected with SARS-CoV-2 in 2020 and reinfected in May-June 2021 (n=246 cases and 492 controls) **Design:** case-control study ▪ Vaccination status of reinfected residents what compared with that of residents who were not reinfected **Results:** ▪ In persons previously infected with COVID-19, the likelihood of reinfection was significantly higher in unvaccinated persons compared to those who were vaccinated (OR = 2.34;95% CI 1.58-3.47) **Limitations:** retrospective study, vaccinated persons less likely to be tested, possibility that some reinfections may not have been distinct virus relative to first infection, possible some vaccination data missing **WH Self et al. MMWR 2021[40]** *(added 9/19/2021)* immunocompetent adults in the US admitted to 21 hospitals in the Influenza and Other Viruses in the Acutely Ill (IVY) Network (n=3689) **Design:** cases control analysis ▪ Case patients admitted with COVID-19-like illness and a positive SARS-CoV-2 test result ▪ Control patients admitted to a hospital with a negative SARS-CoV-2 test result **Results:** ▪ Vaccine efficacy against hospitalization for the full surveillance period (March 11-August 15, 2021) was 93% with Moderna, 88% with Pfizer/BioNTech and 71% with Janssen/J&J ▪ Vaccine efficacy against hospitalization 14-120 after full vaccination was 93% with Moderna and 91% with Pfizer/BioNTech	▪ Interim safety data from the first 288,368 participants in a phase 3b study in South Africa reported adverse events in 5898 (2%); 81% of these were mild to moderate reactogenicity events; 5 arterial, venous thrombotic or embolic events were reported in 5 subjects with risk factors for thromboembolism[26] *(added 6/8/2021)* ▪ Case of death due to TTS reported in a woman in her late 30's who received the J&J vaccine; the patient received the vaccine on August 26, 2021 and died on September 7, 2021[43] *(added 10/7/2021)*	▪ CDC and ACOG state that women <50 years old should be aware of the risk of thrombosis with thrombocytopenia syndrome (TTS) associated with the J&J/Janssen vaccine and that FDA-authorized mRNA vaccines are available that have not been associated with this risk[33,34] *(added 8/12/2021)* ▪ A case-control study using data from Norwegian registries reported no evidence of an increased risk of early pregnancy loss after COVID-19 vaccination[47] *(added 11/7/2021)* **Vaccine Storage:** ▪ Store unpunctured multi-dose vials under refrigeration at 2-8°C (36-46°F) ▪ Vaccine is initially stored frozen by the manufacturer, then shipped refrigerated at 2-8°C ▪ Unpunctured vials can be stored at room temperature (9-25°C; 47-77°F) for up to 12 hours ▪ Punctured vials can be stored at 2-8°C (36-46°F) for up to 6 hours or at room temperature for up to 2 hours ▪ Protect vials from light

VACCINE	EFFICACY	SAFETY	COMMENTS
ADENOVIRUS SEROTYPE 26 (Ad26) VECTOR-BASED COVID-19 VACCINE (Ad26.COV2.S)(JNJ-78436735) (continued)	▪ Vaccine efficacy against hospitalization >120 days after full vaccination was 92% with Moderna and 77% with Pfizer/BioNTech ▪ Efficacy against hospitalization >28 days after vaccination with the Janssen/J&J vaccine was 68% ▪ In a postvaccination antibody analysis in 100 volunteers, anti-receptor binding domain IgG levels were higher with Moderna than with Pfizer/BioNTech or Janssen/J&J and anti-spike IgG levels were higher with Moderna than Janssen/J&J, but not significantly different than with Pfizer/BioNTech **Limitations:** only included immunocompetent adults; only included hospitalized subjects; small number of patients who received Janssen/J&J vaccine; not specific estimates by variant **J&J Booster ENSEMBLE 2 2021**[41] *(added 9/23/2021)* **Population:** adults who received a booster dose of the J&J vaccine 56 days after the primary dose **Design:** phase 3, randomized, double-blind, placebo-controlled ENSEMBLE 2 study **Results:** ▪ Median follow-up 36 days after dose 2 ▪ Efficacy against moderate to severe/critical disease in the US was 94% (95% CI 58-100%; 1 case with vaccine and 14 cases with placebo) ▪ Efficacy against moderate to severe/critical disease globally was 75% (95% CI 55-87%; 14 cases with vaccine and 52 cases with placebo) ▪ Efficacy against severe/critical disease was 100% (95% CI 33-100%; 0 cases with vaccine and 8 cases with placebo)		

VACCINE	EFFICACY	SAFETY	COMMENTS
ADENOVIRUS SEROTYPE 26 (Ad26) VECTOR-BASED COVID-19 VACCINE (Ad26.COV2.S)(JNJ-78436735) (continued)	▪ 4-6-fold increase in antibody levels with booster dose ▪ Booster dose generally well tolerated **Limitations:** not published or peer reviewed **JM Polinski et al. medRxiv 2021** *(added 9/23/2021)* **Population:** adults vaccinated with a single dose of Ad26.COV2.S (n=390,517) compared to matched unvaccinated controls (n=1, 524,153) **Design:** cohort study ▪ Evaluated insurance claims in the US through July 2021 **Results:** Estimated vaccine effectiveness (95%CI): ▪ 79% (77-80%) for COVID-19 infection ▪ 81% (79-84%) for COVID-19 hospitalization ▪ 78% (73-82%) vs Delta infection and 85% (73-91%) vs Delta hospitalization (June-July 2021 in states with high incidence of the variant) ▪ 83% (81-85%) in persons <50 years old ▪ 64% (57-70%) in immunocompromised **Limitations:** not peer reviewed; observational; unclear how definitions of severity line up with RCTs; no sequence-specific information so Delta effectiveness not certain **RL Atmar et al. medRxiv 2021**[44] *(added 10/19/2021)* Vaccine Mixing **Population:** persons in the US with no reported history of SARS-CoV-2 infection who received 1 of 3 COVID-19 vaccines with an FDA Emergency Use Authorization (Pfizer/BioNTech, Moderna, or J&J vaccine) at least 12 weeks prior (n=458) **Design:** phase 1/2 adaptive design, open-label trial sponsored by the NIH		

VACCINE	EFFICACY	SAFETY	COMMENTS
ADENOVIRUS SEROTYPE 26 (Ad26) VECTOR-BASED COVID-19 VACCINE (Ad26.COV2.S)(JNJ-78436735) (continued)	▪ Subjects received a booster dose with one of the 3 vaccines (Pfizer/BioNTech, Moderna, J&J) resulting in 9 vaccine combinations **Results:** ▪ Antibody levels increased in all groups after booster of different vaccine (4.6-56-fold increase) ▪ Neutralizing antibody titers increased 4-20-fold with homologous boost combinations vs 6-76-fold with heterologous boost combinations ▪ Neutralizing antibody titers in J&J primary dose recipients increased 76-fold after Moderna booster, 35-fold after Pfizer booster, and 4-fold after J&J booster ▪ Serum neutralization levels at baseline (before booster) were lower for Pfizer/BioNTech (3-fold) and J&J (10-fold) recipients than for Moderna recipients ▪ Reactogenicity and adverse events similar across all groups **Limitations:** preprint, not peer-reviewed or published; not designed to compare responses between regimens; not representative of general population **ES Rosenberg et al. NEJM 2021[48]** *(added 12/6/2021)* **Population:** adults in New York State vaccinated with BNT162b2, mRNA-1273, or Ad26.COV2.S (n=8,690,825) **Design:** surveillance-based cohort **Results:** ▪ During week of May 1, 2021 (alpha predominance; delta 1.8% of variants), median vaccine effectiveness against COVID-19 was 91.3% for BNT162b2, 96.9% for mRNA-1273, and 86.6% for Ad26.COV2.S		

VACCINE	EFFICACY	SAFETY	COMMENTS
	▪ During week of August 28 (delta predominance; delta 99.6% of variants), median vaccine effectiveness was 72.3% for BNT162b2, 77.8% for mRNA-1273, and 69.4% against Ad26.COV2.S ▪ Effectiveness against hospitalization with COVID-19 remained >86% in adults 18-64 years old, with no apparent time trend **Limitations:** observational, possible confounding, did not account for herd immunity between groups		

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VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA Vaccines			
mRNA-1273 *Spikevax* (Moderna) *(updated 3/29/2022)* **Dosage:**[16] ▪ Primary Series: Two 100 mcg doses given 4-8 weeks apart • 8-week interval may be optimal for certain persons, especially males 18-39 years old[183,184] *(updated 2/28/2022)* • standard 4-week interval should still be used in adults ≥65 years old, moderately or severely immunocompromised, and others who require more rapid protection because of high levels of community spread or high risk of severe COVID-19[183,184] *(updated 2/28/2022)* ▪ A third 100 mcg dose, given 28 days after the 2nd dose, is recommended for certain **immunocompromised** persons (see Immunocompromised 3rd dose below) ▪ Primary doses contain 100 mcg of nucleoside-modified messenger RNA encoding the pre-fusion stabilized Spike glycoprotein (S) of SARS-CoV-2 virus and booster doses contain 50 mcg ▪ Booster:[151,179] One 50-mcg dose ≥5 months after dose 2; in immunocompromised patients, booster can be given ≥3 months after dose 3 *(updated 2/15/2022)*	**Jackson et al. NEJM 2020**[1] *(updated 11/12/2020)* **Population:** healthy adults 18-55 years old (n=45) **Design:** phase 1, dose-escalation, open-label trial ▪ 2 vaccinations delivered 28 days apart at a 25 mcg, 100 mcg, or 250 mcg dose **Results:** ▪ antibody responses higher with the higher dose after 1st vaccination ▪ titers increased after 2nd vaccination ▪ serum-neutralizing activity detected after 2nd vaccination in all participants **Limitations:** preliminary results from a phase 1 trial **Anderson et al. NEJM 2020**[5] *(added 10/1/2020)* **Population:** older adults (≥56 years old) stratified according to age (56-70 years old or ≥71 years old) (n=40) **Design:** phase 1, dose-escalation, open-label trial ▪ 2 doses of 25 mcg or 100 mcg vaccine given 28 days apart **Results:** ▪ Serum neutralizing activity was detected in all participants after the 2nd vaccine dose ▪ Binding- and neutralizing-antibody responses appeared similar to those in adults <55 years old who were given the vaccine and were higher than a panel of convalescent serum controls ▪ Antibody titers were higher with the 100-mcg dose than the 25-mcg dose ▪ Mild to moderate adverse reactions reported; mostly after the 2nd dose	*(section updated 12/17/2020)* ▪ Most common adverse effects were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%) ▪ Severe reactions occurred more frequently after the second dose than the first and occurred less often in subjects ≥65 years compared to younger people ▪ Lymphadenopathy has been reported ▪ Bell's palsy was reported in 3 vaccine recipients and 1 placebo recipient; a causal relationship has not been established; an analysis using the WHO pharmacovigilance database did not detect a signal of disproportionality of facial paralysis with mRNA COVID-19 vaccines compared with other viral vaccines or influenza vaccines alone[65] *(updated 5/3/2021)* ▪ 2 serious events of facial swelling occurred in vaccine recipients ▪ 1 serious event of intractable nausea and vomiting reported in a patient with a history of severe headache and nausea requiring hospitalization ▪ No serious adverse events reported in clinical trials ▪ Anaphylactic reactions were identified as important potential risks; no anaphylactic reactions with close	▪ Lipid nanoparticle-encapsulated, nucleoside-modified messenger RNA (mRNA)-based vaccine ▪ Encodes the SARS-CoV2 spike (S) glycoprotein, which is needed for host cell attachment and viral entry ▪ FDA granted fast track designation ▪ Reduced viral replication in the lungs and noses of primates (KS Corbett et al. NEJM 2020)[2] ▪ Phase 3 trial has begun; expected to enroll about 30,000 participants and use a dose of 100 mcg ▪ Moderna filed for an EUA; FDA advisory committee is scheduled to review on December 17, 2020[16] *(updated 12/16/2020)* ▪ FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) voted (20-0, 1 abstention) to recommended emergency authorization of the Moderna's COVID-19 vaccine; they note more data are needed on long-term safety and efficacy, and in certain populations such as pregnant women and pediatric patients [16] *(updated 12/17/2020)* ▪ FDA issued an Emergency Use Authorization (EUA) to allow administration of the Moderna COVID-19 vaccine for prevention of COVID-19 caused by SARS-CoV-2 in persons ≥18 years old; this is the

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued) ▪ 2nd Booster: One 50 mcg dose ≥4 months after a 1st booster dose of any authorized COVID-19 vaccine for persons ≥50 years old or immunocompromised persons who have undergone solid organ transplantation or have an equivalent level of immunocompromise[185] *(added 3/29/2022)* ▪ FDA and CDC Booster Recommendations: all persons ≥18 years old eligible to receive a booster dose; the CDC recommends everyone ≥18 **should** receive a booster [151,152,167] *(updated 11/30/2021)* ▪ FDA and CDC authorize use of each of the available COVID-19 vaccines as a heterologous (or "mix and match") booster dose in eligible individuals following completion of primary vaccination with a different available COVID-19 vaccine[151,152] *(updated 10/22/2021)* Immunocompromised 3rd Dose: ▪ FDA authorized a 3rd dose to be given 28 days after the 2nd dose in patients who are immunocompromised (patients who have undergone solid organ transplantation or those diagnosed with conditions that are considered to have an equivalent level of immune compromise)[122] *(added 8/13/2021)*	**Limitations:** small number of participants; phase 1 data **A Widge et al. NEJM 2020[10]** *(added 12/3/2020)* **Population:** 34 healthy adults who participated in the phase 1 trial **Design:** phase 1, dose-escalation, open-label trial (interim results reported previously; see Jackson et al and Anderson et al above) ▪ Immunogenicity results 119 days after first vaccination presented ▪ 2 doses of the 100-mcg vaccine given 28 days apart ▪ Stratified according to age: 18-55 yrs, 56-70 yrs, or ≥71 yrs **Results:** ▪ Serum neutralizing antibodies were detected in all participants at day 119 ▪ Expected, slight decrease in antibodies over time **Limitations:** phase 1 data **LR Baden et al. NEJM 2021 (COVE Trial)[8]** *(added 11/17/2020; updated 12/31/2020)* **Population:** adults ≥18 years old in the US, including those at high risk of severe complications of COVID-19 (n=30,420) **Design:** ongoing, phase 3, randomized, observer-blinded, placebo-controlled trial ▪ mRNA-1273 100 mcg vs placebo ▪ 2 doses given 28 days apart **Results:** ▪ 2.2% of subjects had evidence of SARS-CoV-2 infection at baseline ▪ vaccine efficacy 94.1% 14 days after the second vaccine dose (95% CI 89.3-96.8%; p<0.001; 185 cases of COVID-19 in the placebo group and 11 in the vaccine group	temporal relation to the vaccine were reported in the phase 3 clinical trial ▪ Should not be administered to persons with a history of severe allergic reaction to any component of the vaccine ▪ Case of a severe allergic reaction reported in a physician in Boston with a history of shellfish allergy; the patient self-administered an *EpiPen (added 1/1/2021)* ▪ Case of an anaphylactic reaction reported in a healthcare worker in Oregon after vaccination; the patient required hospitalization *(added 1/1/2021)* ▪ CDC recommends that people who experienced an allergic reaction (even if not severe) after administration of the first dose of an mRNA COVID-19 vaccine not be given the second dose[18] *(added 1/1/2021)* ▪ CDC states that allergy to polyethylene glycol (PEG; a vaccine ingredient) is a contraindication to vaccination with an mRNA COVID-19 vaccine[18,22]; an allergy to polysorbate (related to PEG, but not a vaccine ingredient) is a precaution to vaccination[22] *(updated 3/6/2021)* ▪ American College of Allergy, Asthma & Immunology (ACAAI) recommend mRNA COVID-19 vaccines be administered in a healthcare setting where anaphylaxis can be treated, and patients should be observed for at least 15-30 minutes after vaccination[19] *(added 1/1/2021)*	second EUA for a COVID-19 vaccine issued by the FDA[17] *(added 12/18/2020)* ▪ FDA issued a full approval on January 31, 2022 for the 2-dose primary series of the Moderna vaccine *(Spikevax)* for persons ≥18 years old; additional primary dose for immunocompromised persons and booster doses remain authorized under an EUA[182] *(added 2/1/2022)* ▪ Moderna started trials in children 6 months to 11 years old; expected to enroll ~6750 children in US and Canada; manufacturer reports they expect results in 2022 *(added 3/20/2021)* ▪ A NIAIAD trial to investigate whether vaccination prevents transmission has started; expected to enroll 12,000 college students in the US; half will be given Moderna vaccine immediately and half will be vaccinated 4 months later; degree of transmission will be determined by infection rate in close contacts *(added 3/26/2021)* **Variants:** ▪ In an *in vitro* study, sera containing antibodies from people who received the Moderna COVID-19 vaccine showed activity against SARS-CoV-2 with mutations including the B.1.1.7 and B.1.351 variants first identified in the UK and South Africa; there was no impact on neutralizing titers against

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued) ▪ CDC recommends a 3rd dose of an mRNA vaccine for moderately to severely immunocompromised people including people: *(added 8/14/2021)*[123,124] • who have been receiving active cancer treatment for solid tumors or hematologic malignancies • received an organ transplant and are taking immunosuppressants • received a stem cell transplant within the last 2 years or are taking immunosuppressants • with moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome) • who have advanced or untreated HIV infection • are receiving active treatment with high-dose corticosteroids (≥ 20 mg prednisone/day or equivalent), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, TNF blockers, and other biologic agents that are immunosuppressive or immunomodulatory ▪ Available as multiple-dose vials	▪ vaccine efficacy 95.6% in participants 18-<65 years old ▪ vaccine efficacy 86.4% for those ≥65 years old ▪ severe COVID-19 occurred in 30 participants who received placebo (1 fatality) and 0 who received the vaccine **Limitations:** longer-term data needed; more data needed in some subgroups **F Krammer et al. NEJM 2021[43]** *(added 3/15/2021)* ▪ In subjects who were vaccinated with the Moderna or Pfizer/BioNTech mRNA vaccine, those who were seronegative at baseline had variable and relatively low antibody responses 9-12 days after vaccination, while subjects who were seropositive at baseline had rapid development of high antibody titers ▪ Antibody titers were 10-45 times higher in those with preexisting immunity than in those without **BJ Boyarsky et al. JAMA 2021[45]** *(added 3/15/2021)* **Population:** transplant recipients vaccinated against SARS-CoV-2 with 1 dose of an mRNA vaccine in the US (n=436) **Design:** prospective cohort **Results:** ▪ 48% received the Moderna vaccine and 52% received the Pfizer/BioNTech vaccine ▪ Maintenance immunosuppression regimens included tacrolimus (83%), corticosteroids (54%), mycophenolate (66%), azathioprine (9%), sirolimus (4%), everolimus (2%) ▪ 76/436 patients (17%) a had detectable antibody response	▪ ACAAI states that people with common allergies to medications, foods, inhalants, insects and latex are not more likely than the general public to have an allergic reaction to an mRNA COVID-19 vaccine; data on individuals with a history of allergic reactions to previous vaccinations and/or mast call activation syndrome/idiopathic anaphylaxis is limited[19] *(added 1/1/2021)* ▪ A higher number of allergic reactions than expected was reported in California after administration of vaccines from lot 41L20A; and investigation is ongoing *(added 1/23/2021)* ▪ Estimated rate of 2.5 cases of anaphylaxis per million doses administered after administration of 4,014,396 first vaccine doses; based on reports to VAERS[27] *(added 1/25/2021)* ▪ 2 patients who had immediate hypersensitivity reactions to the first dose of Moderna vaccine were successfully administered the second vaccine dose using graded doses[61] *(added 4/20/2021)* CDC analysis of adverse events reported through VAERS and v-safe after administration of 13.8 million vaccine doses (Pfizer-BioNTech and Moderna) found[34] *(added 2/28/2021)*: ▪ most reports were for nonserious events ▪ occurrence of anaphylaxis was within range reported for other vaccines ▪ of 113 reported deaths, most were in residents of long-term care facilities and causes of death were consistent with expected all-cause mortality in this population	B.1.1.7 relative to prior variants, but a 6-fold reduction in neutralizing titers was reported with B.1.351 and a reduction in titers against the P.1 (Brazilian) variant relative to prior variants (titers were still above levels expected to be protective)[28,29,36]; neutralizing titers also reported against the B.1.526 (New York) variant[63,64] ; neutralizing titers against B.1.617 (India) variant were about 4-fold lower, but expected to be protective[80] *(updated 5/20/2021)* ▪ In an *in vitro* study, after vaccination with mRNA-1273, binding and functional antibodies against SARS-CoV-2 variants (B.1.1.7, B.1.351, P.1, B.1.429, B.1.526) were maintained for 6 months[81] *(added 5/20/2021)* ▪ An additional booster dose of the Moderna COVID-19 vaccine (mRNA-1273) is being evaluated to determine if it can increase neutralizing titers against new variants and a booster vaccine (mRNA-1273.351) against the B.1.351 variant (first identified in South Africa) is entering preclinical and phase 1 trials[28] *(added 1/25/2021)*; neutralizing antibody titers against SARS-CoV-2 and the variants B.1.351 and P.1 were increased after a booster dose of mRNA-1273 or mRNA-1273.351 in previously vaccinated individuals[83] *(added 5/20/2021)*

mRNA-1273 (continued)

VACCINE	EFFICACY	SAFETY	COMMENTS
▪ Persons who have received 1 dose of the Moderna COVID-19 vaccine should complete the series with the same vaccine; there is no data on the interchangeability with other COVID-19 vaccines ▪ CDC recommends in exceptional situations when the vaccine product used for the first dose cannot be determined or is no longer available, any mRNA COVID-19 vaccine can be given at least 28 days after the first dose[22] *(added 1/25/2021)* ▪ If the second vaccine dose cannot be given within the recommended interval, CDC now recommends it may be given up to 6 weeks (42 days) after the first dose[22] *(added 1/23/2021)* ▪ CDC states in exceptional situations where a patient received 1 dose of an mRNA vaccine and is unable to complete the series with an mRNA vaccine (e.g., contraindication), a single dose of the Janssen COVID-19 vaccine may be considered at a minimum of 28 days after the first mRNA vaccine dose[22] *(added 3/6/2021)* ▪ COVID-19 vaccines should generally not be given within 14 days of other vaccines[22] *(added 3/6/2021)*	▪ Recipients receiving anti-metabolite maintenance immunosuppression were less likely than those who were not to develop an antibody response (37% vs 63%; adjusted incidence rate ratio [IRR] 0.22, 95% CI 0.15-0.34; p<0.001) ▪ Older patients were less likely to develop an antibody response than younger patients (adjusted IRR 0.83 per 10 years, 95% CI 0.73-0.93, p=0.002) ▪ Antibody response was more likely with Moderna vaccine than Pfizer/BioNTech vaccine (69% vs 31%, IRR 2.15, 95% CI 1.29-3.57; p=0.003) **Limitations:** no control group, convenience sample, lack of serial measurements after vaccine, only response after 1st dose **BJ Boyarsky et al. JAMA 2021[71]** *(added 5/9/2021)* **Population:** transplant recipients vaccinated against SARS-CoV-2 with 2 doses of an mRNA vaccine in the US (n=658) **Design:** prospective cohort **Results:** ▪ 1st dose results in 396 of these patients reported previously (see Boyarsky et al above) ▪ Maintenance immunosuppression regimens included tacrolimus (83%), corticosteroids (54%), mycophenolate (66%), azathioprine (9%), sirolimus (4%), everolimus (2%) ▪ 98/658 patients (15%) a had detectable antibody response at a median of 21 days after dose 1 ▪ 357/658 patients (54%) a had detectable antibody response at a median of 29 days after dose 2	▪ adverse reactions were more common after the second dose ▪ Delayed cutaneous reactions reported in 12 patients given the Moderna vaccine; reactions (≥10 cm in diameter in 5 patients) near the injection site occurred a median of 8 days after the 1st dose; median resolution 6 days; half of patients had recurrent reactions after the 2nd vaccine dose[41] *(added 3/6/2021)* ▪ A case series in Switzerland reported stage III hypertension occurring in 9 patients within minutes of BNT162b2 vaccination; 8 of 9 patients reported well-controlled hypertension before vaccination[51] *(added 3/29/2021)* ▪ Registry-based study reported 414 cutaneous reactions to mRNA COVID-19 vaccines between December 2020 and February 2021; reactions included large local reactions, injection-site reactions, urticarial eruptions, morbilliform eruptions; less common reactions included pernio/chilblains, cosmetic filler reactions, zoster, herpes simplex flares, and pityriasis rosea-like reactions *(added 5/8/2021)* ▪ Of 1422 reports of postvaccination reactions submitted to a COVID-19 vaccine allergy case registry, 510 were delayed large local reactions; of these events, 55 (11%) were in blacks, Indigenous persons, and people of color; most reactions occurred after the first vaccine dose; mean time from vaccination to onset was 8 days; 11 patients had reactions other than at the injection site (diffuse itching, hives,	▪ In a study in Canada, vaccine efficacy against **Alpha** was 89% after 2 doses of Pfizer/BioNTech, 92% after 2 doses of Moderna, and 64% after 1 dose of AstraZeneca; against **Beta/Gamma** 84% after 2 doses of Pfizer/BioNTech, 77% after 1 dose of Moderna, and 48% after 1 dose of AstraZeneca; against **Delta** 87% after 2 doses of Pfizer/BioNTech, 72% after 1 dose of Moderna, and 67% after 1 dose of AstraZeneca[102] *(added 7/15/2021)* ▪ 469 COVID-19 cases were identified following large public gatherings in a Massachusetts town, of these 469 cases, 346 (74%) were in fully vaccinated persons; testing of specimens from 133 patients identified the Delta variant in 90%; among breakthrough cases, 4 (1.2%) were hospitalized and 0 deaths were reported[110] *(added 8/3/2021)* ▪ In a cohort study (see Puranik et al in Efficacy), vaccine effectiveness during a period when Delta variant was prominent was 76% for mRNA-1273 and 46% for BNT162b2; effectiveness against hospitalization remained high[116] *(added 8/11/2021)* ▪ CDC evaluation of data from the HEROES-RECOVER trial that included all available COVID-19 vaccines in the US reported vaccine efficacy of 66% during a period when Delta variant was predominant[129] *(8/24/2021)*

mRNA-1273 (continued)

VACCINE	EFFICACY	SAFETY	COMMENTS
▪ Coadministration of *Fluzone High-Dose* quadrivalent vaccine with the Moderna COVID-19 mRNA booster vaccine resulted in similar immunogenicity responses and safety/tolerability profiles as individual vaccine administration in one trial[148](*added 10/11/2021*)	▪ Of the 658 patients, 98 (15%) had measurable antibody response after dose 1 and 2, 301 (46%) had no antibody response after dose 1 or dose 2, and 259 (39%) had no antibody response after dose 1 but did have antibody response after dose 2 ▪ Of 473 patients receiving anti-metabolites, 38 (8%) had antibody response after dose 1 and 2, 268 (57%) had no antibody response after dose 1 or 2, and 167 (35%) had no antibody response after dose 1 but did have antibody response after dose 2 ▪ Antibody levels were below those reported in immunocompetent persons who were vaccinated **Limitations:** no control group, convenience sample, lack of serial measurements after vaccine **<u>WA Werbel et al. Ann Intern Med 2021</u>[119]** *(added 8/11/2021)* **Population:** solid organ transplant recipients who had a suboptimal response to a standard 2-dose mRNA COVID-19 vaccination series and received a 3rd dose (n = 30) **Design:** case series **Results:** ▪ Primary vaccine series were with Pfizer/BioNTech or Moderna vaccines; 3rd vaccine dose was with J&J/Janssen, Pfizer/BioNTech, or Moderna ▪ 3rd vaccine given a median of 67 days after the 2nd dose ▪ Prior to the 3rd vaccine, 24 patients had negative antibody titers and 6 had low-positive titers ▪ Of the 6 patients with low-positive antibody titers before the 3rd dose, all had high-positive titers after the 3rd dose	other rash, angioedema) *(added 6/9/2021)*[92] ▪ In an analysis of VAERS data, the incidence of sudden sensorineural hearing loss after COVID-19 vaccination did not exceed that of the general population[88] *(added 6/6/2021)* ▪ Case reports of functional neurological disorder after COVID-19 vaccination[127,128] (*added 8/23/2021*) ▪ Interim analysis of surveillance data (Vaccine Safety Datalink [VSD]) from 6.2 million persons who received 11.8 million doses of an mRNA vaccine:[131,132] *(added 9/7/2021)* • No significant associations were found between vaccination and 23 serious health outcomes 1-21 days after vaccination with an mRNA vaccine; confidence intervals were wide for some rate ratio estimates • Vaccination associated with excess risk for myocarditis/pericarditis in persons 12-39 years old; no association reported in overall population • Incidence of anaphylaxis 4.8 (95% CI 3.2-6.9) cases per million doses for Pfizer/BioNTech and 5.1 (95% CI 3.3-7.6) cases per million doses for Moderna **<u>Myocarditis</u>** ▪ CDC investigating reports of myocarditis following mRNA vaccines; currently there are few reports and most cases appear to be mild; according to CDC, these cases seem to occur predominantly in adolescents and young adults, more often in males than females, more often following the 2nd	▪ Data presented at CDC ACIP meeting:[137] *(added 9/8/2021)* --pre-Delta vaccine effectiveness estimates of ≥87% --Delta vaccine effectiveness 39-84% --Delta vaccine effectiveness against hospitalization 75-95% ▪ In a study in nursing home residents, 2 doses of mRNA vaccines were 74.7% effective against infection from March-May 2021 (before Delta was predominant); from June-July 2021 (Delta became predominant), effectiveness declined to 53.1%[138] *(added 9/8/2021)* ▪ Neutralizing antibody titers were ~50 times lower vs **Omicron** than vs original virus (2 doses); a booster (3rd) dose increased titers[175] *(added 12/16/2021)* ▪ Moderna reports a 50-mcg booster dose of mRNA-1273 increased Omicron neutralizing antibody levels ~37-fold and a 100-mcg booster dose increased levels ~83-fold compared to pre-boost levels (based on data including sera from 20 participants in each dose group)[177] *(added 12/21/2021)* ▪ In CDC study, mRNA vaccines 94% effective for preventing emergency department and urgent care visits and 90% effective at preventing COVID-19-associated hospitalizations during Omicron-

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	▪ Of the 24 patients with negative antibody titers before the 3rd dose, 6 had high-positive titers after the 3rd dose, 2 had low-positive titers, and 16 remained negative ▪ Adverse effects included mild-moderate local reactions, fatigue, headache, myalgia ▪ 1 patients had biopsy-proven, antibody-mediated rejection 7 days after the 3rd vaccine dose in the setting of acute volume overload **Limitations:** case series, small sample, no assays for neutralizing antibody, B-cell memory, or T-cell responses **<u>VG Hall et al. NEJM 2021[120]</u>** *(added 8/11/2021)* **Population:** organ transplant recipients who had received a standard 2-dose COVID-19 vaccination series with mRNA-1273 (n=120) **Design:** double-blind, randomized, controlled trial ▪ Patients randomized to receive a 3rd mRNA-1273 dose or a saline placebo given 2 months after the 2nd mRNA-1273 dose **Results:** ▪ Anti-receptor-binding domain (RBD) antibody level ≥100 U/mL at month 4 was present in 55% (33/60) of patients in the mRNA-1273 group and in 18% (10/57) of patients in the placebo group (RR 3.1, 95% CI 1.7-5.8, p<0.001); the primary endpoint ▪ Median percent virus neutralization was 71% in the mRNA-1273 group and 13% in the placebo group ▪ 60% of patients in the mRNA-1273 group and 25% in the placebo group were above the 30% threshold for neutralizing	dose than the 1st, and typically within 4 days after vaccination; rates of myocarditis after vaccination have not exceeded expected baseline rates[87] *(added 5/27/2021)* ▪ CDC reviewing cases of myocarditis/pericarditis after mRNA vaccination (285 of 475 reported cases investigated as of 5/31/2021)[95] *(added 6/15/2021)* ▪ Most cases occurred after 2nd dose ▪ Most occurred in patients 16-24 years old ▪ Median time to onset 2 days (after dose 2) ▪ 79% occurred in males ▪ 81% had full recovery of symptoms ▪ There were more reported cases than expected ▪ A warning statement about the risk of myocarditis is now included in the FDA fact sheets for the Pfizer/BioNTech and Moderna mRNA vaccines[13,96] (*added 6/28/2021*) ▪ In a preprint report, cases of myocarditis after COVID-19 infection were identified from electronic medical records; in 12-17 year-old males, the rate of myocarditis after COVID-19 infection was 450 cases per million; based on these results, the risk of myocarditis in young males after COVID-19 infection was about 6 times higher than after vaccination[113] *(added 8/5/2021)*	predominant periods (*added 1/28/2022*) **Pregnancy and Lactation:** ▪ American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM) recommend all pregnant and breastfeeding individuals be vaccinated against COVID-19 [14]*(added 12/17/2020; updated 8/12/2021)* ▪ CDC strongly recommends COVID-19 vaccination for all pregnant people (and people who are trying get pregnant or plan to become pregnant in the future) and breastfeeding people (on 9/29/2021 CDC recommended urgent action to increase vaccination in these populations); pregnant people are at increased risk for severe illness from COVID-19 compared to non-pregnant people and pregnant people with COVID-19 are at risk for adverse pregnancy outcomes, including preterm birth and admission of neonates to ICU[15,22,146] *(added 3/6/2021; updated 10/4/2021)* ▪ In an analysis of people enrolled in v-safe, among 2456 pregnant persons who received an mRNA COVID-19 vaccine preconception or before 20 weeks of gestation the risk of spontaneous abortion was ~13%; spontaneous abortion typically occurs in ~11-16% of pregnancies[121] *(added 8/12/2021)*
mRNA-1273 (continued)			

antibody positivity (RR 2.4; 95% CI 1.5-4.0)
- Median SARS-CoV-2-specific T-cell counts were greater in the mRNA-1273 group than in the placebo group after the 3rd dose

Limitations: short follow-up, not powered to detect differences in clinical outcomes; anti-RBD cut-off arbitrary

NEJM Correspondence 2021[46-48]
(added 3/23/2021)

2 California Healthcare Systems (UCSD and UCLA)[46]
- 36,659 health care workers were vaccinated with a 1st mRNA vaccine dose between December 16, 2020 and February 9, 2021; 77% received the 2nd dose
- 379 persons tested positive for SARS-CoV-2 ≥1 day after vaccination; most (71%) of positive tests were in the 1st 2 weeks after vaccination
- After both vaccine doses, 37 persons tested positive; 22 were <7days after the 2nd dose; only 8 workers tested positive 8-14 days after the 2nd dose and 7 did so ≥15 days after the 2nd dose

Texas Medical Center (UTSW)
- 59% of 23,234 employees received a 1st mRNA vaccine dose and 30% received a 2nd dose within 31 days of December 15, 2020
- Between December 15, 2020 and January 28, 2021, SARS-CoV-2 infections were reported in 234 of 8969 nonvaccinated employees, 112 of 6144 partially vaccinated employees, and 4 of 8121 fully vaccinated employees

Jerusalem Medical Center (HHUMC)[48]

- CDC analysis of data reported to V-safe in pregnant women who received the Moderna or Pfizer/BioNTech vaccine (>30,000) found that most adverse events in pregnant women were not related to pregnancy (e.g., local and systemic reactions); pregnancy-specific adverse events were within known background rates[44] *(added 3/15/2021)*

- A prospective cohort study including 131 reproductive-age vaccine recipients (84 pregnant, 31 lactating, 16 non-pregnant) reported immunogenicity and reactogenicity in pregnant and lactating women was similar to that in non-pregnant women; antibodies were present in umbilical cord blood and breast milk[50] *(added 3/29/2021)*

CDC evaluated data reported to the v-safe surveillance system, v-safe pregnancy registry, and vaccine adverse event reporting system (VAERS) from December 14, 2020-February 28, 2021[62]
(added 4/22/2021)
- 35,691 participants 16-54 years old identified as pregnant
- Injection-site pain reported more frequently in pregnant women than in non-pregnant women; headache, myalgia, chills, and fever reported less often
- 827 of 3958 women in the v-safe pregnancy registry had a completed pregnancy; of these, 115 (13.9%) resulted in pregnancy loss and 712 (86.1%) resulted in a live birth

mRNA-1273 (continued)

VACCINE	EFFICACY	SAFETY	COMMENTS
	Among workers vaccinated with the Pfizer vaccine the weekly incidence of SARS-CoV-2 infection declined **S Saadat et al. JAMA 2021**[52] *(added 3/29/2021)* **Population:** health care workers who had been previously enrolled in a hospital-wide serosurvey study were randomly contacted based on stratification in 3 groups: SARS-CoV-2 IgG-antibody negative, IgG antibody positive asymptomatic COVID-19, and IgG-positive symptomatic COVID-19 (n=59) **Design:** volunteers were vaccinated with the Pfizer/BioNTech or Moderna vaccine and then had blood drawn on days 0, 7, and 14 **Results:** ▪ At all time points, antibody titer responses were higher in patients who were previously infected with SARS-CoV-2 than in those who did not have prior infection **Limitations:** small sample size, does not demonstrate efficacy **MG Thompson et al. HEROES-RECOVER MMWR 2021**[53] *(added 3/29/2021; updated 6/8/2021)* **Population:** health care personnel, first responders, and other essential/frontline workers in the US who were routinely tested for SARS-CoV-2 for 13 weeks (n=3950) **Design:** prospective cohort **Results:** ▪ 2479 (62.8%) received both mRNA doses and 477 (12.1%) received only 1 dose ▪ There were 1.38 SARS-CoV-2 infections per 1,000 person-days among		(mostly women vaccinated in 3rd trimester) ▪ Preterm birth occurred in 9.4% and small size for gestational age in 3.2% ▪ No neonatal deaths were reported ▪ Calculated proportions of adverse pregnancy and neonatal outcomes in women vaccinated against COVID-19 who had a completed pregnancy were similar to incidences reported in studies in pregnant women before COVID-19; not direct comparison ▪ Among 221 adverse events related to pregnancy that were reported to VAERS, spontaneous abortion was the most frequent (46 cases) ▪ No obvious safety signals found in this preliminary report ▪ Report states more follow-up needed ▪ In a prospective cohort study in 103 women (30 were pregnant and 16 were lactating) who were vaccinated with the Moderna or Pfizer/BioNTech mRNA COVID-19 vaccine, immunogenicity was reported in all women and vaccine-elicited antibodies were found in infant cord blood and breast milk; antibody titers against B.1.1.7 and B.1.351 variants were reduced, but T-cell responses were preserved[74] *(added 5/19/2021)* ▪ In a small study in 7 breastfeeding women, there were no detectable levels of vaccine RNA in breast milk samples collected from 4 to 48

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	unvaccinated persons, 0.04 infections per 1,000 person-days among fully-vaccinated persons, and 0.19 infections per 1,000 person-days among partially immunized persons **Effectiveness under real-world conditions:** ▪ 90% ≥14 days after 2nd dose ▪ 80% ≥14 days after 1st dose, but before second dose ▪ 22.9% of infections were medically attended, including 2 hospitalizations (there were 0 deaths) **Updated Analysis, CDC[91]** *(added 6/9/2021)* ▪ 3975 subjects; completed weekly testing for 17 weeks ▪ Risk of infection reduced by 91% in fully vaccinated ▪ Risk of infection reduced 81% in partially vaccinated ▪ Vaccinated subjects who developed COVID-19 had milder and shorter illness compared to unvaccinated subjects (6 fewer days sick, 2 fewer days sick in bed) ▪ 60% lower risk of developing symptoms in vaccinated persons compared to unvaccinated ▪ 40% lower viral load and 6 fewer days of detectable virus in vaccinated vs unvaccinated **Limitations:** moderately wide confidence intervals partly because of limited number of infections **Doria-Rose et al. NEJM 2021[56]** *(added 4/7/2021)* **Population:** healthy adults (n=33) **Design:** analysis of 33 participants from an ongoing phase 1 trial **Results:**		hours after vaccination[104] *(added 7/15/2021)* ▪ In a case-control surveillance study, among women who had spontaneous abortions, the odds of COVID-19 vaccine exposure in the prior 28 days were not increased compared with women with ongoing pregnancies (adjusted odds ratio 1.02; 95% CI 0.96-1.08); a COVID-19 vaccine was received within 28 days prior to an index date among 8.0% of ongoing pregnancies vs 8.6% of spontaneous abortions[144] *(added 9/23/2021)* ▪ A case-control study using data from Norwegian registries reported no evidence of an increased risk of early pregnancy loss after COVID-19 vaccination[164] *(added 11/7/2021)* **Fertility:** ▪ No adverse effects on sperm parameters (sperm concentration, sperm motility, semen volume) after 2 doses of an mRNA vaccine (Pfizer/BioNTech or Moderna) in 45 men at a median of 75 days after the 2nd vaccine dose[108] *(added 7/22/2021)* **Vaccine Storage:** ▪ Vials are stored frozen (-58 to 5° F/ -50 to -15° C); they should not be stored on dry ice or below -50° C

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	▪ 180 days after the second vaccination there was high antibody activity in all age groups ▪ In a pseudovirus neutralization assay, detectable activity was observed in almost all participants; activity was noted in all participants when a more sensitive test was used ▪ Titers were lower in participants ≥56 years old than in those 18-55 years old **Limitations:** interim analysis; antibody titers and assays that best correlate with vaccine efficacy not known **CDC report (data based on persons vaccinated with any 1 of the 3 vaccines authorized in the US)[60]** *(updated 10/12/2021)* **MMWR Report[85]:** *(added 5/26/2021)* ▪ As of April 30, 2021 10,262 vaccine breakthrough cases reported in the US out of ~101 million vaccinated persons ▪ 6446 (63%) were in women ▪ Median patient age: 58 years ▪ 2725 (27%) were asymptomatic ▪ 995 (10%) were hospitalized; of these 289 (29%) were asymptomatic or unrelated to COVID-19 ▪ 160 (2%) died; of these, 28 (18%) were asymptomatic or unrelated to COVID-19 ▪ Median age of patients who died: 82 years ▪ Sequence data was available for 555 (5%); of these 356 (64%) were variants of concern (B1.1.7 in 199 [56%], B.1.429 in 88 [25%], B1.427 in 28 [8%], P.1 in 28 [8%], and B.1.351 in 13 [4%]) **October 4th Report**		▪ If transport between -50 to -15° C is not possible, vials can be transported at 2-8° C for up to 12 hours; once thawed and transported at 2-8° C vials should not be refrozen and should continue to be stored at 2-8° C until use ▪ Can be stored under refrigeration (2-8° C/ 36-46° F) for 30 days before first use and unpunctured vials can be stored at room temperature for 12 hours and should be discarded after 6 hours ▪ After the first dose has been withdrawn from the vial, it should be stored between 2 to 25° C (36-77° F); discard vial after 12 hours ▪ Vials should be thawed before use; they can be thawed under refrigeration for 2 hours and 30 minutes. Vials should be allowed to stand at room temperature for 15 minutes before administration *(added 12/18/2020)* ▪ Vials can also be thawed at room temperature for 1 hour *(added 12/18/2020)* ▪ Vials should be protected from light ▪ If a vial contains enough liquid after dilution for administration of >10 full doses, those extra doses may be used, but residual vaccine from multiple vials should not be combined to form a full dose *(added 1/19/2021)*

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	(CDC now monitoring only hospitalized or fatal cases instead of all cases) ▪ 30,177 hospitalized or fatal vaccine breakthrough cases out of >185 million fully vaccinated ▪ 5660 (86%) deaths and 15,792 hospitalizations (67%) were ≥65 years old ▪ 2902 (44%) deaths and 11,474 (49%) hospitalizations in women ▪ 968 (15%) deaths and 3483 (15%) hospitalizations asymptomatic or not COVID-related **K Ali et al. (TeenCOVE) NEJM 2021[73]** *(updated 8/11/2021)* **Population:** adolescents 12 to <18 years old (n=3732) **Design:** ongoing phase 2/3 randomized, double-blind trial ▪ Subjects randomized 2:1 to 2 doses of mRNA-1273 (100 mcg/dose) or placebo given 28 days apart **Results:** ▪ 100% efficacy 14 days after the 2nd dose (0 cases in vaccine group and 4 cases in placebo group) using the case definition from the COVE trial ▪ 93% efficacy 14 days after the 2nd dose using the CDC definition (included cases presenting with milder symptoms; 1 COVID symptom and a positive PCR test by nasopharyngeal or saliva sample) ▪ Compared to young adults, immune response in adolescents met criteria for noninferiority ▪ Safety and tolerability profile similar to that in adults; the most common adverse events after the 1st and 2nd vaccine doses were injection site pain (93.1% and		▪ FDA-approved new vials from Moderna that contain up to 15 doses *(added 4/7/2021)*

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	92.4%, respectively), headache (44.6% and 70.2%, respectively), and fatigue (47.9% and 67.8%, respectively) **Limitations:** preliminary data; not published or peer reviewed **SY Wong et al. Gastroenterology 2021[76]** *(added 5/19/2021)* **Population:** Patients with inflammatory bowel disease (IBD) who were vaccinated with the Moderna or Pfizer/BioNTech mRNA COVID-19 vaccine (n=48) **Design:** 48 vaccinated IBD patients were compared to 2 control groups consisting of 14 completely vaccinated healthcare workers and 29 vaccinated healthy volunteers without IBD **Results:** ▪ 85% of patients receiving a biologic (including TNF inhibitors, vedolizumab, and ustekinumab) at time of vaccination ▪ All vaccinated IBD patients demonstrated serological responses **Limitations:** small sample size; single center **EM White et al. NEJM 2021[78]** *(added 5/19/2021)* **Population:** nursing home residents in 280 nursing homes across 21 states in the US **Design:** review of immunization records identified residents who: ▪ received 1 dose of an mRNA vaccine ▪ received 2 doses of an mRNA vaccine ▪ were present on the day of the first facility vaccination clinic but who were not vaccinated **Results:** ▪ 18242 vaccinated residents (80.4% Pfizer/BioNTech and 19.6% Moderna) and 3990 unvaccinated residents		

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	▪ Incidence of SARS-CoV-2 infection decreased over time in residents who were vaccinated and in those who were not vaccinated ▪ After 1st vaccine dose: 822 incident cases (4.5% of vaccinated residents) occurred within 14 days and 250 cases (1.4%) at 15-28 days ▪ After 2nd vaccine dose: 130 cases (1.0%) occurred within 14 days and 38 cases (0.3%) after >14 days ▪ Unvaccinated residents: 173 cases (4.3%) within 14 days of 1st vaccination clinic and 12 cases (0.3%) >42 days after the clinic ▪ Most infections were asymptomatic **Limitations:** observational data **FS Vahidy et al. medRxiv 2021[82]** *(added 5/20/2021)* **Population:** established patients in a healthcare system in the US who were vaccinated with an mRNA vaccine, partially vaccinated with an mRNA vaccine, or not vaccinated through April 4, 2021 (n=91, 134) **Design:** retrospective cohort **Results:** ▪ 70.2% not vaccinated, 4.5% partially vaccinated, 25.4% fully vaccinated ▪ Hospitalization occurred in 0.7% of fully vaccinated patients, 3.4% of partially vaccinated patients, and 2.7% of non-vaccinated patients ▪ 255 deaths occurred in patients hospitalized with COVID-19; of those, 219 (97.3%) were in unvaccinated patients, 5 (2.2%) were in partially vaccinated patients, and 1 (0.0041%) in a fully vaccinated patient ▪ Full vaccination was reported to be 96% effective at preventing COVID-19		

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	hospitalization and 98.7% effective at preventing death ▪ Partial vaccination was reported to be 77% effective at preventing hospitalization and 64.2% effective at preventing death **Limitations:** observational data; not published or peer reviewed **MW Tenforde et al. MMWR 2021[90]** *(added 6/9/2021)* **Population:** adults ≥65 years old at 24 hospitals in 14 states (January-March 2021) (n=417) **Design:** test negative case control **Results:** ▪ Adjusted vaccine efficacy against COVID-19 hospitalization was 94% for full vaccination and 64% for partial vaccination **Limitations:** small sample size; wide confidence intervals; observational; interim analysis with self-reported data **MW Tenforde et al. MMWR 2021[136]** *(added 9/8/2021*) **Population:** adults who received 2 doses of an mRNA vaccine in the US at 21 hospitals in 18 states (March-July 2021) (n=1129) **Design:** case control **Results:** ▪ Median interval of 65 days (range 14-166 days) after receipt of 2nd vaccine dose ▪ 53.3% Alpha and 16.3% Delta ▪ Vaccine efficacy against COVID-19 hospitalization was 86% 2-12 weeks and 84% 13-24 weeks after receipt of 2nd vaccine dose **Limitations:** observational; Delta not predominant; no follow-up past 24 weeks		
mRNA-1273 (continued)	**Benotmane et al. JAMA 2021[112]**		

VACCINE	EFFICACY	SAFETY	COMMENTS
	(added 8/5/2021) **Population:** kidney transplant patients who did not respond to 2 doses of mRNA-1273 vaccine and received a 3rd dose of the vaccine (n=159) Design: antibody responses evaluated after the 3rd vaccine dose **Results:** ▪ 3rd dose was given a median of 51 days after the 2nd dose ▪ Antibody responses measured a median of 28 days after administration of 3rd dose ▪ 78/159 patients (49%) had an antibody response (levels > 50 AU/mL) after administration of a 3rd vaccine dose ▪ Responses were more likely in those who had a weak response after the 2nd dose than in those without a response ▪ Patients taking tacrolimus, mycophenolate, and steroids less likely to develop antibodies than those on other regimens **Limitations:** detailed B- and T-cell studies not performed; antibody level that correlates with protection unknown **AM Cavanaugh et al. MMWR 2021[114]** *(added 8/10/2021)* **Population:** Kentucky residents ≥18 years old infected with SARS-CoV-2 in 2020 and reinfected in May-June 2021 (n=246 cases and 492 controls) **Design:** case-control study ▪ Vaccination status of reinfected residents what compared with that of residents who were not reinfected **Results:** ▪ In persons previously infected with COVID-19, the likelihood of reinfection was significantly higher in unvaccinated persons compared to those who were vaccinated (OR = 2.34;95% CI 1.58-3.47)		

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	**Limitations:** retrospective study, vaccinated persons less likely to be tested, possibility that some reinfections may not have been distinct virus relative to first infection, possible some vaccination data missing **A Puranik et al. medRxiv 2021**[116] *(added 8/11/2021)* **Population:** persons in Mayo Clinic Health system from January 2021-July 2021 **Design:** cohort study ▪ compared the effectiveness of mRNA-1273 and BNT162b2 **Results:** ▪ Delta variant prevalence increased from 0.7% in May 2021 to >70% in July 2021, while the Alpha variant decreased in prevalence from 85% to 13% ▪ Effectiveness estimates over entire study period were 86% with mRNA-1273 and 76% with BNT162b2 ▪ Effectiveness against hospitalization was 91.6% with mRNA-1273 and 85% with BNT162b2 and against ICU admission was 93.3% with mRNA-1273 and 87% with BNT162b2 ▪ No deaths were reported in either cohort ▪ Effectiveness in July (Delta variant prominent) was 76% for mRNA-1273 and 46% for BNT162b2; effectiveness against hospitalization remained high ▪ In matched individuals from multiple states, 2-fold risk reduction against breakthrough infection with mRNA-1273 vaccine vs BNT162b2 vaccine (incidence rate ratio [IRR] 0.50, 95% CI 0.39-0.64) **Limitations:** preprint, not peer reviewed, observational, cohort from limited geographic area, risk of infection relative to date of vaccination not analyzed		

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	**Moderna Investors Report 2021[118]** *(added 8/11/2021)* **Manufacturer Reported:** ▪ Vaccine efficacy of 92.4% ≥4 months after dose 2 (median follow-up 5.3 months) ▪ Neutralizing antibodies remained detectable against wild-type strain 6 months after dose 2 ▪ Neutralizing antibodies against variants of concern started at lower levels than against wild type and waned substantially by 6 months after dose 2 ▪ A booster dose (50 mcg) given >6 months after dose 2 increased geometric mean titers for variants of concern by 32- to 43-fold ▪ After the booster dose, neutralizing titers in subjects ≥65 years old were similar to those in younger subjects **Antonelli et al. Lancet Infect Dis 2021[130]** *(added 9/5/2021)* **Population:** adult users of a COVID Symptom Study mobile phone app in the UK **Design:** prospective, community-based, nested, case-control study ▪ Subjects included persons vaccinated with BNT162b2, mRNA-1273, or ChAdOx1 nCoV-19 **Results**: ▪ Breakthrough COVID-19 cases were reported in 0.5% of people who had received 1 vaccine dose and 0.2% of people who received 2 vaccine doses ▪ Vaccination was associated with reduced odds of hospitalization or having >5 symptoms in the first week of illness compared with no vaccination ▪ Vaccination was associated with reduced odds of long duration symptoms (≥28 days) compared with no vaccination		

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	▪ Vaccinated participants were more likely to be asymptomatic ▪ In older adults (≥60 years old), frailty was associated with breakthrough infection after the 1st vaccine dose **Limitations:** observational study; patient-reported data; some disproportionate demographic characteristics; may not apply to all timepoints post-vaccination or different proportions of variants **Steensels et al. JAMA 2021[139]** *(added 9/17/2021)* **Population:** healthcare workers in Belgium schedule to receive 2 doses of mRNA-1273 or BNT162b2 (n=1647) **Design:** prospective cohort **Results:** ▪ 688 received mRNA-1273 and 959 received BNT162b2 ▪ Higher antibody titers were reported in subjects who received mRNA-1273 compared to BNT162b2 (geometric mean titer 3836 [95% CI 3586-4104] vs 1444 [95% CI 1350-1544]; p<0.001) ▪ Previously infected subjects had higher titers than those who had not been previously infected ▪ The difference in antibody levels according to previous infection was higher than the difference between the 2 vaccines **Limitations:** data on cellular immunity and neutralizing antibodies lacking; limited to healthcare workers **WH Self et al. MMWR 2021[140]** *(added 9/19/2021)* **Population:** immunocompetent adults in the US admitted to 21 hospitals in the Influenza and Other Viruses in the Acutely Ill (IVY) Network (n=3689)		
mRNA-1273 (continued)	**Design:** cases control analysis		

VACCINE	EFFICACY	SAFETY	COMMENTS
	▪ Case patients admitted with COVID-19-like illness and a positive SARS-CoV-2 test result ▪ Control patients admitted to a hospital with a negative SARS-CoV-2 test result **Results:** ▪ Vaccine efficacy against hospitalization for the full surveillance period (March 11-August 15, 2021) was 93% with Moderna, 88% with Pfizer/BioNTech and 71% with Janssen/J&J ▪ Vaccine efficacy against hospitalization 14-120 after full vaccination was 93% with Moderna and 91% with Pfizer/BioNTech ▪ Vaccine efficacy against hospitalization >120 days after full vaccination was 92% with Moderna and 77% with Pfizer/BioNTech ▪ Efficacy against hospitalization >28 days after vaccination with the Janssen/J&J vaccine was 68% ▪ In a postvaccination antibody analysis in 100 volunteers, anti-receptor binding domain IgG levels were higher with Moderna than with Pfizer/BioNTech or Janssen/J&J and anti-spike IgG levels were higher with Moderna than Janssen/J&J, but not significantly different than with Pfizer/BioNTech **Limitations:** only included immunocompetent adults; only included hospitalized subjects; small number of patients who received Janssen/J&J vaccine; not specific estimates by variant **RL Atmar et al. medRxiv 2021[150]** *(added 10/19/2021)* Vaccine Mixing **Population:** persons in the US with no reported history of SARS-CoV-2 infection who received 1 of 3 COVID-19 vaccines with an FDA Emergency Use Authorization		

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	(Pfizer/BioNTech, Moderna, or J&J vaccine) at least 12 weeks prior (n=458) **Design:** phase 1/2 adaptive design, open-label trial sponsored by the NIH ▪ Subjects received a booster dose with one of the 3 vaccines (Pfizer/BioNTech, Moderna, J&J) resulting in 9 vaccine combinations **Results:** ▪ Antibody levels increased in all groups after booster of different vaccine (4.6-56-fold increase) ▪ Neutralizing antibody titers increased 4-20-fold with homologous boost combinations vs 6-76-fold with heterologous boost combinations ▪ Neutralizing antibody titers in J&J primary dose recipients increased 76-fold after Moderna booster, 35-fold after Pfizer booster, and 4-fold after J&J booster ▪ Serum neutralization levels at baseline (before booster) were lower for Pfizer/BioNTech (3-fold) and J&J (10-fold) recipients than for Moderna recipients ▪ Reactogenicity and adverse events similar across all groups **Limitations:** preprint, not peer-reviewed or published; not designed to compare responses between regimens; not representative of general population **<u>Moderna (KidCOVE) 2021</u>** *(added 10/28/2021)* **Population:** children 6 to under 12 years old (n=4753) **Design:** phase 2/3 randomized, observer-blinded, placebo-controlled expansion study ▪ 50 mcg mRNA-1273 IM at day 0 and 28 vs placebo		
mRNA-1273 (continued)	**Results:**		

- Met primary immunogenicity endpoint
- SARS-CoV-2-neutralizing antibody geometric mean ratio (GMR) comparing response in children 6-11 years old to adolescents 12-17 years old (TeenCOVE trial) was 1.5 (95% CI 1.3-1.8), with seroresponse rate 99.3%, difference of 0.6% (95% CI -2.8-2.8) compared to TeenCOVE
- Adverse effects similar to adolescents and adults; most were mild to moderate

Limitations: top line immunogenicity results, not published or peer-reviewed

CH Bozio et al. MMWR 2021[158]
(added 11/3/2021)
Population: hospitalized adults in the US with COVID-like illness who had received testing at least 2x (once associated with hospitalization January -September 2021 and once earlier February 2020 - ≥14 days before hospitalization) (n=7348)
Design: epidemiologic analysis using data from the VISION Network collected from 187 hospitals

- compare odds of receiving a positive SARS-CoV-2 test result between unvaccinated patients with previous SARS-CoV-2 infection and patients vaccinated with an mRNA COVID-19 vaccine

Results:

- Odds of confirmed SARS-CoV-2 infection was 5.49-fold higher in unvaccinated persons with a history of SARS-CoV-2 infection than in vaccinated persons with no prior infection (95% CI 2.75-10.99)

Limitations: observational data; misclassification possible; only hospitalized patients included

BA Dickerman et al. NEJM 2021[168]
(added 12/6/2021)

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA-1273 (continued)	**Population:** U.S. veterans who received a 1st mRNA vaccine dose (BNT162b2 or mRNA-1273) between Jan 4, 2021 and May 14, 2021 (n=219,842 persons/group) **Design:** observational analysis designed to emulate a target trial **Results:** ▪ 24 weeks of follow-up ▪ Estimated risk of documented infection 5.75 events/1000 persons (95% CI 5.39-6.23) with BNT162b2 and 4.52 events/1000 persons (95% CI 4.17-4.84) with mRNA1273 ▪ Excess number of events/1000 persons for BNT162b2 vs mRNA-1273 was • 1.23 for documented infection (95% CI 0.72-1.81) • 0.44 for symptomatic infection (95% CI 0.25-0.70) • 0.55 for hospitalization (95% CI 0.36-0.83) • 0.10 for ICU admission (95% CI 0.00-0.26) • 0.02 for death (95% CI -0.06-0.12) ▪ Corresponding excess risk of documented infection over 12-week follow-up with Delta predominance was 6.54 events/1000 persons (95% CI -2.58-11.82) **Limitations:** observational data; possible outcome misclassification; mostly men **ES Rosenberg et al. NEJM 2021**[169] *(added 12/6/2021)* **Population:** adults in New York State vaccinated with BNT162b2, mRNA-1273, or Ad26.COV2.S (n=8,690,825) **Design:** surveillance-based cohort **Results:** ▪ During week of May 1, 2021 (alpha predominance; delta 1.8% of variants), median vaccine effectiveness against		

VACCINE	EFFICACY	SAFETY	COMMENTS
	COVID-19 was 91.3% for BNT162b2, 96.9% for mRNA-1273, and 86.6% for Ad26.COV2.S ▪ During week of August 28 (delta predominance; delta 99.6% of variants), median vaccine effectiveness was 72.3% for BNT162b2, 77.8% for mRNA-1273, and 69.4% against Ad26.COV2.S ▪ Effectiveness against hospitalization with COVID-19 remained >86% in adults 18-64 years old, with no apparent time trend **Limitations:** observational, possible confounding, did not account for herd immunity between groups		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 ***Comirnaty*** (Pfizer/BioNTech) *(updated 3/29/2022)* **Dosage:**[13] ▪ 5-11 years old: two 0.2-mL (10 mcg; orange cap vial) doses given 3 weeks apart[155] *(added 10/29/2021)* ▪ ≥12 years old: two 0.3-mL (30-mcg; purple cap vial) doses given 3-8 weeks apart *(updated 2/28/2022)* • An 8-week interval may be optimal for certain persons ≥12 years old, especially males 12-39 years old. A standard 3-week interval between the first two doses should still be used in adults ≥65 years old, persons who are moderately or severely immunocompromised, and other persons who require more rapid protection because of high levels of community spread of SARS-CoV-2 infection or a high risk of severe COVID-19[183,184] *(added 2/28/2022)* ▪ A third primary series dose is recommended for **immunocompromised** persons ≥5 years old (see Immunocompromised 3rd dose below for more details) ▪ Each 0.3-mL dose contains 30 mcg of a nucleoside-modified messenger RNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 and each 0.2-mL dose contains 10 mcg of a nucleoside-modified messenger RNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	**Mulligan et al. 2020**[3] **Population:** healthy adults 18-55 years old (n=45) **Design:** phase 1/2 randomized, placebo-controlled, observer-blinded dose escalation study ▪ 2 doses separated by 21 days of 10 mcg, 30 mcg, or 100 mcg of BNT162b1 or placebo **Results:** ▪ At day 28, all subjects in the 10- and 30-mcg groups had significantly elevated RBD-binding IgG antibodies and neutralizing antibodies **Limitations:** phase 1/2 results **Walsh et al. NEJM 2020**[6] *(added 8/23/2020; updated 10/19/20)* **Population:** healthy adults 18-55 and 65-85 years old (n=195) **Design:** phase 1, randomized, observer-blinded, placebo-controlled, dose-escalation trial ▪ 2 vaccinations delivered 21 days apart of 1 of 3 doses (10, 20, or 30 mcg) of BNT162b1 or BNT162b2 or placebo ▪ 1 group received 1 dose of BNT162b1 100 mcg **Results:** ▪ 50% neutralizing antibody titers for the 2 vaccine candidates at the 30-mcg dose on day 28 (7 days after the second dose) or 35 days (14 days after the second dose) ranged from 1.7-4.6 times those of the convalescent serum panel in subjects 18-55 years old; titers ranged from 1.1-2.2 times those of the convalescent serum panel in subjects 65-85 years old ▪ Antibody responses were similar between BNT162b1 and BNT162b2	*(section updated 12/10/2020)* ▪ Local adverse effects included injection-site reactions (84.1%), such as pain, redness, and swelling[11] ▪ Fatigue (62.9%) and headache (55.1%) were the most common systemic adverse effects in the phase 3 trial[11] ▪ Other systemic adverse effects included fever (14.2%), chills (31.9%), muscle pain (38.3%), and joint pain (23.6%)[11] ▪ Local and systemic reactions were more frequent after the second dose[9] ▪ Reactions less common and less severe in older adults than in younger adults[9] ▪ No serious adverse events reported in the clinical trials ▪ The manufacturer has reported mostly mild to moderate adverse reactions in clinical trials; severe or grade 4 reactions have been rare[4] ▪ FDA requested potential anaphylactic reactions be added to pharmacovigilance plans; after vaccination, anaphylaxis occurred in 2 people in the U.K. with a history of allergic reactions[11] ▪ An additional case of anaphylaxis has been reported in the US in a women with no history of allergies *(added 12/17/2020)* ▪ CDC recommends that people who experienced an allergic reaction (even if not severe) after administration of the	▪ Both are lipid nanoparticle-formulated, nucleoside modified mRNA vaccines ▪ BNT162b1 encodes an optimized SARS-CoV-2 receptor-binding domain (RBD) antigen ▪ BNT162b2 encodes an optimized SARS-CoV-2 full-length spike protein antigen ▪ FDA granted fast track designation ▪ The manufacturer advanced BNT162b2 to phase 2/3 clinical trials based on data from phase 1 trials indicating it caused fewer adverse events than BNT1621b1[6] *(added 8/23/2020)* ▪ Phase 3 trial has begun; expected to enroll up to 30,000 participants; manufacturer submitted to FDA to increase to 44,000 participants *(updated 9/18/2020)* ▪ Adolescents 12-17 years old are now being enrolled in clinical trials *(added 11/2/2020)* ▪ Manufacturer plans to submit to FDA for Emergency Use Authorization (EUA) since they report the safety data milestone required by the FDA has been achieved *(updated 11/18/2020)* ▪ The U.K. granted emergency authorization for BNT162b2 *(added 12/2/2020)*

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BNT162b1 and BNT162b2 (continued) ▪ Booster: A booster dose of the Pfizer/BioNTech vaccine for FDA/CDC recommended groups can be given ≥5 months (previously ≥6 months) after completion of a primary series with the Pfizer/BioNTech vaccine; in immunocompromised patients, booster can be given ≥3 months after dose 3 *(updated 2/15/2022)* ▪ 2nd Booster: One 0.3-mL (30 mcg) dose ≥4 months after a 1st booster dose of any authorized COVID-19 vaccine for persons ≥50 years old or immunocompromised persons who have undergone solid organ transplantation or have an equivalent level of immunocompromise[185] *(added 3/29/2022)* ▪ FDA and CDC Booster Recommendations: all persons ≥12 years old should receive a booster dose ≥5 months (≥3 months for immunocompromised) after completion of the primary series [151,152,167,171,172,178] *(updated 2/15/2022)* ▪ FDA and CDC authorize use of each of the available COVID-19 vaccines as a heterologous (or "mix and match") booster dose in eligible individuals following completion of primary vaccination with a different available COVID-19 vaccine[151,152] *(updated 10/22/2021)*	▪ Mild-to-moderate local and systemic reactions were reported with both vaccines; local adverse effects were more frequent after the second dose ▪ Incidence and severity of systemic adverse events was lower with BNT162b2 than with BNT162b1, particularly in older subjects ▪ Data from this trial were used to support use of BNT162b2 in ongoing phase 3 trials **Limitations:** phase 1 data; cannot determine degree of protection against COVID-19 **FP Polack et al. NEJM 2020[7,9]** *(added 11/9/2020; updated 12/10/2020)* **Population:** adults ≥16 years old who were healthy or had stable chronic medical conditions (n=43,448 randomized; 43,448 received injections) ▪ Exclusion criteria included a medical history of COVID-19, immunocompromising conditions or immunosuppressive therapy ▪ Median age 52 years ▪ 42% of subjects > 55 years old **Design:** ongoing, phase 3, multinational, randomized, placebo-controlled, observer-blinded trial ▪ 2 vaccinations delivered 21 days apart of BNT162b2 (30 mcg/dose) or placebo **Results:** ▪ BNT1621b2 vaccine efficacy rate reported to be 95% (95% credible interval, 90.3 to 97.6) at 28 days after the 1st dose ▪ 170 confirmed cases of COVID-19 with onset at least 7 days after the second dose in patients without evidence of existing or prior SARS-CoV-2 infection;	first dose of an mRNA COVID-19 vaccine not be given the second dose[18] *(added 1/1/2021)* ▪ 2 patients who had immediate hypersensitivity reactions to the first dose of Moderna vaccine were successfully administered the second vaccine dose using graded doses[61] *(added 4/20/2021)* ▪ CDC states that allergy to polyethylene glycol (PEG; a vaccine ingredient) is a contraindication to vaccination with an mRNA COVID-19 vaccine[18,22]; an allergy to polysorbate (related to PEG, but not a vaccine ingredient) is a precaution to vaccination[22] *(updated 3/6/2021)* ▪ American College of Allergy, Asthma & Immunology (ACAAI) recommend mRNA COVID-19 vaccines be administered in a healthcare setting where anaphylaxis can be treated, and patients should be observed for at least 15-30 minutes after vaccination[19] *(added 1/1/2021)* ▪ ACAAI states that people with common allergies to medications, foods, inhalants, insects and latex are not more likely than the general public to have an allergic reaction to an mRNA COVID-19 vaccine; data on individuals with a history of allergic reactions to previous vaccinations and/or mast call activation syndrome/idiopathic anaphylaxis is limited[19] *(added 1/1/2021)* ▪ Estimated rate of 11.1 cases of anaphylaxis per million doses administered after administration of 1,893,360 first vaccine doses; based on reports to VAERS[25,26] *(added 1/25/2021)*	▪ Health Canada approved use of BNT162b2 *(added 12/11/2020)* ▪ FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) voted (17-4, 1 abstention) to recommended emergency authorization of the BNT162b2 vaccine; they note more data are needed on long-term safety, prevention of severe disease, and in certain populations such as pregnant women[11] *(updated 12/10/2020)* ▪ FDA issued an Emergency Use Authorization (EUA) to allow administration of the Pfizer-BioNTech COVID-19 vaccine for prevention of COVID-19 caused by SARS-CoV-2 in persons ≥16 years old; this is the first EUA for a COVID-19 vaccine issued by the FDA[12] *(added 12/11/2020)*; on 5/10/2021 FDA authorized use of the vaccine in persons ≥12 years old *(updated 5/10/2021)* ▪ FDA has approved the Pfizer-BioNTech COVID-19 vaccine for prevention of COVID-19 in individuals ≥16 years old; it will continue to be available under an EUA for individuals 12-15 years old; it is the first vaccine to receive an approval from the FDA[126] *(added 8/23/2021)* ▪ FDA advisory committee has voted in favor of authorizing use of the Pfizer/BioNTech vaccine for children 5-11 years old; on October 29, 2021 the FDA updated the EUA

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued) Immunocompromised 3rd Dose: ▪ FDA authorized a 3rd dose to be given 28 days after the 2nd dose in patients who are immunocompromised (patients who have undergone solid organ transplantation or those diagnosed with conditions that are considered to have an equivalent level of immune compromise)[122] *(added 8/13/2021)* ▪ CDC recommends a 3rd dose of an mRNA vaccine for moderately to severely immunocompromised people: *(added 8/14/2021)*[123,124] • receiving active cancer treatment for solid tumors or hematologic malignancies • who received an organ transplant and taking immunosuppressants • who received a stem cell transplant in last 2 years or taking immunosuppressants • with moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome) • with advanced or untreated HIV infection • on high-dose steroids (≥ 20 mg prednisone/day or equivalent), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, severely immunosuppressive cancer	162 observed in the placebo group and 8 in the vaccine group ▪ In participants with and without evidence of prior SARS-CoV-2 infection, 9 cases of COVID-19 occurred in vaccinated subjects and 169 occurred in placebo-treated subjects (94.6% vaccine efficacy) ▪ Vaccine efficacy in adults ≥65 years old was 94.7% ▪ 10 severe cases of COVID-19 reported in the trial; 9 cases in the placebo group and 1 in the vaccine group **Limitations:** preliminary report; not large enough to detect less common adverse events; long-term assessment of efficacy and safety needed; unknown if vaccination prevents asymptomatic infection **S Amit et al. Lancet 2021[33]** *(added 2/27/2021)* **Population:** vaccine-eligible healthcare workers in Israel (n=9109) **Design:** retrospective cohort study comparing vaccinated vs unvaccinated persons **Results:** ▪ 75% reduction in infections (including asymptomatic infections) 15-28 days after the first dose among vaccinated healthcare workers **Limitations:** observational study; possible underestimation of asymptomatic infection **N Dagan et al. NEJM 2021[35]** *(updated 2/27/2021)* **Population:** vaccinated persons ≥16 years old in Israel (n=596,618 vaccinated persons matched to unvaccinated controls)	▪ Lymphadenopathy was reported in 64 patients in the vaccine group and 6 in the placebo group ▪ FDA noted a numerical imbalance in cases of Bell's palsy (4 in the vaccine group vs 0 in the placebo group) [11]; an analysis using the WHO pharmacovigilance database did not detect a signal of disproportionality of facial paralysis with mRNA COVID-19 vaccines compared with other viral vaccines or influenza vaccines alone[65] *(updated 5/3/2021)* ▪ In one case, Bell's palsy was reported in a 61-year-old man 5 hours after administration of the 1st Pfizer/BioNTech vaccine and again 2 days after the 2nd dose[107] *(added 7/22/2021)* CDC analysis of adverse events reported through VAERS and v-safe after administration of 13.8 million vaccine doses (Pfizer-BioNTech and Moderna) found[34] *(added 2/28/2021)*: ▪ most reports were for nonserious events ▪ occurrence of anaphylaxis was within range reported for other vaccines ▪ of 113 reported deaths, most were in residents of long-term care facilities and causes of death were consistent with expected all-cause mortality in this population ▪ adverse reactions were more common after the second dose ▪ A case series in Switzerland reported stage III hypertension occurring in 9 patients within minutes of BNT162b2 vaccination; 8 of 9 patients reported	for the Pfizer/BioNTech vaccine to allow use in children 5-11 years old[155] *(updated 10/29/2021)* ▪ CDC endorsed ACIP vote (14/0) to recommend use of the Pfizer/BioNTech vaccine for children 5-11 years old[157] (*updated 11/2/2021*) ▪ Pfizer/BioNTech report that two 3-mcg doses of the vaccine in **children 2-<5 years old** did not meet the primary efficacy endpoint of non-inferiority compared to the 16-25 year old population in a pre-specified immunogenicity analysis[176] *(added 12/20/2021)* ▪ Pfizer/BioNTech vaccine listed for emergency use by WHO in December 2020[31] *(added 2/16/2021)* ▪ Com-COV study in the UK will evaluate efficacy of using one vaccine for the 1st dose and a different vaccine for the 2nd dose (Oxford/AstraZeneca and Pfizer-BioNTech vaccines will be used) *(added 2/28/2021)* ▪ Pfizer/BioNTech begin trials in children 6 months to 11 years old; expected to enroll >4600 children in US and Europe; manufacturer reports they expect results in the second half of 2021 and authorization request in early 2022 *(added 3/28/2021)* ▪ Vaccine efficacy 92.6% after one dose[38] *(added 2/28/2021)*

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chemotherapy, TNF blockers, other immunosuppressive biologic agents **BNT162b1 and BNT162b2 (continued)** ▪ Available as multiple-dose vials ▪ Persons who have received 1 dose of the Pfizer-BioNTech COVID-19 vaccine should complete the series with the same vaccine; there is no data on the interchangeability with other COVID-19 vaccines ▪ CDC recommends in exceptional situations when the vaccine product used for the first dose cannot be determined or is no longer available, any mRNA COVID-19 vaccine can be given at least 28 days after the first dose[22] *(added 1/25/2021)* ▪ If the second vaccine dose cannot be given within the recommended interval, CDC now recommends it may be given up to 6 weeks (42 days) after the first dose[22] *(added 1/23/2021)* ▪ CDC states in exceptional situations where a patient received 1 dose of an mRNA vaccine and is unable to complete the series with an mRNA vaccine (e.g., contraindication), a single dose of the Janssen COVID-19 vaccine may be considered at a minimum of 28 days after the first mRNA vaccine dose[22] *(added 3/6/2021)*	**Design:** observational trial analyzing data from health care organization in Israel **Results:** ▪ 92% effective at preventing COVID-19 (including asymptomatic infection) ≥7 days after the 2nd dose ▪ 94% effective at preventing symptomatic cases ≥ 7 days after the second dose ▪ 92% effective at preventing severe disease ≥ 7 days after the second dose ▪ After the first dose (14-20 days), the estimated effectiveness was 46% for any infection, 57% for symptomatic infection, 74% for hospitalization, 62% for severe disease, and 72% in preventing death ▪ some have reported this may suggest the vaccine could reduce transmission, but more data are needed ▪ the vaccine was as effective in older patients as it was in younger patients **Limitations:** observational data **MI Samanovic et al medRxiv 2021[39]** *(added 2/28/2021)* **Population:** subjects who received 2 BNT162b2 vaccine doses (n=32) **Design:** evaluation of antibody response using blood samples ▪ Subjects SARS-CoV-2 naïve vs subjects with prior exposure **Results:** ▪ Robust immune response reported after both doses in SARS-CoV-2 naïve subjects ▪ In subjects with prior exposure to SARS-CoV-2 immune responses after the 2nd vaccine dose were lower than after the first dose **Limitations:** not peer reviewed **L Stamatatos et al medRxiv 2021[40]**	well-controlled hypertension before vaccination[51] *(added 3/29/2021)* ▪ Cases of herpes zoster reactivation in patients with autoimmune inflammatory rheumatic diseases[57] *(added 4/17/2021)* ▪ Registry-based study reported 414 cutaneous reactions to mRNA COVID-19 vaccines between December 2020 and February 2021; reactions included large local reactions, injection-site reactions, urticarial eruptions, morbilliform eruptions; less common reactions included pernio/chilblains, cosmetic filler reactions, zoster, herpes simplex flares, and pityriasis rosea-like reactions *(added 5/8/2021)* ▪ Of 1422 reports of postvaccination reactions submitted to a COVID-19 vaccine allergy case registry, 510 were delayed large local reactions; of these events, 55 (11%) were in blacks, Indigenous persons, and people of color; most reactions occurred after the first vaccine dose; mean time from vaccination to onset was 8 days; 11 patients had reactions other than at the injection site (diffuse itching, hives, other rash, angioedema) *(added 6/9/2021)*[92] EMA Pharmacovigilence Risk Assessment Committee (PRAC) investigating reports of myocarditis and CDC evaluated data reported to the v-safe surveillance system, v-safe pregnancy registry, and vaccine adverse event reporting system (VAERS) from December 14, 2020-February 28, 2021[62]	**Variants:** ▪ 2 cases of vaccine breakthrough infections were reported in a cohort of 417 persons who received the 2nd BNT162b2 dose 2 weeks earlier; variants of likely clinical importance including E484K, T95I, del142-144, and D614G were detected *(added 5/9/2021)*[72] ▪ Pfizer developing booster vaccine against variants *(added 1/30/2021)* ▪ In *in vitro* studies, sera containing antibodies from people who received the Pfizer-BioNTech COVID-19 vaccine neutralized SARS-CoV-2 pseudovirus with mutations, including the N501Y mutation identified in the B.1.1.7 strain detected in the UK variant, with mutations including the E484K and N501Y mutations identified in the South Africa variant, and the P.1 variant identified in Brazil [20,21,23,24,30,37]; neutralizing titers also reported against the B.1.526 (New York) variant[63,64]; neutralizing titers against B.1.617 (India) variant were about 4-fold lower, but expected to be protective[80] *(updated 5/20/2021)* ▪ Neutralizing antibody titers 5.8-fold reduced against B.1.617.2 (Delta) vs wild-type; B.1.1.7 (Alpha) titers reduced 2.6-fold vs wild-type; B.1.351 (Beta) reduced 4.9-fold vs wild-type; increased age and time since vaccine correlated with reduced titers[88] *(added 6/6/2021)*

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▪ COVID-19 vaccines should generally not be given within 14 days of other vaccines[22] *(added 3/6/2021)* **BNT162b1 and BNT162b2 (continued)**	*(added 2/28/2021)* **Population:** subjects who were previously infected and recovered from SARS-CoV-2 and then later received 1 mRNA vaccine dose (n=10) **Design:** neutralization study using sera of volunteers **Results:** ▪ Before vaccination sera weakly neutralized Wuhan-Hu-1 and sporadically neutralized the variant virus B.1.351 ▪ Vaccination increased neutralizing antibody titers against both strains by 1000-fold **Limitations:** not peer reviewed **J Lopez Bernal et al. medRxiv 2021[42]** *(added 3/8/2021)* **Population:** older adults in the UK who received the Pfizer/BioNTech or AstraZeneca COVID-19 vaccine **Design:** test negative case control **Results:** ▪ The B.1.117 variant was prominent in the UK during the period of this study ▪ Pfizer/BioNTech vaccine efficacy ~60-70% after 1 dose and ~85-90% after 2 doses; AstraZeneca vaccine was ~60-75% effective after 1 dose ▪ Patients who were infected after 1 dose of the Pfizer/BioNTech vaccine were 43% less likely to be hospitalized and 51% less likely to die compared to those who were not vaccinated; patients who received 1 dose of the AstraZeneca vaccine were 37% less likely to be hospitalized **Limitations:** observational; not peer reviewed **F Krammer et al. NEJM 2021[43]**	▪ pericarditis and recommended adding facial swelling in people with dermal fillers as a side effect of the Pfizer vaccine (*5/8/2021*) ▪ FDA Fact Sheet now has a warning describing a risk of syncope following injection; the risk is higher in adolescents than in adults[13] *(added 5/19/2021)* ▪ In a trial evaluating vaccine mixing, greater systemic reactogenicity (feverishness, chills, fatigue, headache, joint pain, malaise, and muscle ache) was reported following heterologous vaccine schedules compared to their homologous counterparts[77] (see RH Shaw et al in Efficacy column; *added 5/19/2021*) ▪ In an analysis of VAERS data the incidence of sudden sensorineural hearing loss after COVID-19 vaccination did not exceed that of the general population[88] *(added 6/6/2021)* ▪ FDA identified 4 potential adverse events of interest via near real-time surveillance in the Medicare healthcare claims database of persons 65 years and older who received the Pfizer/BioNTech vaccine; the adverse events of interest are: pulmonary embolism, acute myocardial infarction, immune thrombocytopenia, and disseminated intravascular coagulation; other vaccine reporting systems have not identified an association with vaccines and these adverse events of interest; FDA states no need to delay vaccination to wait for investigation results[103] *(added 7/15/2021)*	▪ Pfizer/BioNTech vaccine (2 doses) was 96% effective for preventing hospitalization in patients infected with the Delta variant; based on observational data from England *(added 6/15/2021)*[94] ▪ In observational data from Scotland, the Pfizer/BioNTech vaccine was 79% effective against infection with Delta variant (2 weeks after the 2nd dose)[98] *(added 6/29/2021)* ▪ Israel Ministry of Health reports vaccine effectiveness of 65% with Delta variant circulating in Israel; they not it maintains effectiveness of 93% against serious illness and hospitalization[101] *(added 7/15/2021)* ▪ In a study in Canada, vaccine efficacy against **Alpha** was 89% after 2 doses of Pfizer/BioNTech, 92% after 2 doses of Moderna, and 64% after 1 dose of AstraZeneca; against **Beta/Gamma** 84% after 2 doses of Pfizer/BioNTech, 77% after 1 dose of Moderna, and 48% after 1 dose of AstraZeneca; against **Delta** 87% after 2 doses of Pfizer/BioNTech, 72% after 1 dose of Moderna, and 67% after 1 dose of AstraZeneca[102] *(added 7/15/2021)* ▪ In a test-negative case-control design in England, effectiveness of 1 dose of the BNT162b2 or ChAdOx1 nCoV-19 vaccine against the Delta variant was 30.7% and

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BNT162b1 and BNT162b2 (continued)	*(added 3/15/2021)* ▪ In subjects who were vaccinated with the Moderna or Pfizer/BioNTech mRNA vaccine, those who were seronegative at baseline had variable and relatively low antibody responses 9-12 days after vaccination, while subjects who were seropositive at baseline had rapid development of high antibody titers ▪ Antibody titers were 10-45 times higher in those with preexisting immunity than in those without **BJ Boyarsky et al. JAMA 2021[45]** *(added 3/15/2021)* **Population:** transplant recipients vaccinated against SARS-CoV-2 with 1 dose of an mRNA vaccine in the US (n=436) **Design:** prospective cohort **Results:** ▪ 48% received the Moderna vaccine and 52% received the Pfizer/BioNTech vaccine ▪ Maintenance immunosuppression regimens included tacrolimus (83%), corticosteroids (54%), mycophenolate (66%), azathioprine (9%), sirolimus (4%), everolimus (2%) ▪ 76/436 patients (17%) a had detectable antibody response ▪ Recipients receiving anti-metabolite maintenance immunosuppression were less likely than those who were not to develop an antibody response (37% vs 63%; adjusted incidence rate ratio [IRR] 0.22, 95% CI 0.15-0.34; p<0.001) ▪ Older patients were less likely to develop an antibody response than younger patients (adjusted IRR 0.83 per 10 years, 95% CI 0.73-0.93, p=0.002) ▪ Antibody response was more likely with Moderna vaccine than Pfizer/BioNTech	▪ CDC review of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS) and v-safe (smartphone-based safety surveillance system) for adolescents 12-17 years old; 8.9 million adolescents vaccinated with Pfizer/BioNTech vaccine as of July 16, 2021[109] *(added 8/3/2021)* • 9,246 adverse events reported to VAERS; 90.7% were nonserious and 9.3% were serious, including myocarditis in 4.3% • Common reports to VAERS included dizziness, syncope, and headache • Of 129,000 adolescents enrolled in v-safe, 63.4% reported local reactions and 48.9% reported systemic reactions; frequency similar to clinical trials; systemic reactions more common after dose 2 ▪ Case reports of functional neurological disorder after COVID-19 vaccination[127,128] (*added 8/23/2021*) ▪ Interim analysis of surveillance data (Vaccine Safety Datalink [VSD]) from 6.2 million persons who received 11.8 million doses of an mRNA vaccine:[131,132] *(added 9/7/2021)* • No significant associations were found between vaccination and 23 serious health outcomes 1-21 days after vaccination with an mRNA vaccine; confidence intervals were wide for some rate ratio estimates • Vaccination associated with excess risk for myocarditis/pericarditis in	against the Alpha variant was 48.7%; after 2 doses of BNT162b2 effectiveness against Delta was 88% and against Alpha was 93.7%; after 2 doses of ChAdOx1 nCoV-19 effectiveness against Delta was 67.0% and 74.5% against Alpha[22] *(added 7/22/2021)* ▪ 469 COVID-19 cases were identified following large public gatherings in a Massachusetts town, of these 469 cases, 346 (74%) were in fully vaccinated persons; testing of specimens from 133 patients identified the Delta variant in 90%; among breakthrough cases, 4 (1.2%) were hospitalized and 0 deaths were reported[110] *(added 8/3/2021)* ▪ In a cohort study (see Puranik et al in Efficacy), vaccine effectiveness during a period when Delta variant was prominent was 76% for mRNA-1273 and 46% for BNT162b2; effectiveness against hospitalization remained high[116] *(added 8/11/2021)* ▪ CDC evaluation of data from the HEROES-RECOVER trial that included all available COVID-19 vaccines in the US reported vaccine efficacy of 66% during a period when Delta variant was predominant[129] *(8/24/2021)* ▪ Data presented at CDC ACIP meeting:[137] *(added 9/8/2021)* --pre-Delta vaccine effectiveness estimates of ≥87%

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	vaccine (69% vs 31%, IRR 2.15, 95% CI 1.29-3.57; p=0.003) **Limitations:** no control group, convenience sample, lack of serial measurements after vaccine, only response after 1st dose **BJ Boyarsky et al. JAMA 2021[71]** *(added 5/9/2021)* **Population:** transplant recipients vaccinated against SARS-CoV-2 with 2 doses of an mRNA vaccine in the US (n=658) **Design:** prospective cohort **Results:** ▪ 1st dose results in 396 of these patients reported previously (see Boyarsky et al above) ▪ Maintenance immunosuppression regimens included tacrolimus (83%), corticosteroids (54%), mycophenolate (66%), azathioprine (9%), sirolimus (4%), everolimus (2%) ▪ 98/658 patients (15%) a had detectable antibody response at a median of 21 days after dose 1 ▪ 357/658 patients (54%) a had detectable antibody response at a median of 29 days after dose 2 ▪ Of the 658 patients, 98 (15%) had measurable antibody response after dose 1 and 2, 301 (46%) had no antibody response after dose 1 or dose 2, and 259 (39%) had no antibody response after dose 1 but did have antibody response after dose 2 ▪ Of 473 patients receiving anti-metabolites, 38 (8%) had antibody response after dose 1 and 2, 268 (57%) had no antibody response after dose 1 or 2, and 167 (35%) had no antibody	persons 12-39 years old; no association reported in overall population • Incidence of anaphylaxis 4.8 (95% CI 3.2-6.9) cases per million doses for Pfizer/BioNTech and 5.1 (95% CI 3.3-7.6) cases per million doses for Moderna ▪ In a self-controlled case series in England, there was an increased risk of some adverse thrombotic events leading to hospital admission or death within 28 days after a first vaccine dose (Oxford/AstraZeneca or Pfizer/BioNTech); the risks of most of these events after vaccination were lower than with SARS-CoV-2 infection[133] *(added 9/7/2021)* ▪ In a study in a nationwide mass vaccination setting in Israel involving 2.4 million vaccinated persons, vaccination with BNT162b2 vaccine was associated with an increased risk of myocarditis (2.7 events/100,000 persons), lymphadenopathy (78.4 events), herpes zoster infection (15.8 events), and appendicitis (5.0 events); SARS-CoV-2 infection was associated with an excess risk of myocarditis (11.0 events/100,000 persons) and other adverse events not associated with vaccine use including arrhythmia, acute kidney injury, pulmonary embolism, deep-vein thrombosis, myocardial infarction, pericarditis, and intracranial hemorrhage; in a subsequent analysis stratified by age and sex, the risk of myocarditis after vaccination in males 16-39 years old was 8.2 excess events/100,000 persons (95% CI 2.82-14.35) and the risk after SARS-CoV-2 infection was 11.54 excess	--Delta vaccine effectiveness 39-84% --Delta vaccine effectiveness against hospitalization 75-95% ▪ In a study in nursing home residents, 2 doses of mRNA vaccines were 74.7% effective against infection from March-May 2021 (before Delta was predominant); from June-July 2021 (Delta became predominant), effectiveness declined to 53.1%[138] *(added 9/8/2021)* ▪ In a prospective, longitudinal, cohort study, the secondary attack rate in household contacts exposed to the delta variant was 25% (95% CI 18-33) in fully vaccinated persons and 38% in unvaccinated persons (95%CI 24-53); peak viral load was similar between unvaccinated and vaccinated persons; rate of viral load decline was faster in vaccinated persons[161] *(added 11/7/2021)* ▪ Neutralizing antibody titers ~40% lower against **Omicron**; a third vaccine dose increased antibody titers ~25%[172-174] *(added 12/16/2021)* ▪ Vaccine effectiveness against **Omicron** in small, early study in UK suggest effectiveness of 2 vaccine doses decreased to 30-40% against Omicron variant, but a booster dose may increase effectiveness to 70-75%; effectiveness against hospitalization appears to be ~70%[172-174] *(added 12/16/2021)*

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	response after dose 1 but did have antibody response after dose 2 ▪ Antibody levels were below those reported in immunocompetent persons who were vaccinated **Limitations:** no control group, convenience sample, lack of serial measurements after vaccine **<u>WA Werbel et al. Ann Intern Med 2021</u>**[119] *(added 8/11/2021)* **Population:** solid organ transplant recipients who had a suboptimal response to a standard 2-dose mRNA COVID-19 vaccination series and received a 3rd dose (n = 30) **Design:** case series **Results:** ▪ Primary vaccine series were with Pfizer/BioNTech or Moderna vaccines; 3rd vaccine dose was with J&J/Janssen, Pfizer/BioNTech, or Moderna ▪ 3rd vaccine given a median of 67 days after the 2nd dose ▪ Prior to the 3rd vaccine, 24 patients had negative antibody titers and 6 had low-positive titers ▪ Of the 6 patients with low-positive antibody titers before the 3rd dose, all had high-positive titers after the 3rd dose ▪ Of the 24 patients with negative antibody titers before the 3rd dose, 6 had high-positive titers after the 3rd dose, 2 had low-positive titers, and 16 remained negative ▪ Adverse effects included mild-moderate local reactions, fatigue, headache, myalgia ▪ 1 patients had biopsy-proven, antibody-mediated rejection 7 days after the 3rd vaccine dose in the setting of acute volume overload	events/100,000 persons (95% CI 2.48-22.55)[135,162] *(added 9/8/2021; updated 11/7/2021)* ▪ **Booster** dose safety data from 306 booster recipients (FDA advisory committee meeting 9/17/2021) *(added 9/20/2021)*:[141] • Reactogenicity not increased relative to dose 2 • Lymphadenopathy observed more frequently after booster than after primary series (5.2% vs 0.4%) • No deaths, vaccine-related serious adverse events, myocarditis, pericarditis, anaphylaxis, appendicitis, or Bell's palsy reported ▪ Based on reports to v-safe, adverse reactions after 3rd dose were similar to those after 2nd dose; 79.4% reported local and 74.1% reported systemic reactions after 3rd dose vs 77.6% reported local and 76.5% reported systemic reactions after 2nd dose[149] *(added 10/12/2021)* **<u>Myocarditis:</u>** ▪ CDC investigating reports of myocarditis following mRNA vaccines; currently there are few reports and most cases appear to be mild; according to CDC, these cases seem to occur predominantly in adolescents and young adults, more often in males than females, more often following the 2nd dose than the 1st, and typically within 4 days after vaccination; rates of myocarditis after vaccination have not exceeded expected baseline rates[87] *(added 5/27/2021)*	▪ In CDC study, mRNA vaccines 94% effective for preventing emergency department and urgent care visits and 90% effective at preventing COVID-19-associated hospitalizations during Omicron-predominant periods[180] (*added 1/28/2022*) ▪ In CDC study, vaccination reduced risk of SARS-CoV-2 infection and COVID-19-associated death during Delta and Omicron predominance; protection against infection and death higher in persons who had received booster doses, especially in older patients[181] *(added 1/28/2022)* **Pregnancy and Lactation:** ▪ American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM) recommend all pregnant and breastfeeding individuals be vaccinated against COVID-19 [14]*(added 12/17/2020; updated 8/12/2021)* ▪ CDC strongly recommends COVID-19 vaccination for all pregnant people (and people who are trying get pregnant or plan to become pregnant in the future) and breastfeeding people (on 9/29/2021 CDC recommended urgent action to increase

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	**Limitations:** case series, small sample, no assays for neutralizing antibody, B-cell memory, or T-cell responses **<u>NEJM Correspondence 2021</u>[46-48]** *(added 3/23/2021)* **2 California Healthcare Systems (UCSD and UCLA)[46]** ▪ 36,659 health care workers were vaccinated with a 1st mRNA vaccine dose between December 16, 2020 and February 9, 2021; 77% received the 2nd dose ▪ 379 persons tested positive for SARS-CoV-2 ≥1 day after vaccination; most (71%) of positive tests were in the 1st 2 weeks after vaccination ▪ After both vaccine doses, 37 persons tested positive; 22 were <7days after the 2nd dose; only 8 workers tested positive 8-14 days after the 2nd dose and 7 did so ≥15 days after the 2nd dose **Texas Medical Center (UTSW)** ▪ 59% of 23,234 employees received a 1st mRNA vaccine dose and 30% received a 2nd dose within 31 days of December 15, 2020 ▪ Between December 15, 2020 and January 28, 2021, SARS-CoV-2 infections were reported in 234 of 8969 nonvaccinated employees, 112 of 6144 partially vaccinated employees, and 4 of 8121 fully vaccinated employees **Jerusalem Medical Center (HHUMC)[48]** ▪ Among workers vaccinated with the Pfizer vaccine the weekly incidence of SARS-CoV-2 infection declined	▪ CDC reviewing cases of myocarditis/pericarditis after mRNA vaccination (285 of 475 reported cases investigated as of 5/31/2021)[95] *(added 6/15/2021)* ▪ Most cases occurred after 2nd dose ▪ Most occurred in patients 16-24 years old ▪ Median time to onset 2 days (after dose 2) ▪ 79% occurred in males ▪ 81% had full recovery of symptoms ▪ There were more reported cases than expected ▪ As of 6/21/2021, 616 reports made to VAERS; CDC/FDA confirmed 393 reports *(added 6/28/2021)*[97] ▪ A warning statement about the risk of myocarditis is now included in the FDA fact sheets for the Pfizer/BioNTech and Moderna mRNA vaccines[13,96] (*added 6/28/2021*) ▪ ACIP concludes benefits of vaccine outweigh risk of myocarditis[105] *(added 7/15/2021)* ▪ A review of 13 adolescents (12 male; median age 15 years) with myocarditis after the 2nd dose of Pfizer/BioNTech vaccine reported symptom development a median of 3 days after administration of the 2nd vaccine, all subjects had sudden onset of severe and persistent chest pain, all patients had elevated serum troponin and C-reactive protein, 2 cases had a family history of myocarditis in 1st degree relatives, all patients had evidence of myocardial inflammation and edema on cardiac MRI, 9 patients had abnormal echocardiograms, all patients were given NSAIDs (2 received	vaccination in these populations); pregnant people are at increased risk for severe illness from COVID-19 compared to non-pregnant people and pregnant people with COVID-19 are at risk for adverse pregnancy outcomes, including preterm birth and admission of neonates to ICU[15,22,146] *(added 3/6/2021; updated 10/4/2021)* ▪ In an analysis of people enrolled in v-safe, among 2456 pregnant persons who received an mRNA COVID-19 vaccine preconception or before 20 weeks of gestation the risk of spontaneous abortion was ~13%; spontaneous abortion typically occurs in ~11-16% of pregnancies[121] *(added 8/12/2021)* ▪ CDC analysis of data reported to V-safe in pregnant women who received the Moderna or Pfizer/BioNTech vaccine (>30,000) found that most adverse events in pregnant women were not related to pregnancy (e.g., local and systemic reactions); pregnancy-specific adverse events were within known background rates[44] *(added 3/15/2021)* ▪ A prospective cohort study including 131 reproductive-age vaccine recipients (84 pregnant, 31 lactating, 16 non-pregnant) reported immunogenicity and reactogenicity in pregnant and lactating women was similar to that in non-pregnant women; antibodies were present in

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	**A Angyal et al. Preprints with The Lancet 2021[49]** *(added 3/26/2021)* **Population:** health care workers 22-71 years old in the UK **Design:** observational cohort study ▪ Measurement of antibody and T-cell responses before and after 1 dose of BNT162b2 ▪ Compared responses in subjects with prior SARS-CoV-2 infection to those with no evidence of prior infection **Results:** ▪ Higher antibody titers and T-cell responses reported after a single vaccine dose in persons with previous SARS-CoV-2 infections than in infection-naïve persons ▪ Plasma from previously infected persons showed higher *in vitro* neutralization of the B.1.351 variant compared to infection-naïve persons **Limitations:** preprint; observational data **MG Thompson et al. HEROES-RECOVER MMWR 2021[53]** *(added 3/29/2021; updated 6/8/2021)* **Population:** health care personnel, first responders, and other essential/frontline workers in the US who were routinely tested for SARS-CoV-2 for 13 weeks (n=3950) **Design:** prospective cohort **Results:** ▪ 2479 (62.8%) received both mRNA doses and 477 (12.1%) received only 1 dose ▪ There were 1.38 SARS-CoV-2 infections per 1,000 person-days among unvaccinated persons, 0.04 infections per 1,000 person-days among fully-vaccinated persons, and 0.19 infections	corticosteroids and IVIG), median duration of hospitalization was 2 days, no patient required ICU admission, and all patients recovered[106] *(added 7/21/2021)* ▪ In a preprint report, cases of myocarditis after COVID-19 infection were identified from electronic medical records; in 12-17 year-old males, the rate of myocarditis after COVID-19 infection was 450 cases per million; based on these results, the risk of myocarditis in young males after COVID-19 infection was about 6 times higher than after vaccination[113] *(added 8/5/2021)* ▪ A case series of 15 children (<19 years old) hospitalized with myocarditis after vaccination with BNT162b2 reported most cases were in boys, most occurred after the 2nd dose, 3 patients had ventricular systolic dysfunction, 12 patients had late gadolinium enhancement on cardiac MRI, no patient had pericardial effusion, there were no deaths, no patient required ICU care, median duration of hospitalization was 2 days; 11 patients had resolution of symptoms at follow-up 1-13 days after discharge[117] *(added 8/11/2021)* ▪ In a retrospective review of data from the Israeli Ministry of Health, 5,125,635 persons received 2 doses of BNT162b2 and 136 cases of myocarditis were reported (19 after 1st dose and 117 after 2nd dose); clinical presentation was mild in 129 cases; most cases were in males; rate ratio 30 days after 2nd dose in vaccinated persons, compared with unvaccinated persons, was 2.35[159] *(added 11/6/2021)*	umbilical cord blood and breast milk[50] *(added 3/29/2021)* ▪ Prospective cohort study in Israel reported secretion of SARS-CoV-2 specific IgA and IgG antibodies in breast milk for 6 weeks after breastfeeding women were vaccinated with the Pfizer/BioNTech vaccine; no serious adverse events were reported in mothers or infants during the study period[59] *(added 4/19/2021)* CDC evaluated data reported to the v-safe surveillance system, v-safe pregnancy registry, and vaccine adverse event reporting system (VAERS) from December 14, 2020-February 28, 2021[62] *(added 4/22/2021)* ▪ 35,691 participants 16-54 years old identified as pregnant ▪ Injection-site pain reported more frequently in pregnant women than in non-pregnant women; headache, myalgia, chills, and fever reported less often ▪ 827 of 3958 women in the v-safe pregnancy registry had a completed pregnancy; of these, 115 (13.9%) resulted in pregnancy loss and 712 (86.1%) resulted in a live birth (mostly women vaccinated in 3rd trimester) ▪ Preterm birth occurred in 9.4% and small size for gestational age in 3.2% ▪ No neonatal deaths were reported ▪ Calculated proportions of adverse pregnancy and neonatal outcomes in women vaccinated against COVID-19 who had a completed

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	per 1,000 person-days among partially immunized persons **Effectiveness under real-world conditions:** ▪ 90% ≥14 days after 2nd dose ▪ 80% ≥14 days after 1st dose, but before second dose ▪ 22.9% of infections were medically attended, including 2 hospitalizations (there were 0 deaths) **Updated Analysis, CDC[91]** *(added 6/9/2021)* ▪ 3975 subjects; completed weekly testing for 17 weeks ▪ Risk of infection reduced by 91% in fully vaccinated ▪ Risk of infection reduced 81% in partially vaccinated ▪ Vaccinated subjects who developed COVID-19 had milder and shorter illness compared to unvaccinated subjects (6 fewer days sick, 2 fewer days sick in bed) ▪ 60% lower risk of developing symptoms in vaccinated persons compared to unvaccinated ▪ 40% lower viral load and 6 fewer days of detectable virus in vaccinated vs unvaccinated **Limitations:** moderately wide confidence intervals partly because of limited number of infections **A Britton et al. MMWR 2021[54]** *(added 3/29/2021)* **Population:** residents of 2 skilled nursing facilities in CT (n=463) **Design:** retrospective cohort **Results:** ▪ Efficacy >14 days after dose 1 through 7 days after dose 2 of the Pfizer/BioNTech vaccine was 63% **Limitations:** small sample size	▪ In a retrospective cohort study in Israel, the estimated incidence per 100,000 persons who had at least 1 vaccine dose was 2.13 cases (95% CI 1.56-2.70); highest incidence in 16-29 year old males (10.69 cases/100,000 persons); 76% of cases mild[160] *(added 11/6/2021)*	pregnancy were similar to incidences reported in studies in pregnant women before COVID-19; not direct comparison ▪ Among 221 adverse events related to pregnancy that were reported to VAERS, spontaneous abortion was the most frequent (46 cases) ▪ No obvious safety signals found in this preliminary report ▪ Report states more follow-up needed ▪ In a prospective cohort study in 103 women (30 were pregnant and 16 were lactating) who were vaccinated with the Moderna or Pfizer/BioNTech mRNA COVID-19 vaccine, immunogenicity was reported in all women and vaccine-elicited antibodies were found in infant cord blood and breast milk; antibody titers against B.1.1.7 and B.1.351 variants were reduced, but T-cell responses were preserved[74] *(added 5/19/2021)* ▪ A retrospective cohort study in Israel compared 7350 vaccinated pregnant women with 7530 matched unvaccinated controls; SARS-CoV-2 infection was reported in 118 women in the vaccinated group and in 202 women in the unvaccinated group; adjusted hazard ratio 0.22 (95% CI 0.11-0.43); no severe adverse events were reported[100] *(added 7/13/2021)* ▪ In a small study in 7 breastfeeding women, there were no detectable

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	**RW Frenck et al. NEJM 2021[55]** *(added 3/31/3021; updated 5/27/2021)* **Population:** adolescents 12-15 years of age, with or without prior evidence of SARS-CoV-2 infection, in the US (n=2260) **Design:** randomized, double-blind, placebo-controlled phase 3 trial ▪ 2 doses of BNT162b2 or placebo 21 days apart **Results:** ▪ Vaccine efficacy 100%; 16 cases of COVID-19 in the placebo group (n=1129) vs 0 in the vaccine group (n=1131) ≥7 days after the second dose ▪ SARS-CoV-2-neutralizing antibody geometric mean titers (GMTs) of 1239.5 reported one month after the 2nd dose (GMTs were 705.1 in earlier trial in participants 16-25 years old); the geometric mean ratio of SARS-CoV-2 50% neutralizing titers after dose 2 in subjects 12 to 15 years old relative to subjects 16-25 years old was 1.76 and met the criteria for noninferiority ▪ Side effects consistent with those observed in participants 16-25 years old in previous trials; injection-site pain, fatigue, and headache were most common **Limitations:** only short-term data on safety and efficacy available **T Kustin et al. medRxiv 2021[58]** *(added 4/17/2021)* **Population**: individuals with documented SARS-CoV-2 infection (symptomatic or asymptomatic) identified in a health care organization in Israel **Design:** case-control study ▪ Investigated whether persons with SARS-CoV-2 infection who had received a BNT162b2 vaccine were more likely to		levels of vaccine RNA in breast milk samples collected from 4 to 48 hours after vaccination[104] *(added 7/15/2021)* ▪ In a case-control surveillance study, among women who had spontaneous abortions, the odds of COVID-19 vaccine exposure in the prior 28 days were not increased compared with women with ongoing pregnancies (adjusted odds ratio 1.02; 95% CI 0.96-1.08); a COVID-19 vaccine was received within 28 days prior to an index date among 8.0% of ongoing pregnancies vs 8.6% of spontaneous abortions[144] *(added 9/23/2021)* ▪ A case-control study using data from Norwegian registries reported no evidence of an increased risk of early pregnancy loss after COVID-19 vaccination[164] *(added 11/7/2021)* **Fertility:** ▪ No adverse effects on sperm parameters (sperm concentration, sperm motility, semen volume) after 2 doses of an mRNA vaccine (Pfizer/BioNTech or Moderna) in 45 men at a median of 75 days after the 2nd vaccine dose[108] *(added 7/22/2021)* **Vaccine Storage:** **Purple Cap Vials (≥12 years old):** ▪ Ultra-cold (-76 to -130° F/-60 to -90° C) freezer conditions required for vaccine storage

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	become infected with B.1.1.7 or B.1.351 compared with unvaccinated controls ▪ 2 categories of vaccinated carriers: those with a positive test between 14 days after the 1st dose and a week after the 2nd dose and those with a positive test at least 1 week after the 2nd dose **Results:** ▪ B.1.1.7 was predominant strain in Israel during sample period ▪ Frequency of B.1.351 infection was less than 1% ▪ Vaccinated persons who were infected ≥1 week after the 2nd dose were disproportionately infected with B.1.351 (OR 8.1) ▪ Vaccinees infected between 2 weeks after the 1st dose and 1 week after the second dose were disproportionality infected with B.1.1.7 (OR 26.10) **Limitations:** not peer reviewed; observational data; only able to evaluate high viral load cases; not intended to determine efficacy **CDC report (data based on persons vaccinated with any 1 of the 3 vaccines authorized in the US)[60]** *(updated 10/12/2021)* **MMWR Report[85]:** *(added 5/26/2021)* ▪ As of April 30, 2021 10,262 vaccine breakthrough cases reported in the US out of ~101 million vaccinated persons ▪ 6446 (63%) were in women ▪ Median patient age: 58 years ▪ 2725 (27%) were asymptomatic ▪ 995 (10%) were hospitalized; of these 289 (29%) were asymptomatic or unrelated to COVID-19 ▪ 160 (2%) died; of these, 28 (18%) were asymptomatic or unrelated to COVID-19		▪ Cartons of the vaccine arrive in thermal containers with dry ice; vials should be removed immediately and stored in ultra-cold freezers; if ultra-cold freezer storage is not available, the thermal container may be used for temporary storage when consistently re-filled to the top with dry ice[13] *(added 12/11/2020)* ▪ FDA has authorized transportation and storage of undiluted vaccine vials at common pharmaceutical freezer temperatures of -25 to -15°C (-13 to 5° F) for a total period of up to 2 weeks; frozen vials stored at this alternative freezer temperature may be returned one time to the recommended ultra-cold storage conditions[32] *(added 2/27/2021)* ▪ Vials may be thawed and then stored undiluted in the refrigerator (35-46° F /2 -8° C) for up to 1 month[13,79] *(updated 5/20/2021)* ▪ For immediate use, undiluted vials may be thawed and stored at room temperature for no more than 2 hours; vials must reach room temperature before dilution[13] *(added 12/11/2020)* ▪ After dilution, vials may be stored be at 35 to 77° F (2 to 25° C) and used within 6 hours from the time of dilution[13] *(added 12/11/2020)* ▪ Vaccine must be diluted with 0.9% Sodium Chloride Injection, USP that

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	▪ Median age of patients who died: 82 years ▪ Sequence data was available for 555 (5%); of these 356 (64%) were variants of concern (B1.1.7 in 199 [56%], B.1.429 in 88 [25%], B1.427 in 28 [8%], P.1 in 28 [8%], and B.1.351 in 13 [4%]) **October 4th Report** (CDC now monitoring only hospitalized or fatal cases instead of all cases) ▪ 30,177 hospitalized or fatal vaccine breakthrough cases out of >185 million fully vaccinated ▪ 5660 (86%) deaths and 15,792 hospitalizations (67%) were ≥65 years old ▪ 2902 (44%) deaths and 11,474 (49%) hospitalizations in women ▪ 968 (15%) deaths and 3483 (15%) hospitalizations asymptomatic or not COVID-related **VJ Hall et al. Lancet 2021[66]** *(added 5/5/2021)* **Population:** health care staff ≥18 years old working in publicly-funded hospitals in the UK (n=23,324) **Design:** prospective cohort ▪ Patients assigned to positive cohort (antibody positive or history of infection [previous positivity of antibody or PCR tests] or negative cohort (antibody negative with no previous positive test) **Results:** ▪ Dominant variant in circulation during this study was B.1.1.7		is not supplied with the vaccine[13] *(added 12/11/2020)* ▪ Vials should be protected from light ▪ If a vial contains enough liquid after dilution for administration of >5 full doses, those extra doses may be used, but residual vaccine from multiple vials should not be combined to form a full dose *(added 1/19/2021)* ▪ FDA fact sheet updated to indicate vials contain 6 doses of 0.3 mL; a low dead-volume syringe and/or needle is recommended to withdraw the 6 doses from the vial *(added 1/25/2021)* **Orange Cap Vials (5-11 years old):** ▪ Transport in ultra-cold freezer conditions (-25 to -15°C/-13 to 5°F) ▪ Once received, vials can be refrigerated (35-46° F /2 -8° C) and stored for up to 10 weeks; alternatively, store vials at ultra-low freezer temperature (-76 to -130° F/-60 to -90° C) ▪ Undiluted vials may be thawed and stored at room temperature (8-25°C/35-77°F) for no more than 12 hours ▪ After dilution, vials may be stored be at 35 to 77° F (2 to 25° C) and used within 12 hours from the time of dilution

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	▪ Vaccine coverage was 89% (94% of those received the BNT162b2 vaccine) ▪ Total follow-up was 2 months ▪ 977 new infections in the unvaccinated cohort (incidence density 14 infections per 10,000 person-days) ▪ 71 new infections 21 or more days after 1st vaccine dose (incidence density 8 infections per 10,000 person-days) and 9 infections 7 days after the second dose (incidence density 4 infections per 10,000 person-days) in the vaccinated cohort ▪ In the unvaccinated cohort: 543 (56%) of participants had typical COVID-19 symptoms and 140 (14%) were asymptomatic on or 14 days before positive PCR ▪ In the vaccinated cohort: 29 (36%) had typical COVID-19 symptoms and 15 (19%) were asymptomatic ▪ Vaccine effectiveness was 70% at 21 days after the first dose and 85% at 7 days after the second dose **Limitations:** timing of testing may have influenced results; high vaccine coverage in study population may not be generalizable **Y Angel et al. JAMA 2021** *(added 5/8/2021)* **Population:** health care workers in Israel who were regularly screened for SARS-CoV-2 infection via PCR testing (n=6710) **Design:** retrospective cohort study ▪ Compared incidence of infection between fully vaccinated and unvaccinated health care workers **Results:** ▪ 5953 (88.7%) received at least 1 dose, 5517 (82.2%) received 2 doses, and 757 (11.3%) were not vaccinated		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	▪ Lower incidence of symptomatic and asymptomatic SARS-CoV-2 infection ▪ Symptomatic infection occurred in 8 vaccinated health care workers and 38 unvaccinated health care workers (incidence rate of 4.7 vs 149.8 per 100,000 person-days, respectively) ▪ Asymptomatic infection occurred in 19 fully vaccinated health care workers and 17 unvaccinated health care workers (incidence rate 11.3 vs 67.0 per 100,000 person-days) ▪ Adjusted incidence rate ratio (IRR) of 0.03 for symptomatic infection (95% CI 0.01-0.06) and 0.14 for asymptomatic infection (95% CI 0.07-0.31) >7 days after the 2nd dose ▪ Adjusted IRR corresponding to estimated vaccine effectiveness of 97% for symptomatic infection and 86% for asymptomatic infection **Limitations:** observational study **Abu-Raddad et al. NEJM 2021[69]** *(added 5/8/2021)* **Population:** cases of SARS-CoV-2 in persons vaccinated with the Pfizer/BioNTech BNT162b2 vaccine compared to unvaccinated persons in Qatar **Design:** test-negative case-control **Results:** ▪ Estimated vaccine effectiveness against infection with B.1.1.7 variant was 89.5% and against the B.1.351 variant was 75.0% ≥14 days after the second dose ▪ Vaccine effectiveness against severe, critical, or fatal disease due to infection with any SARS-CoV-2 variant was 97.4% (B.1.1.7 and B.1.351 were predominant) **Limitations:** observational; limited data		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	**L Tang et al. JAMA 2021[70]** *(added 5/9/2021)* **Population:** routinely screened health care workers eligible for vaccination at St. Jude Children's Research Hospital (n=5217) **Design:** observational cohort study **Results:** ▪ 3052 (58.5%) received 1 vaccine dose, 2776 (53.2%) received 2 vaccine doses, 2165 (41.5%) unvaccinated ▪ Median follow-up 81 days in unvaccinated group and 72 days in vaccinated group ▪ 51 vaccinated health care workers had a positive SARS-CoV-2 test result; 29 (56.9%) were diagnosed through asymptomatic screening ▪ 185 unvaccinated health care workers tested positive; 79 (42.7%) were asymptomatic ▪ The incidence rate ratio (IRR) was 0.21 (95% CI 0.15-0.28) for any SARS-CoV-2 infection, 0.28 (95% CI 0.18-0.42) for asymptomatic cases, and 0.16 (95% CI 0.10-0.25) for symptomatic or known exposure cases **Limitations:** observational; small cohort; short follow-up **H Parry et al. MedRxiv 2021[75]** *(added 5/19/2021)* **Population**: 172 people >80 years old who were vaccinated with BNT162b2 with either a standard 3 weeks interval between doses or an extended interval schedule (12 weeks) **Design:** population-based cohort study **Results:** ▪ Peak antibody response was 3.5-fold higher in subjects who were vaccinated on the extended interval schedule		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	▪ Cellular immune responses were 3.6-fold lower **Limitations:** small sample size; cohort study; not published or peer-reviewed **SY Wong et al. Gastroenterology 2021[76]** *(added 5/19/2021)* **Population:** Patients with inflammatory bowel disease (IBD) who were vaccinated with the Moderna or Pfizer/BioNTech mRNA COVID-19 vaccine (n=48) **Design:** 48 vaccinated IBD patients were compared to 2 control groups consisting of 14 completely vaccinated healthcare workers and 29 vaccinated healthy volunteers without IBD **Results:** ▪ 85% of patients receiving a biologic (including TNF inhibitors, vedolizumab, and ustekinumab) at time of vaccination ▪ All vaccinated IBD patients demonstrated serological responses **Limitations:** small sample size; single center **RH Shaw Lancet 2021[77]** *(added 5/19/2021)* **Population:** subjects ≥50 years old with no or mild-to-moderate, well controlled comorbidity in the UK (n=830) **Design:** multicenter, participant-masked, randomized heterologous prime-boost COVID-19 vaccination study Subjects randomized to 1 of 4 vaccine schedules administered 28 or 84 days apart: ▪ AstraZeneca/AstraZeneca ▪ AstraZeneca/Pfizer-BioNTech ▪ Pfizer-BioNTech/Pfizer-BioNTech ▪ Pfizer-BioNTech/AstraZeneca **Results:**		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	▪ Reactogenicity results reported for 436 subjects who received vaccines at 28-day intervals ▪ Greater systemic reactogenicity was reported following heterologous vaccine schedules compared to their homologous counterparts ▪ Adverse effects that were reported in more subjects who received a heterologous vaccine schedule included feverishness, chills, fatigue, headache, joint pain, malaise, and muscle ache ▪ There were no hospitalizations due to these adverse reactions ▪ No thrombocytopenia was reported in any group at 7 days post-boost ▪ Efficacy results expected in June 2021 **Limitations:** interim results; only subjects ≥ 50 years old **EM White et al. NEJM 2021[78]** *(added 5/19/2021)* **Population:** nursing home residents in 280 nursing homes across 21 states in the US **Design:** review of immunization records identified residents who: ▪ received 1 dose of an mRNA vaccine ▪ received 2 doses of an mRNA vaccine ▪ were present on the day of the first facility vaccination clinic but who were not vaccinated **Results:** ▪ 18242 vaccinated residents (80.4% Pfizer/BioNTech and 19.6% Moderna) and 3990 unvaccinated residents ▪ Incidence of SARS-CoV-2 infection decreased over time in residents who were vaccinated and in those who were not vaccinated		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	▪ After 1st vaccine dose: 822 incident cases (4.5% of vaccinated residents) occurred within 14 days and 250 cases (1.4%) at 15-28 days ▪ After 2nd vaccine dose: 130 cases (1.0%) occurred within 14 days and 38 cases (0.3%) after >14 days ▪ Unvaccinated residents: 173 cases (4.3%) within 14 days of 1st vaccination clinic and 12 cases (0.3%) >42 days after the clinic ▪ Most infections were asymptomatic **Limitations:** observational data **FS Vahidy et al. medRxiv 2021[82]** *(added 5/20/2021)* **Population:** established patients in a healthcare system in the US who were vaccinated with an mRNA vaccine, partially vaccinated with an mRNA vaccine, or not vaccinated through April 4, 2021 (n=91, 134) **Design:** retrospective cohort **Results:** ▪ 70.2% not vaccinated, 4.5% partially vaccinated, 25.4% fully vaccinated ▪ Hospitalization occurred in 0.7% of fully vaccinated patients, 3.4% of partially vaccinated patients, and 2.7% of unvaccinated patients ▪ 255 deaths occurred in patients hospitalized with COVID-19; of those, 219 (97.3%) were in unvaccinated patients, 5 (2.2%) were in partially vaccinated patients, and 1 (0.0041%) in a fully vaccinated patient ▪ Full vaccination was reported to be 96% effective at preventing COVID-19 hospitalization and 98.7% effective at preventing death ▪ Partial vaccination was reported to be 77% effective at preventing		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	hospitalization and 64.2% effective at preventing death **Limitations:** observational data; not published or peer reviewed **J Lopez Bernal et al. 2021[84]** *(added 5/26/2021)* **Population:** subjects vaccinated with the BNT162b2 or ChAdOx1 vaccine in the UK (n=12,675 sequenced cases) **Design:** test negative case control **Results:** ▪ Of 12,675 cases, 11,621 were B.1.1.7 and 1054 were B.1.617.2 ▪ Vaccine effectiveness after 2 doses of BNT162b2 against the B.1.617.2 variant was 87.9% compared to 93.4% against B.1.1.7 ▪ Vaccine effectiveness after 1 dose of BNT162b2 was 33.2% against B.1.617.2 and 49.2% against B.1.1.7 **Limitations:** observational data; preprint report **RH Haberman et al. Ann Rheum Dis 2021[86]** *(added 5/27/2021)* **Population:** ▪ established patients in a New York Hospital system with immune-mediated inflammatory diseases receiving methotrexate, anti-cytokine biologics or both who were receiving the BNT162b2 vaccine (n=51) ▪ healthy subjects served as controls (n=26) ▪ a second, independent validation cohort of controls (n=182) and patients with immune-mediated inflammatory diseases (n=31) evaluated for humoral immune response **Design:** cohort study		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	**Results:** ▪ After vaccination, adequate antibody responses were observed in 98.1% of healthy controls, 91.9% of patients on biologic treatments and 62.2% of patients taking methotrexate (p<0.001) ▪ Activated CD8+ T cell response was not induced after vaccination in subjects on methotrexate **Limitations:** observational, small sample size **MW Tenforde et al. MMWR 2021[90]** *(added 6/9/2021)* **Population:** adults ≥65 years old at 24 hospitals in 14 states (n=417) **Design:** test negative case control **Results:** ▪ Adjusted vaccine efficacy against COVID-19 hospitalization was 94% for full vaccination and 64% for partial vaccination **Limitations:** small sample size; wide confidence intervals; observational; interim analysis with self-reported data **MW Tenforde et al. MMWR 2021[136]** *(added 9/8/2021)* **Population:** adults who received 2 doses of an mRNA vaccine in the US at 21 hospitals in 18 states (March-July 2021) (n=1129) **Design:** case control **Results:** ▪ Median interval of 65 days (range 14-166 days) after receipt of 2nd vaccine dose ▪ 53.3% Alpha and 16.3% Delta ▪ Vaccine efficacy against COVID-19 hospitalization was 86% 2-12 weeks and 84% 13-24 weeks after receipt of 2nd vaccine dose		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	**Limitations:** observational; Delta not predominant; no follow-up past 24 weeks **L Monin et al. Lancet Oncol 2021[93]** *(added 6/9/2021)* **Population:** cancer patients and healthy controls recruited from 3 London hospitals who were vaccinated with the Pfizer/BioNTech vaccine (n=151 cancer patients and 54 healthy controls) **Design:** prospective observational study **Results:** ▪ Proportion of positive anti-S IgG titers at 21 days following vaccine dose 1 were 32 of 34 (94%) healthy controls, 21 of 56 (38%) of patients with solid cancer, and 8 of 44 (18%) of patients with hematological cancer ▪ 2 weeks after vaccine dose 12 of 12 (100%) healthy controls, 18 of 19 (95%) of patients with solid cancer, and 3 of 5 (60%) of patients with hematological cancers were seropositive ▪ Injection-site pain was the most common adverse reaction ▪ No vaccine-related toxicities were reported **Limitations:** interim analysis; insufficient power to assess 21-day boost; no matched control group or nonvaccinated control group **AM Borobia et al. Lancet 2021[99]** *(added 6/29/2021)* **Population:** adults 18-60 years old in Spain who were vaccinated with a single dose of ChAdOx1-S 8-12 weeks before screening (n=676) **Design:** phase 2, open-label, randomized trial ▪ Subjects randomized 2:1 to BNT162b2 or maintain observation (control group) **Results:**		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	▪ At day 14, geometric mean titres of receptor binding domain antibodies, and IgG against trimeric spike protein were significantly increased from baseline ▪ Injection-site pain and induration, headache, and myalgia were the most common adverse events **Limitations:** ongoing trial; not compared to a control group that received a 2nd dose of ChAdOx1-S **Bergwerk et al. NEJM 2021[111]** *(added 8/3/2021)* **Population:** health care workers in Israel who were fully vaccinated with the Pfizer/BioNTech vaccine **Design:** prospective cohort study to assess effectiveness of BNT162b2 **Results:** ▪ 39 SARS-CoV-2 breakthrough infections occurred among 1497 fully vaccinated health care workers for which RT-PCR data were available ▪ Neutralizing antibody titers in cases patients were lower than those in matched uninfected controls during the peri-infection period ▪ Most breakthrough infections were mild or asymptomatic ▪ 19% had symptoms >6 weeks ▪ 85% of samples tested were Alpha variant (B.1.1.7) **Limitations:** observational; small number of cases; mostly young healthy persons **AM Cavanaugh et al. MMWR 2021[114]** *(added 8/10/2021)* **Population:** Kentucky residents ≥18 years old infected with SARS-CoV-2 in 2020 and reinfected in May-June 2021 (n=246 cases and 492 controls) **Design:** case-control study		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	▪ Vaccination status of reinfected residents what compared with that of residents who were not reinfected **Results:** ▪ In persons previously infected with COVID-19, the likelihood of reinfection was significantly higher in unvaccinated persons compared to those who were vaccinated (OR = 2.34;95% CI 1.58-3.47) **Limitations:** retrospective study, vaccinated persons less likely to be tested, possibility that some reinfections may not have been distinct virus relative to first infection, possible some vaccination data missing **SJ Thomas et al. NEJM 2021**[115] *(updated 11/6/2021)* **Population:** participants from ongoing randomized controlled trial (44,165 participants ≥16 years old and 2264 participants 12-15 years old) **Design:** ongoing, placebo-controlled, observer-blinded, multinational, pivotal efficacy study ▪ BNT162b2 given as 2 doses (30 mcg/dose) 21 days apart ▪ Data up to 6 months post-vaccination **Results:** At up to 6 months of follow-up: ▪ Vaccine efficacy was 91.3% (95% CI 89.0-93.2) ▪ Vaccine efficacy against severe disease was 96.7% (95% CI 80.3-99.9) ▪ Vaccine efficacy in South Africa (Beta variant predominant) was 100% (95% CI 53.5-100) **Limitations:** ability to collect data in blinded, placebo-controlled manner limited by need to immunize placebo recipients under EUA; **A Puranik et al. medRxiv 2021**[116]		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	*(added 8/11/2021)* **Population:** persons in Mayo Clinic Health system from January 2021-July 2021 **Design:** cohort study ▪ compared the effectiveness of mRNA-1273 and BNT162b2 **Results:** ▪ Delta variant prevalence increased from 0.7% in May 2021 to >70% in July 2021, while the Alpha variant decreased in prevalence from 85% to 13% ▪ Effectiveness estimates over entire study period were 86% with mRNA-1273 and 76% with BNT162b2 ▪ Effectiveness against hospitalization was 91.6% with mRNA-1273 and 85% with BNT162b2 and against ICU admission was 93.3% with mRNA-1273 and 87% with BNT162b2 ▪ No deaths were reported in either cohort ▪ Effectiveness in July (Delta variant prominent) was 76% for mRNA-1273 and 46% for BNT162b2; effectiveness against hospitalization remained high ▪ In matched individuals from multiple states, 2-fold risk reduction against breakthrough infection with mRNA-1273 vaccine vs BNT162b2 vaccine (incidence rate ratio [IRR] 0.50, 95% CI 0.39-0.64) **Limitations:** preprint, not peer reviewed, observational, cohort from limited geographic area, risk of infection relative to date of vaccination not analyzed **Antonelli et al. Lancet Infect Dis 2021[130]** *(added 9/5/2021)* **Population:** adult users of a COVID Symptom Study mobile phone app in the UK **Design:** prospective, community-based, nested, case-control study		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	▪ Subjects included persons vaccinated with BNT162b2, mRNA-1273, or ChAdOx1 nCoV-19 **Results**: ▪ Breakthrough COVID-19 cases were reported in 0.5% of people who had received 1 vaccine dose and 0.2% of people who received 2 vaccine doses ▪ Vaccination was associated with reduced odds of hospitalization or having >5 symptoms in the first week of illness compared with no vaccination ▪ Vaccination was associated with reduced odds of long duration symptoms (≥28 days) compared with no vaccination ▪ Vaccinated participants were more likely to be asymptomatic ▪ In older adults (≥60 years old), frailty was associated with breakthrough infection after the 1st vaccine dose **Limitations:** observational study; patient-reported data; some disproportionate demographic characteristics; may not apply to all timepoints post-vaccination or different proportions of variants **YM Bar-On et al. NEJM 2021[134]** *(updated 9/17/2021)* **Population:** individuals in Israel ≥60 years old eligible for a 3rd (booster) dose of the Pfizer/BioNTech vaccine (vaccinated at least 5 months earlier) **Design:** dynamic cohort ▪ Individuals start in "non-booster" cohort and switched to "booster" cohort 12 days after administration of 3rd dose **Results:** ▪ Delta variant dominant ▪ Rate of confirmed infection lower in booster group vs nonbooster group by a factor 11.3-fold (95% CI 10.4-12.3) ≥12 days after administration of booster dose		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	▪ Rate of severe illness was lower in the booster group vs nonbooster group by a factor of 19.5 (95% CI 12.9-29.5) ≥12 days after administration of booster ▪ At least 12 days after booster dose the rate of infection was lower than the rate after 4-6 days by a factor of 5.4 (95% CI 4.8-6.1) **Limitations:** potential confounding and detection bias **Steensels et al. JAMA 2021**[139] *(added 9/17/2021)* **Population:** healthcare workers in Belgium schedule to receive 2 doses of mRNA-1273 or BNT162b2 (n=1647) **Design:** prospective cohort **Results:** ▪ 688 received mRNA-1273 and 959 received BNT162b2 ▪ Higher antibody titers were reported in subjects who received mRNA-1273 compared to BNT162b2 (geometric mean titer 3836 [95% CI 3586-4104] vs 1444 [95% CI 1350-1544]; p<0.001) ▪ Previously infected subjects had higher titers than those who had not been previously infected ▪ The difference in antibody levels according to previous infection was higher than the difference between the 2 vaccines **Limitations:** data on cellular immunity and neutralizing antibodies lacking; limited to healthcare workers **Pfizer Booster Data FDA Meeting 2021** *(added 9/17/2021)* ▪ In an immunogenicity analysis of adults 18-55 years old in a phase 2/3 study who received a primary series of BNT162b2 followed by a booster dose about 6 months later (n=306), the primary		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	immunogenicity endpoint (neutralizing antibody geometric mean titers measured after a booster dose compared to after the 2-dose primary series) met the prespecified criteria for noninferiority ▪ In a phase 1 exploratory analysis, geometric mean titers vs Delta increased from 241.0 at 1 month post-dose 2 to 1321.0 at 1 month post-booster in persons 18-55 years old and from 123.4 to 1478.9 in people 65-85 years old; geometric mean titers vs wild type virus increased from 310.1 to 1546.4 in persons 18-55 years old and from 195.8 to 1612.7 in those 65-85 years old ▪ Post-hoc analysis of efficacy during the Delta variant surge (July-August 2021): incidence 70.3 cases/1000 person years in subjects a mean of 9.8 months post-dose 2 and 51.6 cases/1000 persons years in subjects a mean of 4.7 months post-dose 2 **WH Self et al. MMWR 2021**[140] *(added 9/19/2021)* immunocompetent adults in the US admitted to 21 hospitals in the Influenza and Other Viruses in the Acutely Ill (IVY) Network (n=3689) **Design:** cases control analysis ▪ Case patients admitted with COVID-19-like illness and a positive SARS-CoV-2 test result ▪ Control patients admitted to a hospital with a negative SARS-CoV-2 test result **Results:** ▪ Vaccine efficacy against hospitalization for the full surveillance period (March 11-August 15, 2021) was 93% with		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	Moderna, 88% with Pfizer/BioNTech and 71% with Janssen/J&J ▪ Vaccine efficacy against hospitalization 14-120 after full vaccination was 93% with Moderna and 91% with Pfizer/BioNTech ▪ Vaccine efficacy against hospitalization >120 days after full vaccination was 92% with Moderna and 77% with Pfizer/BioNTech ▪ Efficacy against hospitalization >28 days after vaccination with the Janssen/J&J vaccine was 68% ▪ In a postvaccination antibody analysis in 100 volunteers, anti-receptor binding domain IgG levels were higher with Moderna than with Pfizer/BioNTech or Janssen/J&J and anti-spike IgG levels were higher with Moderna than Janssen/J&J, but not significantly different than with Pfizer/BioNTech **Limitations:** only included immunocompetent adults; only included hospitalized subjects; small number of patients who received Janssen/J&J vaccine; not specific estimates by variant **Walter et al. (children 5-11 years old) NEJM 2021**[142,154,165] *(updated 11/20/2021)* **Population:** children 5-11 years old (n=2268) **Design:** phase 2/3 clinical trial ▪ 2 doses (10 mcg each) of vaccine about 21 days apart vs placebo (2:1 randomization) **Results:** ▪ Neutralizing antibody geometric mean titer (GMT) 1 month after dose 2 in children 5-11 years old (1197.6 [95% CI 1106.1-1296.6]) was noninferior to the GMT (1146.5 [95% CI 1045.5-1257.2]) in		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	participants in 16-25 years old (control group) ▪ 99.2% of participants achieved seroresponse at 1 month after dose 2 in both age groups ▪ In a descriptive efficacy analysis in 1450 participants who received BNT162b2 and 936 who received placebo, vaccine efficacy was 90.7% (16 COVID-19 cases occurred ≥7 days after dose 2 in the placebo group vs 3 cases in the vaccine group); no cases were severe ▪ Most cases were in July-August 2021; all were in the US except 1 in Spain ▪ Asymptomatic disease/transmission not assessed ▪ No virus sequence analysis available ▪ Median follow-up time 2.3 months ▪ Most common adverse reaction was injection-site pain (71-74%) ▪ Most common systemic events were fatigue and headache ▪ Systemic adverse events reported more often after dose 2 than after dose 1 ▪ Lymphadenopathy more often in vaccine group than placebo group ▪ No reports of anaphylaxis; hypersensitivity (rash) and angioedema reported in more vaccine recipients than placebo recipients ▪ No cases of myocarditis/pericarditis were reported, but sample size was too small to detect this adverse event **Limitations**: lack of longer-term follow-up; not powered to detect rare side effects **SY Tartof et al. Lancet 2021**[147] *(added 10/5/2021)* **Population:** healthcare records of persons ≥12 years old who were members of the Kaiser Permanente Southern California health system; individuals assessed for		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	eligibility between December 14, 2020 and August 8, 2021 (n=3,436,957) **Design:** retrospective cohort study **Results:** <u>Effectiveness against SARS-CoV-2 infection in fully vaccinated:</u> ▪ 73% (95% CI 72-74) over the entire study period ▪ 88% (95% CI 86-89) during the first month after full vaccination ▪ 47% (95% CI 43-51) after 5 months <u>Effectiveness against hospitalization in fully vaccinated:</u> ▪ 90% (95% CI 89-92) over the entire study period ▪ 87% (95% CI 82-91) during the first month after full vaccination ▪ 88% (95%CI 82-92) after 5 months <u>Effectiveness against Delta vs other variants:</u> ▪ 75% (95% CI 71-78) against Delta vs 91% (95% CI 88-92) against other variants over entire study period ▪ 93% (95% CI 85-87) against Delta vs 97% (95-99) against other variants during first month after full vaccination ▪ 53% (95% CI 39-65) against Delta vs 67% (95% CI 45-80) against other variants at 4 months ▪ Difference in rate of decline in effectiveness between Delta and other variants was not statistically significant (p=0.30) ▪ Effectiveness against hospitalization 93% (95% 84-96) for Delta up to 6 months and 95% (90-98) for other variants **Limitations:** retrospective study, differences between groups in testing patterns and other characteristics, sequencing more likely to fail in vaccinated persons with lower viral loads		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	**RL Atmar et al. medRxiv 2021[150]** *(added 10/19/2021)* Vaccine Mixing **Population:** persons in the US with no reported history of SARS-CoV-2 infection who received 1 of 3 COVID-19 vaccines with an FDA Emergency Use Authorization (Pfizer/BioNTech, Moderna, or J&J vaccine) at least 12 weeks prior (n=458) **Design:** phase 1/2 adaptive design, open-label trial sponsored by the NIH ▪ Subjects received a booster dose with one of the 3 vaccines (Pfizer/BioNTech, Moderna, J&J) resulting in 9 vaccine combinations **Results:** ▪ Antibody levels increased in all groups after booster of different vaccine (4.6-56-fold increase) ▪ Neutralizing antibody titers increased 4-20-fold with homologous boost combinations vs 6-76-fold with heterologous boost combinations ▪ Neutralizing antibody titers in J&J primary dose recipients increased 76-fold after Moderna booster, 35-fold after Pfizer booster, and 4-fold after J&J booster ▪ Serum neutralization levels at baseline (before booster) were lower for Pfizer/BioNTech (3-fold) and J&J (10-fold) recipients than for Moderna recipients ▪ Reactogenicity and adverse events similar across all groups **Limitations:** preprint, not peer-reviewed or published; not designed to compare responses between regimens; not representative of general population **Y Goldberg et al. NEJM 2021[156]** *(added 10/30/2021)*		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	**Population:** Israeli residents fully vaccinated with Pfizer/BioNTech before June 2021 (4, 791,398) **Design:** Poisson regression model comparing rates of SARS-CoV-2 infection and severe COVID-19 among persons vaccinated during different time periods ▪ Data collected from Israeli national database from July 11-31, 2021 **Results:** ▪ Adults ≥60 years old who completed a 2-dose primary series of the Pfizer/BioNTech vaccine in the second half of January 2021 had a significantly higher rate of infection than those who completed their series in the second half of March 2021 (3.2 vs 1.6 cases/1000 persons) ▪ Adults ≥60 years old who completed their series in January had a significantly higher rate of severe COVID-19 than those who completed it in March (0.29 vs 0.15 cases/1000 persons) **Limitations:** observational; did not separate waning immunity vs change in dominant variant from Alpha to Delta		
	CH Bozio et al. MMWR 2021[158] *(added 11/3/2021)* **Population:** hospitalized adults in the US with COVID-like illness who had received testing at least 2x (once associated with hospitalization January -September 2021 and once earlier February 2020 - ≥14 days before hospitalization) (n=7348) **Design:** epidemiologic analysis using data from the VISION Network collected from 187 hospitals		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	▪ compare odds of receiving a positive SARS-CoV-2 test result between unvaccinated patients with previous SARS-CoV-2 infection and patients vaccinated with an mRNA COVID-19 vaccine **Results:** ▪ Odds of confirmed SARS-CoV-2 infection was 5.49-fold higher in unvaccinated persons with a history of SARS-CoV-2 infection than in vaccinated persons with no prior infection (95% CI 2.75-10.99) **Limitations:** observational data; misclassification possible; only hospitalized patients included **SM Olson et al. MMWR 2021**[163] *(added 11/7/2021)* **Population:** hospitalized patients 12-18 years old in the US (n=464) **Design:** test-negative, case-control study **Results:** ▪ During period June-September 2021 ▪ Delta variant predominant during study period ▪ Vaccine efficacy against COVID-19 hospitalization 93% (95% CI 83-97%) ▪ 97% of adolescents hospitalized with COVID-19 were unvaccinated ▪ 43% of unvaccinated adolescents admitted to ICU and no vaccinated adolescents admitted to ICU **Limitations:** not able to assess efficacy directly against specific variants; not able to assess subgroups; self-reported data from some participants; most patients in Southern US **R Lazarus et al. Lancet 2021** *(added 11/21/2021)* **Population:** adults in the UK receiving a 2nd dose of the Oxford/AstraZeneca vaccine or the Pfizer/BioNTech vaccine		

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2 (continued)	**Design: randomized, controlled, phase 4 trial** ▪ COVID vaccine plus an age-appropriate influenza vaccine or placebo **Results:** ▪ Concomitant administration of influenza vaccine with one of the COVID-19 vaccines was non-inferior to COVID-19 vaccine alone for any systemic adverse reaction 7 days after vaccination in 4 cohorts; in 2 cohorts (BNT162b2 plus adjuvanted trivalent influenza vaccine and ChAdOx1 plus recombinant quadrivalent influenza vaccine the upperlimit of the 95% CI exceeded the 0.25 non-inferiority margin ▪ Most systemic reactions mild or moderate in all cohorts ▪ Immune responses were preserved for both vaccines **Limitations:** participant-reported primary outcome; influenza vaccine more likely to cause local reactions than placebo, possibly unmasking allocation **BA Dickerman et al. NEJM 2021[168]** *(added 12/6/2021)* **Population:** U.S. veterans who received a 1st mRNA vaccine dose (BNT162b2 or mRNA-1273) between Jan 4, 2021 and May 14, 2021 (n=219,842 persons/group) **Design:** observational analysis designed to emulate a target trial **Results:** ▪ 24 weeks of follow-up ▪ Estimated risk of documented infection 5.75 events/1000 persons (95% CI 5.39-6.23) with BNT162b2 and 4.52 events/1000 persons (95% CI 4.17-4.84) with mRNA1273 ▪ Excess number of events/1000 persons for BNT162b2 vs mRNA-1273 was		

- 1.23 for documented infection (95% CI 0.72-1.81)
- 0.44 for symptomatic infection (95% CI 0.25-0.70)
- 0.55 for hospitalization (95% CI 0.36-0.83)
- 0.10 for ICU admission (95% CI 0.00-0.26)
- 0.02 for death (95% CI -0.06-0.12)

- Corresponding excess risk of documented infection over 12-week follow-up with Delta predominance was 6.54 events/1000 persons (95% CI -2.58-11.82)

Limitations: observational data; possible outcome misclassification; mostly men

ES Rosenberg et al. NEJM 2021[169]
(added 12/6/2021)
Population: adults in New York State vaccinated with BNT162b2, mRNA-1273, or Ad26.COV2.S (n=8,690,825)
Design: surveillance-based cohort
Results:

- During week of May 1, 2021 (alpha predominance; delta 1.8% of variants), median vaccine effectiveness against COVID-19 was 91.3% for BNT162b2, 96.9% for mRNA-1273, and 86.6% for Ad26.COV2.S
- During week of August 28 (delta predominance; delta 99.6% of variants), median vaccine effectiveness was 72.3% for BNT162b2, 77.8% for mRNA-1273, and 69.4% against Ad26.COV2.S
- Effectiveness against hospitalization with COVID-19 remained >86% in adults 18-64 years old, with no apparent time trend

Limitations: observational, possible confounding, did not account for herd immunity between groups

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VACCINE	EFFICACY	SAFETY	COMMENTS
Adjuvanted Recombinant Nanoparticle Vaccine			
NVX-CoV2373 (Novavax) *(updated 12/21/2021)*	**Keech et al. NEJM 2020**[1] *(updated 9/20/2020)* **Population:** healthy adults 18-59 years old (n=131) **Design:** phase 1/2, randomized, observer-blinded, placebo-controlled trial ▪ 2 vaccinations (5 or 25 mcg) given 21 days apart with or without *Matrix-M1* adjuvant or placebo **Results:** ▪ The adjuvanted vaccine induced neutralizing antibody responses and antigen-specific T cells ▪ Neutralizing antibody responses after the second vaccination exceeded levels in COVID-29 convalescent serum **Limitations:** phase 1/2 trial **UK Phase 3 Trial 2021**[3] *(added 1/30/2021; updated 3/13/2021)* **Population:** adults 18-84 years old (n=>15,000) **Design:** phase 3, randomized, double-blind, controlled trial **Results:** **Interim Analysis (1/30/2021)** ▪ 56 cases of COVID-19 in the placebo group and 6 cases in the NVX-CoV2373 group, resulting in a vaccine efficacy of 89.3% ▪ 61 cases were mild or moderate and 1 was severe (in the placebo group) ▪ UK variant strain detected in >50% of PCR-confirmed symptomatic cases ▪ Efficacy against original strain was 95.6% and against the UK variant strain was 85.6% **Final Analysis** *(updated 3/13/2021)*	▪ Tenderness and pain at the injection site ▪ Headache, fatigue, myalgia ▪ No serious adverse events reported ▪ In PREVENT-19 trial, injection-site pain and tenderness were the most common local symptoms and fatigue, headache, and muscle pain were the most common systemic symptoms; most adverse reactions were mild to moderate severity and lasted <3 days	▪ Recombinant nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins[2] ▪ Contains saponin-based *Matrix-M* adjuvant ▪ Phase 2b trial ongoing in South Africa ▪ Phase 3 trial initiated in the UK; expected to enroll up to 10,000 participants *(added 9/27/2020)* ▪ Novavax announced initiation of phase 3 trial in the US and Mexico on December 28, 2020; expected to enroll up to 30,000 participants *(added 1/1/2021)* ▪ In a sub-study, co-administration with influenza vaccine resulted in no change to influenza vaccine immune response and a reduction in antibody response to the Novavax COVID-19 vaccine; Novavax COVID-19 vaccine efficacy was 87.5% (95% CI -0.2,98.4) in the sub-study and 89.8% (95% CI 79.7, 95.5) in the main study *(added 6/16/2021)* ▪ Two-dose vaccine (21 days apart) ▪ Stored under refrigeration ▪ Shipped in ready-to-use liquid formulation

VACCINE	EFFICACY	SAFETY	COMMENTS
NVX-CoV2373 (continued)	▪ 96 cases of COVID-19 in the placebo group and 10 cases in the vaccine group, resulting in a vaccine efficacy of 89.7% ▪ 5 cases of severe disease were reported, all in the placebo group ▪ Efficacy against original virus strain was 96.4% and against the UK variant strain (B.1.1.7/501Y.V1) was 86.3% **Limitations:** not peer reviewed or published **Shinde et al. South Africa Phase 2b Trial NEJM 2021**[3,4] *(added 1/30/2021; updated 5/7/2021)* **Population:** adults 18-84 years old (n=6324) **Design:** phase 2b, randomized, placebo-controlled trial **Results:** **Interim Analysis** *(added 1/30/2021)* ▪ 60% efficacy for prevention of mild, moderate, and severe COVID-19 in HIV-negative subjects (94% of study population) ▪ 29 cases of COVID-19 in the placebo group and 15 cases in the NVX-CoV2373 group; 1 severe case was in placebo group ▪ South Africa variant strain detected in 92.6% of cases **Complete Analysis** *(updated 3/13/2021)* ▪ 51 cases in the vaccine group and 96 in the placebo group, resulting in an overall vaccine efficacy of 48.6% against predominantly variant strains (majority were B.1.351/501Y.V2) ▪ 5 cases of severe disease were all in the placebo group ▪ Efficacy in HIV-negative subjects was 55.4%		

VACCINE	EFFICACY	SAFETY	COMMENTS
NVX-CoV2373 (continued)	▪ Vaccine induced protection began 14 days after the 1st dose; increased efficacy was observed 7 days after the 2nd dose **Published Data NEJM 2021 (*updated 5/7/2021*):[5]** ▪ In 2684 baseline seronegative participants, 15 cases of COVID-19 were reported in vaccinated subjects and 29 cases in those given placebo; vaccine efficacy 49.4% ▪ In HIV-negative subjects, vaccine efficacy was 60.1%; 92.7% of cases were the B.1.351 variant ▪ Post hoc vaccine efficacy against B.1.351 was 51.0% (in HIV negative subjects) and 43.0% in the overall population **Limitations:** preliminary results, limited followup **PREVENT-19 Trial. Novavax 2021[6]** *(added 6/16/2021)* **Population:** participants ≥18 years old in the US and Mexico (n=29,960) **Design:** 2:1 randomized, placebo-controlled, observer-blinded trial ▪ NVX-CoV2373 vs placebo **Results:** ▪ 90.4% overall efficacy (7 days after 2nd dose); 77 cases observed (63 in placebo group and 14 in vaccine group; all cases in vaccine group were mild) ▪ 100% efficacy against moderate or severe disease; 10 moderate cases and 4 severe cases occurred, all in the placebo group ▪ 91.0% efficacy in "high-risk" populations (>65 years or <65 years with certain comorbidities or frequent COVID-19 exposure); 62 cases in placebo group and 13 in vaccine group ▪ All hospitalizations and death occurred in placebo group Variants:		

VACCINE	EFFICACY	SAFETY	COMMENTS
NVX-CoV2373 (continued)	▪ Sequence data available for 54 of 77 cases; 35 (65%) were variants of concern; 9 (17%) variants of interest; 10 (19%) other variants ▪ 93.2% efficacy against variants of concern and variants of interest ▪ 100% efficacy against variants not considered variants of concern or variants of interest **Limitations:** top-line results from manufacturer; not yet published or peer-reviewed		

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VACCINE	EFFICACY	SAFETY	COMMENTS
Inactivated Vaccine			
Whole-Virus Inactivated SARS-CoV-2 Vaccine (WIV04 strain) (Sinopharm) *(updated 5/26/2021)*	**Xia et al. JAMA 2020[1]** **Population:** healthy adults 18-59 years old in China (phase 1 trial n=96; phase 2 trial n=224) **Design:** randomized, double-blind, placebo-controlled phase 1 and 2 trials ▪ Phase 1: 3 injections at day 0, 28, and 56 of a 2.5, 5, or 10 mcg vaccine or aluminum hydroxide adjuvant only ▪ Phase 2: 5 mcg vaccine at days 0 and 14, 5 mcg vaccine at days 0 and 21, or aluminum hydroxide adjuvant only **Results:** ▪ Neutralizing antibodies reported in all dose groups 14 days after completion of 3 injections in phase 1 and 2 injections in phase 2 ▪ 100% seroconversion in patients in the phase 1 trial and in those who received injections on days 0 and 21 in phase 2 ▪ Antibody titers increased after second and third injections **Limitations:** phase 1/2 interim data; did not use comparator group of convalescent serum samples **N Al Kaabi et a. JAMA 2021[2]** *(added 5/26/2021)* **Population:** healthy adult volunteers without a history of COVID-19 in the United Arab Emirates and Bahrain (n=40382) **Design:** ongoing, randomized, double-blind phase 3 trial ▪ Participants randomized to receive 1 of 2 inactivated vaccines developed from SARS-CoV-2 WIV04 (5 mcg/dose; n=13459) and HBO2 (4 mcg/dose; 13465) or an aluminum hydroxide (alum)-only control (n=13458)	▪ Pain at the injection site, fever ▪ In the phase 3 trial, the most common adverse reactions were pain at the injection site and headache ▪ Serious adverse events occurred at similar rates in the vaccine and alum-only groups ▪ 1 case of possible demyelinating myelitis and 1 case of severe emesis were reported in the phase 3 trial	▪ Whole-virus inactivated vaccine ▪ Phase 3 trial enrolling 15,000 volunteers started in Abu Dhabi in July

VACCINE	EFFICACY	SAFETY	COMMENTS
Whole-Virus Inactivated SARS-CoV-2 Vaccine (WIV04 strain)	▪ Administered as 2 IM injections 21 days apart **Results:** ▪ Primary analysis included 38,206 subjects ▪ 26 cases of symptomatic COVID-19 occurred in the WIV04 group, 21 in the HB02 group, and 95 in the alum-only group ▪ Efficacy 14 days after the 2nd dose was 72.8% for WIV04 and 78.1% for HBO2 compared with alum-only ($p<0.001$ for both) ▪ Severe COVID-19 occurred in 2 subjects in the alum-only group and in no patients in the vaccine groups **Limitations:** interim analysis		

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VACCINE	EFFICACY	SAFETY	COMMENTS
DNA Vaccine			
INO-4800 (Inovio) *(added 11/29/2020)*	**Inovio Phase 1 Trial**[1] **Population:** healthy adult volunteers (n=40) **Design:** phase 1 trial ▪ 1 mg or 2 mg vaccine each given 4 weeks apart **Results:** ▪ 94% of participants had an overall immune response	▪ Redness at the injection site ▪ No serious adverse events reported in phase 1 trial	▪ DNA vaccine ▪ Manufacturer has another DNA vaccine in clinical trials for MERS ▪ Vaccine administered directly into cells via a proprietary smart device *(Cellectra 2000)* that uses a brief electrical pulse to reversibly open small pores in the cell, allowing plasmids to enter[1] ▪ Phase 2 trial expected to include 400 participants received FDA approval to begin ▪ Phase 3 portion of the clinical trials is on hold until the manufacturer resolves questions from the FDA regarding the vaccine delivery device ▪ Does not need to be frozen for transport or storage

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Adjuvanted Recombinant Protein-Based Vaccine			
Adjuvanted Recombinant Protein-Based Vaccine (GSK/Sanofi) *(added 12/3/2020)*	**Phase 1/2 Trial**[1] ▪ Enrolled 440 healthy adults in the US ▪ Results anticipated in December	▪ Not yet available	▪ Recombinant protein-based technology is the same as one of Sanofi's influenza vaccines and ▪ Use of GSK's pandemic adjuvant technology may reduce amount of vaccine protein required per dose ▪ Expected to begin phase 3 trials in December

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