COVID-19 Evidence Digest 12/18/20

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine (NEJM)

Bottom Line: A two-dose administration of the BNT162b2 mRNA vaccine has been determined to be safe and effective in preventing Covid-19 among those who are 16 years of age or older.

Details: This was a phase 2/3 randomized control trial of the Pfizer BNT162b2 mRNA vaccine. mRNA vaccines teach our cells how to make a protein which causes our bodies to produce antibodies against a virus. 43,548 participants who were ≥16 years old were randomized to either receive the vaccine (n=21,720) or a placebo (n=21,728). Participants received two doses, 21 days apart. The BNT162b2 vaccine was 95% effective in preventing Covid-19 (95% CI [90.3,97.6]). The vaccine was also found to be 90 to 100% effective across different ages, sex, race/ethnicity, BMI (body mass index), and comorbidities. After seven days of the second dose, only eight participants who received the vaccine got Covid-19, compared to 162 participants who received a placebo. Among these participants, ten had severe Covid-19, nine of whom received the placebo. The vaccine was found to be safe, with the most common reactions to the vaccine being mild-to-moderate pain at the injection site, fatigue, and headache. Severe fatigue was reported in 4% of participants who received the vaccine. A median 2-month follow up, safety of this vaccine was similar to that of other viral vaccines. One limitation of this trial is that long-term effectiveness and the duration of protection from Covid-19 has yet to be determined. Additionally, this trial did not include anyone under 16 years of age, pregnant women, and those with additional risk, like immunocompromised persons. The safety and effectiveness of this vaccine among those between the ages of 12 and 15 years old will be reported on. Additional studies are being planned to determine the safety and effectiveness of the vaccine in those less than 12 years old, pregnant women, and other risk groups.

Key Takeaways:

- In a trial conducted by Pfizer, the vaccine was found to be 95% effective and safe in the prevention of Covid-19 among those who are 16 years of age or older.
- This vaccine has not yet been determined to be safe and effective among those younger than 16 years of age, pregnant women, and other risk groups (e.g. immunocompromised persons).

The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine — United States, December 2020 (MMWR)

Bottom Line: The Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation for use of the Pfizer-BioNTeck COVID-19 vaccine for individuals 16 years and older for prevention of COVID-19 (BNT162b2) on December 12, 2020.

Details: On December 11, 2020 the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine (BNT162b2). On December 12, 2020, the ACIP issued an interim recommendation for use of the Pfizer-BioNTeck COVID-19 vaccine for individuals 16 years and older for prevention of COVID-19 (BNT162b2). The vaccination includes 2 doses (30ug, 0.3mL each) of the Pfizer-BioNTech COVID-19 vaccine administered intramuscularly, 3 weeks apart.

The recommendation should be implemented along with the ACIP's interim recommendation for allocating initial supplies of the COVID-19 vaccine. This is an interim recommendation and will be updated as additional information is available. The ACIP COVID-19 Vaccines Work Group

conducted a systematic review of the literature and used the GRADE approach to assess the evidence for vaccine related outcomes. Most evidence came from one randomized, double-blind, placebo controlled Phase II/III clinical trial. Additional clinical considerations should be taken for administration in special populations, such as individuals you are pregnant, immunocompromised or severe allergies. Additional safety and efficacy studies are planned and will inform future ACIP recommendations.

Key Takeaways:

- On December 11, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine (BNT162b2).
- ACIP issued interim recommendation for use of the vaccine on persons >=16 years to prevent COVID-19. Additional clinical considerations should be made for administration in special populations, such as individuals you are pregnant, immunocompromised or severe allergies. This recommendation will be updated as additional information is available.
- Recommendation should be implemented along with the ACIP's interim recommendation for initial supplies of COVID-19 vaccine.

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19 (NEJM)

Bottom Line: In this randomized controlled trial, patients hospitalized with Covid-19 who received baricitinib plus remdesivir had reduced time to recovery and fewer adverse events compared to patients who received remdesivir alone.

Details: This double-blind, randomized, placebo-controlled trial enrolled 1033 patients hospitalized with Covid-19 to either remdesivir plus baricitinib (a JAK inhibitor) or remdesivir plus placebo. The primary outcome was time to recovery, and secondary outcome was clinical status at day 15. Of the patients randomized to baricitinib plus remdesivir, median time to recovery was 7 days (95% CI 6 to 8), compared to patients receiving remdesivir plus placebo who had median time to recovery of 8 days (95% CI 7 to 9). Findings among patients receiving high-flow oxygen or non-invasive ventilation were more notable, where median time to recovery was 10 days with baricitinib plus remdesivir versus 18 days with remdesivir alone. Overall, patients receiving baricitinib plus remdesivir had higher odds of improvement in clinical status at day 15 (OR 1.3, 95% CI 1.0 to 1.6). Patients receiving combination therapy also had fewer serious adverse events (16% vs 21%, p=0.03), and fewer new infections (5.9% vs 11.2%, p=0.003). Mortality at 28 days was 5.1% in the combination group versus 7.8% in the control group, but this difference did not reach statistical significance (HR 0.65, 95% CI 0.39 to 1.09).

Key Takeaways:

- Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status.
- Combination therapy was associated with more significant improvements in patients receiving high-flow oxygen or non-invasive mechanical ventilation.
- A randomized, head-to-head comparison would be needed to compare remdesivir plus baricitinib to remdesivir plus dexamethasone to more fully understand differences in safety and efficacy of the two treatment combinations.

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NYC HEALTH + HOSPITALS | POPULATION HEALTH

Early initiation of prophylactic anticoagulation for prevention of COVID-19 mortality (MedRxIV)

Bottom Line: Among patients hospitalized with COVID-19, those who were started on prophylactic anticoagulation within the first 24 hours of admission had lower risk of death.

Details: This observational cohort study evaluated 4,297 patients hospitalized with COVID-19 from 3/1-7/31 within the VA health system and compared mortality rates between those who did and did not receive prophylactic dose anticoagulation within the first 24 hours of admission. 84.4% of the cohort received prophylactic anticoagulation within the first 24 hours (most commonly heparin based). At time of hospital presentation the group who received prophylactic anticoagulation tended to be sicker with a higher proportion having an oxygen saturation < 93%, elevated heart rate at ≥ 90 or temperature ≥ 100.4 F. This group had lower burden of comorbidities, however. 622 patients died within 30 days of hospital admission (14.5% of total cohort). 14.1% of the group receiving prophylactic anticoagulation died compared to 16.3% of the group who did not receive prophylactic anticoagulation. Inverse probability weighting was used to account for baseline differences in those receiving anticoagulation and those not. Adjusted analyses showed that patients receiving prophylactic anticoagulation within 24 hours of admission were 27% less likely to die within 30 days of hospital admission compared to patients who did not receive early prophylactic anticoagulation (HR 0.73, CI 0.66-0.81).

Key Takeaways: In an observational study of patients hospitalized with COVID-19 within the VA health system, those who received early (within 24 hours) prophylactic anticoagulation (mostly with heparin-based treatment) had less risk of dying than those who did not receive this treatment.

Efficacy of pulmonary rehabilitation in severe and critical-ill COVID-19 patients: a controlled study (MedRxiv)

Bottom Line: This small case control study suggested that pulmonary habitation could be effective among COVID-19 patients, regardless of the disease severity.

Details: High proportion of critically ill COVID-19 patients with mechanical ventilation need in the ICU will often develop ICU-acquired weakness, and thus need rehabilitation. This retrospective, case control study compared the rehabilitation efficacies between 51 COVID-19 patients referred to inpatient pulmonary rehabilitation from March 23, 2020 to May 29, 2020 with 51 patients above the age of 40 with common pneumonia and completed the same rehabilitation protocol in 2019. The performances of six-min walk test (6MWT), chronic respiratory questionnaire (CRQ), and functional independence measure (FIM) were measured at entrance and re-measured at discharge. An above 30-m difference for 6MWT and an above ten-point difference for CRQ between the two measurements was considered as clinically relevant improvement. The proportional of patients failed to achieve such clinical significant improvements was compared between the COVID-19 and the control group while controlling for baseline values, age, sex, and cumulative illness rating scale. The study found 1) similar performance at discharge for 6MWT ($p = 0.14$) and CRQ ($p = 0.55$) but a significantly higher ($p = 0.004$) value of 4.16 points for FIM in the COVID-19 group compared to the control group; 2) no significant difference were found in the 19 patients admitted in the ICU and required mechanical ventilation compared to the control group; 3) Odds ratio of non-improvement in

6MWT was 0.30 (p = 0.13) and 3.02 times higher in CRQ comparing the COVID-19 group and the control group.

Key Takeaways:

- In-house rehabilitation can be effective for COVID-19 patients, regardless of illness severity.
- Further studies are needed to evaluate the discrepancy between high physical improvement and low gains in disease related quality of life.

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All-Cause Excess Mortality and COVID-19–Related Mortality Among US Adults Aged 25-44 Years, March-July 2020 (JAMA)

Bottom Line: The COVID-19 pandemic was associated with increases in deaths due to any cause among 25-44 year olds in the US from March-July.

Details: This study looked at excess deaths (the difference between observed and expected deaths) due to any cause and COVID-19 associated deaths among US adults 25-44 years of age from March-July 2020, comparing excess deaths to those in previous years (2015-2019). As unintentional opioid deaths are usually the leading cause of death in this age cohort, they were also compared with COVID-19 associated deaths for the corresponding months in 2018. Death data were obtained from the National Center for Health Statistics. From March-July 2020, 76,088 deaths due to any cause occurred among 25-44 year olds in the US; there were 11,899 deaths more than what was expected (incident rate ratio = 1.19). Excess deaths occurred in every month and overall in all 10 US Department of Health and Human Services regions. 4,535 deaths due to COVID-19 were recorded, which made up over one-third (38%) of excess deaths. In the NY/NJ region, the incident rate for deaths due to any case was 2.30, with 80% of deaths related to COVID-19. By comparison, from March-July of 2018, 10,347 deaths due to unintentional opioid overdose occurred among 25-44 year olds. In the NY/NJ region, COVID-19 associated deaths in April 2020 exceeded unintentional opioid overdose deaths in April 2018 and were similar to these overdose deaths throughout the study period. While non-COVID-19 attributed deaths during the study period are unexplained, inadequate SARS-CoV-2 testing likely played a role.

Key Takeaways:

- 38% of excess deaths overall among 25-44 year olds were attributed directly to COVID-19. While causes for remaining excess deaths are unknown, inadequate SARS-CoV-2 testing may have played a role, suggesting an underdetection of COVID-19-associated deaths in this population.
- In NY/NJ and two other US regions, COVID-19 associated deaths during March-July 2020 exceeded or were similar to unintentional opioid overdose deaths in March-July 2018.

COVID-19 is 10 Times Deadlier for People with Down Syndrome, Raising Calls for Early Vaccination (Science)

Bottom Line: People with Down syndrome (DS) are 5 times more likely to be hospitalized and 10 times more likely to die from COVID-19 than the general population due to anatomical, chromosomal, and immune system features.

Details: This article summarizes recent studies on COVID-19 morbidity and mortality among people with Down syndrome (DS). A recent UK study found that if infected with SARS-CoV-2, people with DS are 5 times more likely to be hospitalized and 10 times more likely to die from COVID-19 than the general population. These findings remained after controlling for other factors that may contribute to risk, including heart disease, obesity, diabetes, and living in a group home. Another study (pre-print) found that people with DS

>40 years of age hospitalized with COVID-19 are most at risk, with a mortality of 51% versus 7% for people with DS <40 hospitalized with COVID-19. Explanations for higher risk of severe COVID-19 among people with DS include: typical anatomy that may explain higher rates of respiratory infections in general; extra copies of chromosome 21, which codes for an enzyme that slices the SARS-CoV-2 spike protein, allowing for host cell entry; and immune system abnormalities, including T cell development, low levels of circulating B cells and a protein that prevents immune cells from attacking the body, and high levels of inflammation-causing proteins, which contribute to chronic inflammation even with no infection. While the interferon response, a first line of defense against viruses, is initially helpful in fighting COVID-19, elevated activity among people with DS can lead to a hyperinflammatory state (e.g., cytokine storm) that is common in severe and fatal COVID-19. Given these findings, some experts have called for the prioritization of people with DS over 40 years of age in COVID-19 vaccination efforts; of note, the CDC does not include DS in its list of underlying conditions associated with severe COVID-19, and has not yet defined which medically vulnerable groups may be prioritized in vaccine allocation. Given their poorer outcomes and underlying mechanisms for them, some physicians have also called for people with DS over 40 to be prioritized for monoclonal antibody treatments and treatment with baricitinib in combination with remdesivir.

Key Takeaways:

- Given the significantly elevated risk for severe and fatal COVID-19 among people with DS (particularly those over the age of 40), some experts have called for the prioritization of particular treatments and early vaccination.

Household Transmission of SARS-CoV-2 A Systematic Review and Meta-analysis (JAMA)

Bottom Line: In this systematic review and analysis of findings across multiple studies, the estimated SARS-CoV-2 secondary attack rate (spread of infection from an initial case to others) within households and families was 17%.

Details: Given the high-risk nature of crowded indoor settings for the transmission of SARS-CoV-2, the authors of this study conducted a systematic review and meta-analysis (combined analysis of results from multiple studies) to examine what is known about transmission within households and families, and compare it with other coronaviruses (SARS-CoV and Middle East Respiratory Syndrome (MERS)). All articles with data to estimate the SARS-CoV-2 secondary attack rate (spread of infection from an initial case to others) within households and families were included. 54 relevant studies were included, reflecting 77,758 participants. Across studies, the combined estimated household and family secondary attack rate was 16.6%, though variation between studies was significant. This estimate is substantially higher than what has been estimated for SARS-CoV (7.5%) and MERS (4.7%). Higher secondary attack rates were estimated for the following household configurations and contacts: from symptomatic vs asymptomatic index cases (18% vs 0.7%), in adult vs child contacts (28.3% vs 16.8%), in spouses vs other household contacts (37.8% vs 17.8%), and in households with 1 contact vs 3 or more contacts (41.5% vs 22.8%).

Key Takeaways:

- In this study, higher secondary attack rates were reported in some household configurations and contacts, including: in households with symptomatic vs asymptomatic index cases; among adult contacts vs child contacts; among spouses vs other family members; and in households with 1 contact vs those with 3 or more contacts.
- Precautionary measures to minimize SARS-CoV-2 transmission in households, including improved ventilation, increased mask-wearing at home, isolation at home if possible or in external facilities, should be explored further.