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SYNOPSIS

Review of "Safety of the BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Setting"

09/2/2021

Article citation: Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA covid-19 vaccine in a nationwide setting. N Engl J Med. 2021 Aug 25 [Epub ahead of print]. Available from: https://doi.org/10.1056/NEJMoa2110475

One-minute summary

- Based on data from the largest health care organization in Israel, the BNT162b2 (Pfizer-BioNTech) mRNA Coronavirus Disease 2019 (COVID-19) vaccine was most strongly associated with an elevated risk of:
    - Myocarditis (risk ratio [RR], 3.24; 95% confidence interval [CI], 1.55 to 12.44; risk difference [RD], 2.7 more events per 100,000 persons; 95% CI, 1.0 to 4.6)
        - The incidence of myocarditis spiked mainly after the second dose of vaccine and among the 21 cases, the median age was 25 and 91% were male
    - Lymphadenopathy (RR, 2.43; 95% CI, 2.05 to 2.78; RD, 78.4 more events per 100,000 persons; 95% CI, 64.1 to 89.3)
        - Spikes in the incidence of lymphadenopathy were seen after both the first and second doses of vaccine
    - Herpes zoster infection (RR, 1.43; 95% CI, 1.20 to 1.73; RD, 15.8 more events per 100,000 persons; 95% CI, 8.2 to 24.2)
    - Bell's palsy (RR 1.32, 95% CI, 092-1.86; RD, 8 more events per 100,000 persons)
        - Herpes zoster infection is one potential cause of Bell's palsy
    - Appendicitis (RR, 1.40; 95% CI, 1.02 to 2.01; RD, 5.0 more events per 100,000 persons; 95% CI, 0.3 to 9.9)
- Vaccination was substantially protective against:
    - Anemia (RR, 0.79; 95% CI, 0.67 to 0.93; RD, 18.7 fewer events per 100,000 persons; 95% CI, 6.1 to 32.1)
    - Intracranial hemorrhage (RR, 0.48; 95% CI, 0.20 to 0.89; RD, 2.988 fewer events per 100,000 persons; 95% CI, 0.5 to 5.7)
    - Acute kidney injury (RR, 0.44; 95% CI, 0.23 to 0.73; RD, 4.6 fewer events per 100,000 persons; 95% CI, 1.8 to 7.8)

    - Lymphopenia (RR, 0.26; 95% CI, 0.00 to 1.03; RD, 0.9 fewer events per 100,000 persons; 95% CI, <0.1 more to 2.0 fewer)

- SARS-CoV-2 infection was associated with a substantially increased risk of:
    - Myocarditis (RR, 18.28; 95% CI, 3.95 to 25.12; RD, 11.0 more events per 100,000 persons; 95% CI, 5.6 to 15.8)
    - Acute kidney injury (RR, 14.83; 95% CI, 9.24 to 28.75; RD, 125.4 more events per 100,000 persons; 95% CI, 107.0 to 142.6)
    - Pulmonary embolism (RR, 12.14; 95% CI, 6.89 to 29.20; RD, 61.7 more events per 100,000 persons; 95% CI, 48.5 to 75.4)
    - Intracranial hemorrhage (RR, 6.89; 95% CI, 1.90 to 19.16; RD, 7.6 more events per 100,000 persons; 95% CI, 2.7 to 12.6)
    - Pericarditis (RR, 5.39; 95% CI, 2.22 to 23.58; RD, 10.9 more events per 100,000 persons; 95% CI, 4.9 to 16.9)
    - Myocardial infarction (RR, 4.47; 95% CI, 2.47 to 9.95; RD, 25.1 more events per 100,000 persons; 95% CI, 16.2 to 33.9)
    - Thrombocytopenia (RR, 4.24; 95% CI, 2.57 to 7.65; RD, 39.0 more events per 100,000 persons, 95% CI, 26.5 to 51.3)
    - Deep vein thrombosis (RR, 3.78; 95% CI, 2.50 to 6.59; RD, 43.0 more events per 100,000 persons; 95% CI, 29.9 to 56.6)
    - Arrhythmia (RR, 3.83; 95% CI, 3.07 to 4.95; RD, 166.1 more events per 100,000 persons; 95% CI, 139.6 to 193.2)
- SARS-CoV-2 infection was not protective against any adverse event.
- Authors conclude that the BNT162b2 vaccine was not associated with an elevated risk of most of the twenty-five short- and medium-term (up to 42 days) adverse events examined.

Additional information

- Health data (collected between December 20, 2020 until May 24, 2021) was derived from Israel's largest payer-provided health care organization that insures approximately 52% of the population of Israel, of which 1,736,832 (nearly 20% of the total population) were eligible for inclusion (final study population size differed for each adverse event).
    - Adverse events recorded wherein a previous diagnosis of an adverse event of the same type had occurred were excluded from analysis due to difficulty determining whether the event was a recoding of previous events or a true new event.
    - Population included was 16 years or older, had at least one year of health data, no previous SARS-CoV-2 infection, and no contact with the health care system in the previous 7 days (except for the comparison of infected and uninfected matches).
    - Additionally excluded were long-term care facility residents, persons confined to their homes for medical reasons, health care workers, and persons for whom data on body mass

index or residential area were missing, in which confounding could not adequately be addressed.

- Vaccinated and unvaccinated subjects were matched according to socio-demographic (age, sex, place of residence, socioeconomic status, population sector) and clinical variables (general clinical condition and disease load including number of pre-existing chronic conditions (those considered to be risk factors for severe COVID-19 by the United States Centers for Disease Control and Prevention), number of previous outpatient visits in the past year, pregnancy status).
    - Unvaccinated infected and uninfected matched comparisons were also assessed to determine adverse events related to infection without vaccination.
- RRs and RDs at 42 days after vaccination (21 days of follow-up data after each vaccination dose) or 42 days after diagnosis with SARS-CoV-2 were calculated using a Kaplan-Meier estimator.
- Adverse events included acute kidney injury, anemia, appendicitis, arrhythmia, arthritis, arthropathy, Bell's Palsy, cerebrovascular accident, deep vein thrombosis, herpes simplex, herpes zoster, intracranial hemorrhage, lymphadenopathy, lymphopenia, myocardial infarction, myocarditis, neutropenia, other thrombosis, paresthesia, pericarditis, pulmonary embolus, seizures, syncope, thrombocytopenia, uveitis, and vertigo.
    - For each adverse event, follow-up was conducted until the adverse event occurred, 42 days, the end of the study calendar period, death, the unvaccinated matched pair received a first dose of vaccine, or either vaccinated or unvaccinated pair was diagnosed with SARS-CoV-2 infection.
- Authors include the following limitations and notes:
    - Protective effects of vaccination compared to unvaccinated, uninfected individuals may be a result of undiagnosed SARS-CoV-2 infections (lack of testing or because of false negative PCR test results) in the unvaccinated comparison groups.
    - Study participants were not randomly assigned according to exposures, which may introduce selection bias at censoring and confounding at baseline.
    - The matching process created a study population with a difference in median age of 5 compared to the eligible population, which given that younger groups are more likely to report myocarditis, could skew adverse events reporting between these two groups.
    - Populations such as health care workers and residents in long term care facilities that could be at higher risk of certain adverse events were excluded which affects the generalizability of the results.
    - Some diagnoses could be missed if reporting from out-of-network hospitals was not appropriately entered in the database used.
    - Vaccinated individuals may be more likely to have health care-seeking behaviours, thus identifying more adverse events; this applies similarly to individuals who are infected with SARS-CoV-2.

- Authors acknowledge that there cannot be a true direct comparison of the data from the vaccinated/unvaccinated and infected/uninfected matched pairs because comparisons were derived from different cohorts and made up of different compositions.
- The study does not address risk among persons with prior medical history of a particular adverse event.
- The study does not address adverse events that may occur after 42 days.

PHO reviewer's comments

- While the risk of myocarditis is increased following vaccination with Pfizer-BioNTech (1 to 5 events per 100,000 persons); however, the risk of myocarditis following SARS-CoV-2 infection was substantially increased, as was the risk for other adverse events.
- This study did not find an association between BNT162b2 vaccine and various thromboembolic events.
- This study does not include adverse outcomes for vaccinated, infected individuals. Therefore, any effect of vaccination either increasing or decreasing risk of adverse outcomes compared to unvaccinated infected individuals cannot be made from this data; however, vaccination is well known to reduce severe outcomes related to SARS-CoV-2 infection and related hospitalization and death.

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Review of “Safety of the BNT162b2 mRNA covid-19 vaccine in a nationwide setting”. Toronto, ON: Queen’s Printer for Ontario; 2021.

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