COVID-19: Prevention

A Crawley BSP, M LeBras PharmD, L Regier BSP © www.RxFiles.ca Nov 2022

Vaccines: Strong evidence for ↓hospitalizations & death.[50] Myth busting: ℹ even "low risk" adults can be hospitalized if unprotected (**Table 2**); ℹ safety signals allow a tailored choice (**Table 1**); ℹ vaccines protect you **& others**.
Pearls: vaccines may help ↓"long COVID" risk;[51] if immunocompromised, give an extra dose to complete initial series; vaccination still recommended post-COVID-19 infection (after isolation); mix-and-match OK & may ↑ response.[52]

Table 1. COVID-19 Vaccines

Primary Series

- **1st-line**: any mRNA vaccine due to favourable risk-benefit profile.[NACI]
- **1st-line, age 12-30yrs**: **COMIRNATY** due to ?↓myocarditis risk vs **SPIKEVAX**.[NACI,26]

Booster Doses

Fall 2022: *Offer new booster to all ≥12yrs if >3-**6**mos since last dose or COVID infection.*[NACI]

- **1st-line**: mRNA vaccine, **SPIKEVAX bivalent/COMIRNATY bivalent** preferred if available.

Booster Dose 1: 3-6 months after initial vaccine series.
All adults ≥18 years of age.[NACI]
All high-risk children age 5-17 years.[NACI]
Any child age 5-17 years if ↑ local infection rate.[NACI]

Booster Dose 2: 6 months after first booster
High-risk adults (e.g. ↑age, Indigenous, in long-term care, immunocompromised).[NACI]

Table 2. Monovalent Vaccine Efficacy in Adults (Omicron variant)

	Infection risk if exposed to COVID-19	**Hospitalization** risk if ~first infection	**Mortality** risk if ~first infection
Unvaccinated adults	**~100%?** (if infection-naïve)	**Wide range of risk (see Table 3)** **1%** to **30%+** [30,47]	**0.1%** to **30%+** [30,47]
Adults vaccinated w/ initial series	↓ risk by 20-33% [36,42]	↓ risk by 65% [38]	↓ risk by 79% [37]
Adults vaccinated + 1 booster	↓ risk by 54-69% [36]	↓ risk by 85% [38]	↓ risk by 94% [37]
Adults vaccinated + 2 boosters	↓ risk by 75-83% [39]	↓ risk by 95% [39]	↓ risk by **99%?** [39]

Notes: Estimates only. Vaccine efficacy wanes over time; in general, a booster "renews" a patient nearly back to a previous level of protection. Efficacy (esp. infection risk) dependent on virus variant; future vaccines likely to target specific variants.

Vaccines

Intervention	Initial Dosing (Primary Series)	Booster Dosing
Pfizer-BioNTech mRNA vaccines ❄ **COMIRNATY** BNT162b2 (PfL) purple cap: six 30mcg doses/vial; requires dilution grey cap: six 30mcg doses/vial; do not dilute orange cap: ten 10mcg doses/vial; requires dilution maroon cap: ten 3mcg doses/vial; requires dilution	≥12 yrs: 30mcg IM (0.3mL of purple or grey cap vial) 5-11 years: 10mcg IM (0.2mL of orange cap vial) 6 mos to <5 yrs: 3 mcg IM (0.2mL of maroon cap vial) **Initial ≥5yrs**: 2 doses given 3-**8** wks apart. If immunocompromised, give a 3rd dose 4-8 wks later. **Initial 6mos to <5yrs**: 2 doses given 3-**8** weeks apart, then 3rd dose given ≥8 wks after 2nd dose. If immunocompromised, give a 4th dose 4-8 wks later.	**Booster ≥12yrs**: 30mcg IM (0.3mL of purple or grey cap vial) **Booster 5-11yrs**: 10mcg IM (0.2mL of orange cap vial)
COMIRNATY Original / Omicron BA.4/BA.5 BIVALENT grey cap: six 30mcg doses/vial; do not dilute	Not Health Canada approved for primary series. *(SK: may be used if requested & pt consent obtained)*	**Booster ≥12y**: 30mcg IM (0.3mL of grey cap vial)
Moderna mRNA vaccines ❄ **SPIKEVAX** mRNA-1273 (PfL) red cap: 0.2mg/mL (**100mcg**/0.5mL or **50mcg**/0.25mL doses) x 5mL blue cap: 0.1mg/mL (**50mcg**/0.5mL or **25mcg**/0.25mL doses) x 2.5mL	≥12 yrs: 100mcg IM (0.5mL of red cap vial) 6-11 years: 50mcg IM (0.25mL of red cap vial **OR** 0.5mL of blue cap vial) 6 mos to 5 yrs: 25mcg IM (0.25mL of blue cap vial) **Initial**: 2 doses given 4-**8** weeks apart. If immunocompromised, give a 3rd dose 4-8 wks later.	**Booster ≥70yrs or LTC or immunocompromised**: 100mcg IM (0.5mL of red cap vial) off-label, but studied. **Booster ≥18yrs**: 50mcg IM (0.25mL of red cap vial **OR** 0.5mL of blue cap vial)
Original/Omicron BA.1 BIVALENT blue cap: five 0.5mL doses/vial **Original/Omicron BA.4/5 BIVALENT** blue cap: five 0.5mL doses/vial	Not Health Canada approved for primary series. *(SK: may be used if requested & pt consent obtained)*	**Booster ≥18yrs**: 50mcg (0.5mL of blue cap vial)
Novavax recombinant spike protein **NUVAXOVID** ❄ (PfL) one vial containing ten 0.5mL doses	≥18 yrs: 0.5mL IM **Initial**: 2 doses given 3-**8** weeks apart. Consider 3rd dose if immunocompromised.[NACI 54]	Not preferred. Reserve if CI others.[NACI] **Booster ≥18yrs**: 0.5mL IM CDN: off-label [FDA approval Oct'22 eg mRNA hesitant]
Janssen (J&J) adenoviral vector **JCOVDEN** Ad.26.COV2.S (PfL) one vial containing five 0.5mL doses ❄	≥18 yrs: 0.5mL IM **Initial**: 1 dose. If immunocompromised, give a 2nd dose 4 weeks later of an mRNA vaccine.	Not preferred. Reserve if CI others.[NACI] **≥18yrs, Booster dose**: 0.5mL IM -booster 1: give 2mos post initial series.
Medicago recombinant spike protein **COVIFENZ** ❄ two vials; after mixing = ten 0.5mL doses	18-64 yrs: 0.5mL IM **Initial**: 2 doses given 3-**8** weeks apart. Consider 3rd dose if immunocompromised.[NACI 54]	Off-label for use as booster dose.

mAB

Intervention	Initial Dosing (Primary Series)	Booster Dosing
Tixagevimab-Cilgavimab EVUSHELD ❄ (PfL) dark grey cap 150mg tixagevimab vial white cap 150mg cilgavimab vial	**UNCERTAINTIES**: Sask: routine use **not** recommended. Potential for emerging antiviral resistance.[HC] **On-label dosing** 150mg/150mg if immunocompromised or vaccination not recommended.[32] **Off-label:** ≥12yrs & ≥40kg: 300mg tixagevimab IM + 300mg cilgavimab IM.[expert opinion for Omicron] ➔ Give **separate injections** into each gluteal muscle	Repeat dosing unstudied. FDA: repeat q6mos in those who require ongoing protection.[Expert opinion]

Masking and Physical Distancing

Effective.[59] Face mask use ↓ transmission by 82% (3.1% vs 17.4%, **NNT≈7**) and physical distancing ↓ transmission by 80% (2.6% vs 12.8%, **NNT≈10**) compared to no intervention.[44] N95 masks more effective than disposable masks.[43,44] Physical distancing 2m more effective than 1m.[44] Eye protection (e.g. face shield, goggles) also associated with ↓ infection risk.[44]

Adverse Effects AE / Contraindications CI / Drug Interactions DI Monitoring M

- **AE**: For all vaccines: injection site reactions (>50%, and more common with second dose);[21] fever 20%, headache 50%, fatigue 50%, chills 20%, myalgia 50%, arthralgia 20%. ↑AE in younger patients.[57] The vast majority of AE resolve within 2 days. Typically do **not** pre-dose with antipyretics as ?may limit immune response. **Uncertain**: asthenia (**COMIRNATY**), facial nerve paralysis (**COMIRNATY**).

Link: Tips to Avoid Shoulder Injury Related to Vaccine Administration (Waterloo).

Table 1. Serious Adverse Events with COVID-19 Vaccines.[22-26]

Cumulative serious AE rate ≈ **0.01%**, which is << COVID-19 hospitalization risk.[58]

	Myocarditis (± pericarditis)	**VITT** (clots with ↓ platelets)	**GBS** (nerve damage)
COMIRNATY	< 1 in 10,000 (in males age 12-30yr)	**not detected**	**not detected**
SPIKEVAX	< 1 in 100,000 (all other patients)	**not detected**	**not detected**
NUVAXOVID	lack of data	lack of data	lack of data
JCOVDEN	**not detected**	< 1 in 100,000 (♀ 30-49yr)	< 1 in 100,000
COVIFENZ	lack of data	lack of data	lack of data

For more details on the risk of myocarditis, VITT, and GBS, see **Online Extras Table 5**.

- **CI for all vaccines**: anaphylaxis to a component or previous COVID-19 vaccine of the same platform. **Precautions**: history of immediate allergic reaction to any other vaccine or injection; if one COVID-19 vaccine is **CI**, other platforms are precautioned. History of myocarditis (mRNA vaccines). **Kids**: history of MIS-C. **Additional warnings for adenoviral vector vaccines**: **Contraindicated** if history of VITT or CLS; **Cautione** if history of thromboembolic disease.
- Usually OK to still give vaccine if mild acute illness (e.g. cough & cold).
- **DI**: None. May give a COVID-19 vaccine **at any time** in relation to other vaccines (exception 6mos to <5yrs, ideally wait 14d between but ok to give at same visit).
- **M**: Observe for 15 minutes after vaccine; observe for 30 minutes if precautions or past anaphylaxis history.
- Report vaccine adverse events here.
- **COVIFENZ**: developed in Canada 🇨🇦. Plant-based.
- Low dead-volume syringes helps ↑ # of doses/vial.

Unclear benefit for hospitalization or mortality endpoints with prophylactic use.
↓ incidence of symptomatic COVID-19 by 83% (0.3% tix-cil vs 1.8% placebo, **NNT≈67** over ~6 mos) for high-risk COVID-19-**negative**. See RxFiles **PROVENT** Trial Summary.

- **AE**: Injection site reactions, ?cardiac events e.g. MI **NNH≈263**/6mos.[PROVENT]
- **CI**: **Caution**: History of CVD e.g. CAD, MI, HF, stroke, etc.; hypersensitivity to COVID-19 vaccine. **DI**: None known. Wait ≥14 days after COVID-19 vaccine dose.

Vitamin D: did not prevent COVID-19 in those with low vitamin D levels.[69] **CORONAVIT** Not available: **VAXZEVRIA AstraZeneca**.

CLS=capillary leak syndrome **GBS**=Guillain-Barré syndrome **mRNA**=messenger ribonucleic acid **mAB**=monoclonal antibody **MIS-C**=multisystem inflammatory syndrome in children **r**=ritonavir **VITT**=vaccine-induced immune thrombotic thrombocytopenia

COVID-19: Outpatient Treatment Therapies

A Crawley BSP, M LeBras PharmD, L Regier BSP © www.RxFiles.ca Nov 2022

Clinical Pearls

- COVID-19 therapies are not a substitute for vaccination. If mRNA vaccine-hesitant, consider non-mRNA vaccine. Deferring a COVID-19 vaccine for 3 months after infection may maximize vaccine response; however consider offering immediately after a severe infection to help overcome vaccine hesitancy.
- Nirmatrelvir/ritonavir **PAXLOVID** has numerous critically important drug interactions. Consult ≥2 sources. Complete a full medication history (including herbal and OTC products) prior to prescribing.
- COVID-19 therapies typically target pts at highest risk for severe COVID-19 complications. Most data for **unvaccinated** pts; expert opinion/observational data suggests role in **vaccinated but high-risk** pts too.[33-35]

Supportive Care for COVID-19 Outpatients

- Analgesics/antipyretics (e.g. acetaminophen); antitussives (e.g. dextromethorphan).
- Close monitoring for new/worsening dyspnea; progression from dyspnea to hospitalization can be rapid. Lying in prone position (rather than supine) may help. Patients in SK may call 811.
- Quarantine from family and/or wear mask; handwash; disinfect.
- Drink fluids regularly to avoid dehydration; rest to promote recovery.

Table 3. Risk Factors for Severe COVID-19.[29]

Age (esp. ≥65yrs & **≥75yrs**), obesity, diabetes, immunocompromised, CKD, asthma, COPD, CVD, cancer, HIV, Indigenous, neurologic conditions, cystic fibrosis, smoking, liver dx, pregnancy, sickle cell disease, tuberculosis.
See Risk Calculator from BC CTC.

Drug	Indications / Role in Therapy	Dosing	Cost	Adverse Effects AE / Contraindications CI / Drug Interactions DI / Comments
Nirmatrelvir-Ritonavir **PAXLOVID** 150mg nirmatrelvir tabs and 100mg ritonavir tabs (in blister cards) PL	✓ 1st line for high-risk outpatients (≥18yrs) with mild-to-moderate COVID-19. Give within 5 days and if no contraindications/overriding DIs. **Link**: Eligibility criteria in Sask. ❶ immunocompromised ❷ under or unvaccinated ❸ ≥70y with risk factors **Link**: Sask prescriber assessment form. See RxFiles **EPIC-HR** Trial Summary.	**eGFR ≥ 60mL/min**: 300mg nirmatrelvir (two pink tabs) + 100mg ritonavir (one white tab) **po q12h x 5 days** **eGFR 30-59mL/min**: 150mg nirmatrelvir (one pink tab) + 100mg ritonavir (one white tab) **po q12h x 5 days** **eGFR < 30mL/min ± dialysis (off-label)**: Evolving data. SK: **CI** based on prescribing guidelines.[71]	Federally acquired medication	↓ hospitalization/death by 89% (0.8% nirmatrelvir/r vs 6.3% placebo, **NNT≈18**) when given to high-risk patients within 5 days of symptom onset.[EPIC-HR, Cochrane'22] Minimal benefits in low-risk patients.[EPIC-SR, 35] Most benefit in older adults ≥65 years.[63] • **AE**: **Bad taste** (common); nausea/vomiting/diarrhea; headache; myalgia; ↑BP. Serious adverse effects are rare. Rebound infection after 5-day tx documented; do not re-treat. • **CI**: severe liver dx (Child-Pugh C); some antiepileptics e.g. phenytoin • **DI**: CYP3A4 substrate & strong inhibitor. **MANY**: atorvastatin, rosuvastatin, apixaban, amlodipine, tamsulosin, clopidogrel, ticagrelor, colchicine, clozapine. Nirmatrelvir/r should not be dose adjusted to manage DIs. **Useful checkers**: Liverpool, medSask, BC CTC. Assess harm of disrupting current drug tx relative to expected nirmatrelvir/r benefit!
Remdesivir **VEKLURY** 100mg vial PL	✓ high-risk outpatients (≥18yrs) if **CI** or **DI** to nirmatrelvir/r.[1] ✓ hospitalized patients (≥12yrs & ≥40kg) with pneumonia & requiring O_2. See RxFiles **PINETREE** Trial Summary.	**Outpatients**: 200mg IV day 1, then 100mg IV days 2 & 3. If **eGFR <30mL/min**: 200mg IV day 1, then 100mg IV 48-72hr later.[61] **Inpatients**: 200mg IV day 1, then 100mg IV day 2 & onwards for total duration of **5**-10d.	Federally acquired medication	↓ hospitalization by 87% (0.7% remdesivir vs 5.3% placebo, **NNT≈22**) when given to high-risk outpatients within 7 days of symptom onset.[PINETREE] No proven (outpatient) ↓ in mortality. • **AE**: **Nausea**, headache, ↑LFTs, rash, ↓BP, ↓HR, anaphylaxis. Serious adverse effects rare. • **CI**: ALT > 5x ULN. • **DI**: Strong 3A4 inducers (e.g. CBZ, rifampin) ↓ levels. Hydroxychloroquine may ↓efficacy.
Sotrovimab **XEVUDY** 500mg vial PL	**Utilization on hold in Sask due to uncertain efficacy vs Omicron.[WHO'22]** ✓ mild-to-moderate outpatient COVID-19 in high-risk patients age ≥12yrs & ≥40kg. See RxFiles **COMET-ICE** Trial Summary.	500mg IV once over 60 minutes May slow rate of infusion if reaction occurs.	Federally acquired medication	↓ hospitalization by 85% (1% sotrovimab vs 7% placebo, **NNT≈17**) when given to high-risk patients within 7 days of symptom onset.[COMET-ICE] **Guidelines suggest may not be effective against Omicron BA.2 variant.**[1] • **AE**: Infusion reactions, diarrhea, anaphylaxis (treat with epinephrine). Serious AE rare. • **CI**: Hypersensitivity to any components. **DI**: None known.
Tixagevimab-Cilgavimab **EVUSHELD** ❄ 150mg tixagevimab vial and 150mg cilgavimab vial PL	✓ for high-risk outpatients (≥12yrs & ≥40kg) with mild-to-moderate COVID-19. See RxFiles **TACKLE** Trial Summary.	≥18yrs: 300mg tixagevimab IM (dark grey vial cap) + 300mg cilgavimab IM (white vial cap) **Requires separate injections** (3mL each drug).	Federally acquired medication	↓ hospitalization by 57% (4.1% tix-cil vs 9.5% placebo, *interim result*) when given to unvaccinated (& mainly high risk) patients within 7 days of symptom onset.[TACKLE] Possible role in acute treatment, but potential for emerging antiviral resistance.[HC] For **AE**, **CI**, & **DI** for tixagevimab-cilgavimab, see previous page.
Bebtelovimab 175mg vial PL	**Currently not authorized** in Canada. Studied in mild-to-moderate outpatient COVID-19 in low-risk pts age ≥12yrs.	175mg IV once over >30 seconds	Unavailable in Canada	**BLAZE-4** unpublished data: faster COVID-19 symptom resolution (6 days with bebtelovimab vs 8 days placebo), but no change in hospitalizations when given to low-risk outpatients.[9] • **AE**: Infusion reactions, itch, rash. **DI**: None known.
Molnupiravir **LAGEVRIO** 200mg capsule PL	**Currently not authorized** in Canada. Studied in mild-to-moderate outpatient COVID-19 in high-risk pts age ≥18yrs.	800mg (4 caps) q12h po x 5 days	Unavailable in Canada	↓ hospitalization/death by 30% (6.8% molnupiravir vs 9.7% placebo, **NNT≈33**) when given to high-risk patients within 5 days of symptom onset.[MOVe-OUT] • **AE**: Diarrhea, nausea, dizziness, ?impaired bone/cartilage growth. • **CI**: Use contraception (♂ & ♀) during tx. **DI**: None known.
Inhaled Budesonide **PULMICORT TURBUHALER** 100, 200, 400mcg inhaler PL	**Uncertain benefit.** Off-label & **not recommended for routine use**.[IDSA] Studied in high-risk, mostly unvaxxed adults ≥50yrs. Continue ICS in asthma!	800mcg inhaled BID x 7-14 days (until symptoms resolve)	$130 (1 inhaler)	Faster COVID-19 symptom resolution (12 days budesonide vs 15 days usual care) when given to high-risk outpatients within 14 days; mixed data for hospitalizations.[PRINCIPLE,17] • **AE**: Sore throat, dysphonia, cough, thrush. Rinse mouth after use. • **DI**: ↑levels by CYP3A4 inhibitors (e.g. ritonavir, ketoconazole).
Fluvoxamine **LUVOX, g** 50, 100mg tabs PL	**Uncertain benefit.** Off-label & **not recommended for routine use**.[IDSA, WHO] Studied in high-risk, unvaxxed pts ≥18yr.	100mg BID po x 10 days See Fact Sheet from Waterloo	$20 (1 course)	↓ hospitalization by ~30% (11% fluvox vs 16% placebo) when given to high-risk outpatients within 7d of symptoms, but methodology issues.[TOGETHER] No benefit at 50mg BID.[COVID-OUT] • **AE**: Nausea, constipation, sedation. **DI**: Many. See RxFiles Antidepressants.
Colchicine, g 0.6mg tab PL	**Uncertain benefit.** Off-label & **not recommended for routine use**. Studied in high-risk, unvaccinated outpatients age ≥40yrs. No benefit for inpatients.[60]	0.5-0.6mg BID po x 3 days, then daily x 27 days	$20 (1 course)	↓ hospitalization/death by 25% (4.5% colchicine vs 5.9% placebo, **NNT≈71**) when given to high-risk outpatients within 1 day of positive COVID-19 test.[COLCORONA] • **AE**: Diarrhea 14% **NNH≈15**,[18] nausea, rash. **Serious**: ?pulmonary embolism 0.5%, neutropenia. • **CI**: Blood dyscrasias, transplant pts, CrCl<30mL/min. **DI**: P-gp & CYP3A4 inhibitors.
Hydroxychloroquine	✗ Ineffective. (Initial evidence mixed; subsequent meta-analysis showed inefficacy.[11])			Ineffective in preventing infection & ↑harms;[11] no clinical benefit in hospitalized patients.[12]
Ivermectin	✗ Ineffective. (Initial positive RCT data was fabricated;[48] subsequent showed inefficacy.[13, COVID-OUT])			Failed to prevent COVD-19 hospitalization when given within 7 days of symptom onset.[13]

Other agents (not routinely available in SK): casirivimab-imdevimab, bamlanivimab-etesevimab, regdanvimab, high-titer convalescent plasma. **Vitamin D**:[27,28] inconsistent benefit in hospitalized patients.[64,66]

*Note: real-world **NNT**s will vary based on patient risk level, current COVID-19 wave, variant, etc.*

COVID-19 Online Extras

Acknowledgements: Written by Alex Crawley, Marlys LeBras, and Loren Regier. Thanks to our reviewers: the SHA COVID-19 Therapeutic Expert Group (TEG), Marc Legge, Sachin Duggal, Trish Rawn, Christina DeLonghi, Satchan Takaya, Carmen Bell, Kelsey Boechler, Stephen Lee, Shanna Fenton, Janice Norfield.
Disclosures: No conflicts of interest are reported by Alex Crawley, Marlys LeBras, or Loren Regier.

Table 4. Useful Links and Resources

Guidelines & Reviews	Clinical Tools
NIH COVID-19 Guidelines **IDSA** COVID-19 Guidelines **WHO** COVD-19 Guidelines **Saskatchewan** COVID-19 Outpatient Treatment Guidelines **Medical Letter** COVID-19 Treatments and COVID-19 Vaccines **Pharmacist Letter** COVID-19 Treatments and COVID-19 Vaccines **UpToDate** COVID-19 Review **British Columbia** COVID-19 Treatments **Ontario Science Table** Nirmatrelvir/Ritonavir (Paxlovid) Briefing	**medSask Paxlovid Center:** immunocompromising medications, prescriber assessment tool (prescription), paxlovid patient handout **SHA Outpatient** COVID-19 management **Drug Interactions checkers**: Liverpool, medSask, BC CTC, Ontario Science Table, IDSA Drug Interaction Guidance **Sask Paxlovid Dispensing +/- Prescribing** Pharmacies **medSask COVID-19 vaccine** doses, eligibility, and intervals **Health Canada** COVID Vaccines Components **Health Canada** Approved COVID-19 Therapies in Canada **Centre for Effective Practice** COVID-19 Resource Centre **Sask Health** Vaccine Clinics in Saskatchewan [or call 1-833-727-5829] **Sask Health** Vaccine Comparison Chart **Health Canada** Where to Book a Vaccine Appointment **Waterloo**: Tips to Avoid Shoulder Injury Related to Vaccine Administration **ACFP**: COVID Tools for Practice

Table 5. Adverse Events with COVID-19 Vaccines: Additional Information.

Myocarditis with mRNA vaccines	VITT (Vaccine-Induced Immune Thrombotic Thrombocytopenia) with adenoviral vector vaccines	Guillain-Barré syndrome (GBS) with adenoviral vector vaccines
• Most common in young adult males. For example, with a second mRNA dose: ➜ up to 69 cases per million in males 12-17yrs.[22] ➜ up to 4 cases per million in males >30yrs.[22] ➜ up to 4 cases per million in males 5-11yrs.[49] • Ask patients to monitor for new chest pain, shortness of breath, or palpitations. • Myocarditis cases are usually mild, with onset <1 week after vaccine. The vast majority of cases resolve after supportive care in a hospital setting. • Myocarditis risk is greater with a COVID-19 **infection** than a vaccine (1500 cases per million patients).[23] • Myocarditis risk may be greater with **SPIKEVAX** than **COMIRNATY** (one analysis suggested a ~5x higher risk with **SPIKEVAX**).[26]	• Most common in adult females (e.g. 3.8 cases per million doses of Janssen vaccine in general population vs up to 10.6 cases per million in females 30-49yrs).[24] • Ask patients to monitor for signs and symptoms: e.g. new petechiae or bruising, shortness of breath, chest pain, lower extremity edema, abdominal pain, unabating severe headache, severe backache, new focal neurologic symptoms, seizures. • Fatal in up to 20% of cases. Onset typically within 2 weeks of vaccine. • Some evidence that mRNA vaccines are safe in patients who have previously experienced VITT.[62]	• In reports, median age of 56 years, 13 days after Janssen vaccination. Fatal in <1% of cases. Overall rate of 9.8 cases per million doses (4x background rate).[25] • Ask patients to monitor for tingling in extremities; weakness; difficulty with facial movements, breathing, or swallowing. • Causal relationship not yet established. Of note, other vaccines (e.g. for influenza) have previously been associated with GBS.[31]

References for COVID-19 Chart

1. NIH Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available from https://www.COVID19treatmentguidelines.nih.gov/ . Accessed May 16, 2022.
2. NICE COVID-19 Rapid Guideline. Available from https://www.nice.org.uk/guidance/ng191 . Accessed May 16, 2022.
3. IDSA. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Available from http://www.idsociety.org/COVID19guidelines. Last updated March 23, 2022.
4. **PINETREE**. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, Oguchi G, Ryan P, Nielsen BU, Brown M, Hidalgo A. Early remdesivir to prevent progression to severe COVID-19 in outpatients. New England Journal of Medicine. 2022 Jan 27;386(4):305-15.
5. **COMET-ICE**. Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, Sarkis E, Solis J, Zheng H, Scott N, Cathcart AL. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. New England Journal of Medicine. 2021 Nov 18;385(21):1941-50.
6. **PROVENT**. Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, Yuan Y, Seegobin S, Ellery A, Levinson DJ, Ambery P. Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of COVID-19. New England Journal of Medicine. 2022 Apr 20.
7. Beb monograph: https://www.fda.gov/media/156152/download
8. Evusheld monograph: https://COVID-vaccine.canada.ca/info/pdf/evusheld-pm-en.pdf
9. Orders M. An EUA for Bebtelovimab for Treatment of COVID-19. Med Lett Drugs Ther. 2022 Mar 21;64(1646):41-2.
10. **MOVe-OUT**. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martín-Quirós A, Caraco Y, Williams-Diaz A, Brown ML, Du J. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. New England Journal of Medicine. 2022 Feb 10;386(6):509-20.
11. Bartoszko JJ, Siemieniuk RA, Kum E, Qasim A, Zeraatkar D, Ge L, Han MA, Sadeghirad B, Agarwal A, Agoritsas T, Chu DK. Prophylaxis against COVID-19: living systematic review and network meta-analysis. bmj. 2021 Apr 26;373.
12. RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with COVID-19. New England Journal of Medicine. 2020 Nov 19;383(21):2030-40.
13. Reis G, Silva EA, Silva DC, Thabane L, Milagres AC, Ferreira TS, Dos Santos CV, Campos VH, Nogueira AM, de Almeida AP, Callegari ED. Effect of early treatment with ivermectin among patients with COVID-19. New England Journal of Medicine. 2022 Mar 30.
14. **EPIC-HR**. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, Baniecki M, Hendrick VM, Damle B, Simón-Campos A, Pypstra R. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. New England Journal of Medicine. 2022 Apr 14;386(15):1397-408.
15. **TOGETHER**. Reis G, dos Santos Moreira-Silva EA, Silva DC, Thabane L, Milagres AC, Ferreira TS, Dos Santos CV, de Souza Campos VH, Nogueira AM, de Almeida AP, Callegari ED. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. The Lancet Global Health. 2022 Jan 1;10(1):e42-51.
16. Medical Letter. Treatments Considered for COVID-19. Available from https://secure.medicalletter.org/downloads/1595e_table.pdf. Accessed May 16, 2022.
17. Moe SS, Allan GM, Train A. Budesonide bests COVID-19. Canadian Family Physician. 2022 May 1;68(5):355-.
18. **COLCORONA**. Tardif JC, Bouabdallaoui N, L'Allier PL, Gaudet D, Shah B, Pillinger MH, Lopez-Sendon J, da Luz P, Verret L, Audet S, Dupuis J. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. The Lancet Respiratory Medicine. 2021 Aug 1;9(8):924-32.
19. **PRINCIPLE**. Yu LM, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, Van Hecke O, Ogburn E, Evans PH, Thomas NP, Patel MG. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. The Lancet. 2021 Sep 4;398(10303):843-55.
20. **STOIC**. Ramakrishnan S, Nicolau Jr DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, Krassowska K, Fox R, Binnian I, Glover V, Bright S. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. The Lancet Respiratory Medicine. 2021 Jul 1;9(7):763-72.
21. Rosenblum HG, Gee J, Liu R, Marquez PL, Zhang B, Strid P, Abara WE, McNeil MM, Myers TR, Hause AM, Su JR. Safety of mRNA vaccines administered during the initial 6 months of the US COVID-19 vaccination programme: an observational study of reports to the Vaccine Adverse Event Reporting System and v-safe. The Lancet Infectious Diseases. 2022 Mar 7.
22. Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, Broder KR, Gee J, Weintraub E, Shimabukuro T, Scobie HM. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices—United States, June 2021. Morbidity and Mortality Weekly Report. 2021 Jul 7;70(27):977. Available from https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm#T2_down
23. Boehmer TK, Kompaniyets L, Lavery AM, et al. Association Between COVID-19 and Myocarditis Using Hospital-Based Administrative Data — United States, March 2020-January 2021. MMWR Morb Mortal Wkly Rep. 2021;70(35):1228–1232. doi: 10.15585/mmwr.mm7035e5.
24. Updates on Thrombosis with Thrombocytopenia Syndrome (TTS). ACIP Meeting December 16, 2021. Available from https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-12-16/02-COVID-See-508.pdf
25. Woo EJ, Mba-Jonas A, Dimova RB, Alimchandani M, Zinderman CE, Nair N. Association of receipt of the Ad26. COV2. S COVID-19 vaccine with presumptive Guillain-Barré syndrome, February-July 2021. Jama. 2021 Oct 26;326(16):1606-13.
26. Abraham N, Spruin S, Rossi T, Fireman B, Zafack J, Blaser C, Shaw A, Hutchings K, Ogunnaike-Cooke S. Myocarditis and/or pericarditis risk after mRNA COVID-19 vaccination: a Canadian head to head comparison of BNT162b2 and mRNA-1273 vaccines. Vaccine. 2022 May 25.
27. De Smet D, De Smet K, Herroelen P, Gryspeerdt S, Martens GA. Serum 25 (OH) D level on hospital admission associated with COVID-19 stage and mortality. American journal of clinical pathology. 2021 Mar;155(3):381-8.
28. Hosseini B, El Abd A, Ducharme FM. Effects of Vitamin D Supplementation on COVID-19 Related Outcomes: A Systematic Review and Meta-Analysis. Nutrients. 2022 Jan;14(10):2134.
29. CDC. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. Available from https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html
30. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, Felix SE, Tie Y, Fullerton KE. Coronavirus disease 2019 case surveillance—United States, january 22–may 30, 2020. Morbidity and Mortality Weekly Report. 2020 Jun 6;69(24):759.

31. CDC. Guillain-Barré Syndrome and Vaccines. Available from https://www.cdc.gov/vaccinesafety/concerns/guillain-barre-syndrome.html
32. medSask. Evusheld (tixagevimab and cilgavimab) for Pre-Exposure Prophylaxis Clinical Practice Guideline. Available from https://medsask.usask.ca/documents/COVID-documents/evusheld-cpg.pdf
33. Najjar-Debbiny R, Gronich N, Weber G, Khoury J, Amar M, Stein N, Goldstein LH, Saliba W. Effectiveness of Paxlovid in Reducing Severe COVID-19 and Mortality in High Risk Patients. Clinical Infectious Diseases. 2022.
34. Young-Xu Y, Epstein L, Marconi VC, Davey V, Zwain G, Smith J, Korves C, Cunningham F, Bonomo R, Ginde AA. Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data. medRxiv. 2022 Jan 1.
35. Arbel R, Sagy YW, Hoshen M, Battat E, Lavie G, Sergienko R, Friger M, Peretz A, Yaron S, Serby D, Hammerman A. Oral Nirmatrelvir and Severe Covid-19 Outcomes During the Omicron Surge.
36. Accorsi EK, Britton A, Shang N, Fleming-Dutra KE, Link-Gelles R, Smith ZR, Derado G, Miller J, Schrag SJ, Verani JR. Effectiveness of Homologous and Heterologous COVID-19 Boosters against Omicron. New England Journal of Medicine. 2022 May 25.
37. Tenforde MW, Self WH, Gaglani M, Ginde AA, Douin DJ, Talbot HK, Casey JD, Mohr NM, Zepeski A, McNeal T, Ghamande S. Effectiveness of mRNA Vaccination in Preventing COVID-19–Associated Invasive Mechanical Ventilation and Death—United States, March 2021–January 2022. Morbidity and Mortality Weekly Report. 2022 Mar 25;71(12):459.
38. Lauring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, McNeal T, Ghamande S, Douin DJ, Talbot HK, Casey JD, Mohr NM. Clinical severity of, and effectiveness of mRNA vaccines against, COVID-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. bmj. 2022 Mar 9;376.
39. a. Magen O, Waxman JG, Makov-Assif M, Vered R, Dicker D, Hernán MA, Lipsitch M, Reis BY, Balicer RD, Dagan N. Fourth dose of BNT162b2 mRNA COVID-19 vaccine in a nationwide setting. New England Journal of Medicine. 2022 Apr 28;386(17):1603-14. This study compared 4 doses of the Pfizer vaccine to 3 doses of the Pfizer vaccine. For our Table 2, the rates of 45%, 68%, and 74% were applied to the "vaccinated + 1 booster" row in order to compare to an unvaccinated population.
b. A booster is your best shot now. Topol, E. Available from https://erictopol.substack.com/p/a-booster-is-your-best-shot-now. Data consistently show two vaccine booster doses having greater efficacy than one vaccine booster dose.
c. McConeghy KW. Effectiveness of a Second COVID-19 Vaccine Booster Dose Against Infection, Hospitalization, or Death Among Nursing Home Residents—19 States, March 29–July 25, 2022. MMWR. Morbidity and Mortality Weekly Report. 2022;71. In this study a second booster dose dramatically reduced the risk of death compared to a single booster dose in nursing home residents.
40. NACI 2021 Rapid Response. Updated recommendation on the use of authorized COVID-19 vaccines in individuals aged 12 years and older in the context of myocarditis and pericarditis reported following mRNA COVID-19 vaccination. Available from https://www.canada.ca/content/dam/phac-aspc/documents/services/immunization/national-advisory-committee-on-immunization-naci/rapid-response-recommendation-use-COVID-19-vaccines-individuals-aged-12-years-older-myocarditis-pericarditis-reported-following-mrna-vaccines/summary.pdf
41. NACI 2022 Advisory Committee Statement. Initial guidance on a second booster dose of COVID-19 vaccines in Canada. Available from https://www.canada.ca/content/dam/phac-aspc/documents/services/immunization/national-advisory-committee-on-immunization-naci/naci-guidance-second-booster-dose-COVID-19-vaccines.pdf
42. Discovery Health releases at-scale real-world analysis of Omicron outbreak; including collaboration with the SA Medical Research Council (SAMRC) to analyse vaccine effectiveness. Available from https://www.discovery.co.za/corporate/health-insights-omicron-outbreak-analysis
43. Tools for Practice #259. Unmasking the evidence around masks for healthcare workers. Available from https://gomainpro.ca/wp-content/uploads/tools-for-practice/1587394057_tfp259COVIDmasksfv.pdf
44. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ, El-Harakeh A, Bognanni A, Lotfi T, Loeb M, Hajizadeh A. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. The Lancet. 2020 Jun 27;395(10242):1973-87.
45. **TACKLE**. Montgomery H, Hobbs FR, Padilla F, Arbetter D, Templeton A, Seegobin S, Kim K, Campos JA, Arends RH, Brodek BH, Brooks D. Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Respiratory Medicine. 2022 Jun 7.
46. NACI 2022 Interim Guidance. Interim guidance on planning considerations for a fall 2022 COVID-19 vaccine booster program in Canada. Available from https://www.canada.ca/content/dam/phac-aspc/documents/services/immunization/national-advisory-committee-on-immunization-naci/naci-summary-june-29-2022.pdf
47. Estimated COVID-19 risk if diagnosed in the United States. The Economist. Available from https://www.economist.com/graphic-detail/COVID-pandemic-mortality-risk-estimator
48. The Guardian. "Huge study supporting ivermectin as COVID treatment withdrawn over ethical concerns." Available from https://www.theguardian.com/science/2021/jul/16/huge-study-supporting-ivermectin-as-COVID-treatment-withdrawn-over-ethical-concerns
49. Su JR. COVID-19 vaccine safety updates: Primary series in children and adolescents ages 5–11 and 12–15 years, and booster doses in adolescents ages 16–24 years. Centers for Disease Control and Prevention Advisory Committee on Immunization Practices Meeting January 5, 2022.
50. Huang YZ, Kuan CC. Vaccination to reduce severe COVID-19 and mortality in COVID-19 patients: A systematic review and meta-analysis. Eur. Rev. Med. Pharmacol. Sci. 2022 Mar 1;26:1770-6.
51. a. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Impact of vaccination on post-acute COVID-19 syndrome (PACS) – what we know so far. Toronto, ON: Queen's Printer for Ontario; 2022. Available from https://www.publichealthontario.ca/-/media/Documents/nCoV/COVID-WWKSF/2022/04/impact-vaccination-post-acute-COVID-19-syndrome.pdf?sc_lang=en
b. Notarte KI, Catahay JA, Velasco JV, Pastrana A, Ver AT, Pangilinan FC, Peligro PJ, Casimiro M, Guerrero JJ, Gellaco MM, Lippi G. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review. EClinicalMedicine. 2022 Nov 1;53:101624.
52. a. Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, Rostad CA, Martin JM, Johnston C, Rupp RE, Mulligan MJ. Homologous and heterologous COVID-19 booster vaccinations. New England Journal of Medicine. 2022 Mar 17;386(11):1046-57.
b. Rashedi R, Samieefar N, Masoumi N, Mohseni S, Rezaei N. COVID-19 vaccines mix-and-match: The concept, the efficacy and the doubts. *J Med Virol*. 2022;94(4):1294-1299. doi:10.1002/jmv.27463
c. Bánki Z, Mateus J, Rössler A, Schäfer H, Bante D, Riepler L, Grifoni A, Sette A, Simon V, Falkensammer B, Ulmer H. Heterologous ChAdOx1/BNT162b2 vaccination induces stronger immune response than homologous ChAdOx1 vaccination: The pragmatic, multi-center, three-arm, partially randomized HEVACC trial. EBioMedicine. 2022 Jun 1;80:104073.
d. Heinzel A, Schretzenmeier E, Regele F, Hu K, Raab L, Eder M, Aigner C, Jabbour R, Aschauer C, Stefanski AL, Dörner T. Three-Month Follow-Up of Heterologous vs. Homologous Third SARS-CoV-2 Vaccination in Kidney Transplant Recipients: Secondary Analysis of a Randomized Controlled Trial. Frontiers in medicine. 2022;9.
53. FDA authorizes revisions to Evusheld dosing. Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-revisions-evusheld-dosing
54. NACI COVID-19 Canadian Immunization Guide. Available from https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-26-covid-19-vaccine.html#t2

55. World Health Organization. Therapeutics and COVID-19: living guideline. Version 11.0. Section 6.2: Fluvoxamine for patients with non-severe COVID-19 (published July 14, 2022). (accessed July 21, 2022). Available from https://app.magicapp.org/#/guideline/nBkO1E/rec/EgOQwE
56.
57. Patel R, Kaki M, Potluri VS, Kahar P, Khanna D. A comprehensive review of SARS-CoV-2 vaccines: Pfizer, moderna & Johnson & Johnson. Human Vaccines & Immunotherapeutics. 2022 Jan 31;18(1):2002083.
58. Health Canada. Reported side effects following COVID-19 vaccination in Canada. Accessed August 3, 2022 from https://health-infobase.canada.ca/covid-19/vaccine-safety/#a1
59. Andrejko KL, Pry JM, Myers JF, Fukui N, DeGuzman JL, Openshaw J, Watt JP, Lewnard JA, Jain S, COVID C, COVID C. Effectiveness of face mask or respirator use in indoor public settings for prevention of SARS-CoV-2 infection—California, February–December 2021. Morbidity and Mortality Weekly Report. 2022 Feb 11;71(6):212.
60. **RECOVERY**. Group RC. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet Respiratory Medicine. 2021 Dec 1;9(12):1419-26.
61. BC Covid Therapeutics Committee. Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19. Accessed August 15, 2022 from http://www.bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/ClinicalPracticeGuide_Therapeutics_MildModerateCOVID.pdf
62. Schönborn L, Seck SE, Thiele T, Warkentin TE, Greinacher A. SARS-CoV-2 Infection in Patients with a History of VITT. N Engl J Med. 2022 Jun 27. doi: 10.1056/NEJMc2206601. Epub ahead of print. PMID: 35759529.
63. Arbel R et al D. Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge. N Engl J Med. 2022 Sep 1;387(9):790-798.
64. Murai IH, Fernandes AL, Sales LP, 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 Mar 16;325(11):1053-1060.
65. Bramante CT, et al. **COVID-OUT** Trial Team. Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19. N Engl J Med. 2022 Aug 18;387(7):599-610.
66. De Niet S, et al. Positive Effects of Vitamin D Supplementation in Patients Hospitalized for COVID-19: A Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients. 2022 Jul 26;14(15):3048.
67. Reis_S, et al. Nirmatrelvir combined with ritonavir for preventing and treating COVID-19. Cochrane Database of Systematic Reviews 2022, Issue 9. Art. No.: CD015395. DOI:10.1002/14651858.CD015395.pub2.
68. Health Canada: EVUSHELD (tixagevimab and cilgavimab for injection) - Risk of Prophylaxis or Treatment Failure due to Antiviral Resistance - Canada.ca. Accessed Oct 27, 2022.
69. Jolliffe D A, Holt H, Greenig M, Talaei M, Perdek N, Pfeffer P et al. Effect of a test-and-treat approach to vitamin D supplementation on risk of all cause acute respiratory tract infection and covid-19: phase 3 randomised controlled trial (**CORONAVIT**) BMJ 2022; 378 :e071230 doi:10.1136/bmj-2022-071230.
70. FDA. FDA authorizes revisions to Evusheld dosing. June 29, 2022. Available at: https://bit.ly/3K5AcNc.
71. COVID-19 Supplemental Clinical Guidance #4: Nirmatrelvir/Ritonavir (Paxlovid) Use in Patients With Advanced Chronic Kidney Disease and Patients on Dialysis with COVID19. Accessed Nov 7, 2022. https://www.ontariohealth.ca/sites/ontariohealth/files/2022-04/PaxlovidClinicalGuide.pdf