RESEARCH LETTER

Myocardial Infarction, Stroke, and Pulmonary Embolism After BNT162b2 mRNA COVID-19 Vaccine in People Aged 75 Years or Older

The BNT162b2 mRNA vaccine (Pfizer-BioNTech) was the first SARS-CoV-2 vaccine authorized and most widely used in older persons in France. Although no increases in cardiovascular events were reported in the phase 3 trials,[1] questions emerged once the vaccine was used on a large scale because older people were underrepresented in the trials. We evaluated the short-term risk of severe cardiovascular events among French people aged 75 years or older after the administration of the BNT162b2 mRNA vaccine.

Supplemental content

Methods | This population-based study used the French National Health Data System linked to the national COVID-19 vaccination database. Eligible participants were all persons unvaccinated or vaccinated with the BNT162b2 vaccine, aged 75 years or older, admitted to the hospital between December 15, 2020, and April 30, 2021, for acute myocardial infarction, hemorrhagic stroke, ischemic stroke, or pulmonary embolism (diagnoses identified using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,* codes) (**Table 1** and eTable in the Supplement).

We undertook within-person comparisons using a self-controlled case series method adapted to cardiovascular event-dependent exposures and high-event-related mortality that can cancel or defer subsequent vaccination or increase short-term mortality[2] (eMethods in the Supplement). Only exposures preceding the event were considered. Exposure risk intervals were the 1 through 14 days following each of the 2 vaccine doses. The exposure risk interval was further subdivided into days 1 through 7 and 8 through 14. Except for the vaccination day, the remaining periods were regarded as nonrisk periods. Unvaccinated persons were

Table 1. Baseline Characteristics and Vaccination: Description of Cardiovascular Events That Occurred in Hospitals in France Between December 15, 2020, and April 30, 2021

	No. (%)			
	Acute myocardial infarction	Stroke		Pulmonary embolism
		Ischemic	Hemorrhagic	
Total No. of events	11 489	17 386	4891	7296
No. of persons with the event	11 113	17 014	4804	7221
No. of persons with ≥1 dose of the vaccine[a]	6510 (58.6)	9162 (54.0)	2050 (42.7)	3993 (55.3)
Month of event occurrence				
December 15, 2020-January 31, 2021	1312 (20.2)	2112 (23.0)	564 (27.5)	963 (24.1)
February 2021	1135 (17.4)	1657 (18.1)	424 (20.7)	675 (16.9)
March 2021	2640 (40.6)	3297 (36.0)	688 (33.6)	1450 (36.3)
April 2021	1423 (21.8)	2096 (22.9)	374 (18.2)	905 (22.7)
No. of persons with 2 doses of the vaccine[a]	4843 (43.6)	6531 (38.0)	1366 (28.4)	2889 (40.0)
Month of event occurrence				
December 15, 2020-January 31, 2021	20 (0.4)	44 (0.7)	9 (0.7)	18 (0.6)
February 2021	1242 (25.6)	1947 (29.8)	477 (34.9)	890 (30.8)
March 2021	1219 (25.2)	1610 (24.6)	352 (25.8)	683 (23.6)
April 2021	2362 (48.8)	2930 (44.9)	528 (38.6)	1298 (44.9)
No. of unvaccinated persons	4603 (41.4)	7852 (46.0)	2754 (57.3)	3228 (44.7)
Month of event occurrence				
December 15, 2020-January 31, 2021	2010 (43.7)	3304 (42.1)	1273 (46.2)	1347 (41.7)
February 2021	900 (19.5)	1648 (21.0)	591 (21.4)	687 (21.3)
March 2021	954 (20.7)	1720 (21.9)	569 (20.7)	669 (20.7)
April 2021	739 (16.1)	1180 (15.0)	321 (11.7)	525 (16.3)
Age at onset of the first event, y				
Mean (SD)	84 (6)	85 (6)	85 (6)	85 (6)
Median (IQR)	84 (79-88)	85 (81-90)	85 (80-89)	84 (80-89)
Women	5110 (46)	9986 (59)	2557 (53)	4534 (63)
Men	6003 (54)	7028 (41)	2247 (47)	2687 (37)
Died	2059 (19)	3971 (23)	2336 (49)	1234 (17)

[a] For vaccinated individuals between December 27, 2020 (the starting day of the vaccination campaign against SARS-CoV-2 in France) and April 30, 2021 (the end of the observation period).

Table 2. Relative Incidence of Severe Cardiovascular Events During the 14-Day Risk Periods After Exposure to the First and Second Dose of BNT162b2 Vaccine vs the Nonrisk Periods

	Acute myocardial infarction		Stroke				Pulmonary embolism	
			Ischemic		Hemorrhagic			
	No. of cases	RI (95% CI)	No. of cases	RI (95% CI)	No. of cases	RI (95% CI)	No. of cases	RI (95% CI)
Nonrisk periods	5233	1 [Reference]	7407	1 [Reference]	1548	1 [Reference]	3264	1 [Reference]
Mean No. of days per person	123.5		122.8		119.4		123.5	
Risk period after first dose, d								
0[a]	13	0.23 (0.13-0.40)	24	0.29 (0.20-0.44)	7	0.30 (0.14-0.64)	6	0.18 (0.08-0.41)
1-14	717	0.97 (0.88-1.06)	991	0.90 (0.84-0.98)	274	0.90 (0.78-1.04)	379	0.85 (0.75-0.96)
Subintervals								
0[a]	13	0.23 (0.13-0.40)	24	0.29 (0.20-0.44)	7	0.30 (0.14-0.64)	6	0.18 (0.08-0.41)
1-7	326	0.84 (0.75-0.95)	505	0.90 (0.82-0.99)	142	0.91 (0.75-1.09)	188	0.82 (0.70-0.96)
8-14	391	1.08 (0.97-1.21)	486	0.90 (0.82-0.99)	132	0.89 (0.73-1.07)	191	0.88 (0.75-1.02)
Risk period after second dose, d								
0[a]	9	0.22 (0.11-0.42)	22	0.37 (0.24-0.56)	8	0.45 (0.22-0.93)	12	0.51 (0.29-0.91)
1-14	538	1.04 (0.93-1.16)	718	0.92 (0.84-1.02)	213	0.97 (0.81-1.15)	332	1.10 (0.95-1.26)
Subintervals								
0[a]	9	0.22 (0.11-0.42)	22	0.37 (0.24-0.56)	8	0.45 (0.22-0.93)	12	0.51 (0.29-0.91)
1-7	269	0.97 (0.84-1.11)	363	0.87 (0.78-1.00)	113	0.95 (0.76-1.17)	167	1.04 (0.86-1.25)
8-14	269	1.11 (0.97-1.28)	355	0.96 (0.85-1.08)	100	0.99 (0.79-1.23)	165	1.15 (0.97-1.37)

Abbreviation: RI, relative incidence.

[a] Day 0 refers to the day of the vaccine injection.

included to account for temporal effects. Unbiased estimating equations were used to calculate the relative incidence (RI) adjusted for temporality (in 7-day increments) to consider any changes in background rates of both events and vaccination. All analyses were performed using the SCCS package in R, version 3.6.1. A 95% CI around the RI that did not include 1 defined statistical significance.

The research group has permanent regulatory access to the data from the French National Health Data System (French decree No. 2016-1871 of December 26, 2016, on the processing of personal data called National Health Data System and French law). No informed consent was required because data are anonymized.

Results | As of April 30, 2021, nearly 3.9 million persons 75 years or older had received at least 1 dose of the BNT162b2 vaccine and 3.2 million had received 2 doses. Over the observation period, 11 113 persons 75 years or older were hospitalized for an acute myocardial infarction, 17 014 for an ischemic stroke, 4804 for a hemorrhagic stroke, and 7221 for pulmonary embolism, of whom 58.6%, 54.0%, 42.7%, and 55.3%, respectively, received at least 1 dose of the vaccine (Table 1). In the 14 days following either dose, no significant increased risk was found for any outcome: the RI for myocardial infarction for the first dose was 0.97 (95% CI, 0.88-1.06) and for the second dose, 1.04 (95% CI, 0.93-1.16); for ischemic stroke for the first dose, 0.90 (95% CI, 0.84-0.98) and for the second dose, 0.92 (95% CI, 0.84-1.02); for hemorrhagic stroke for the first dose, 0.90 (95% CI, 0.78-1.04) and for the second dose, 0.97 (95% CI, 0.81-1.15); or for pulmonary embolism for the first dose, 0.85 (95% CI, 0.75-0.96) and the second dose, 1.10 (95% CI, 0.95-1.26) (**Table 2**). No significant increase for any of the cardiovascular events was observed in the 2 subdivided exposure intervals (1-7 days and 8-14 days) (Table 2).

Discussion | In this nationwide study involving persons aged 75 years or older in France, no increase in the incidence of acute myocardial infarction, stroke, and pulmonary embolism was detected 14 days following each BNT162b2 mRNA vaccine dose.

Israeli and US studies reported that persons receiving the BNT162b2 vaccine were not at increased risk of myocardial infarction, pulmonary embolism, or cerebrovascular events in the 42 days[3] and 21 days[4] following vaccination. Based on a self-controlled case-series design that compensates for the lack of randomization by eliminating the effect of time-invariant confounding factors, this study provides further evidence regarding the risk of serious cardiovascular adverse events in older people. Limitations of the study include the possibility of residual time-dependent confounding.

Further investigations are needed to measure these risks in younger populations and for other types of vaccines against SARS-CoV-2.

Marie Joelle Jabagi, PharmD, PhD
Jérémie Botton, PharmD, PhD
Marion Bertrand, MSc
Alain Weill, MD
Paddy Farrington, PhD
Mahmoud Zureik, MD, PhD
Rosemary Dray-Spira, MD, PhD

Author Affiliations: EPI-PHARE, French National Agency for Medicines and Health Products Safety, French National Health Insurance, Saint-Denis, France (Jabagi, Botton, Bertrand, Weill, Zureik, Dray-Spira); School of Mathematics and Statistics, the Open University, Milton Keynes, United Kingdom (Farrington).

Corresponding Author: Marie Joelle Jabagi, PharmD, PhD, EPI-PHARE, 143-147 Boulevard Anatole France, F-93285 Saint-Denis CEDEX (marie-joelle.jabagi@ansm.sante.fr).

Accepted for Publication: November 15, 2021.

Published Online: November 22, 2021. doi:10.1001/jama.2021.21699

Author Contributions: Drs Jabagi and Bertrand had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Jabagi, Botton, Bertrand, Weill, Zureik, Dray-Spira.
Drafting of the manuscript: Jabagi, Bertrand, Zureik.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Jabagi, Botton, Bertrand, Farrington.
Supervision: Botton, Weill, Zureik, Dray-Spira.

Conflict of Interest Disclosures: None reported.

Additional Contributions: Stephane Le Vu, PharmD, PhD, and Kim Bouillon, MD, PhD, EPI-PHARE, Saint-Denis, France, reviewed the manuscript without compensation. Bérangère Baricault, Msc, and Jerome Drouin, Msc, EPI-PHARE, Saint-Denis, France, provided unpaid technical support related to data management.

1. Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577

2. Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures. *Biostatistics*. 2009;10(1):3-16. doi:10.1093/biostatistics/kxn013

3. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. *N Engl J Med*. 2021;385(12):1078-1090. doi:10.1056/NEJMoa2110475

4. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA*. 2021;326(14):1390-1399. doi:10.1001/jama.2021.15072