TGIF to all. I hope everyone has had a terrific week.

Under COVID-19 News a report from AAP/CHA shows new cases reported in children were up for the fourth time in 5 weeks, but severe disease and mortality remains extremely low. The second report is a very good interim report on Novavax vaccine. Today the CDC ACIP meets again on the J&J vaccine.

Under Journal Review, the first article looks at safety and efficacy of 1 dose of the J&J. This is a very good vaccine with a very rare side effect. This vaccine does not require the cold storage, requires only 1 dose, and is relatively inexpensive. The use of this vaccine in the homeless, migrants, rural areas, and low and middle income countries could make a significant difference in not only reaching herd immunity here, but around the world. The next article demonstrated that mRNA vaccines are safe in pregnancy, and the last article looks at use of convalescent plasma for treatment of hospitalized patients with COVID-19.

Have a safe and relaxing weekend – more good articles and news on Monday.

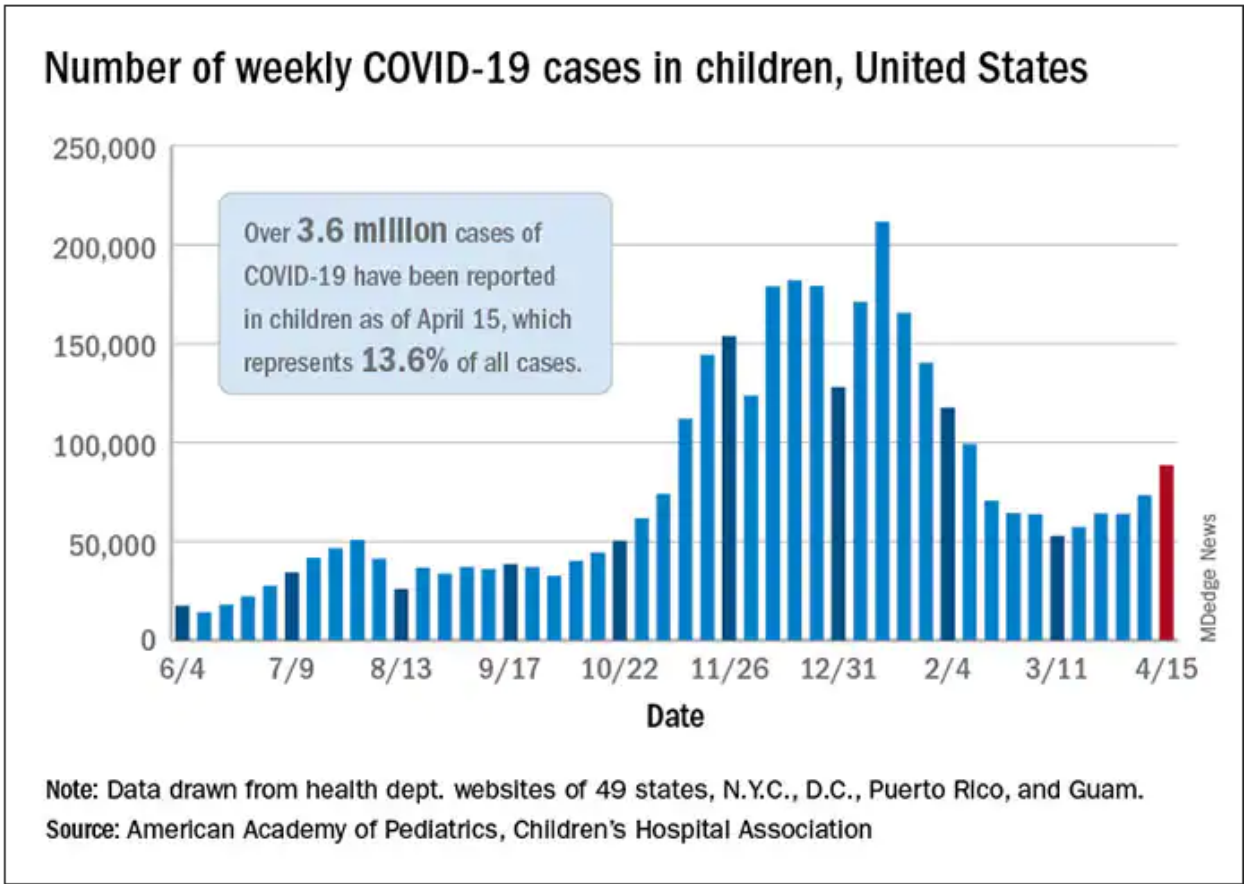
Ed

## COVID-19 News

**Children and COVID-19: State Data Report:**
A joint report from the American Academy of Pediatrics and the Children's Hospital Association
April 15, 2021

New cases reported in children were up for the fourth time in 5 weeks, rising from 73,000 to over 88,000 for the week of April 9-15. That represented 20.6% of all new cases for the week, eclipsing the previous high of 19.1% recorded just 3 weeks ago, based on data collected by the AAP and CHA from 49 states, the District of Columbia, New York City, Puerto Rico, and Guam. Cumulative cases of COVID-19 in children exceed 3.6 million in those jurisdictions, which is 13.6% of the total reported among all ages, and the overall rate of coronavirus infection is 4,824 cases per 100,000 children in the population, the AAP and CHA. [children make up ~22% of population] Since the beginning of April, the largest local increases in cases reported came in Michigan (21.6%), Vermont (15.9%), and Maine (15.6%). Nationally, the increase over those same 2 weeks is just under 5%. There were 5 deaths among children during the week of April 9-15, bringing the total to 297, but the recent increases in cases have not affected the long-term trends for serious illness. The death rate for children with COVID-19 has been 0.01% since early November — 43 states, New York City, Puerto Rico, and Guam are reporting such data — and the hospitalization rate has been 0.8% since mid-January in 24 states and New York City, the AAP/CHA data show.

**Comment:** This is not surprising as adult vaccinations now reach over 2 million with at least 1 shot. Transmission in children have in part been fueled by group sports and relaxation of restrictions. Although children have an extremely low risk of severe disease and death, they can transmit to vulnerable people who have not been vaccinated. The more people that are vaccinated, including children, the faster we get to herd immunity.




**Comment:** This is not surprising as adult vaccinations now reach over 2 million with at least 1 shot. Children make up ~20% of persons <16. Currently vaccines are only approved for individuals 16 years and older so it is not surprising that younger age groups will represent an increasing percentage of new infections. Hopefully, the FDA will give EUA for children 12 and up in the next month. Hospitalizations and mortality remain low. Transmission in children have in part been fueled by group sports and relaxation of restrictions. Although children have an extremely low risk of severe disease and death, they can transmit to vulnerable people who have not been vaccinated. The more people that are vaccinated, including children, the faster we get to herd immunity.

**Novavax Covid-19 Vaccine Update**

A final analysis from phase 3 trials in the UK show the vaccine is 96% efficacious against mild, moderate, and severe disease against the wild-type SARS-CoV-2 strain. In addition, Novavax released the results of phase 2b trial in South Africa which demonstrated a 55.4% efficacious rate among subjects where the majority of cases were due to the B.1.351 variant. However, in both trials the vaccine was 100% efficacious against severe disease including severe disease and death.

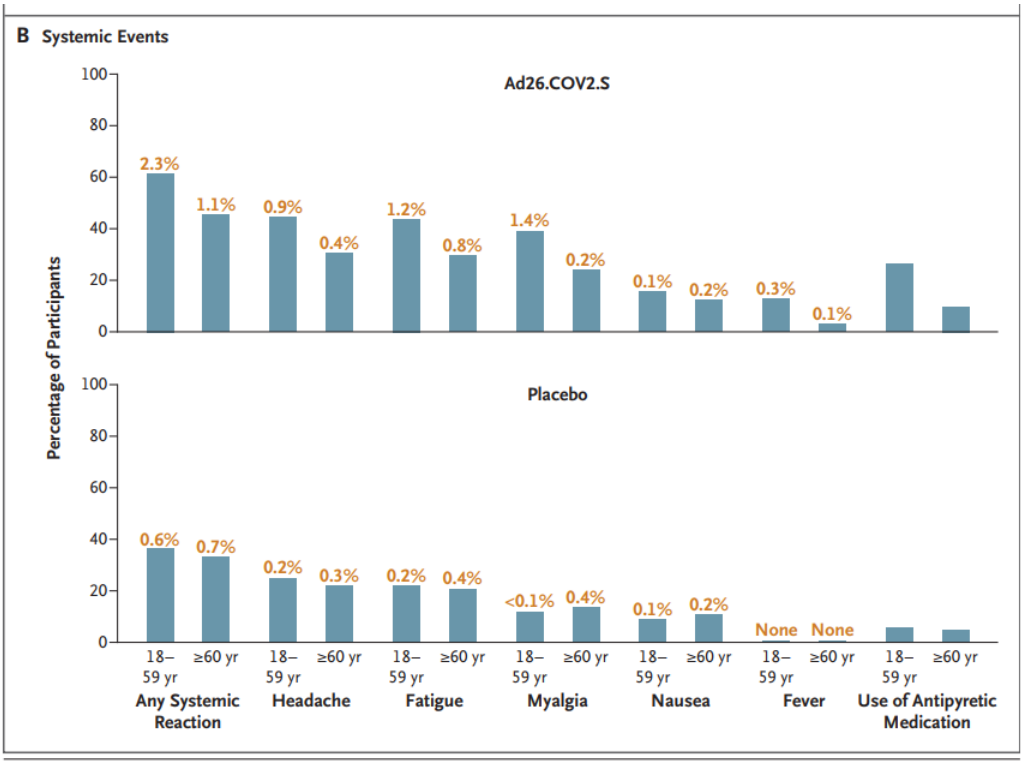
According to released analysis, the vaccine-induced protection began 14 days after the initial dose and increased efficacy occurred 7 days after the second dose of vaccine.

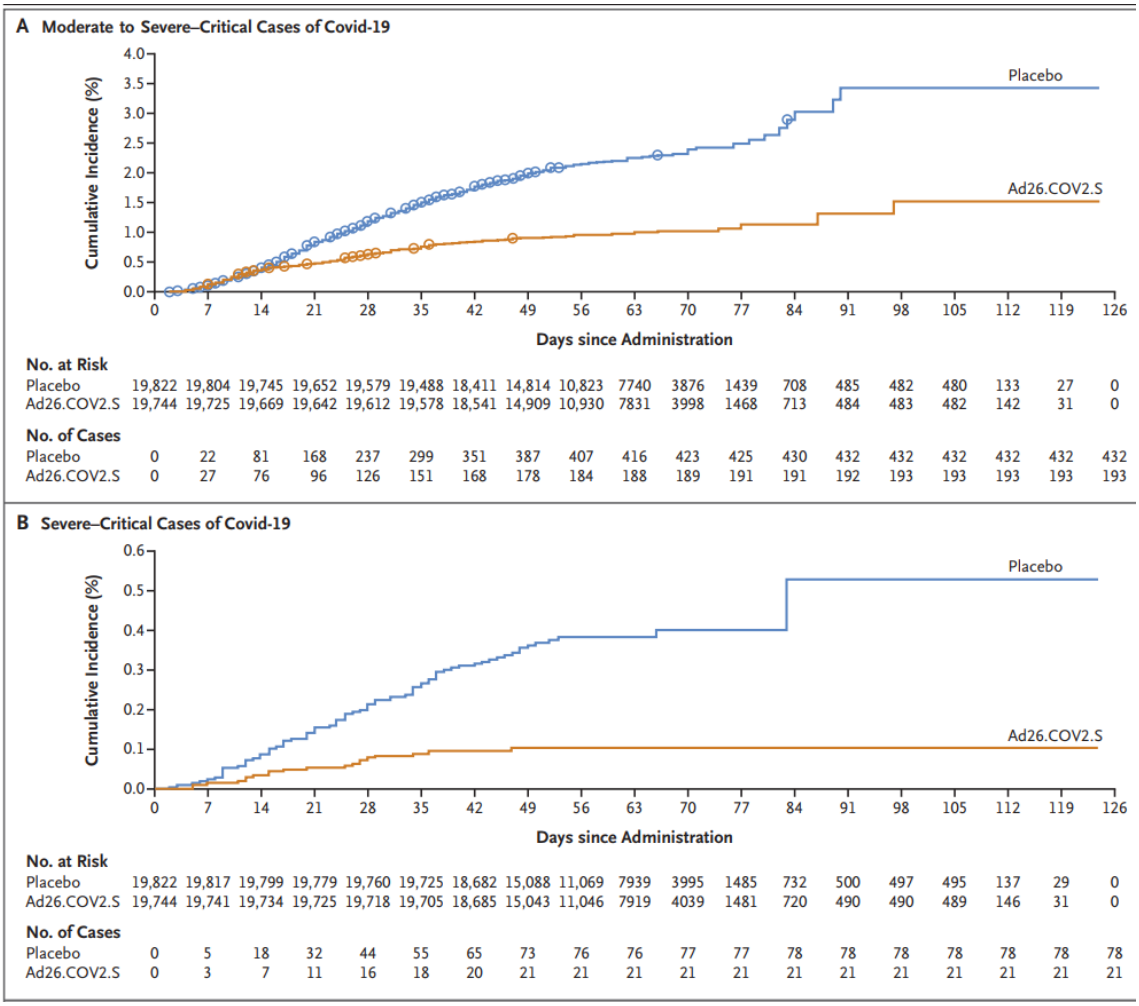
**Comment:** This is incredibly good news. Novavax is a more traditional protein vaccine complexed with an adjuvant. If approved we will have the option of 3 different technologies, mRNA, viral vector, and protein.

## Journal Review

**Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine Against Covid-19**
N Engl J Med published online April 21, 2021
DOI: 10.1056/NEJMoa210154
This is an international, randomized, double-blind, placebo-controlled, phase 3 trial. Investigators randomly assigned adult participants in a 1:1 ratio to receive a single dose of Ad26.COV2.S (J&J) or placebo. The primary end points were vaccine efficacy against moderate to severe-critical coronavirus disease 2019 (Covid-19) with an onset at least 14 days and at least 28 days after administration among participants in the per-protocol population who had tested negative for SARS-CoV-2. Safety was also assessed.

Overall 19,630 SARS-CoV-2-negative participants received Ad26.COV2.S and 19,691 who received placebo. Ad26.COV2.S protected against moderate to severe-critical Covid-19 with onset at least 14 days after administration (116 cases in the vaccine group vs. 348 in the placebo group; efficacy, 66.9%; adjusted 95% confidence interval [CI], 59.0 to 73.4) and at least 28 days after administration (66 vs. 193 cases; efficacy, 66.1%; adjusted 95% CI, 55.0 to 74.8). Vaccine efficacy was higher against severe-critical Covid-19 (76.7% [adjusted 95% CI, 54.6 to 89.1] for onset at ≥14 days and 85.4% [adjusted 95% CI, 54.2 to 96.9] for onset at ≥28 days). Despite 86 of 91 cases (94.5%) in South Africa with sequenced virus having the 20H/501Y.V2 variant, vaccine efficacy was 52.0% and 64.0% against moderate to severe-critical Covid-19 with onset at least 14 days and at least 28 days after administration, respectively, and efficacy against severe-critical Covid-19 was 73.1% and 81.7%, respectively. Three deaths occurred in the vaccine group (none were Covid-19–related), and 16 in the placebo group (5 were Covid-19–related). Systemic side effects were limited.






**Comment:** A single dose of Ad26.COV2.S protected against symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection and was effective against severe-critical disease, including hospitalization and death. There were no deaths attributed to Covid-19 in the vaccinated group and protection increased over time. This trial was conducted during a time of extremely high rates of SARS-CoV-2 infection. This situation, combined with the emergence of viral variants, makes comparison of vaccine trials inappropriate. ACIP is meeting today to determine if the J&J vaccine will be reinstated. As discussed on Wednesday the European Union (EMA) concluded the overall benefits of J&J COVID-19 Vaccine in preventing COVID-19 outweigh the risks of side effects.

**Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons**
N Engl J Med published online April 21, 2021.
DOI: 10.1056/NEJMoa2104983
From December 14, 2020, to February 28, 2021, the authors used data from the "v-safe after vaccination health checker" surveillance system, the v-safe pregnancy registry, and the Vaccine Adverse Event Reporting System (VAERS) to characterize the initial safety of mRNA Covid-19 vaccines in pregnant persons.

A total of 35,691 v-safe participants 16 to 54 years of age identified as pregnant. Among 3958 participants enrolled in the v-safe pregnancy registry, 827 had a completed pregnancy, of which 115

(13.9%) resulted in a pregnancy loss and 712 (86.1%) resulted in a live birth (mostly among participants with vaccination in the third trimester). Adverse neonatal outcomes included preterm birth (in 9.4%) and small size for gestational age (in 3.2%); no neonatal deaths were reported. The expected proportions of adverse pregnancy and neonatal outcomes in persons vaccinated against Covid-19 who had a completed pregnancy were similar to incidences reported in studies involving pregnant women that were conducted before the Covid-19 pandemic. Among 221 pregnancy-related adverse events reported to the VAERS, the most frequently reported event was spontaneous abortion (46 cases).

**Table 4. Pregnancy Loss and Neonatal Outcomes in Published Studies and V-safe Pregnancy Registry Participants.**

| Participant-Reported Outcome | Published Incidence* | V-safe Pregnancy Registry† |
|---|---|---|
| | % | *no./total no. (%)* |
| Pregnancy loss among participants with a completed pregnancy | | |
| Spontaneous abortion: <20 wk[15-17] | 10–26 | 104/827 (12.6)‡ |
| Stillbirth: ≥ 20 wk[18-20] | <1 | 1/725 (0.1)§ |
| Neonatal outcome among live-born infants | | |
| Preterm birth: <37 wk[21,22] | 8–15 | 60/636 (9.4)¶ |
| Small size for gestational age[23,24]‖ | 3.5 | 23/724 (3.2) |
| Congenital anomalies[25]** | 3 | 16/724 (2.2) |
| Neonatal death[26]†† | <1 | 0/724 |

* The populations from which these rates are derived are not matched to the current study population for age, race and ethnic group, or other demographic and clinical factors.
† Data on pregnancy loss are based on 827 participants in the v-safe pregnancy registry who received an mRNA Covid-19 vaccine (BNT162b2 [Pfizer–BioNTech] or mRNA-1273 [Moderna]) from December 14, 2020, to February 28, 2021, and who reported a completed pregnancy. A total of 700 participants (84.6%) received their first eligible dose in the third trimester. Data on neonatal outcomes are based on 724 live-born infants, including 12 sets of multiples.
‡ A total of 96 of 104 spontaneous abortions (92.3%) occurred before 13 weeks of gestation.
§ The denominator includes live-born infants and stillbirths.
¶ The denominator includes only participants vaccinated before 37 weeks of gestation.

**Comment:** This preliminary finding did not show any obvious safety signals among pregnant persons who received mRNA Covid-19 vaccines. This is certainly good news since pregnancy has been identified as a risk factor for serious Covid-19 infection. However, more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, will be necessary to assure maternal, pregnancy, and infant outcomes.

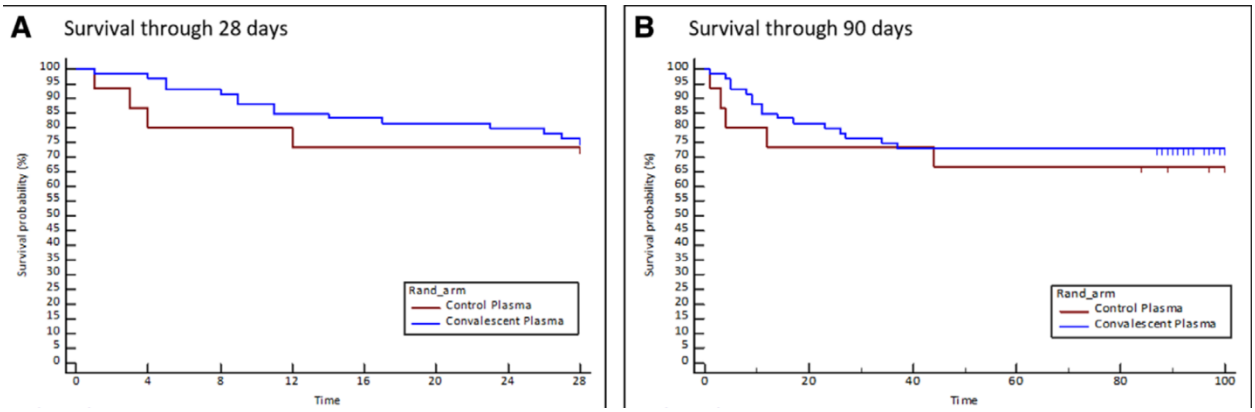
**Severe Acute Respiratory Syndrome Coronavirus 2 Convalescent Plasma Versus Standard Plasma in Coronavirus Disease 2019 Infected Hospitalized Patients in New York: A Double-Blind Randomized Trial**

Crit Care Med published online April 16, 2021.
DOI: 10.1097/CCM.0000000000005066

This is a double-blind RCT. Covid19 + patients were randomized (4:1) to receive 2 U of convalescent plasma versus standard plasma. Antibodies to SARS-CoV-2 were measured in plasma units and in trial recipients.

Unfortunately, enrollment was terminated after EUA was granted for convalescent plasma. Seventy-four patients were randomized. At baseline, mean Apache II was (23.4 [5.6] and 22.5 [6.6]),

percent of patients intubated (19% and 20%), and median (interquartile range) days from symptom onset to randomization of 9 (6–18) and 9 (6–15), were similar in the convalescent plasma versus standard plasma arms, respectively. Convalescent plasma had high neutralizing activity (median [interquartile range] titer 1:526 [1:359–1:786]) and its administration increased antibodies to SARS-CoV-2 by 14.4%, whereas standard plasma administration led to an 8.6% decrease ($p$ = 0.005). No difference was observed for ventilator-free days through 28 days (primary study endpoint): median (interquartile range) of 28 (2–28) versus 28 (0–28; $p$ = 0.86) for the convalescent plasma and standard plasma groups, respectively. All-cause mortality through 90 days was numerically lower in the convalescent plasma versus standard plasma groups (27% vs 33%; $p$ = 0.63) but did not achieve statistical significance.




**Comment:** This small RCT, administration of convalescent plasma to hospitalized patients with Covid-2019 infection increased antibodies to SARS-CoV-2 but was not associated with improved outcomes. The duration of estimated symptom onset to randomization was 9 days (median) in both study arms, and consistent with this fact, most patients had already generated antibodies to SARS-CoV-2 at baseline. Indeed, 80% and 87% of patients in our CP and SP arms, respectively. Results involving early administration (within 72 hr. after symptom onset) with high tittered CP vs saline showed benefit in some series, which contrasts with the apparent ineffectiveness of CP for “late” treatment of COVID-19 infection. This study was underpowered to rule out a potential benefit that might exist. However, there are 11 published randomized trials, and at least two other notable COVID-19 convalescent plasma treatment trials that researchers halted based on the recommendation of analysis performed by independent data and safety monitoring boards. Preliminary data from the RECOVERY trial (10,406 randomized patients) demonstrated no difference in the primary endpoint of 28-day mortality. Therefore, the current preponderance of randomized clinical trial data shows little or no significant benefits independent of antibody titers. The NIH says there are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.