Good morning and TGIF. In the middle of virtual ID Week so this is a little late.

Today under Covid-19 News, I report on preliminary result of the Pfizer phase 2/3 trial in children ages 5-11. Next, I share the number of pediatric Covid-19 cases in the US. Next the Kaiser Foundation update on their vaccine dashboard. Some positive changes. Finally, the press release on the efficacy of RDV in the outpatient setting.

Under Journal Review the first two are on RDV. The next article confirms the efficacy of MCA in the outpatient arena. The last article explores the maternal-neonatal transfer of SARS CoV-2 IgG antibodies.

Have a wonderful weekend.

Ed

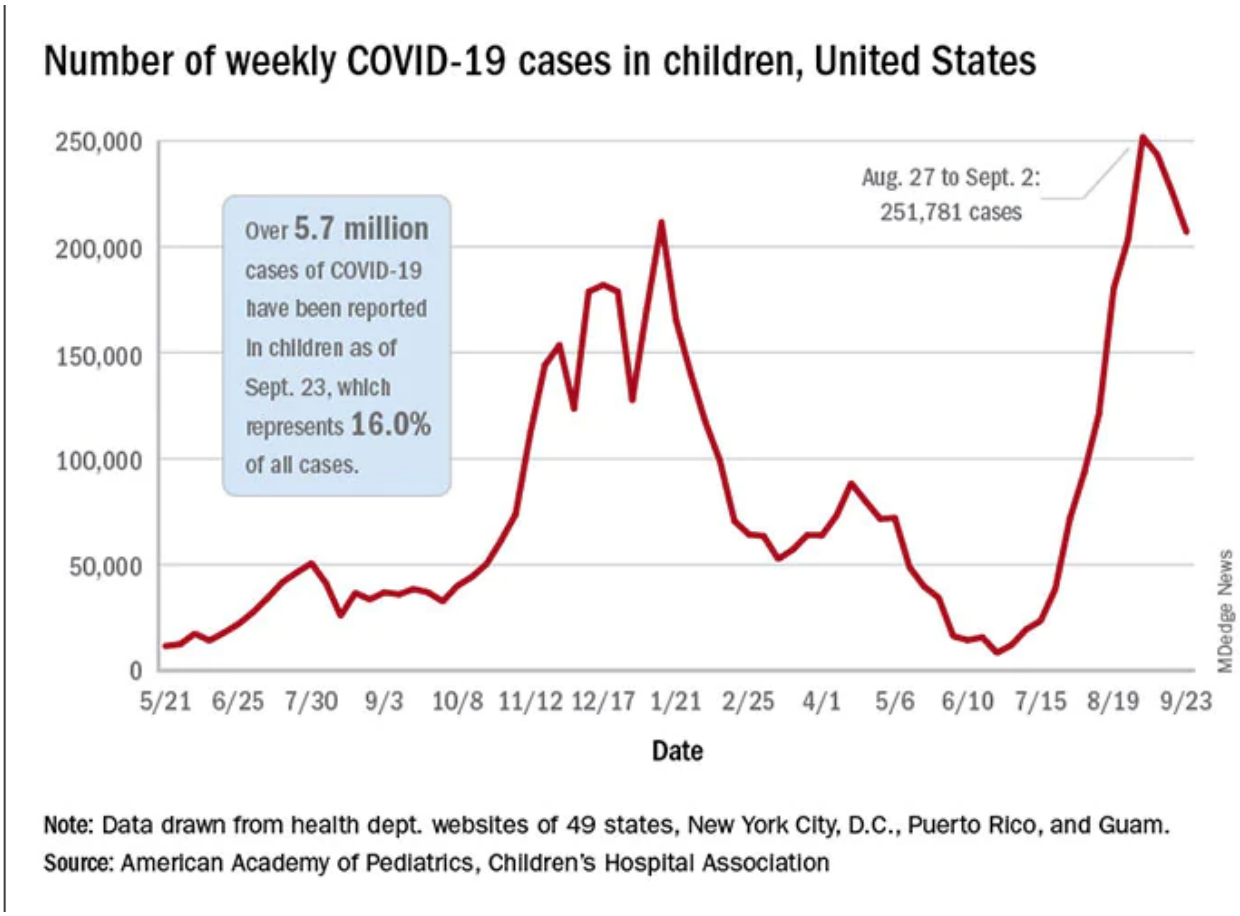
COVID-19 News

Preliminary Result of Pfizer Vaccine in 5-11 Year Olds
Pfizer and BioNTech submitted initial data from a phase 2/3 trial of their mRNA COVID-19 vaccine for children ages 5 to 11 years to the Food and Drug Administration (FDA), and said an application for emergency use authorization of the vaccine in that age-group will likely follow in the coming weeks.

On September 20th, the company shared promising results in children in that age range of two doses of the mRNA vaccine, which contains 10 micrograms (μg) of active ingredient, compared with 30 μg contained in the currently FDA-approved vaccine. Researchers found a two-dose course of the vaccine to be safe and generate a robust immune response in children 5 to 11 years old. Antibody levels in the children who received the shot were similar to those measured in younger adults in a separate study. Pfizer said the company will have data on vaccines in children ages 6 months to 2 years, and 2 years to 5 years, as soon as the fourth quarter of 2021. Children under age 5 received a lower 3-μg dose for each injection in the phase 2/3 study, the company said.

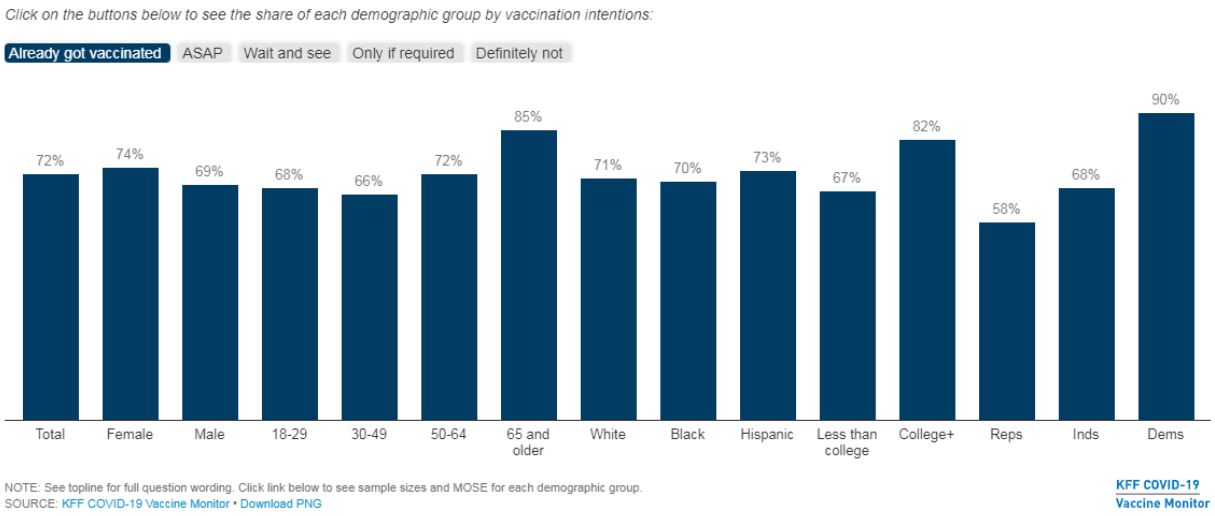
Children 11 and younger are the only group of Americans not yet eligible for COVID-19 vaccination, and pediatric cases of the virus have increased significantly since the Delta variant became the dominant strain in the United States this summer. For the fifth consecutive week, more than 200,000 pediatric cases were reported across the country during the week of Sep 16 to the 23. The latest update from AAP shows that nearly 207,000 child COVID-19 cases were reported last week. See below.

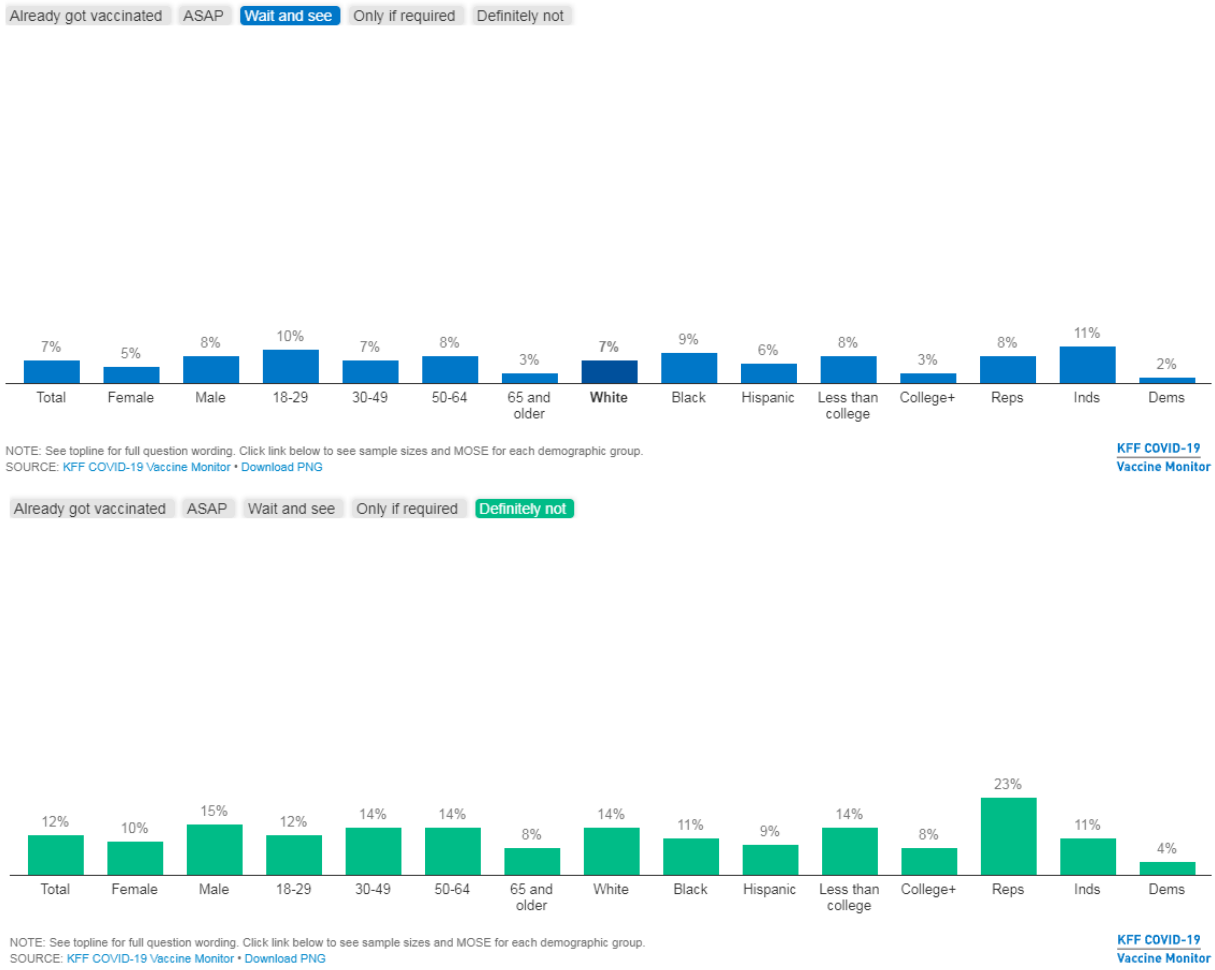
Since the pandemic began, children represented 16.0% of total cumulated cases. For the week ending September 23, children were 26.7% of reported weekly COVID-19 cases (children, under age 18, make up 22.2% of the US population)," the AAP said.



Comment: It now appears Pfizer will not finish its application for 5-11 years old until mid-October, however, which means the FDA may probably not make its decision until after Halloween.

Kaiser Family Foundation COVID-19 Vaccine Monitor Dashboard
September 28,2021





Comment: The latest survey data reveal 73% of Hispanic adults reported being at least partially vaccinated, along with 70% of Black adults and 71% of white adults, while the same survey in May showed rates of only 57%, 56%, and 65%, respectively. Unfortunately, the definitely not outnumber the wait and see. Mandates do seem to be making a difference with a clear uptake of persons getting vaccinated.

Remdesivir Sharply Cuts COVID Hospitalization Risk
Gilead Press Release September 22, 2021

Remdesivir was found to reduce some COVID-19 patients' risk of hospitalization by 87% in a phase 3 trial, the drug's manufacturer announced Wednesday. The randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of a 3-day course of intravenous remdesivir in an analysis of 562 nonhospitalized patients at high risk for disease progression. Remdesivir demonstrated a statistically significant 87% reduction in risk for COVID-19-related hospitalization or all-cause death by Day 28 (0.7% [2/279]) compared with placebo (5.3% [15/283]) *P* = .008. Participants were assigned 1:1 to remdesivir or the placebo group.

Comment: The results of this trial are similar to MCA. The results suggest that antivirals given early in infection can prevent progression. MCA are a one-time infusion or SQ injection vs 3 days of IV RDV. Currently MCA are distributed from the federal government and are free. See Journal Review.

Journal Review

Remdesivir Plus Standard of Care Versus Standard of Care Alone for the Treatment of Patients Admitted to Hospital with COVID-19 (DisCoVeRy): A Phase 3, Randomised, Controlled, Open-Label Trial

Lancet Infect Dis published online September 14, 2021 – article suggested by Shivani Patel
doi.org/10.1016/ S1473-3099(21)00485-0

DisCoVeRy was a phase 3, open-label, adaptive, multicenter, randomized, controlled trial conducted in 48 sites in Europe (France, Belgium, Austria, Portugal, Luxembourg). Adult patients (aged =18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection and illness of any duration were eligible if they had clinical evidence of hypoxemic pneumonia or required oxygen supplementation. Participants were randomly assigned (1:1:1:1:1) to receive standard of care alone or in combination with remdesivir, lopinavir-ritonavir, lopinavir-ritonavir and interferon beta-1a, or hydroxychloroquine. Randomization used computer-generated blocks of various sizes; it was stratified on severity of disease at inclusion and on European administrative region. Remdesivir was administered as 200 mg intravenous infusion on day 1, followed by once daily, 1-h infusions of 100 mg up to 9 days, for a total duration of 10 days. [US protocol is 5 days] It could be stopped after 5 days if the participant was discharged. The primary outcome was the clinical status at day 15 measured by the WHO seven-point ordinal scale, assessed in the intention-to-treat population. Safety was assessed in the modified intention-to-treat population and was one of the secondary outcomes.

Between March 22, 2020, and Jan 21, 2021, 857 participants were enrolled and randomly assigned to remdesivir plus standard of care (n=429) or standard of care only (n=428). At day 15, the distribution of the WHO ordinal scale was: (1) not hospitalized, no limitations on activities (61 [15%] of 414 in the remdesivir group vs 73 [17%] of 418 in the control group); (2) not hospitalized, limitation on activities (129 [31%] vs 132 [32%]); (3) hospitalized, not requiring supplemental oxygen (50 [12%] vs 29 [7%]); (4) hospitalized, requiring supplemental oxygen (76 [18%] vs 67 [16%]); (5) hospitalized, on non-invasive ventilation or high flow oxygen devices (15 [4%] vs 14 [3%]); (6) hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (62 [15%] vs 79 [19%]); (7) death (21 [5%] vs 24 [6%]). The difference between treatment groups was not significant (odds ratio 0·98 [95% CI 0·77-1·25]; p=0·85). There was no significant difference in the occurrence of serious adverse events between treatment groups (remdesivir, 135 [33%] of 406 vs control, 130 [31%] of 418; p=0·48). This finding could be due to a genuine absence of effect but could also reflect that treatment was administered too late to be effective (median 9 days after onset of symptoms). See next article.

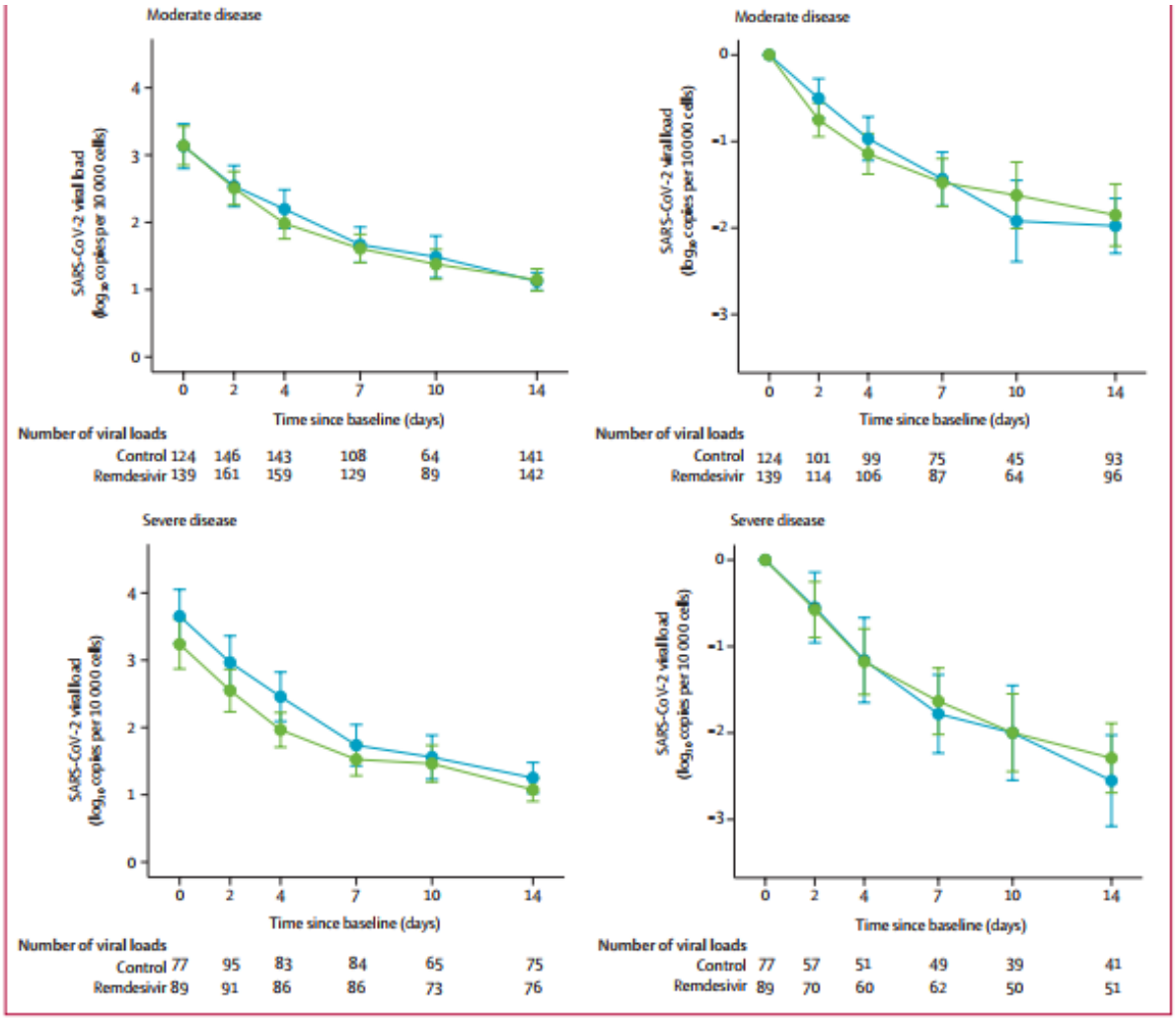


Figure 3: **Normalised SARS-CoV-2 viral loads in nasopharyngeal swabs in the intention-to-treat population at each timepoint and as change from baseline, according to treatment group and COVID-19 severity at random assignment**

Data are mean (95% CI). Green lines show the remdesivir group. Blue lines show the control group. LSMD=least-square mean difference.

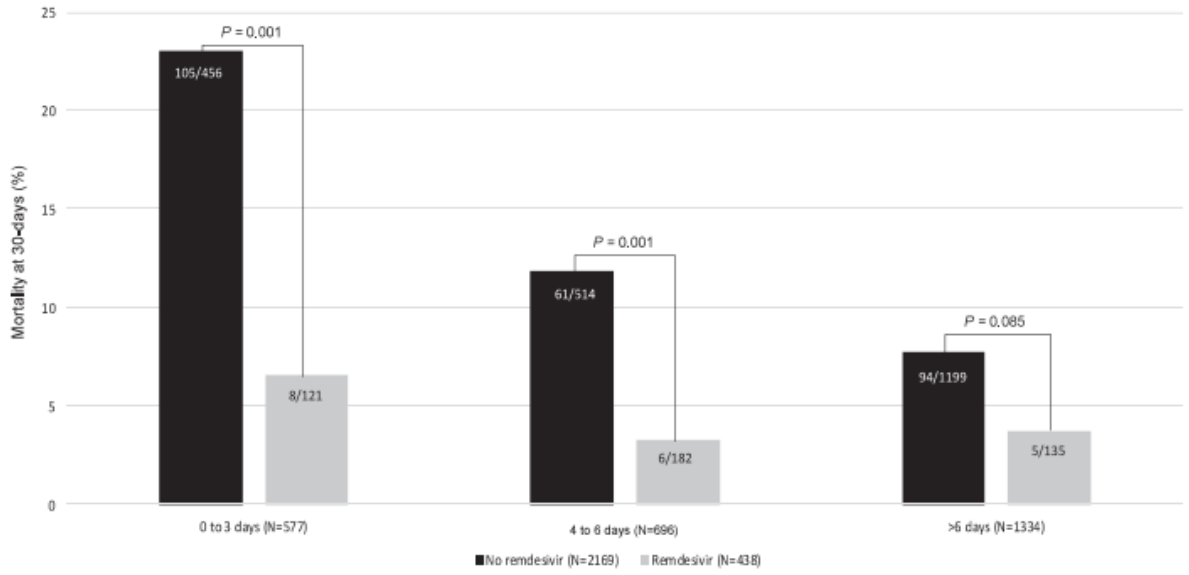
Comment: The faster time to recovery previously reported was not observed in the DisCoVeRy trial. Together with previous evidence, results from the DisCoVeRy trial do not support the use of remdesivir in hospitalized patients with COVID-19 in a population with symptoms for more than a week and requiring oxygen support. This was open-label and not placebo-controlled. Indeed, several treatments were concomitantly evaluated at the beginning of the trial, and masking was thus impossible due to the different modes of administration (intravenous, subcutaneous, or oral) of the different treatment groups. This might have introduced bias in the follow-up and management of patients. The decision to begin corticosteroids in patient management or to begin mechanical ventilation might have been influenced by the knowledge of the treatment group, even unconsciously. Only 1/3 of patients received steroids as SOC. I had to look at the supplemental material to tease this important variable.

	All patients			Moderate			Severe		
	Overall (N=832)	Remdesivir (N=414)	Control (N=418)	Overall (N=504)	Remdesivir (N=253)	Control (N=251)	Overall (N=328)	Remdesivir (N=161)	Control (N=167)
Corticosteroids (general route) — no. (%)	333 (40.0%)	164 (39.6%)	169 (40.4%)	201 (39.9%)	96 (37.9%)	105 (41.8%)	132 (40.2%)	68 (42.2%)	64 (38.3%)
- Dexamethasone	271 (32.6%)	139 (33.6%)	132 (31.6%)	166 (32.9%)	86 (34.0%)	80 (31.9%)	105 (32.0%)	53 (32.9%)	52 (31.1%)
- Hydrocortisone	24 (2.9%)	10 (2.4%)	14 (3.3%)	8 (1.6%)	4 (1.6%)	4 (1.6%)	16 (4.9%)	6 (3.7%)	10 (6.0%)
- Methylprednisolone	47 (5.6%)	23 (5.6%)	24 (5.7%)	26 (5.2%)	11 (4.3%)	15 (6.0%)	21 (6.4%)	12 (7.5%)	9 (5.4%)

This article and others before it seem to point to the same conclusion. If RDV is administered at the start of the inflammatory process, RDV is unlikely to change the course by itself. At that point anti-inflammatories such as steroids are now the SOC. Based on the late breaking abstract from Gilead (see above) early administration before the inflammatory phase does seem to prevent progression, but by the time most of our patients are hospitalized they have symptoms of > 7days and are oxygen dependent therefore, they have already crossed into the inflammatory phase. This finding could be due to a genuine absence of effect but could also reflect that treatment was administered too late to be effective (median 9 days after onset of symptoms). See next article.

Impact of Remdesivir According to the Pre-Admission Symptom Duration in Patients with COVID-19
J Antimicrob Chemother published online September 2021
doi:10.1093/jac/dkab321
Patients admitted for >48 h in our hospital for a SARS-CoV-2 confirmed or suspected infection from February 2020 to February 2021 were retrospectively analyzed. The primary outcome of the study was mortality at 30 days. Univariate and multivariate analyses were performed to identify predictors of mortality.

In total, 2607 patients (438 receiving remdesivir and 2169 not) were included with a median (IQR) age of 65 (54-77) years and 58% were male. Four hundred and seventy-six were admitted to the ICU (18.3%) and 264 required invasive mechanical ventilation (10.1%). The global 30-day mortality rate was 10.7%. Pre-admission symptom duration of 4-6 days and 3 days was associated with a 1.5- and 2.5-fold increase in the mortality rate, respectively, in comparison with >6 days and treatment with remdesivir was independently associated with a lower mortality rate (OR = 0.382, 95% CI = 0.218–0.671). The analysis showed that the major difference was among patients with shorter pre-admission symptom duration (<6 days).



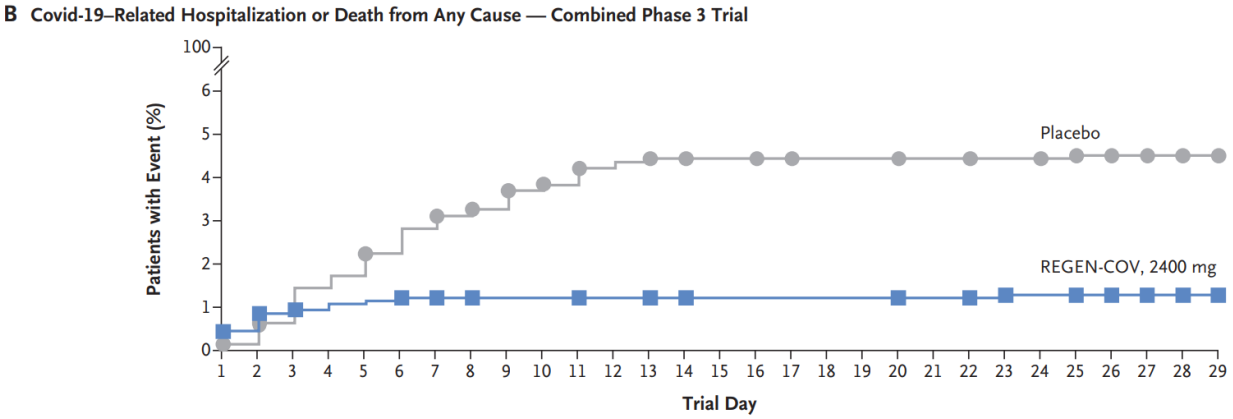
Comment: Patients with 3 days and 4-6 days from symptom onset to admission are associated with a 2.5- and 1.5-fold higher risk of death, respectively. Remdesivir was associated with 62% reduced odds of

death versus standard-of-care and its survival benefit increased with shorter duration of symptoms. Steroids were used in <15% of patients during this study. This study shows that the beneficial effect of remdesivir is linked to the number of days from symptom onset. The shorter the pre-admission duration of symptoms the higher the difference in the mortality rate between patients receiving or not receiving remdesivir that probably represents the subpopulation in whom the expected viral load is higher and the type I IFN production lower. I think this is the first report assessing the mortality rate of COVID-19 patients receiving or not receiving remdesivir according to the pre-admission duration of symptoms. Our results show a low mortality rate (4.3% versus 12%, respectively) in hospitalized patients receiving remdesivir. This result is in line with that reported in the ACTT-1 study that randomized patients to remdesivir or placebo. [N Engl J Med 2020; 383: 1813–26] The patients in this trial mainly correspond to those in the ACTT-1 study with a baseline ordinal score of 5 (hospitalized patients requiring supplemental oxygen) who had a mortality rate of 4% in the remdesivir arm versus 12.7% in the control arm, perfectly matching with the results in this paper. The primary endpoint of the ACTT-1 study was the time to recovery and the authors showed that the major difference was observed in patients with <6 days of symptoms; however, the impact on the mortality rate was not reported in this subgroup. However, a post hoc analysis did show a mortality benefit in this subgroup only. The main limitation of this study is its retrospective design. Another limitation was the lack of information about the viral load to better define the efficacy of remdesivir, but unfortunately the Ct of PCR was not available from the EHR. The result in this study and others suggests remdesivir needs to be given in the first week of symptom onset to impact outcomes.

REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19

N Engl J Med published September 29, 2021
DOI: 10.1056/NEJMoa2108163

This is a phase 3 portion of an adaptive trial. Patients were randomly assigned outpatients with Covid-19 and risk factors for severe disease to receive various doses of intravenous REGEN-COV or placebo. Patients had to be 18years of age or older and were not hospitalized. These patients had a confirmed local SARS-CoV-2-positive diagnostic test result no more than 72 hours before randomization, with the onset of any Covid-19 symptom, as determined by the investigator, occurring no more than 7 days before randomization. The phase 3 primary efficacy analysis presented here involved cohort patients who were assigned to receive either 2400 mg or 1200 mg of REGEN-COV, with their concurrent placebo groups serving as a control. Covid-19-related hospitalization or death from any cause occurred in 18 of 1355 patients in the REGEN-COV 2400-mg group (1.3%) and in 62 of 1341 patients in the placebo group who underwent randomization concurrently (4.6%) (relative risk reduction [1 minus the relative risk], 71.3%; P<0.001); these outcomes occurred in 7 of 736 patients in the REGEN-COV 1200-mg group (1.0%) and in 24 of 748 1 patient in the placebo group who underwent randomization concurrently (3.2%) (relative risk reduction, 70.4%; P=0.002). The median time to resolution of symptoms was 4 days shorter with each REGEN-COV dose than with placebo (10 days vs. 14 days; P<0.001 for both comparisons). REGEN-COV was efficacious across various subgroups, including patients who were SARS-CoV-2 serum antibody-positive at baseline. Both REGEN-COV doses reduced viral load faster than placebo.



Comment: This had been previously reported by Regeneron, but this publication is the peer reviewed report on this study. I think it is clear, MCA have a role early on in infection in high-risk persons. This study reported a 70% relative risk reduction in the risk of Covid-19-related hospitalization or death from any cause, and it resolved symptoms and reduced the SARS-CoV-2 viral load more rapidly than placebo.

Maternal-Neonatal Transfer of SARS CoV-2 IgG Antibodies among Parturient Women Treated with BNT162b2 mRNA Vaccine during Pregnancy
published online September 2021 Am J Ob & Gyn MFM
doi.org/10.1016/j.ajogmf.2021.100492
This is a prospective cohort study in a single tertiary medical center in Israel between February and March 2021. Parturient women who had been vaccinated with Pfizer vaccine during pregnancy were included and compared to COVID-19 recovered parturient women. SARS CoV-2 IgG antibodies were measured in maternal and cord sera, dried blood spot samples taken from newborns, and breast-milk samples. The primary outcome was to determine whether neonatal cord and dried blood spot samples were positive for SARS CoV-2 antibodies and to evaluate transfer ratio defined as cord blood IgG divided by maternal IgG levels.

The study included 64 vaccinated parturient women and 11 parturient women who had COVID-19 disease during pregnancy. All maternal blood sera samples and 98.3% of cord blood sera samples were positive for SARS Cov-2 IgG with median concentrations of 26.1 (IQR 22.0;39.7) and 20.2 (IQR 12.7;29.0) respectively. Similarly, 96.4% of neonatal blood spot samples and all breast milk samples were positive for SARS CoV-2 IgG with median concentrations of 11.0 (IQR 7.2;12.8) and 4.9 (IQR 3.8;6.0), respectively. There was a significant positive correlation between maternal serum levels of SARS Cov-2 IgG and cord blood (R=0.483, p=0.0001), neonatal blood spot (R=0.515, p=0.004), and breast milk levels (R=0.396, p=0.005) of SARS CoV-2 IgG. The median placental transfer ratio of SARS-COV-2 IgG was 0.77. Comparison of vaccinated with recovered COVID-19 patients revealed significantly higher SARS CoV-2 IgG levels in maternal serum and cord blood among vaccinated women (p<0.0001).

Comment: SARS-CoV-2 IgG antibodies were detected in samples of cord blood, newborn dried blood spot and breast milk. Neonatal and breast milk antibody levels were positively correlated with maternal serum antibody levels. Higher levels of cord blood antibodies were detected among vaccinated women compared to COVID-19 recovered women, but there were only 11 women in this category. However, this later finding highlights the uneven immunity from natural disease and supports the Israeli guidance on administering one dose of vaccine to boost immunity. Several studies suggest only one dose may be needed.