Incidence Rates of Safety Outcomes in a Post-Approval Study of the Pfizer-BioNTech Monovalent COVID-19 Vaccine in the United States, Booster Dose Analysis

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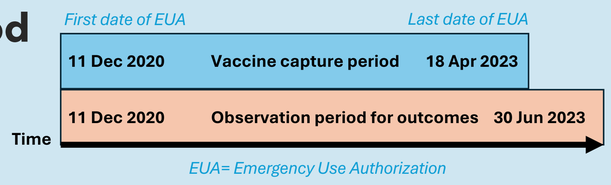
Background and Objective

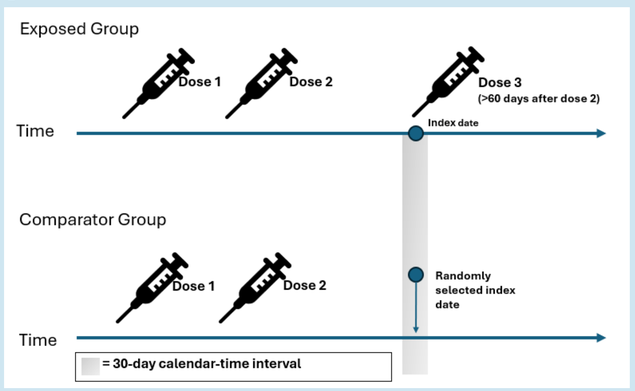
- A post-approval safety study [EUPAS43468] is ongoing in the US to assess the safety of the original Pfizer-BioNTech monovalent COVID-19 vaccine (BNT162b2) as a booster dose using data from immunization registries and 5 health insurers participating in the FDA's Sentinel System
- Among a cohort of individuals who have received 2 BNT162b2 doses, the study will compare the incidence of 26 safety events of interest in those who have received a 3rd dose of BNT162b2 to those who have not received a 3rd dose of any COVID-19 vaccine
- As a part of an interim analysis conducted to inform final study implementation, we estimated incidence rates (IR) of myocarditis/pericarditis (myo/peri) in those who received a 3rd dose of BNT162b2 and matched comparators and calculated pooled IR for 25 additional safety events regardless of exposure status

Methods

Study Period



Population



- Individuals aged ≥6 months who previously received 2 monovalent BNT162b2 doses in a homologous series
- BNT162b2 booster recipients (3rd dose >60 days after 2nd dose) were matched to those who had not received a 3rd dose of any COVID-19 vaccine as of the same calendar interval using a 1:2 variable matching ratio by age, sex, US state, calendar time, time since last BNT162b2 dose, and propensity score

Eligibility Criteria

- Had at least 12 months of continuous medical and prescription drug coverage before the index date (or from birth, if < 12 months of age)
- Enrolled from the first date they were eligible to receive the vaccine, based on age-eligibility requirements
- Were within the age-authorized range for vaccination on the index date
- Before the index date, received 2 monovalent BNT162b2 doses in a homologous series

Covariates

- Calendar time, demographics (age, sex, state), comorbidities, comedications, vaccines targeting infections other than SARS-CoV-2, healthcare utilization, and time since 2nd BNT162b2 dose

Follow-up

- Individuals were followed from the day after index date (except anaphylaxis which started on index date) until the earliest of the following: safety event of interest; end of the outcome-specific risk interval; receipt of another brand of COVID-19 vaccine, Pfizer-BioNTech bivalent vaccine, or unknown brand of COVID-19 vaccine; disenrollment from the health plan; receipt of a later dose before the recommended dosing spacing* or death

Safety Events of Interest

- Algorithms to define 26 safety events and risk windows were informed by studies from the FDA's Biologics Effectiveness and Safety (BEST) Initiative and CDC's Vaccine Safety Datalink (VSD)

Statistical Analyses

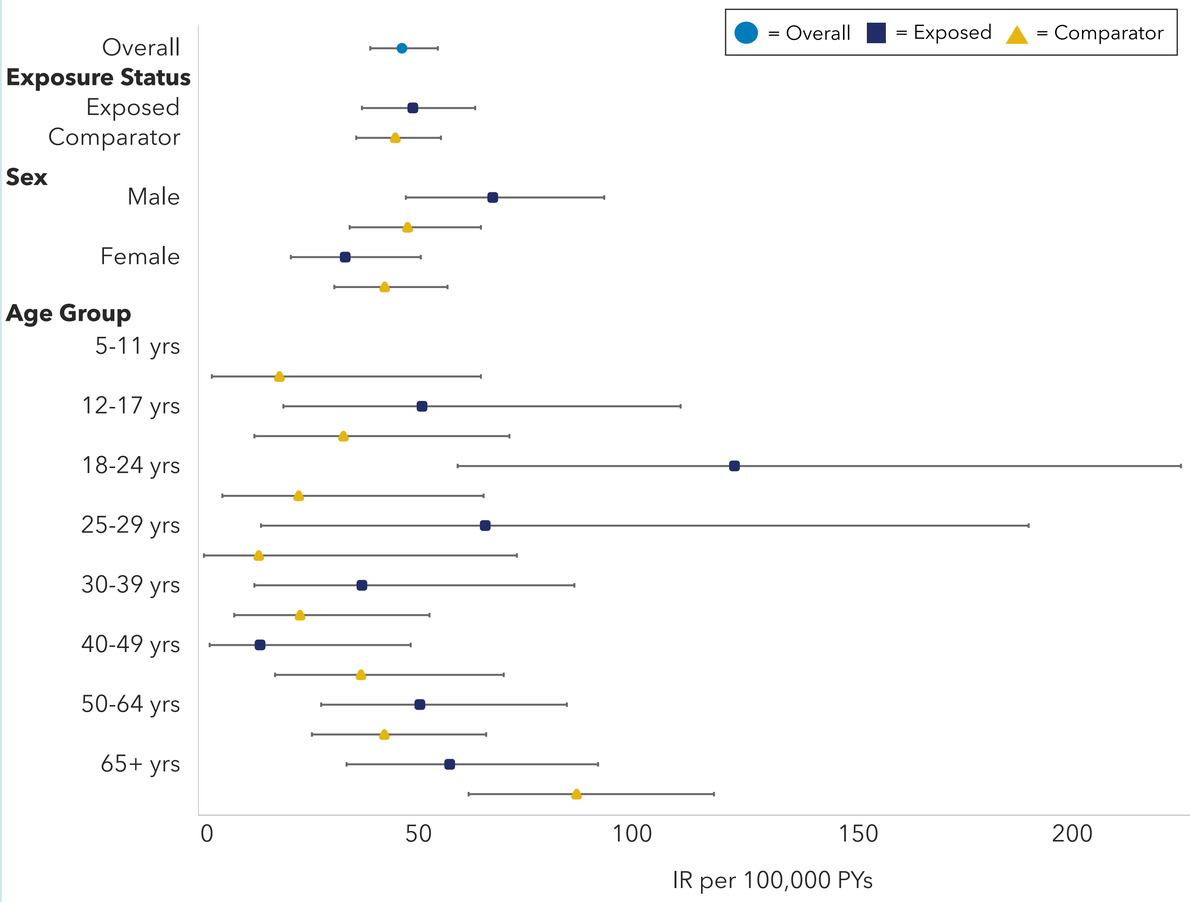
- In the matched population, IRs per 100,000 person years (PYs) and 95% confidence intervals (95% CI) were estimated overall (combined exposed and comparator groups) and in age-defined subgroups (5-11, 12-17, 18-64, 65+ years). For myo/peri, IR were stratified by exposure status, sex and additional age groups (5-11, 12-17,18–24, 25-29, 30-39, 40-49, 50-64, 65+ years)

**Recommended dose spacing: For 2nd dose was defined as receipt ≥ 17 days after dose 1, for 3rd dose was defined as receipt ≥ 24 days after dose 2*

Results

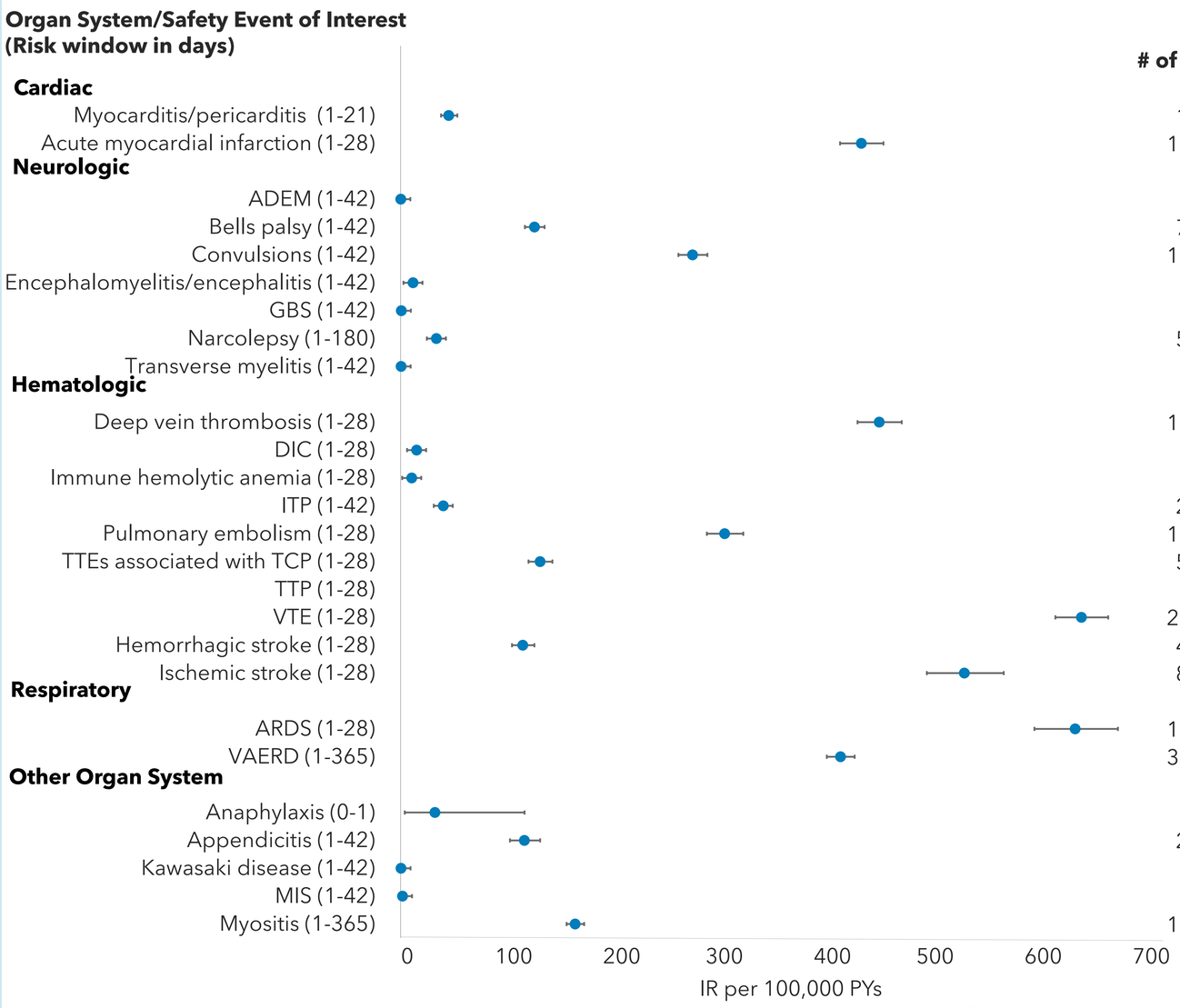
Study Population: Before matching: ~3.1 million booster recipients, ~6.8 million eligible comparators
After matching: ~ 2.1 million booster recipients, ~ 3.5 million comparators

Figure 1. IR of Myocarditis/Pericarditis (21-day risk window) Overall (Exposed and Comparator Combined), and by Exposure Status, Sex, and Age Group



	# of Events	IR (95%CI)
Overall	141	45.4 (38.2, 53.6)
Exposure Status		
Exposed	57	47.9 (36.3, 62.1)
Comparator	84	43.9 (35, 54.3)
Sex		
Male	36	66.1 (46.3,91.5)
	41	46.7 (33.5,63.4)
Female	21	32.5 (20.1,49.7)
	43	41.5 (30.0,55.8)
Age Group		
5-11 yrs	0	N/A
12-17 yrs	2	17.5 (2.1,63.4)
	6	50.0 (18.4,108.9)
18-24 yrs	6	32.1 (11.8,69.9)
	10	121.2 (58.1,222.9)
25-29 yrs	3	21.9 (4.5,64.0)
	3	64.4 (13.3,188.2)
30-39 yrs	1	12.8 (0.3,71.6)
	5	36.3 (11.8,84.7)
40-49 yrs	5	22.2 (7.2,51.7)
	2	13.1 (1.6,47.4)
50-64 yrs	9	36.1 (16.5,68.6)
	14	49.5 (27.0,83.0)
65+ yrs	19	41.4 (24.9,64.6)
	17	56.3 (32.8,90.1)
	39	85.2 (60.6,116.5)

Figure 2. IR of Safety Events of Interest (Exposed and Comparator Combined)



Organ System/Safety Event of Interest (Risk window in days)	# of Events	IR (95%CI)
Cardiac		
Myocarditis/pericarditis (1-21)	141	45.4 (38.2,53.6)
Acute myocardial infarction (1-28)	1,749	435.2 (415.1,456.1)
Neurologic		
ADEM (1-42)	1	0.2 (0.0,1.0)
Bells palsy (1-42)	725	126.4 (117.4,136.0)
Convulsions (1-42)	1,581	275.8 (262.4,289.8)
Encephalomyelitis/encephalitis (1-42)	67	11.7 (9.1,14.8)
GBS (1-42)	4	0.7 (0.2,1.8)
Narcolepsy (1-180)	568	33.8 (31.1,36.7)
Transverse myelitis (1-42)	3	0.5 (0.1,1.5)
Hematologic		
Deep vein thrombosis (1-28)	1,817	452.1 (431.6,473.4)
DIC (1-28)	61	15.1 (11.5,19.4)
Immune hemolytic anemia (1-28)	60	10.5 (8.0,13.5)
ITP (1-42)	231	40.3 (35.3,45.8)
Pulmonary embolism (1-28)	1,232	306.1 (289.3,323.7)
TTEs associated with TCP (1-28)	532	131.8 (120.8,143.4)
TTP (1-28)	0	N/A
VTE (1-28)	2,576	643.1 (618.5,668.4)
Hemorrhagic stroke (1-28)	466	115.4 (105.2,126.4)
Ischemic stroke (1-28)	841	532.5 (497.1,569.7)
Respiratory		
ARDS (1-28)	1,020	637.2 (598.7,677.6)
VAERD (1-365)	3,888	415.6 (402.6,428.9)
Other Organ System		
Anaphylaxis (0-1)	2	32.4 (3.9,117.1)
Appendicitis (1-42)	266	116.9 (103.3,131.8)
Kawasaki disease (1-42)	1	0.4 (0.0,2.4)
MIS (1-42)	4	1.8 (0.5,4.5)
Myositis (1-365)	1,544	164.9 (156.8,173.4)

ADEM = Acute disseminated encephalomyelitis; ARDS= Acute respiratory distress syndrome; DIC = Disseminated intravascular coagulation; GBS= Guillain-Barré syndrome; ITP = Immune thrombocytopenia; MIS = Multisystem inflammatory syndrome; N/A = Not applicable; TTEs associated with TCP = Thromboembolic events associated with thrombocytopenia; TTP = Thrombotic thrombocytopenic purpura; VAERD = Vaccine-associated enhanced respiratory disease; VTE= Venous thromboembolism

- The most common events in children were appendicitis [5-11 yrs: 14 events, IR: 150.2 (95% CI, 82.1-252.1); 12-17 yrs: 34 events, IR: 215.4 (95% CI,149.1-300.9)] and convulsions [5-11 yrs: 44 events, IR: 130.7 (95% CI, 94.9-175.4); 12-17 yrs: 92 events, IR: 157.1 (95% CI, 126.7-192.7)]
- VTE was the most common event in adults with event counts of 928 in individuals aged 18-64 [IR: 388.5 (95% CI, 363.9-414.3)] and 1,641 in individuals 65+ [IR: 1,695.9 (95% CI, 1,614.8-1,780.0)]. Among all age groups, <5 safety events were observed for ADEM, GBS, transverse myelitis, TTP, anaphylaxis, Kawasaki disease, and MIS
- In children 5-11 and 12-17 yrs, <5 safety events were observed for acute myocardial infarction, DIC, immune hemolytic anemia, pulmonary embolism, TTEs associated with TCP, hemorrhagic stroke, ischemic stroke, ARDS, and VAERD
- Additionally, in children 5-11 yrs, <5 safety events were observed for myo/peri, narcolepsy, deep vein thrombosis (DVT), ITP, and VTE

Discussion

Myocarditis/Pericarditis

- In the overall study population, the IR for myo/peri was similar in the exposed and comparator groups
- Consistent with findings from the VSD, the IR was numerically higher in the exposed group than in the comparator group among males and among younger individuals
- No cases of myo/peri were observed among exposed individuals aged 5-11 years

All Outcomes

- In the overall study population, there were at least 5 events each for most safety events of interest, but <5 events were observed for ADEM, GBS, transverse myelitis, anaphylaxis, Kawasaki disease, TTP and MIS
- Safety events of interest were uncommon among individuals aged 5 to 11 and 12 to 17 years

Conclusions

- Interim results suggest sufficient sample size to estimate robust effect estimates for many safety events in the final analysis
- Precision of hazard ratio estimates for rare outcomes may be limited in younger age groups, especially for myo/peri, narcolepsy, DVT, ITP and VTE in children ages 5-11 years

Disclosure Statement: This project was funded by Pfizer; some co-authors are employees and stockholders of Pfizer, the company that produced the vaccine being evaluated. Some co-authors are or were employed at nonprofit organizations (RTI Health Solutions, Harvard Pilgrim Health Care Institute, and HealthPartners) that conduct work for government and private organizations, including pharmaceutical companies. Some co-authors are employees of Optum and may own stock in UnitedHealth Group. Some co-authors are employees at CVS Health and may own stock in this company. One co-author was employed at CVS Health at the time of this study and is currently at Glade Oak. Some co-authors are employees at Carelon Research and may own stock in Elevance Health. Some co-authors are employees of Humana and may own stock in this company. Some co-authors are employed at StatLog

Acknowledgements: Pfizer COVID safety team: Heather Rubino, Cynthia de Luise, Susan Mather, Henry Goebe, Claudia Ianos, RTI Health Solutions: Kim Wideman, Harvard Pilgrim Health Care Institute: Shannon Walsh, Elizabeth Messenger-Jones, Maria Michaelidis, CVS Health: Harpreet Dhillon Kaur, Xi Wang, Smita Bhatia, Jim Marshall, Darshana Jaiswal, Anuj Saini, Yi Liu, Aparna Srikanti

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Presented at 41st Annual ISPE Meeting, 2025; Washington D.C., USA

Poster# A-334
COV-VAX-5939