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Largest real-world study of COVID-19 vaccine safety published

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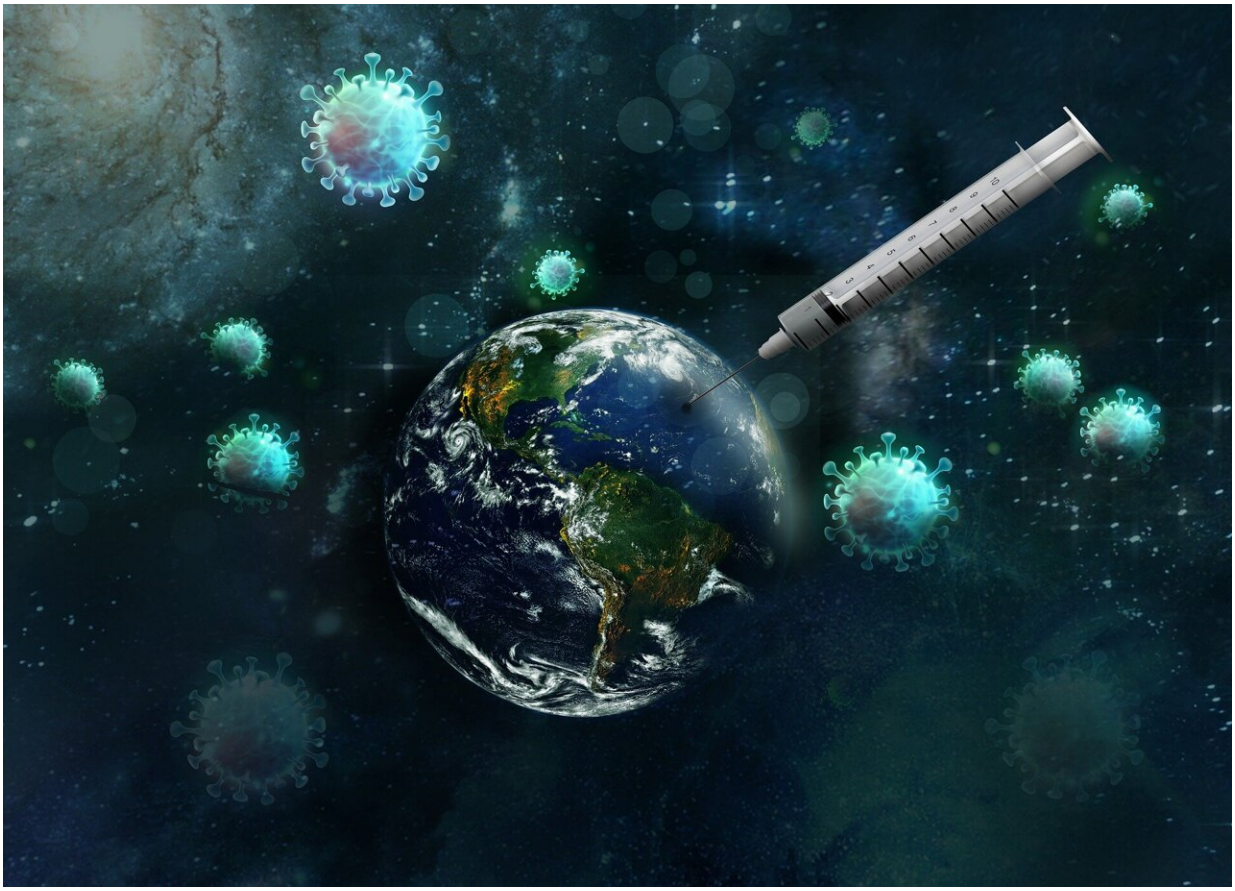

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The Clalit Research Institute, in collaboration with researchers from Harvard University, analyzed one of the world's largest integrated health

record databases to examine the safety of the Pfizer/BioNTech BNT162B2 vaccine against COVID-19. The study provides the largest peer-reviewed evaluation of the safety of a COVID-19 vaccine in a nationwide mass-vaccination setting. The study was conducted in Israel, an early global leader in COVID-19 vaccination rates.

Previous efforts to characterize vaccine safety have relied on voluntary active reporting by vaccinated individuals, which is known to be incomplete. The present study relies on the analysis of millions of anonymized electronic medical records, which are far more comprehensive.

Furthermore, in order to provide the necessary context for interpreting vaccine safety findings, this study is the first to examine a wide range of adverse events both among vaccinated individuals and among unvaccinated individuals who were infected with the coronavirus. Thus, two separate analyses were conducted:

1. Vaccination Outcomes Analysis: 884,828 vaccinated individuals aged 16 and over were carefully matched with 884,828 unvaccinated individuals based on an extensive set of sociodemographic, geographic and health-related attributes. Individuals were assigned to each group dynamically based on their changing vaccination status (235,541 individuals moved from the unvaccinated cohort into the vaccinated cohort during the study). Rates of the 25 potential adverse events within three weeks following either vaccine dose were compared between the two groups. This analysis took place from December 20, 2020, the launch of Israel's national vaccination campaign, through May 24, 2021.
2. Infection Outcomes Analysis: To provide context for the vaccine safety findings above, a separate analysis was conducted that estimated the rates of the same 25 potential adverse events

> among 173,106 unvaccinated individuals who were infected with the coronavirus, compared to 173,106 carefully matched controls who were not infected with the coronavirus. This analysis took place from March 1, 2020 (the beginning of the COVID-19 pandemic in Israel) through May 24, 2021.

The vaccine was found to be safe: Out of 25 potential side effects examined, 4 were found to have a strong association with the vaccine.

Myocarditis was found to be associated with the vaccine, but rarely—2.7 excess cases per 100,000 vaccinated individuals. (The myocarditis events observed after vaccination were concentrated in males between 20 and 34.) In contrast, coronavirus infection in unvaccinated individuals was associated with 11 excess cases of myocarditis per 100,000 infected individuals.

Other adverse events moderately associated with vaccination were swelling of the lymph nodes, a mild side effect that is part of a standard immune response to vaccination, with 78 excess cases per 100,000, appendicitis with 5 excess cases per 100,000 (potentially as a result of swelling of lymph nodes around the appendix), and herpes zoster with 16 excess cases per 100,000.

In contrast to the relatively small number of adverse effects associated with the vaccine, high rates of multiple serious adverse events were associated with coronavirus infection among unvaccinated patients, including: Cardiac arrhythmias (a 3.8-fold increase to an increase of 166 cases per 100,000 infected patients), kidney damage (14.8-fold increase; 125 excess cases per 100,000), pericarditis (5.4-fold increase; 11 excess cases per 100,000), pulmonary embolism (12.1-fold increase; 62 excess cases per 100,000), deep vein thrombosis (3.8-fold increase; 43 excess cases per 100,000), myocardial infarction (4.5-fold increase; 25 excess cases per 100,000), and stroke (2.1-fold increase; 14 excess cases per

100,000).

The research was conducted by Dr. Noam Barda, Dr. Noa Dagan, Yair Ben-Shlomo, Dr. Eldad Kepten, Dr. Jacob Waxman, Reut Ohana and Prof. Ran Balicer from the Clalit Research Institute, Dr. Doron Netzer of Clalit Health Services, as well as Prof. Miguel Hernán and Prof. Marc Lipsitch of the Harvard T.H. Chan School of Public Health, Prof. Isaac Kohane of the Department of Biomedical Informatics at Harvard Medical School, and Prof. Ben Reis of Boston Children's Hospital and Harvard Medical School.

This study focused on adverse events that may develop in the short to medium term after vaccination, and those with clinical significance. The study did not focus on common immediate symptoms such as redness and discomfort at the injection site or fever. Symptoms that occurred within 6 weeks of the vaccine (three weeks after each vaccine dose) were defined as an adverse event of the vaccine if they occurred more frequently among the vaccinated group compared to the control group.

The results of this study validate and complement the previously reported findings of the Pfizer/BioNTech Phase-III randomized clinical trial, which, with 21,720 vaccinated individuals, could not precisely and comprehensively assess vaccine safety. The present study's large size allows a more detailed assessment of the vaccine's safety across a wider range of adverse events.

"The extensive nationwide rollout of Israel's COVID-19 vaccination campaign provided the Clalit Research Institute with a unique opportunity to assess, through its rich and comprehensive digital datasets, the safety of the vaccine in a real-world setting, without needing to rely on individual-driven active reporting of side-effects" said Prof. Ran Balicer, senior author of the study, Director of the Clalit Research Institute and Chief Innovation Officer for Clalit. "These results

show convincingly that this mRNA vaccine is very safe and that the alternative of 'natural' morbidity caused by the coronavirus puts a person at significant, higher and much more common risk of serious adverse events. These data should facilitate informed individual risk-benefit decision-making, and, in our view, make a strong argument in favor of opting-in to get vaccinated, especially in countries where the virus is currently widespread," added Prof. Balicer, who also serves as Chairman of Israel's National Expert Advisory Team on COVID-19 response.

"This study sheds light for the first time on the significant side effects of the coronavirus vaccine. Since this is a more comprehensive analysis based on electronic medical records, these are more reliable assessments than those published to date which have relied on voluntary active reporting systems," explains Doron Netzer, Chief Medical Officer of Clalit's Community Health Division.

Prof. Ben Reis, Director of the Predictive Medicine Group at the Boston Children's Hospital Computational Health Informatics Program and Harvard Medical School, said, "To date, one of the main drivers of vaccine hesitancy has been a lack of information regarding potential side effects of the vaccine. This careful epidemiological study provides reliable information on vaccine safety, which we hope will be helpful to those who have not yet decided about vaccination." He continued, "Those who have hesitated until now to get vaccinated due to concerns about very rare side effects—such as myocarditis—should be aware that the risks for this very same side effect are actually higher among unvaccinated infected individuals."

Prof. Miguel Hernán, Director of the CAUSALab and Professor at the Harvard T.H. Chan School of Public Health, said, "This research is a perfect example of how randomized trials and observational healthcare databases complement each other. The original trial of the Pfizer/BioNTech vaccine provided evidence of its safety, but the

estimates were too imprecise given the small sample size. This analysis of Clalit's high-quality database emulates the design of the original trial, uses its findings as a benchmark, and expands upon them to confirm the vaccine's safety on a wide range of adverse events. This combination of evidence from randomized trials and observational studies is a model for efficient medical research, something which is especially important in COVID times."

Prof. Marc Lipsitch, Director of the Center for Communicable Disease Dynamics and Professor at the Harvard T.H. Chan School of Public Health, said, "In all studies of vaccine safety, a major challenge is to ensure that those we are comparing to identify the vaccine's side effects are similar in the other characteristics that may predict whether they will experience these side effects. This is especially hard in the context of a rapidly growing, age-targeted vaccine campaign. Clalit's extraordinary database made it possible to design a study that addressed these challenges in a way that provides tremendous confidence in the inferences that come out of the study."

The research was funded in part by the newly announced Ivan and Francesca Berkowitz Family Living Laboratory Collaboration at Harvard Medical School and Clalit Research Institute. "The strengthening of the scientific collaboration between Harvard and Clalit made possible by the Berkowitz Living Laboratory Collaboration is already bearing fruit and giving us a foretaste of the value of healthcare systems instrumented for research," said Prof. Isaac Kohane, Chair of the Department of Biomedical Informatics at Harvard Medical School and co-Director of the Ivan and Francesca Berkowitz Family Living Laboratory Collaboration along with Professor Balicer. "Israel offers a unique environment in which to study the vaccine and its effects, and this study is an excellent example of what can be accomplished through such close scientific collaborations."

More information: Noam Barda et al, Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting, *New England Journal of Medicine* (2021). DOI: 10.1056/NEJMoa2110475