COVID-19 Literature Review
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1. There is decreased vaccine protection of AstraZeneca against COVID-19 3 months after 2nd jab is given.
2. Thromboprophylaxis with Xarelto for 35 days decreased risk of symptomatic or fatal VTE from 9% to 3% after COVID hospitalization
3. Early treatment with Molnupiravir reduced the risk of hospitalization or death in at-risk, unvaccinated adults with Covid-19 from 9.7% to 6.8%
4. Novavax new 2-dose vaccine had 90% efficacy in general, 100% efficacy for moderate to severe disease against COVID19
5. In hospitalized hypoxic COVID-19 patients, Methylprednisolone had better results compared to Dexamethasone
6. Vaccination was associated with a smaller reduction in transmission of the delta variant compared to Alpha, and reductions in transmission of Delta declined overtime becoming similar to unvaccinated individuals at 12 weeks.
7. Neutralization efficiency of 2 doses of mRNA vaccine at 5 months is low for Alpha and Delta variants, and there is NO neutralization efficiency against Omicron. after 3rd jab, neutralization increases, however, against Omicron it is still lower than neutralization against Delta by a factor of 4. Durability of effect after 3rd jab is still to be determined.
8. Two doses of mRNA vaccine demonstrated 70% effectiveness against COVID hospitalization compared to 93% compared to other variants.
    1. It is important not to confuse viral neutralization (#7) vs clinical effectiveness against hospitalization (#8) - especially since we are learning that Omicron may indeed cause less severe disease but at higher numbers.
9. Among non-hospitalized patients who were at high risk for Covid-19 progression, a 3-day course of Remdesivir resulted in an 87% lower risk of hospitalization or death than placebo from 5/3% decreased to 0.7%
10. 8.7 million doses of mRNA vaccine have been administered to 5-12 year old with serious adverse events rarely reported
11. Protection afforded by prior infection in preventing symptomatic reinfection with Alpha, Beta, or Delta is robust, at about 90% but decreases to 56% with Omicron. Prior-infection protection against hospitalization or death at reinfection appears robust, regardless of variant
12. A different pattern of characteristics and outcomes is noted in patients hospitalized with Omicron in South Africa, compared to previous variants.
    1. Younger patients
    2. Fewer comorbidities
    3. Fewer hospitalizations and respiratory diagnoses
    4. Decrease in severity and mortality
13. Neither Sotrovimab nor BRII-196 plus BRII-198 (monoclonal Antibody infusion) showed efficacy for improving clinical outcomes among adults hospitalized with COVID-19

LANCET - 12/20/2021 - AstraZeneca protection after 2 doses.	• 1 972 454 adults received two doses of ChAdOx1 nCoV-19 in Scotland and 42 558 839 in Brazil, with longer follow-up in Scotland because two-dose vaccination began earlier in Scotland than in Brazil. • In Scotland, RRs for severe COVID-19 increased to 2·01 (95% CI 1·54–2·62) at 10–11 weeks, 3·01 (2·26–3·99) at 14–15 weeks, and 5·43 (4·00–7·38) at 18–19 weeks after the second dose. The pattern of results was similar in Brazil, with RRs of 2·29 (2·01–2·61) at 10–11 weeks, 3·10 (2·63–3·64) at 14–15 weeks, and 4·71 (3·83–5·78) at 18–19 weeks after the second dose. • In Scotland, vaccine effectiveness decreased from 83·7% (95% CI 79·7–87·0) at 2–3 weeks, to 75·9% (72·9–78·6) at 14–15 weeks, and 63·7% (59·6–67·4) at 18–19 weeks after the second dose. • In Brazil, vaccine effectiveness decreased from 86·4% (85·4–87·3) at 2–3 weeks, to 59·7% (54·6–64·2) at 14–15 weeks, and 42·2% (32·4–50·6) at 18–19 weeks

	• vaccine protection of AstraZeneca against COVID-19 hospital admissions and deaths in both Scotland and Brazil decreases with time, becoming evident within three months of the second vaccine dose • https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02754-9/fulltext
LANCET - 12/16/2021 - Xarelto prophylaxis after COVID 19 hospitalization	• From Oct 8, 2020, to June 29, 2021, 997 patients were screened. Of these patients, 677 did not meet eligibility criteria; the remaining 320 patients were enrolled and randomly assigned to receive Rivaroxaban (n=160 [50%]) or no anticoagulation (n=160 [50%]). • All patients received thromboprophylaxis with standard doses of heparin during hospitalization. • 165 (52%) patients were in the intensive care unit while hospitalized. 197 (62%) patients had an IMPROVE score of 2–3 and elevated D-dimer levels and 121 (38%) had a score of 4 or more. Two patients (one in each group) were lost to follow-up due to withdrawal of consent and not included in the intention-to-treat primary analysis. • The primary efficacy outcome occurred in five (3%) of 159 patients assigned to Rivaroxaban and 15 (9%) of 159 patients assigned to no anticoagulation (relative risk 0·33, 95% CI 0·12–0·90; p=0·0293). No major bleeding occurred in either study group. Allergic reactions occurred in two (1%) patients in the Rivaroxaban group • In patients at high risk discharged after hospitalization due to COVID-19, thromboprophylaxis with Rivaroxaban 10 mg/day for 35 days improved clinical outcomes compared with no extended thromboprophylaxis • https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02392-8/fulltext
NEJM - 12/16/2021 - Molnupiravir for oral Treatment of non-hospitalized COVID pts.	• A total of 1433 participants underwent randomization; 716 were assigned to receive Molnupiravir and 717 to receive placebo. With the exception of an imbalance in sex, baseline characteristics were similar in the two groups. • The superiority of Molnupiravir was demonstrated at the interim analysis; the risk of hospitalization for any cause or death through day 29 was **lower with Molnupiravir (28 of 385 participants [7.3%]) than with placebo (53 of 377 [14.1%])** (difference, −6.8 percentage points; 95% confidence interval, −11.3 to −2.4; P=0.001). • In the analysis of all participants who had undergone randomization, the percentage of participants who were hospitalized or died through day 29 was lower in the Molnupiravir group than in the placebo group (**6.8%** [48 of 709] vs. **9.7%** [68 of 699]; difference, −3.0 percentage points; 95% confidence interval, −5.9 to −0.1). Results of subgroup analyses were largely consistent with these overall results; in some subgroups, such as patients with evidence of previous SARS-CoV-2 infection, those with low baseline viral load, and those with diabetes, the point estimate for the difference favored placebo. One death was reported in the Molnupiravir group and 9 were reported in the placebo group through day 29. Adverse events were reported in 216 of 710 participants (30.4%) in the Molnupiravir group and 231 of 701 (33.0%) in the placebo group. • Early treatment with Molnupiravir reduced the risk of hospitalization or death in at-risk, unvaccinated adults with Covid-19 • https://www.nejm.org/doi/full/10.1056/NEJMoa2116044?query=featured_coronavirus
NEJM - 12/15/2021 - Novavax adjuvant recombinant spike protein nanoparticle vaccine efficacy and safety	• Of the 29,949 participants who underwent randomization between December 27, 2020, and February 18, 2021, a total of 29,582 (median age, 47 years; 12.6% ≥65 years of age) received at least one dose: 19,714 received vaccine and 9868 placebo. • Over a period of 3 months, 77 cases of Covid-19 were noted — 14 among vaccine recipients and 63 among placebo recipients (**vaccine efficacy, 90.4%**; 95% confidence interval [CI], 82.9 to 94.6; P<0.001). Ten moderate and 4 severe cases occurred, all in placebo recipients, yielding **vaccine efficacy against moderate-to-severe disease of 100%** (95% CI, 87.0 to 100). Most sequenced viral genomes (48 of 61, 79%) were variants of concern or interest — largely B.1.1.7 (alpha) (31 of the 35 genomes for

	variants of concern, 89%). Vaccine efficacy against any variant of concern or interest was 92.6% (95% CI, 83.6 to 96.7). • Reactogenicity was mostly mild to moderate and transient but was more frequent among NVX-CoV2373 recipients than among placebo recipients and was more frequent after the second dose than after the first dose • Novavax vaccine had 90% efficacy in general, 100% efficacy for moderate to severe disease. • https://www.nejm.org/doi/full/10.1056/NEJMoa2116185?query=featured_coronavirus
BMC ID - 4/2021 - methylprednisolone vs dexamethasone	• There were no significant differences between the groups on admission. However, the • intervention group demonstrated significantly better clinical status compared to the control group at day 5 (4.02 vs. 5.21, $p = 0.002$) and day 10 (2.90 vs. 4.71, $p = 0.001$) of admission. There was also a significant difference in the overall mean score between the intervention group and the control group, (3.909 vs. 4.873 respectively, $p = 0.004$). The mean length of hospital stay was 7.43 ± 3.64 and 10.52 ± 5.47 days in the intervention and control groups, respectively ($p = 0.015$). • The need for a ventilator was significantly lower in the intervention group than in the control group (18.2% vs 38.1% $p = 0.040$) • In hospitalized hypoxic COVID-19 patients, methylprednisolone demonstrated better results compared to dexamethasone • https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-021-06045-3
NEJM - 1/5/2022 - vaccination and effects on delta transmission	• Among 146,243 tested contacts of 108,498 index patients, 54,667 (37%) had positive SARS-CoV-2 polymerase-chain-reaction (PCR) tests. • In vaccinated index patients who became infected with the alpha variant, two vaccinations with either BNT162b2 or ChAdOx1 nCoV-19 (also known as AZD1222), as compared with no vaccination, were independently associated with reduced PCR positivity in contacts (adjusted rate ratio with BNT162b2, 0.32; 95% confidence interval [CI], 0.21 to 0.48; and with ChAdOx1 nCoV-19, 0.48; 95% CI, 0.30 to 0.78). • Vaccine-associated reductions in transmission of the delta variant were smaller than those with the alpha variant, and reductions in transmission of the delta variant after two BNT162b2 vaccinations were greater (adjusted rate ratio for the comparison with no vaccination, 0.50; 95% CI, 0.39 to 0.65) than after two ChAdOx1 vaccinations (adjusted rate ratio, 0.76; 95% CI, 0.70 to 0.82). Variation in cycle-threshold (Ct) values (indicative of viral load) in index patients explained 7 to 23% of vaccine-associated reductions in transmission of the two variants. • The reductions in transmission of the delta variant declined over time after the second vaccination, reaching levels that were similar to those in unvaccinated persons by 12 weeks in index patients who had received ChAdOx1 nCoV-19 and attenuating substantially in those who had received BNT162b2. Protection in contacts also declined in the 3-month period after the second vaccination • Vaccination was associated with a smaller reduction in transmission of the delta variant than of the alpha variant, and the effects of vaccination decreased over time • https://www.nejm.org/doi/full/10.1056/NEJMoa2116597?query=featured_coronavirus
NEJM - 12/29/2022 - neutralization of Omicron after third dose of mRNA vaccine.	• We analyzed the neutralization efficiency of the BNT162b2 vaccine against wild-type SARS-CoV-2 and the beta, delta, and omicron variants of concern. Limitations of the study include the small cohort tested and the fact that the test was only an in vitro assay. Nevertheless, • we found l**ow neutralization** efficiency with two doses of the BNT162b2 vaccine against the wild-type virus and the delta variant, assessed more than 5 months after receipt of the second dose, and **no neutralization efficiency against the omicron variant**. • The importance of a third vaccine dose is clear, owing to the higher neutralization efficiency (by a factor of 100) against the omicron variant after the third dose than after the second dose; however, even with three vaccine doses, neutralization against

	the omicron variant was lower (by a factor of 4) than that against the delta variant. The durability of the effect of the third dose of vaccine against Covid-19 is yet to be determined • https://www.nejm.org/doi/full/10.1056/NEJMc2119358?query=featured_coronavirus
NEJM - 12/29/2022 - effectiveness of 2 doses of mRNA vaccine against Omicron	• During the proxy omicron period, we found a vaccine effectiveness of 70% (95% confidence interval [CI], 62 to 76), a finding that was supported by the results of all sensitivity tests. • This measure of vaccine effectiveness was significantly different from that during the comparator period, when the rate was 93% (95% CI, 90 to 94) against hospitalization for Covid-19 • https://www.nejm.org/doi/full/10.1056/NEJMc2119270?query=featured_coronavirus • https://www.nejm.org/doi/full/10.1056/NEJMc2119270?query=featured_coronavirus
NEJM - 12/22/2022 - Early Remdesivir to prevent progression against severe COVID	• A total of 562 patients who underwent randomization and received at least one dose of Remdesivir or placebo were included in the analyses: 279 patients in the Remdesivir group and 283 in the placebo group. The mean age was 50 years, 47.9% of the patients were women, and 41.8% were Hispanic or Latino. The most common coexisting conditions were diabetes mellitus (61.6%), obesity (55.2%), and hypertension (47.7%). • Covid-19–related hospitalization or death from any cause occurred in 2 patients (0.7%) in the Remdesivir group and in 15 (5.3%) in the placebo group (hazard ratio, 0.13; 95% confidence interval [CI], 0.03 to 0.59; **P=0.008**). A total of 4 of 246 patients (1.6%) in the Remdesivir group and 21 of 252 (8.3%) in the placebo group had a Covid-19–related medically attended visit by day 28 (hazard ratio, 0.19; 95% CI, 0.07 to 0.56). No patients had died by day 28. Adverse events occurred in 42.3% of the patients in the Remdesivir group and in 46.3% of those in the placebo group • Among non-hospitalized patients who were at high risk for Covid-19 progression, a 3-day course of Remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death than placebo • https://www.nejm.org/doi/full/10.1056/NEJMoa2116846?query=featured_coronavirus
CDC - 12/31/2021 - Vaccine safety in 5-12 year olds	• After authorization of Pfizer-BioNTech COVID-19 vaccine for children aged 5–11 years during October 2021, and administration of approximately 8 million doses, local and systemic reactions after vaccination were commonly reported to VAERS and v-safe for vaccinated children aged 5–11 years. Serious adverse events were rarely reported • https://www.cdc.gov/mmwr/volumes/70/wr/mm705152a1.htm?s_cid=mm705152a1_x
MedRxIV - 1/6/2022 - protection from prior infection without vaccination against Omicron	• prior infection in preventing reinfection (PES) against symptomatic reinfection was estimated at • 90.2% (95% CI: 60.2-97.6) for Alpha, • 84.8% (95% CI: 74.5-91.0) for Beta, • 92.0% (95% CI: 87.9-94.7) for Delta, and • **56.0%** (95% CI: 50.6-60.9) for **Omicron**. Only 1 Alpha, 2 Beta, 0 Delta, and 2 Omicron reinfections progressed to severe COVID-19. None progressed to critical or fatal COVID-19. PES against hospitalization or death due to reinfection was estimated at 69.4% (95% CI: -143.6-96.2) for Alpha, 88.0% (95% CI: 50.7-97.1) for Beta, 100% (95% CI: 43.3-99.8) for Delta, and 87.8% (95% CI: 47.5-97.1) for Omicron. • CONCLUSIONS: Protection afforded by prior infection in preventing symptomatic reinfection with Alpha, Beta, or Delta is robust, at about 90%. While such protection against reinfection with Omicron is lower, it is still considerable at nearly 60%. • Prior-infection protection against hospitalization or death at reinfection appears robust, regardless of variant • https://www.medrxiv.org/content/10.1101/2022.01.05.22268782v1
JAMA - 12/30/2022 - characteristics of hospitalized pts	• The number of patients treated in the hospitals during the same early period of each wave differed (2351 in wave 4 vs maximum 6342 in wave 3); however,

with Omicron in South Africa	• 68% to 69% of patients presenting to the emergency department with a positive COVID-19 result were admitted to the hospital in the first 3 waves vs 41.3% in wave 4 (Table 1).
	• Patients hospitalized during wave 4 were younger (median age, 36 years vs maximum 59 years in wave 3; *P* < .001) with a higher proportion of females. Significantly fewer patients with comorbidities were admitted in wave 4, and the proportion presenting with an acute respiratory condition was lower (31.6% in wave 4 vs maximum 91.2% in wave 3, *P* < .001).
	• Of 971 patients admitted in wave 4,
	  ○ 24.2% were vaccinated,
	  ○ 66.4% were unvaccinated, and vaccination status was unknown for 9.4%.
	• The proportion of patients requiring oxygen therapy significantly decreased (
	  ○ 17.6% in wave 4 vs
	  ○ 74% in wave 3, *P* < .001) as did the percentage receiving mechanical ventilation (Table 2).
	• Admission to intensive care was
	  ○ 18.5% in wave 4 vs
	  ○ 29.9% in wave 3 (*P* < .001).
	• The median LOS (between 7 and 8 days in previous waves)
	  ○ decreased to 3 days in wave 4.
	• The death rate was between
	  ○ 19.7% in wave 1 and
	  ○ 29.1% in wave 3 and decreased to
	  ○ 2.7% in wave 4
	• different pattern of characteristics and outcomes in patients hospitalized with COVID-19 was observed in the early phase of the fourth wave compared with earlier waves in South Africa, with younger patients having fewer comorbidities, fewer hospitalizations and respiratory diagnoses, and a decrease in severity and mortality
	• https://jamanetwork.com/journals/jama/fullarticle/2787776

JAMA - 12/28/2022 - pulmonary pathogenesis of COVID	• Individuals who died more than 20 days following initial COVID-19 symptoms exhibited high levels of pulmonary fibrosis. Furthermore, several individuals had widespread thrombosis, and each had diffuse alveolar damage—a potentially fatal condition that prevents adequate oxygenation of the blood and ultimately stiffens the lungs, according to the study • https://jamanetwork.com/journals/jama/fullarticle/2787569
Lancet - 12/23/2022 - efficacy and safety of sotrovimab against COVID	• Between Dec 16, 2020, and March 1, 2021, 546 patients were enrolled and • randomly assigned to • sotrovimab (n=184), • BRII-196 plus BRII-198 (n=183), or • placebo (n=179), of whom 536 received part or all of their assigned study drug (sotrovimab n=182, BRII-196 plus BRII-198 n=176, or placebo n=178; median age of 60 years [IQR 50–72], 228 [43%] patients were female and 308 [57%] were male). At this point, • enrolment was halted on the basis of the interim futility analysis. • At day 5, neither the sotrovimab group nor the BRII-196 plus BRII-198 group had significantly higher odds of more favorable outcomes than the placebo group on either the pulmonary scale (adjusted odds ratio sotrovimab 1·07 [95% CI 0·74–1·56]; BRII-196 plus BRII-198 0·98 [95% CI 0·67–1·43]) or the pulmonary-plus complications scale (sotrovimab 1·08 [0·74–1·58]; BRII-196 plus BRII-198 1·00 [0·68–1·46]). By day 90, sustained clinical recovery was seen in 151 (85%) patients in the placebo group compared with 160 (88%) in the sotrovimab group (adjusted rate ratio 1·12 [95% CI 0·91–1·37]) and 155 (88%) in the BRII-196 plus BRII-198 group (1·08 [0·88–1·32]). The composite safety outcome up to day 90 was met by 48 (27%) patients in the placebo

	group, 42 (23%) in the sotrovimab group, and 45 (26%) in the BRII-196 plus BRII-198 group. 13 (7%) patients in the placebo group, 14 (8%) in the sotrovimab group, and 15 (9%) in the BRII-196 plus BRII-198 group died up to day 90 • Neither sotrovimab nor BRII-196 plus BRII-198 showed efficacy for improving clinical outcomes among adults hospitalized with COVID-19 • https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00751-9/fulltext