Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Self-controlled case series analysis

Since vaccinated and unvaccinated subjects may vary by characteristics such as frailty and risk factors for cardiovascular events that are difficult to measure and control for, we undertook within-person comparisons using the self-controlled case-series method. The advantages of this method are that only cases are needed, and it is self-matched so that time-invariant multiplicative confounders are necessarily adjusted. The method[1] was initially described in 1995 by Paddy Farrington and has been frequently adopted for vaccine safety evaluation.[2,3,4,5,6]

However, in order to take into consideration that the occurrence of severe cardiovascular events may delay or cancel post-event vaccination and the fact that these events may increase short-term mortality, we used an adaptation of the self-controlled case-series method: the SCCS model for event-dependent exposures.[7] In this approach, only exposures preceding the event's occurrence are considered to model the risk. In addition, the observation period of every case ended on April 30, 2021, irrespective of whether they died.

The observation period extended from December 15, 2020, to April 30, 2021, and included all four events of interest (acute myocardial infarction, hemorrhagic stroke, ischemic stroke, or pulmonary embolism) occurring in vaccinated and unvaccinated individuals of 75 years and over. Diagnoses were identified in the database using the ICD-10 codes (etable 1). Subjects vaccinated with a Covid-19 vaccine other than the BNT162b2 mRNA vaccine were excluded from the analysis. The inclusion of the unvaccinated individuals is required for this specific SCCS approach. Lack of vaccination may indicate cancellation of vaccination and may tend to occur more often for earlier events. Thus, to obtain the correct temporal effect and avoid bias in the relative incidence, unvaccinated cases must be included.

The exposure risk intervals, defined as the 15 days following each of the 1st and second doses of the vaccine, were subdivided into two sub-periods: a specific sub-interval corresponding to the same day of vaccination (day 0) and a sub-interval extending from 1 to 14 days after vaccination. The exposure risk interval was further subdivided into three sub-intervals: day 0; days 1 through 7; and 8 through 14. Day 0 was defined as a separate risk period to ensure it is not included in the control periods or the primary interest risk period (since a case is unlikely to be vaccinated when admitted to the hospital for an acute event). Unbiased estimating equations are used to calculate the relative incidence at each dose by comparing the incidence in the risk interval (1 to 14 days after each of the two vaccine doses) with the incidence in other post-exposure periods (non–risk periods), as required for the SCCS model for event-dependent exposure. In this model, all exposures that occur after an event are disregarded and treated as missing because their timing may depend on the event. Additional unbiased estimating equations using all observation time contribute to estimating the temporal effects. The estimating equations are derived under a counterfactual in which no exposures can occur after an event. Measures of the relative incidence were derived using R software (package SCCS)[8] adjusted for seasonality (in 7-days increments) to take into account any temporal changes in background rates.

eTable. *ICD-10* codes used to define severe cardiovascular events of interest

ICD - 10 codes				
Acute myocardial infarction				
I21	Acute myocardial infarction			
Ischemic stroke				
I63	Cerebral infarction			
I64	Stroke, not specified as hemorrhagic or infarction			
Hemorrhagic stroke				
I60	Subarachnoid hemorrhage			
I61	Intracerebral hemorrhage			
I62	Other non-traumatic intracranial hemorrhages			
Pulmonary embolism				
I26	Pulmonary embolism			

eReferences

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