Good morning. Today the big news is the FDA release of their internal analysis of the Pfizer vaccine data. As stated, tomorrow a group of distinguished outside experts will review the data.

I have reviewed multiple publications. The first article suggests that patients on metformin have a lower risk of mortality in COVID-19 patients admitted to the hospital. The authors suggest that metformin reduces TNFα and other inflammatory adipokines that are high in people with obesity and type 2 diabetes and contribute to COVID-19 severity, while it boosts levels of the anti-inflammatory cytokine IL-10. The second article reports admission hyperglycemia was a strong predictor of all-cause mortality in non-critically hospitalized COVID-19 patients regardless of prior history of diabetes. The third article reports on the AstraZeneca vaccine interim results. As has been reported further work is clearly needed to determine the mechanism of the increased efficacy with an LD/SD (low dose/standard dose) regimen. The next article confirms prior reports on the safety of rooming in and breast feeding for COVID-19 positive mothers providing infection prevention measures are in place. The last article is a review on the role of children in household clusters.

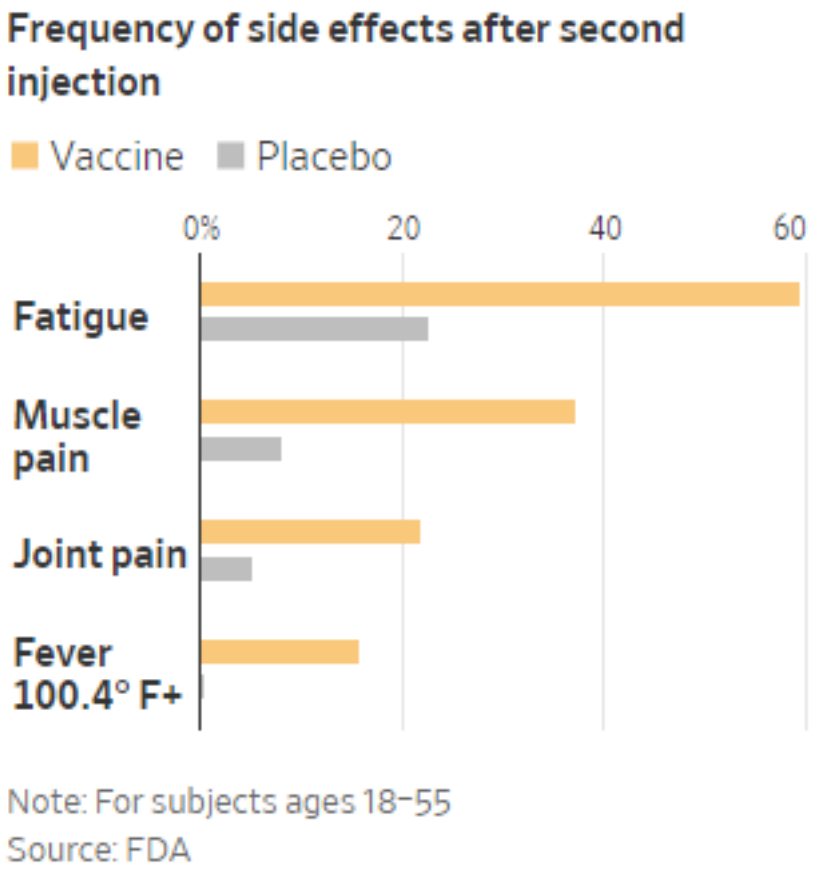
Have a great day

Ed

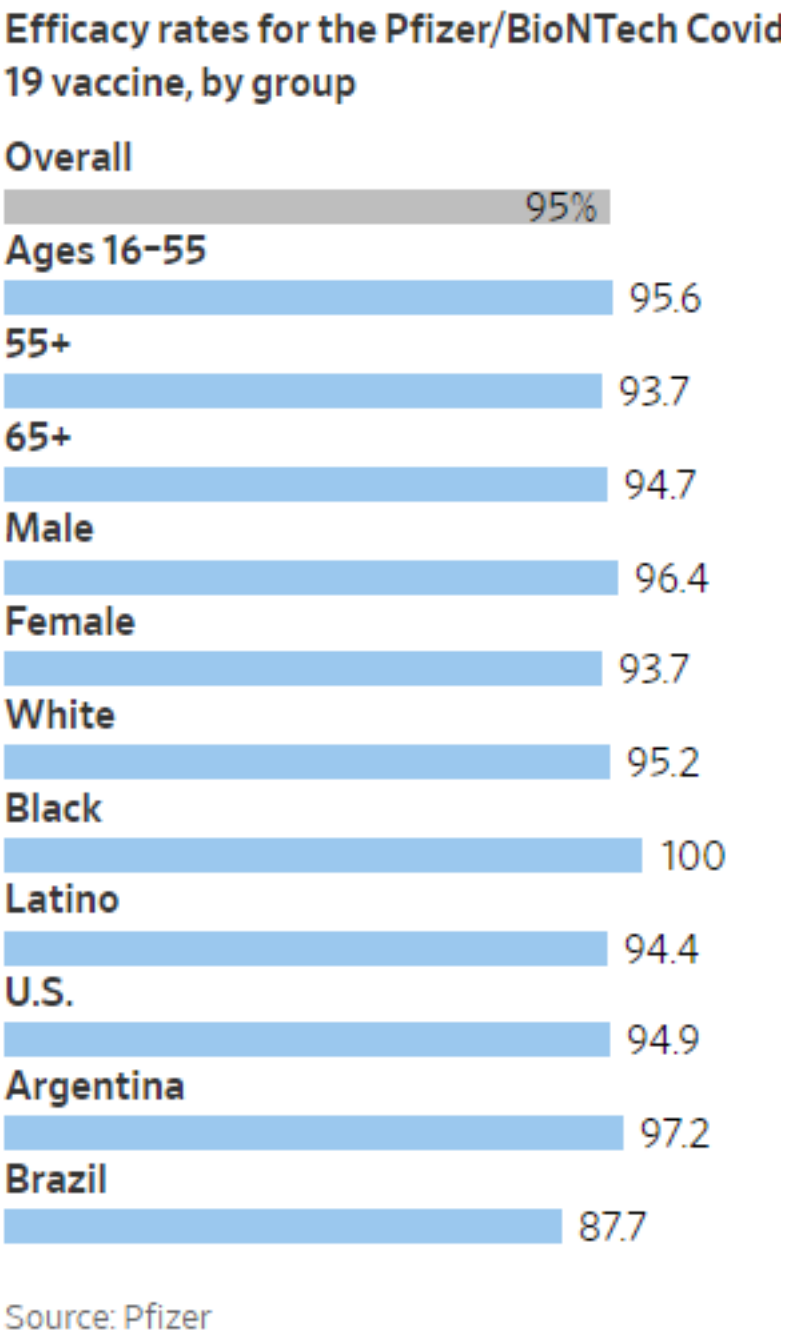
COVID-19 News

The big news today revolves around the FDA report released yesterday on their review of the Pfizer vaccine. Tomorrow a group of outside experts will discuss if the FDA should grant EUA for the Pfizer vaccine. Next week will be Moderna's turn.

Here is what we know. The FDA reported that the two-dose vaccine provided benefits even after just the first injection—cutting the risk of getting Covid-19 by about half. The vaccine was found to be 95% effective after the second dose, three weeks later. FDA scientists also found that the vaccine was effective in reducing the risk of confirmed severe disease even after the first dose. Side effects were common. The most common complaint was fatigue, followed by muscle pain and joint pain. (see graph below) Severe "adverse reactions" were rare, most frequent after the second dose, and generally less frequent in older adults greater than 55 years of age.



The vaccine was found to be effective across race, age, and ethnicity, and that its analyses found no safety concerns in subgroups by race, age, ethnicity or people with comorbidities such as pre-existing conditions. (see below)



Pfizer would begin shipping the first of 25 million doses this year, the equivalent for 12.5 million people because it requires two doses. The government had hoped to deliver enough vaccine for about 20 million people.

Comment: News remains very positive [in fact exciting!] for the first of 2 mRNA vaccines. People's hesitancy to get vaccinated could be a big hurdle including some HCWs. For us to get back to "normal" it will take all of us to follow public recommendations [3 Ws] until we can reach at least 70% vaccination rates.

Literature Review

Metformin and Risk of Mortality in Patients Hospitalised with COVID-19: A Retrospective Cohort Analysis

Lancet Healthy Longevity published online December 3, 2020
doi.org/10.1016/S2666-7568(20)30033-7

Researchers conducted a retrospective cohort analysis using claims data from the UnitedHealth Group (UHG)'s Clinical Discovery Claims Database, which includes de-identified data for individuals with COVID-19 admissions in all 50 US states, covering a diverse range of ages, ethnicities and regions.

They found that 6,256 of the 15,380 individuals with pharmacy claims data were eligible for inclusion in the study. Patients had to be over 18, have at least 6 months of continuous enrolment in UHG last year, and be admitted to hospital with COVID-19 between January 1 and June 7, 2020. Among this cohort of 6256 individuals, the median age was 73 years, and 52.8% were women. Type 1 diabetics were excluded from the analysis.

The primary outcome was in-hospital mortality from COVID-19, with the independent variable being home metformin use, defined as more than 90 days of prescription claims during the year before admission to hospital for COVID-19. The exploratory independent variable of interest was home use of TNFα inhibitors. The UHG database did not include outcomes related to in-hospital complications, intensive care unit, or ventilator use, so an analysis on these endpoints was not possible.

Of the 2,333 people in the metformin group, 394 (16.9%) died of COVID-19 during admission to hospital for the disease, compared with 791 (20.2%) of 3923 in the non-metformin group. Metformin use was not associated with significantly decreased mortality in the overall sample of both men and women by either Cox proportional hazards stratified model (hazard ratio [HR] 0.887 [95% CI 0.782–1.008]) or propensity matching (odds ratio [OR] 0.912 [95% CI 0.777–1.071], *P* =0.15).

However, among women, the drug was associated with lower death rates by Cox proportional hazards (HR 0.785, 95% CI 0.650–0.951) and propensity matching (OR 0.759, 95% CI 0.601–0.960, *P* =0.021). There was no significant reduction in mortality among men (HR 0.957, 95% CI 0.82–1.14; *P* =0.689 by Cox proportional hazards).

The authors noted that metformin reduces TNFα and other inflammatory adipokines that are high in people with obesity and type 2 diabetes and contribute to COVID-19 severity, while it boosts levels of the anti-inflammatory cytokine IL-10. They also highlighted previous research showing that metformin causes these beneficial effects significantly more in females than males in both animal and human studies.

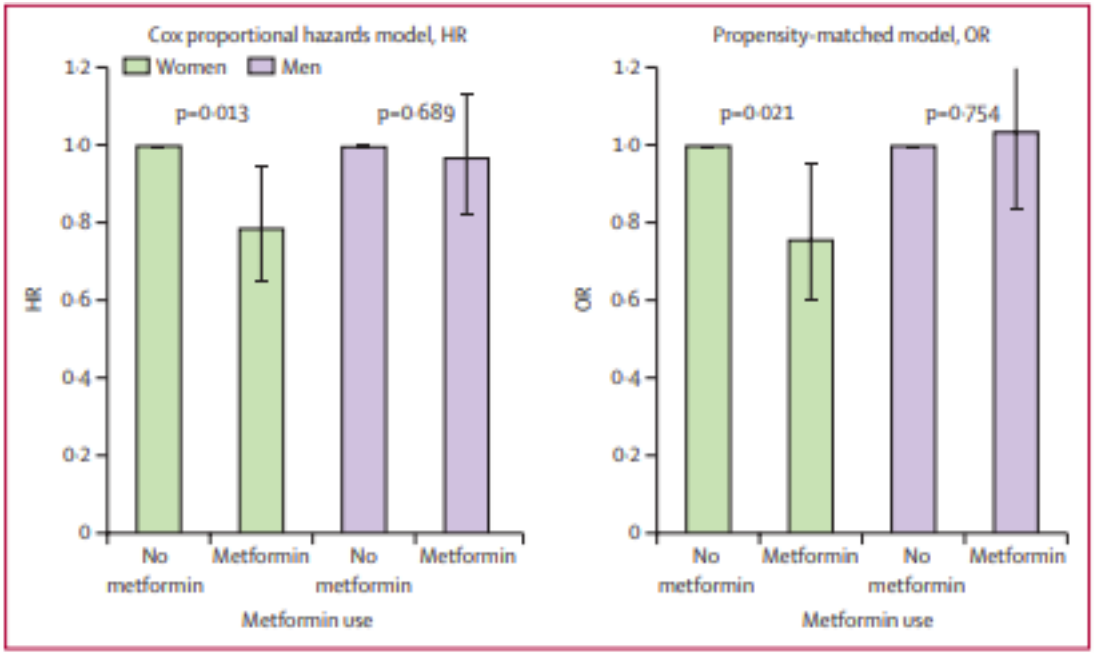
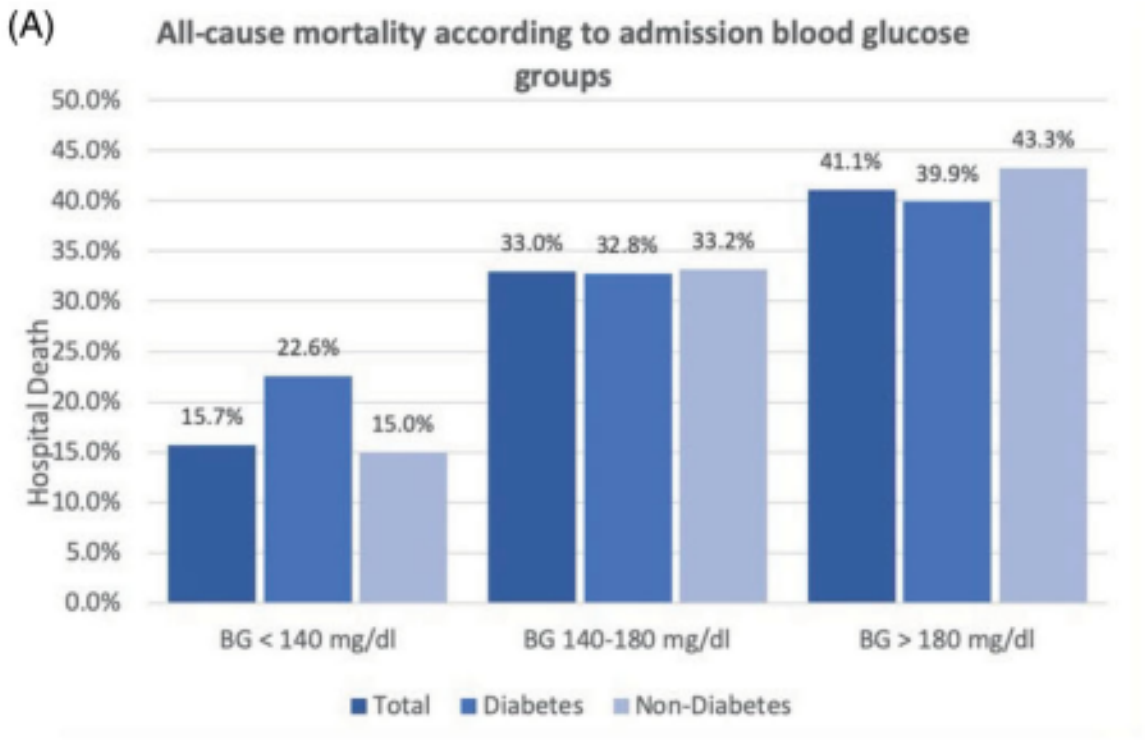


Figure 3: **Survival among women and among men, comparing those without metformin to those with metformin**

Comment: If these findings are supported in other analyses and prospective trials, metformin could be widely distributed for prevention of severe COVID-19 in people with diabetes or a BMI of at least 30 especially in women. Limitations included the retrospective nature of the analysis, and the inability to assess outcomes other than mortality, such as length of stay or need for mechanical ventilation. Moreover, while claims data show metformin was prescribed as a home medication for at least 90 days within the last 12 months, they do not give information about adherence.

Admission Hyperglycaemia as a Predictor of Mortality in Patients Hospitalized with COVID-19 Regardless of Diabetes Status: Data from the Spanish SEMI-COVID-19 Registry
Ann Med published online November 4, 2020
doi.org/10.1080/07853890.2020.1836566
The aim of this study was to evaluate the association between blood glucose (BG) levels and in-hospital mortality in non-critically ill patients hospitalized with COVID-19. The investigators performed a retrospective multi-center study involving patients hospitalized with SARS-CoV-2 infection. Patients were categorized into three groups according to admission BG levels: <140 mg/dL, 140–180 mg/dL and >180 mg/dL. The primary endpoint was all-cause in-hospital mortality.

Of the 11,312 patients, only 2128 (18.9%) had diabetes and 2289 (20.4%) died during hospitalization. The in-hospital mortality rates were 15.7% (<140 mg/dL), 33.7% (140–180 mg) and 41.1% (>180 mg/dL), p<.001. The cumulative probability of mortality was significantly higher in patients with hyperglycemia compared to patients with normoglycemia (log rank, p<.001), independently of pre-existing diabetes. Hyperglycemia (after adjusting for age, diabetes, hypertension and other confounding factors) was an independent risk factor of mortality (BG >180 mg/dL: HR 1.50; 95% confidence interval (CI): 1.31–1.73) (BG 140–180 mg/dL; HR 1.48; 95%CI: 1.29–1.70). Hyperglycemia was also associated with requirement for mechanical ventilation, intensive care unit (ICU) admission and mortality.



Comment: In this retrospective study, admission hyperglycemia was a strong predictor of all-cause mortality in non-critically hospitalized COVID-19 patients regardless of prior history of diabetes. Unfortunately, insufficient evidence is available on the benefits of strict glycemic control in patients hospitalized with COVID-19 due to the fact that glycemic management was underestimated during outbreak and the difficulties of multiple daily insulin injections and frequent point-of-care glucose testing in areas with high burden of COVID-19 patients. Besides hyperglycemia, after performing a multivariate stepwise regression analysis, age, male gender, hypertension, COPD, dependency/frailty, creatinine levels, CRP > 60 U/L and LDH > 400 U/L were also independently associated with all-cause mortality in this study. This study has several limitations. First, it is an observational retrospective cohort study conducted during an outbreak, so there may be residual or unmeasured confounding factors. Second, most patients did not have an HbA1c measurement and as such, some patients classified as non-diabetic could have unknown diabetes. In addition, based on a study reviewed last week in the Daily Briefing, the incidence of critically ill cases and mortality rate were significantly higher in the insufficient glycemic control group (HbA1c ≥6.5%), and HbA1c was a significant independent risk factor associated with in-hospital death of patients with COVID-19. (J Diab Invest 11.20) Another unanswered question is whether hyperglycemia plays any role in the pathophysiology of the disease or if it is just an inflammatory bystander. Lastly with routine use of steroids in hospitalized patients with COVID-19, does controlling glucose have an additional benefit.

Safety and Efficacy of the ChAdOx1 nCoV-19 Vaccine (AZD1222) Against SARS-CoV-2: An Interim Analysis of Four Randomised Controlled Trials in Brazil, South Africa, and the UK
Lancet published online December 8, 2020
doi.org/10.1016/S0140-6736(20)32661-1
The present publication is an interim primary efficacy analysis which includes data from 7,548 participants from the United Kingdom and 4,088 participants from Brazil. Between April 23, 2020, and November 4, 2020, a total of 23,848 participants were enrolled and randomized to receive the ChAdOx1

nCoV-19 vaccine or the meningococcal group A, C, W, and Y conjugate vaccine. Participants in the ChAdOx1 nCoV-19 group received 2 doses containing 5×10^{10} viral particles; a subset of participants in the UK trial received a half dose as their first dose (low-dose) and a standard dose as their second dose.

The primary efficacy analysis included symptomatic COVID-19 in seronegative participants with a NAAT positive swab more than 14 days after a second dose of vaccine. Overall vaccine efficacy across both groups was 70.4%. In participants who received 2 standard doses, vaccine efficacy was 62.1%. However, participants who received a low dose followed by a standard dose, efficacy was 90%. Vaccine efficacy in older age groups could not be assessed but needs to be determined. From 21 days after the first dose, there were ten cases hospitalized for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death.

There were 74341 person-months of safety follow-up (median 3·4 months, IQR 1·3–4·8): 175 adverse events occurred in 168 participants, 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group. A case of transverse myelitis was reported 14 days after ChAdOx1 nCoV-19 booster vaccination as being possibly related to vaccination, with the independent neurological committee considering the most likely diagnosis to be of an idiopathic, short segment, spinal cord demyelination.

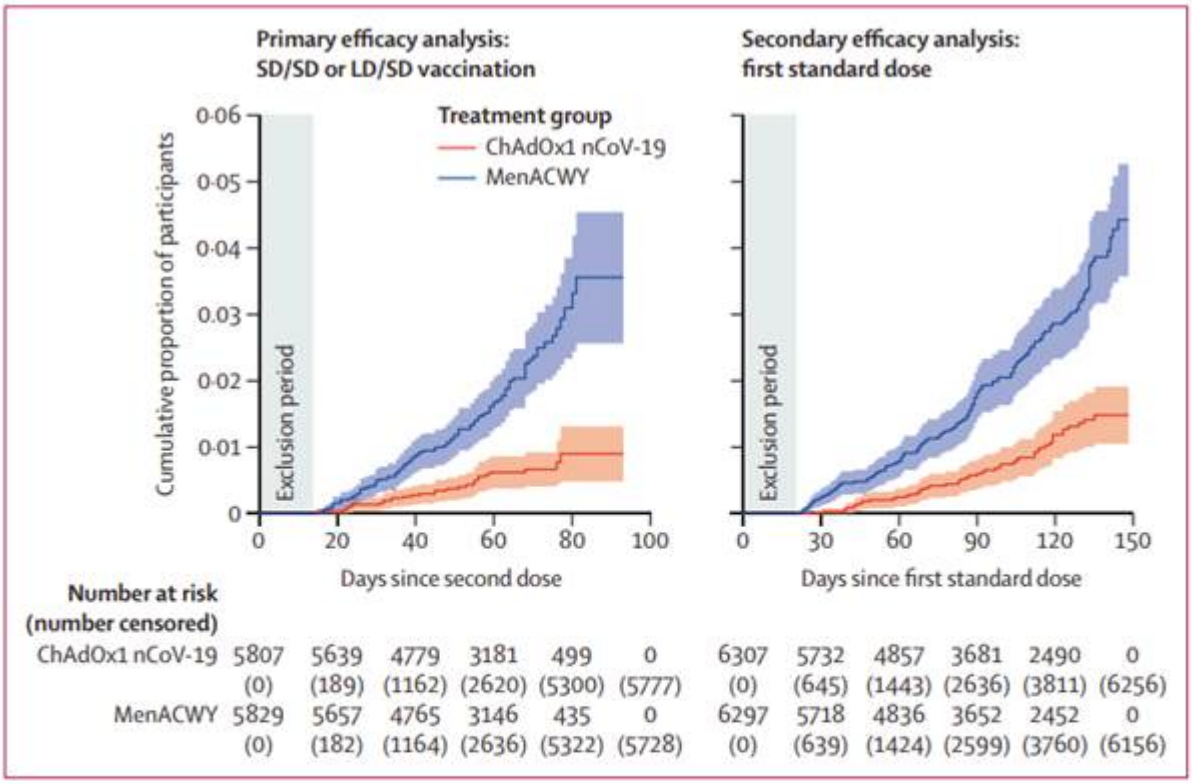


Figure: **Kaplan-Meier cumulative incidence of primary symptomatic, NAAT-positive COVID-19**
Cumulative incidence of symptomatic COVID-19 after two doses (left) or after first standard dose in participants receiving only standard-dose vaccines (right). Grey shaded areas show the exclusion period after each dose in which cases were excluded from the analysis. Blue and red shaded areas show 95% CIs. LD/SD=low-dose prime plus standard-dose boost. MenACWY=meningococcal group A, C, W, and Y conjugate vaccine. NAAT=nucleic acid amplification test. SD/SD=two standard-dose vaccines given.

Comment: Further work is clearly needed to determine the mechanism of the increased efficacy with a LD/SD regimen. The authors propose it might be due to higher levels of neutralizing antibody, lower levels of anti-vector immunity with lower vector-derived antigen content of the first dose, or differential antibody functionality or cellular immunity, including altered avidity or immunodominance. While the data presented here show that ChAdOx1 nCov-19 is efficacious against symptomatic disease most cases in this report were in adults younger than 55 years of age. An important public health need is to reduce morbidity and mortality of the disease in an older adult population and thus the potential efficacy in this age group is critical. In a prior publication immunogenicity data appeared similar immune responses following vaccination with two doses of ChAdOx1 nCov-19 in older adults, including those older than 70 years of age, when compared with those younger than 55 years. The vaccine can be stored and distributed at 2–8°C making distribution and storage easier and the vaccine is less expensive.

Evaluation of Rooming-in Practice for Neonates Born to Mothers with Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Italy

JAMA Pediatrics published online December 7, 2020
doi:10.1001/jamapediatrics.2020.5086

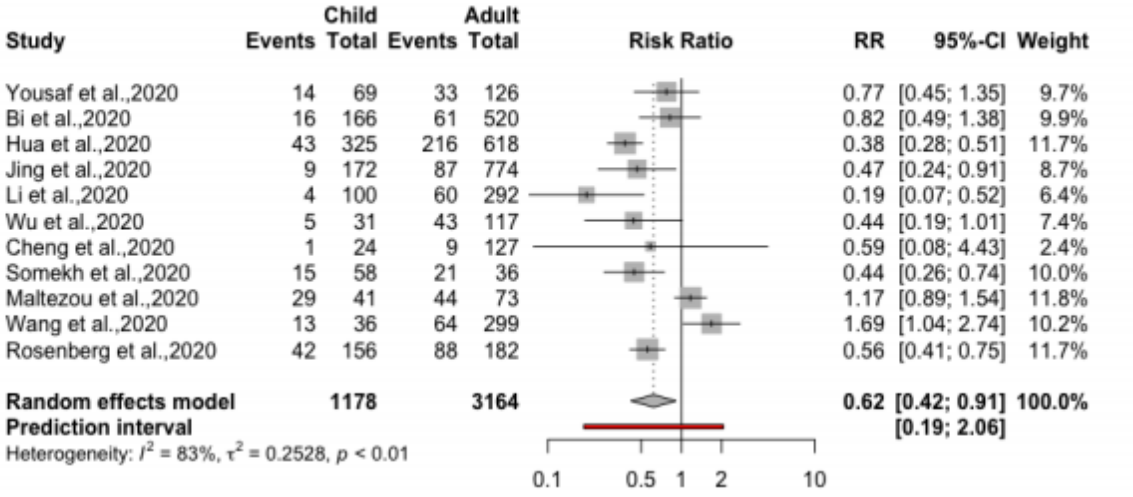
This is a prospective, multicenter study enrolling mother-infant dyads from March 19 to May 2, 2020, followed up for 20 days of life (range, 18-22 days), was performed. Participants included 62 neonates born to 61 mothers with SARS-CoV-2 infection who were eligible for rooming-in practice based on the clinical condition of the mother and infants whose results of nasopharyngeal swabs were negative at birth. Forty-six of the 61 mothers (75%) delivered vaginally. Forty-four (72%) were diagnosed as having COVID-19 before delivery, while 14 (23%) were suspected of being infected at delivery, and 3 (5%), including the 1 who had twins, were diagnosed 2 to 5 days after delivery based on symptoms. Of all the newborns in the study, 95% were breastfed. Neonates were tested for SARS-CoV-2 by PCR on a nasopharyngeal swab collected within 24 hours after birth. They underwent a physical examination daily and mother-infant pairs received nurse and midwife care many times a day. On day 7 of life, neonates underwent a second nasopharyngeal swab and were discharged from the hospital if they were in good clinical condition. Based on guidance a formal document regarding protected rooming-in rules was provided to the mothers, especially concerning handwashing, surgical facemask donned during breastfeeding or when providing care for the infant, and otherwise physical distancing (2 m) from the infant.

Of the 62 neonates enrolled (25 boys), born to 61 mothers (median age, 32 years; interquartile range, 28-36 years), only 1 infant (1.6%; 95% CI, 0%-8.7%) was diagnosed as having SARS-CoV-2 infection at post birth checks. In that case, rooming-in was interrupted on day 5 of life because of severe worsening of the mother's clinical condition. The neonate became positive for the virus on day 7 of life and developed transient mild dyspnea. Ninety-five percent of the neonates enrolled were breastfed.

Comment: The findings of this study suggest that mother-to-infant transmission of SARS-CoV-2 during rooming-in practice is rare, provided that adequate infection prevention guidance such as droplet and contact precautions are in place. Registry data show that about 60% of the mother and child pairs roomed together, with less than 2% of newborns testing positive for coronavirus. Recent placental studies suggest that the placenta is an unlikely route of mother-to-child SARS-CoV-2 transmission. The sample size was relatively small, and a proper control group was lacking, limiting the generalizability of our findings.

A Meta-Analysis on the Role of Children in SARS-CoV-2 in Household Transmission Clusters
Clin Infect Dis published online December 6, 2020
doi.org/10.1093/cid/ciaa1825
The investigators performed a meta-analysis of the published literature on household SARS-CoV-2 transmission clusters (n=213 from 12 countries). Only 8 (3.8%) transmission clusters were identified as having a pediatric index case. Asymptomatic index cases were associated with a lower secondary attack in contacts than symptomatic index cases (estimate risk ratio [RR], 0.17; 95% confidence interval [CI], 0.09-0.29). To determine the susceptibility of children to household infections the secondary attack rate (SAR) in pediatric household contacts was assessed. The secondary attack rate in pediatric household contacts was lower than in adult household contacts (RR, 0.62; 95% CI, 0.42- 0.91). These data have important implications for the ongoing management of the COVID-19 pandemic, including potential vaccine prioritization strategies.

Below: Relative risk (RR) for the secondary attack rate of children and adults in household SARS-CoV-2 transmission clusters. Events describe the number of SARS-CoV2 positive individuals identified in the study.



Comment: While the data suggests that children may be less susceptible to SARS-CoV-2 infection than adults, the researchers cautioned that children may be infrequently identified as index cases because of limited interaction outside the home during the study period, a higher probability of adult travel to COVID-19–endemic areas, and datasets that include few children younger than 16 years old. Interestingly, they found that older children were not significantly more likely than younger children to acquire the virus, in contrast to previous pre-print suggestions. Once infected, it remains to be determined as to whether children are more or less likely to transmit the SARS-CoV-2 to a family member as an infected adult. There is an emerging evidence that mild or asymptomatic patients are less infectious than those with pronounced clinical symptoms (Pediatrics 2020; 146(2). The Lancet Microbe 2020). Indeed, this meta-analysis showed that an asymptomatic index case was associated with a significantly lower secondary attack rate compared to a symptomatic. This study assumed that SARSCoV-2 infections in the household contacts of infected individuals were the result of a direct transmission event. However, it is possible that the household contact acquired the virus from another source (e.g., from community exposure) and that the first in the family to develop symptoms was not necessarily the index case.