Largest real-world study of third dose of COVID-19 vaccine effectiveness shows Delta resistance

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The Clalit Research Institute, in collaboration with researchers from Harvard University, analyzed one of the world's largest integrated health

record databases to examine the effectiveness of the third dose of the Pfizer/BioNTech BNT162B2 vaccine against the Delta variant of SARS-CoV-2. The study provides the largest peer-reviewed evaluation of the effectiveness of a third "booster" dose of a COVID-19 vaccine in a nationwide mass-vaccination setting. The study was conducted in Israel. It is published in *The Lancet* journal.

Many countries are currently experiencing a resurgence of SARS-CoV-2 infections despite hitherto successful vaccination campaigns. This may be due to the greater infectiousness of the Delta (B.1.617.2) variant of SARS-CoV-2, and to waning immunity of vaccines administered months earlier. In the face of the current resurgence, several countries are planning to administer a third booster dose of mRNA COVID-19 vaccine.

This study suggests that a third vaccine dose is effective in reducing severe COVID-19-related outcomes compared to individuals who have received two vaccine doses at least 5 months ago. It is the first to estimate the effectiveness of a third dose of an mRNA COVID-19 vaccine—BNT162b2 specifically—against severe outcomes with adjustment for various possible confounders, including comorbidities and behavioral factors. The study's large size also allows a more precise assessment of the vaccine's effectiveness across different time periods, different subpopulations (by sex, age and number of comorbidities), and different severe outcomes (which are rarer and thus require greater sample size). A recent clinical trial conducted by BioNTech included a smaller sample size and did not estimate the third-dose's effects for more severe outcomes.

The study took place from July 30, 2021 through Sept 23, 2021, coinciding with Israel's fourth wave of coronavirus infection and illness, during which the Delta (B.1.617.2) variant was the dominant strain in the country for new infections (with very few exceptions).

Researchers reviewed data from 728,321 individuals aged 12 or above who had received the third dose of the BNT162b2 vaccine. These individuals were carefully matched 1:1 with 728,321 individuals who had received only two shots of the BNT162b2 vaccine at least five months prior. The matching was based on an extensive set of demographic, geographic and health-related attributes associated with risk of infection, risk of severe disease, health status and health seeking behavior. Individuals were assigned to each group dynamically based on their changing vaccination status (198,476 individuals moved from the unvaccinated cohort into the vaccinated cohort during the study). Multiple analyses were conducted to ensure that the estimated vaccine effectiveness was robust to potential biases. The study included a total of over 12,000,000 person-days of follow-up.

The results show that, compared with individuals who received only two doses five months prior, individuals who received three doses of the vaccine (7 days or more after the third dose) had 93% lower risk of COVID-19-related hospitalization, 92% lower risk of severe COVID-19 disease, and 81% lower risk of COVID-19-related death. Vaccine effectiveness was found to be similar for different sexes, age groups (ages 40-69 and 70+) and number of comorbidities.

The study also included a population-level analysis which found that infection rates began to drop for each age group 7-10 days after that age group became eligible for the third dose.

"These results show convincingly that the third dose of the vaccine is highly effective against severe COVID-19-related outcomes in different age groups and population subgroups, one week after the third dose. These data should facilitate informed policy decision-making," said Prof. Ran Balicer, senior author of the study, Director of the Clalit Research Institute and Chief Innovation Officer for Clalit.

Prof. Ben Reis, Director of the Predictive Medicine Group at the Boston Children's Hospital Computational Health Informatics Program and Harvard Medical School, said that "to date, one of the main drivers of vaccine hesitancy has been a lack of information regarding the effectiveness of the vaccine. This careful epidemiological study provides reliable information on third-dose vaccine effectiveness, which we hope will be helpful to those who have not yet decided about vaccination with a third dose."

More information: Ran Balicer et al, Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study, *The Lancet*, 2021.

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