

MedCheck in English No.27

COVID-19 Information

Vaccine increases venous thrombosis mortality

Supplementary appendix

2023-9-15

MedCheck Editorial team

Table. Venous thrombosis mortality risk after SARS-CoV-2 vaccination (Data: England)

General population (2015-2019) for reference			Vaccinated population (28 days after first dose)					Mortality rate ratio (Vaccinated/reference)	
Population total five years (N)	Venous thrombosis		Vaccine type	Vaccinated population (N)	Person- time (100,000 p-ys)	Venous thrombosis		Point estimate *	95% confidence interval
	Deaths (N)	Mortality rate (/100,000 p-ys)				Deaths (N)	Mortality rate (/100,000 p-ys)		
227,832,793	10,967	4.81	Pfizer	9,513,625	729,812	338	46.31	6.89 *	6.29-7.54
			AstraZeneca	19,608,007	1,504,176	499	33.17	9.63 *	8.61-10.72

- If the age distributions of death from venous thrombosis in vaccinee were equal to that in the venous thrombosis patients reported in the ref. [12], standardised mortality ratios (SMRs) were 5.64 (Pfizer) and 6.30 (AstraZeneca). If they were equal to that in the reference population, SMRs were 5.41 (Pfizer) and 7.02 (AstraZeneca) (Appendix 7-9)

p-ys : person-years

Appendix 1 : Calculation of venous thrombosis deaths following SARS-CoV-2 vaccination.

Table 3 | Incidence rate ratios (95% confidence intervals) for primary composite and risk periods immediately before and after exposure to vaccine and before and after adjusted for calendar time from 1 December 2020 to 24 April 2021

Outcome and time period	ChAdOx1 nCoV-19 vaccine		BNT162b2 mRNA vaccine	
	No of events	Incidence rate ratio (95% CI)	No of events	Incidence rate ratio (95% CI)
Composite primary outcomes				
Thrombocytopenia				
Baseline	3851	1.00	2009	1.00
-28 to -1 days	910	0.67 (0.62 to 0.72)	504	0.63 (0.56 to 0.69)
0 day	19	0.39 (0.25 to 0.62)	13	0.41 (0.23 to 0.70)
1-7 days	331	0.97 (0.87 to 1.10)	243	1.02 (0.89 to 1.18)
8-14 days	438	1.33 (1.19 to 1.47)	254	1.02 (0.89 to 1.17)
15-21 days	337	1.08 (0.96 to 1.22)	259	1.06 (0.93 to 1.22)
22-28 days	356	1.26 (1.13 to 1.42)	241	1.08 (0.94 to 1.23)

Supplementary table 7a: Incidence rate ratios (IRR) and after exposure to vaccination, adjusted for calendar time and sensitivity analyses.

		Sensitivity 1*	
		events	IRR (95% CI)
Thrombocytopenia			
ChAdOx1nCoV-19 vaccine	baseline	3840	1.00
	-28 to -1 days	909	0.67 (0.62, 0.72)
	0 day	19	0.41

- Hippisley-Cox's paper's subjects were vaccinees for first dose aged 16 years and over in England.
- Table 1 of the paper lists the number of vaccinees and Table 3 of the paper lists the number of cases of venous thrombosis within 28 days of vaccination.
- There were the number of venous thrombosis within 28 days after vaccination, excluding deaths in supplementary table 7a (Sensitivity analysis - 1) ; therefore by subtracting cases excluding deaths from cases including deaths, deaths can be calculated.
- There are case definitions for venous thrombosis in supplementary table 1 ; these are pulmonary embolism, portal vein thrombosis and other venous embolisms (ICD-10: I26, I81, I82).

Appendix2: Venous thrombosis mortality rate in general population in England (2015-2019)

Age group (years)	Venous thrombosis deaths within five years[15] (N)	Population for total five years[14] (N)	Venous thrombosis mortality rate (/100,000 pys)
16-29	65	52,397,619	0.12
30-39	176	36,952,299	0.48
40-49	427	36,556,960	1.17
50-59	872	36,793,199	2.37
60-69	1,668	29,533,992	5.65
70-79	2,742	21,976,076	12.48
80-89	3,558	11,148,041	31.92
>90	1,459	2,474,607	58.96

pys: person-years

Appendix3: Subjects and outcome in this research

England population aged over 16 years

SARS-CoV-2
Unvaccinated persons

SARS-CoV-2 vaccinee
(first dose)



Venous thrombosis mortality within 28 days after vaccine dose . . . (a)

Comparison for this research

Population in 2015-2019
(general population)*



Venous thrombosis mortality during 2015-2019 five years . . . (b)

Venous thrombosis mortality rate ratio=**(a)**/**(b)** . . . **Outcome**

Supplementary table 6a: Background crude incidence rates per 100,000 person years (95% CI) of primary outcomes in people aged 16+ for the 5 calendar years 2015-2019 using primary care data from the QResearch database (representative 20% sample of England) linked to hospital and mortality records

	Thrombocytopenia			Venous thromboembolism			Arterial thromboembolism		
	count	pyrs (100,000)	Rate (95% CI)	count	Pyrs (100,000)	Rate (95% CI)	count	Pyrs (100,000)	Rate (95% CI)

* Venous thrombosis incidence was written on supplementary table 6 in reference [12].

Appendix 4-1: diagnostic overlap

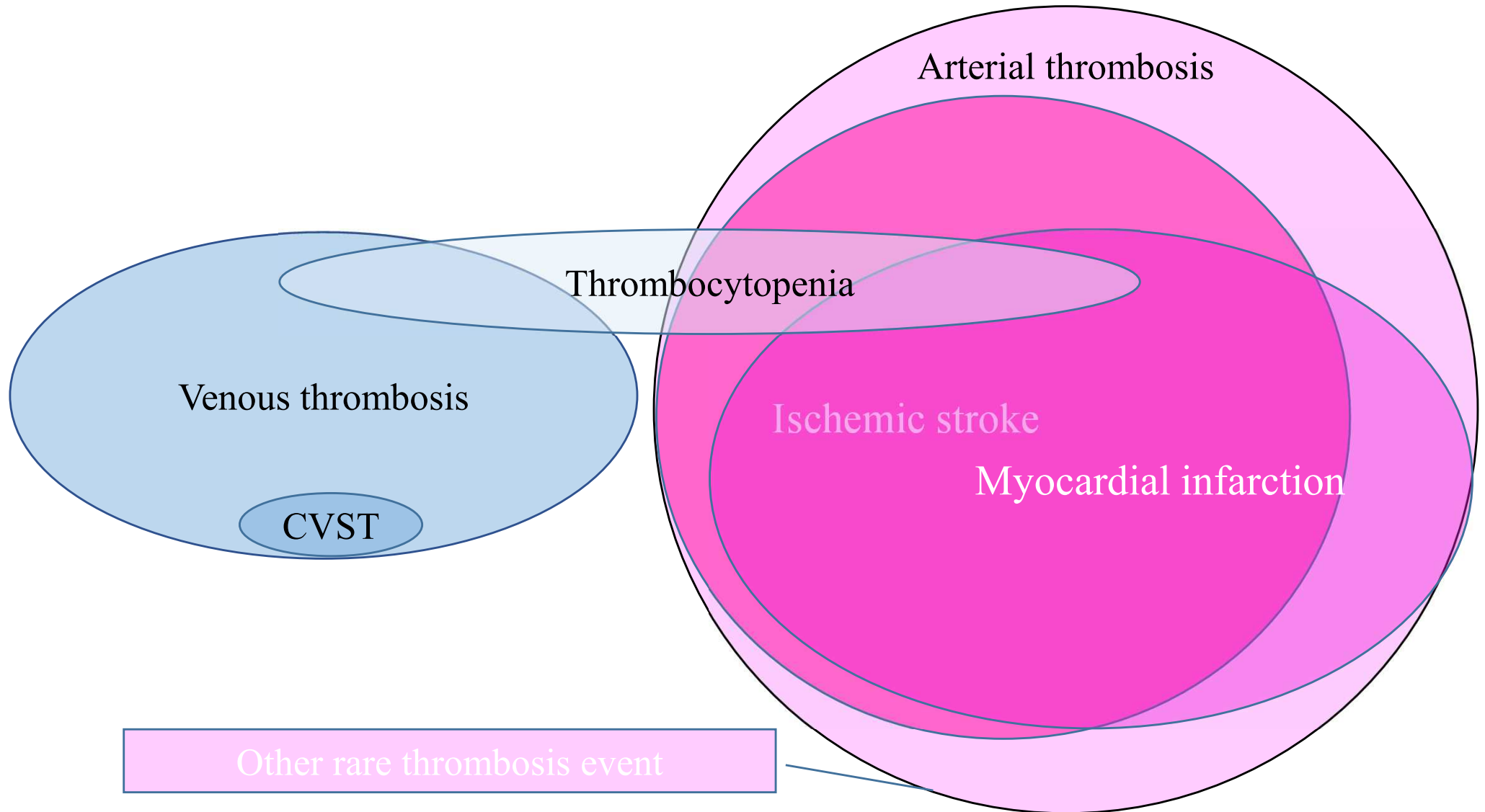
Supplementary table 3: Incidence rate ratio for thromboembolism; thrombocytopenia + vaccination and before and after a positive test

	Time period
Composite primary outcomes	
Thrombocytopenia + Venous thromboembolism	baseline
	-28 to -1 days
	0 day
	1-7 days
	8-14 days
	15-21 days
	22-28 days
Thrombocytopenia + Arterial thromboembolism	baseline
	-28 to -1 days
	0 day
	1-7 days
	8-14 days
	15-21 days
	22-28 days

Results

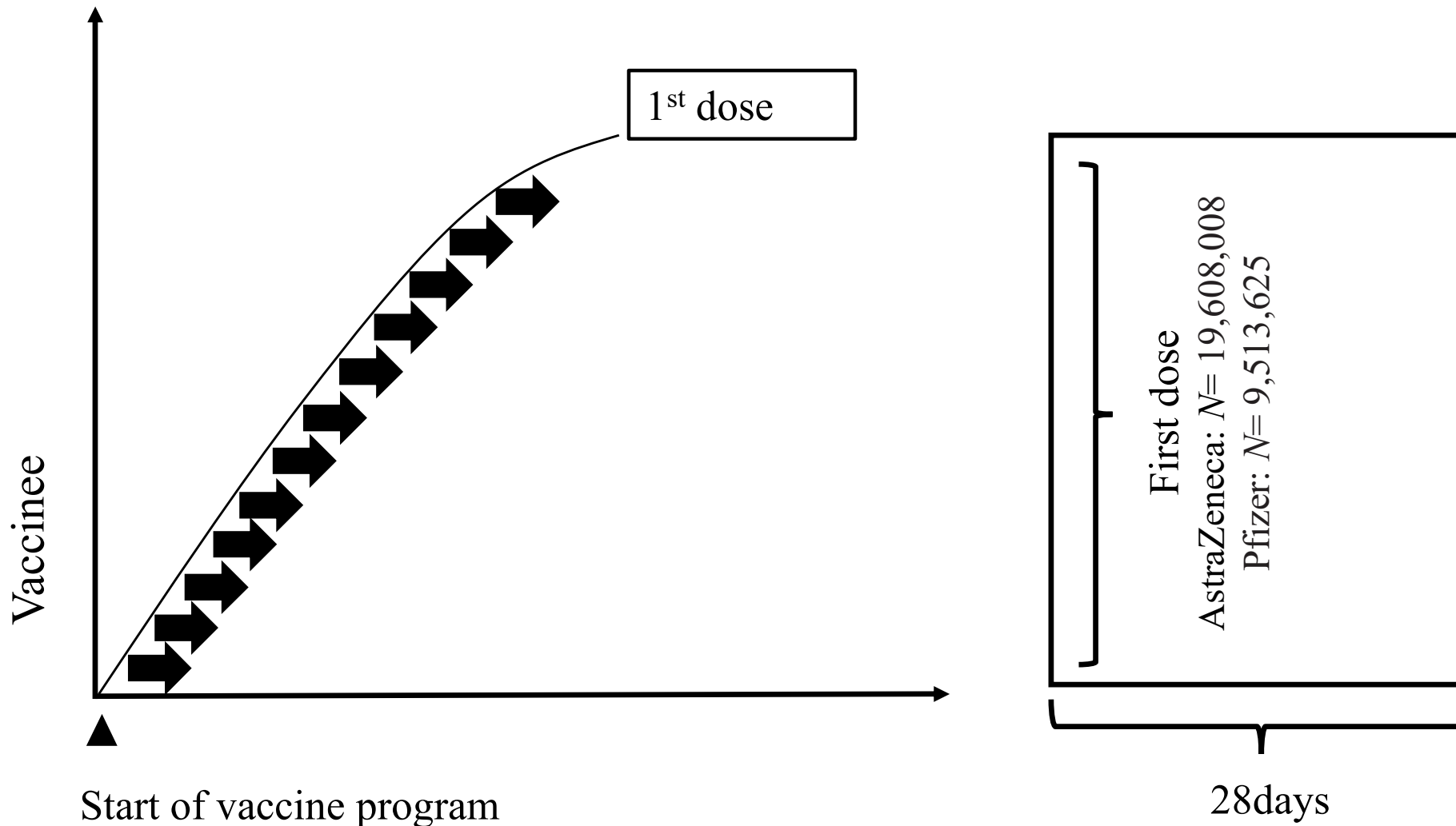
Table 1 shows the characteristics of 19 608 008 people who had the ChAdOx1 nCoV-19 vaccine, 9 513 625 who had the BNT162b2 mRNA vaccine, and 1 758 095 with a SARS-CoV-2 positive test. During the study period, among those vaccinated, 9764 people had a hospital admission related to thrombocytopenia (52 deaths) and 23 390 people were admitted to hospital with venous thromboembolism (1871 deaths); this included 119 people with CVST related hospital admissions (no deaths). Hospital admission related to arterial thromboembolic events occurred in 89 321 people (6533 deaths); these included 28 222 ischaemic strokes (4204 deaths), 62 699 with myocardial infarction (2875 deaths), and 3655 with other rare arterial thrombotic events (84 deaths). Table 2 shows

Appendix 4-2 : Image of diagnostic overlap



- Venous thrombosis includes cerebral venous sinus thrombosis and overlaps some thrombocytopenia cases. However, the number of cerebral venous sinus thrombosis(CVST) deaths(AstraZeneca:0, Pfizer:0) and thrombocytopenia deaths (AstrZeneca:20 ,Pfizer:5) are sufficiently small compared to venous thrombosis deaths (AstraZeneca: 499, Pfizer: 338) within 28 days following vaccination. Therefore, it is reasonable to compare venous sinus thrombosis mortality between the vaccinee and the reference population.
- Ischemic heart disease and myocardial infarction are included in arterial thrombosis, and there is likely to be diagnostic overlap between ischemic heart disease and myocardial infarction.

Appendix 5: Calculation for person-time following SARS-CoV-2 vaccination



The area enclosed by the rectangle indicates the observed person-years of first-time vaccine recipients.

Appendix6-1: Percent coverage of Pfizer's vaccine by age group

Age group (years)	Vaccinated [12] (N)	Population in 2021 [14] (N)	Percent coverage of vaccine (%)
16-29	685,100	9,674,878	7.08%
30-39	786,815	7,753,274	10.15%
40-49	1,030,833	7,166,966	14.38%
50-59	1,486,062	7,724,309	19.24%
60-69	1,692,935	6,057,542	27.95%
70-79	1,934,771	4,875,028	39.69%
80-89	1,619,781	2,307,038	70.21%
≥ 90	277,328	509,436	54.44%
Total	9,513,625	46,068,471	20.65%

Appendix6-2: Percent coverage of AstraZeneca's vaccine by age group

Age group (years)	Vaccinated [12] (N)	Population in 2021 [14] (N)	Percent coverage of vaccine (%)
16-29	1,060,982	9,674,878	10.97%
30-39	1,551,528	7,753,274	20.01%
40-49	3,803,176	7,166,966	53.07%
50-59	5,564,739	7,724,309	72.04%
60-69	3,988,397	6,057,542	65.84%
70-79	2,782,590	4,875,028	57.08%
80-89	643,058	2,307,038	27.87%
≥ 90	213,537	509,436	41.92%
Total	19,608,007	46,068,471	42.56%

Appendix 7. Predicted venous thrombosis deaths by age group (sensitivity analysis-1)

Age group (years)	Venous thrombosis cases ^{*1} (N)	Predicted venous thrombosis deaths ^{*2} (N)
16-29	a_1	$A_1 = T \times a_1 / t_1$
30-39	b_1	$B_1 = T \times b_1 / t_1$
40-49	c_1	$C_1 = T \times c_1 / t_1$
50-59	d_1	$D_1 = T \times d_1 / t_1$
60-69	e_1	$E_1 = T \times e_1 / t_1$
70-79	f_1	$F_1 = T \times f_1 / t_1$
80-89	g_1	$G_1 = T \times g_1 / t_1$
≥ 90	h_1	$H_1 = T \times h_1 / t_1$
Total	$t_1 (= a_1 + b_1 + c_1 + d_1 + e_1 + f_1 + g_1 + h_1)$	T

*1: $a_1, b_1, c_1, d_1, e_1, f_1, g_1,$ and h_1 were calculated from supplementary table 6 reported in the ref.[12].

*2: “T” was calculated according to the method in Appendix 1.

Appendix 8. Predicted venous thrombosis deaths by age group (sensitivity analysis-2)

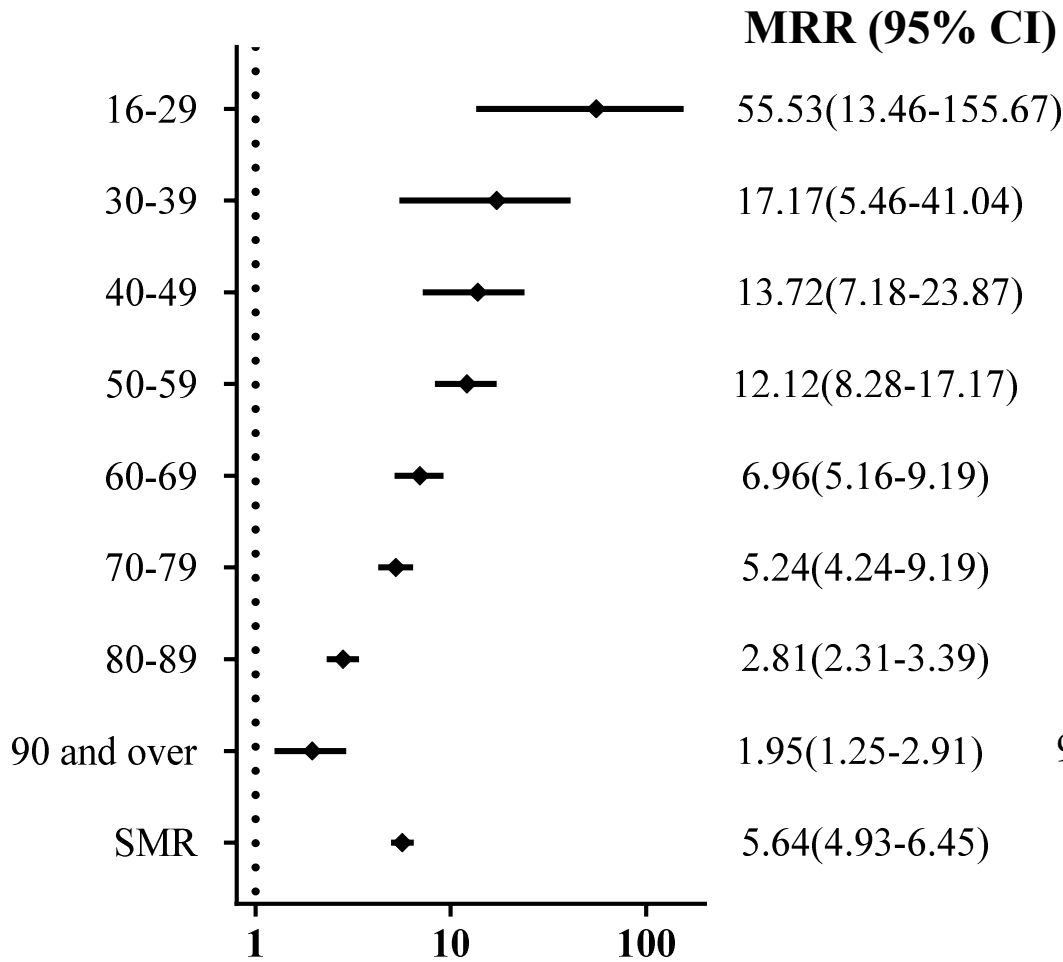
Age group (years)	Venous thrombosis deaths in the reference population ^{*1} (N)	Anticipated venous thrombosis deaths ^{*2} (N)
16-29	a ₂	A ₂ =T × a ₂ /t ₂
30-39	b ₂	B ₂ =T × b ₂ /t ₂
40-49	c ₂	C ₂ =T × c ₂ /t ₂
50-59	d ₂	D ₂ =T × d ₂ /t ₂
60-69	e ₂	E ₂ =T × e ₂ /t ₂
70-79	f ₂	F ₂ =T × f ₂ /t ₂
80-89	g ₂	G ₂ =T × g ₂ /t ₂
≥ 90	h ₂	H ₂ =T × h ₂ /t ₂
Total	t ₂ (=a ₂ +b ₂ +c ₂ +d ₂ +e ₂ +f ₂ +g ₂ +h ₂)	T

*1: a₂, b₂, c₂, d₂, e₂, f₂, g₂, and h₂ were calculated from the reference population [15].

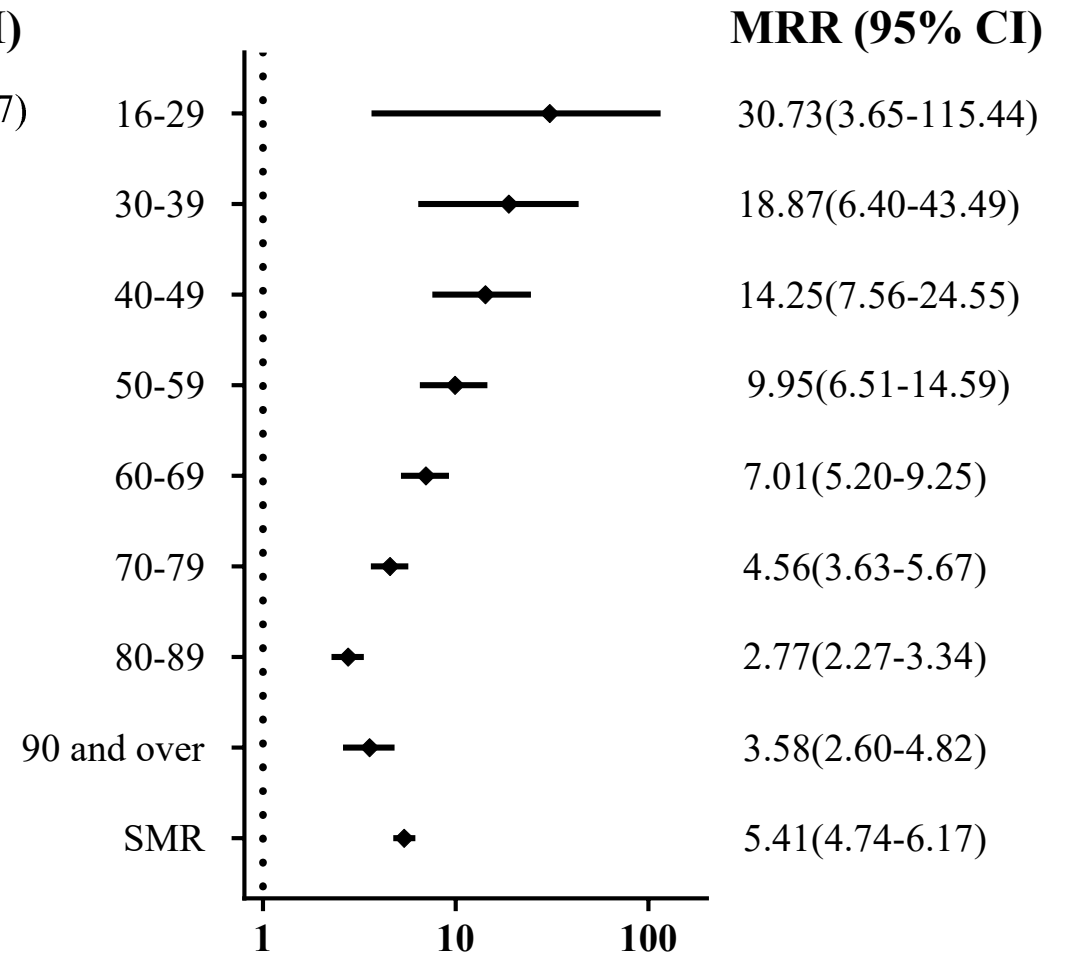
*2: “T” was calculated according to the method in Appendix 1.

Appendix9-1: Sensitivity analysis for Pfizer's vaccine

Sensitivity analysis-1



Sensitivity analysis-2

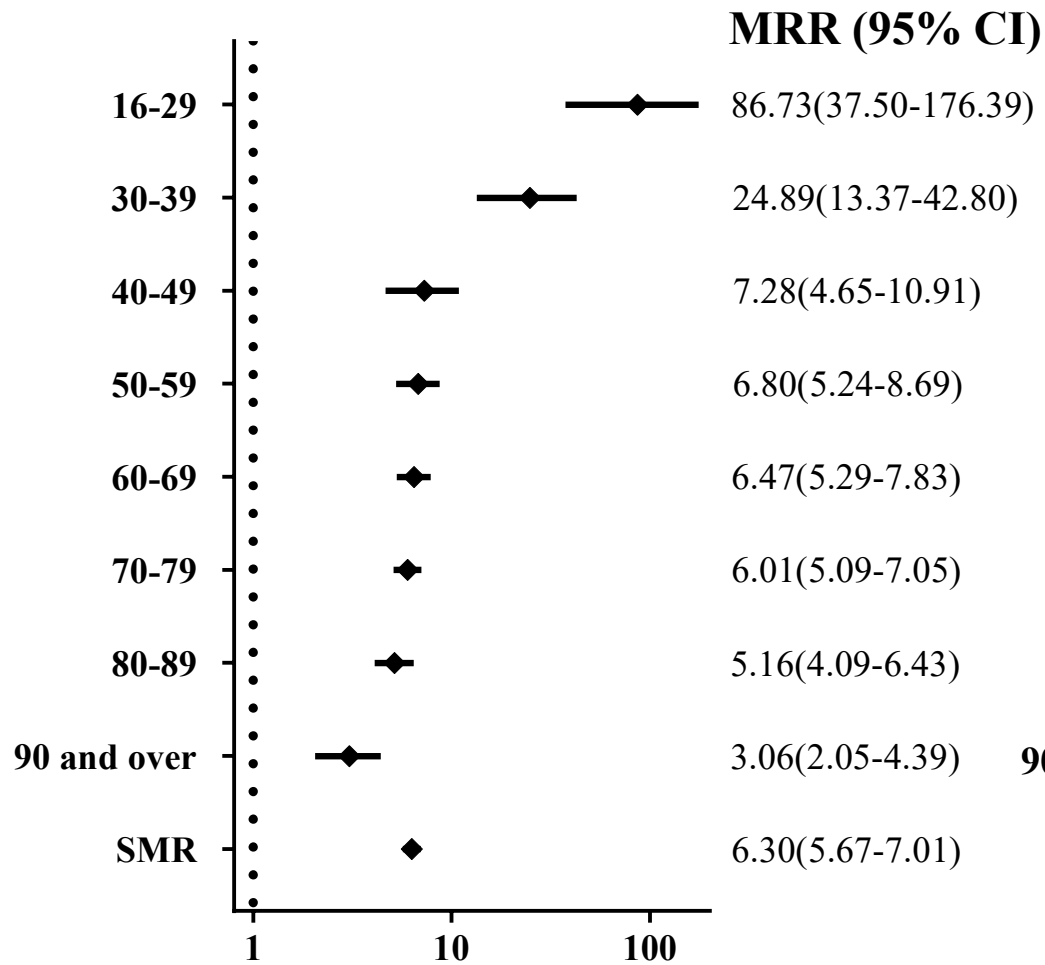


Abbreviations

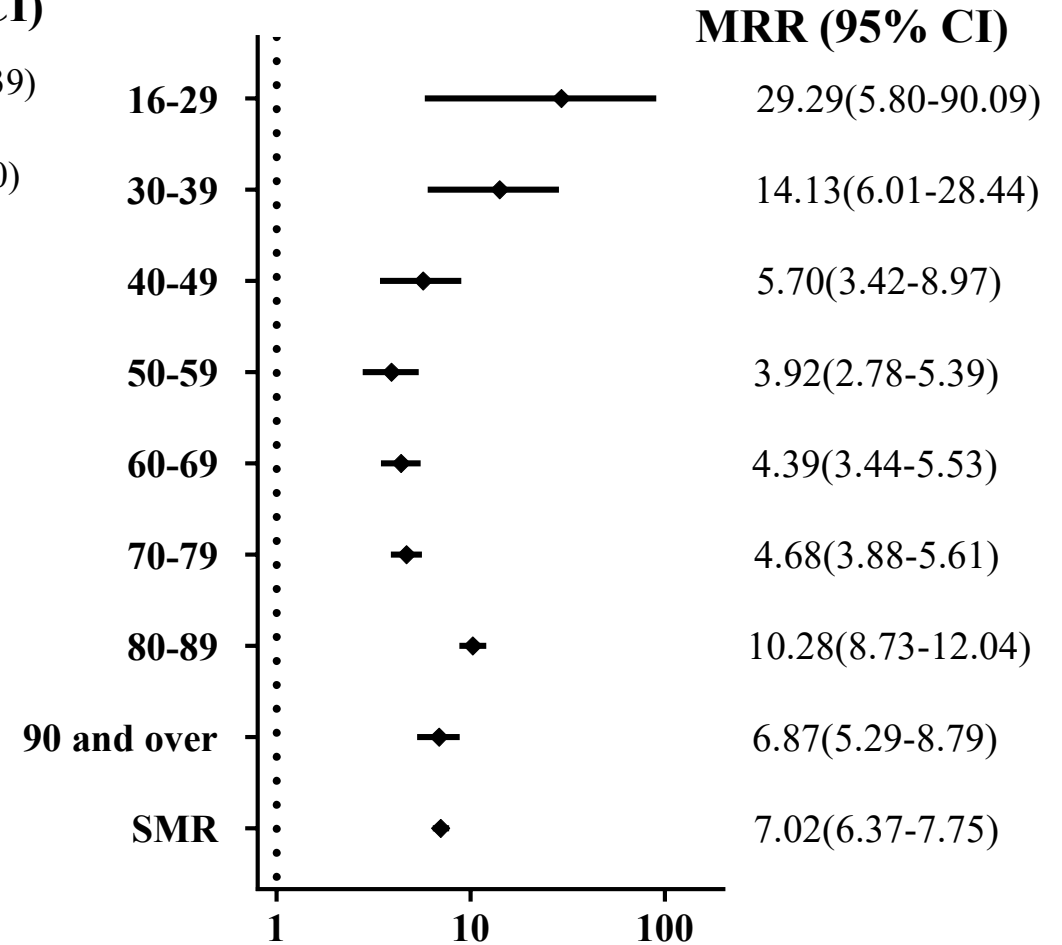
MRR: mortality rate ratio, 95%CI: 95% confidence interval, SMR: standardized mortality ratio

Appendix9-2: Sensitivity analysis for AstraZeneca's vaccine

Sensitivity analysis-1



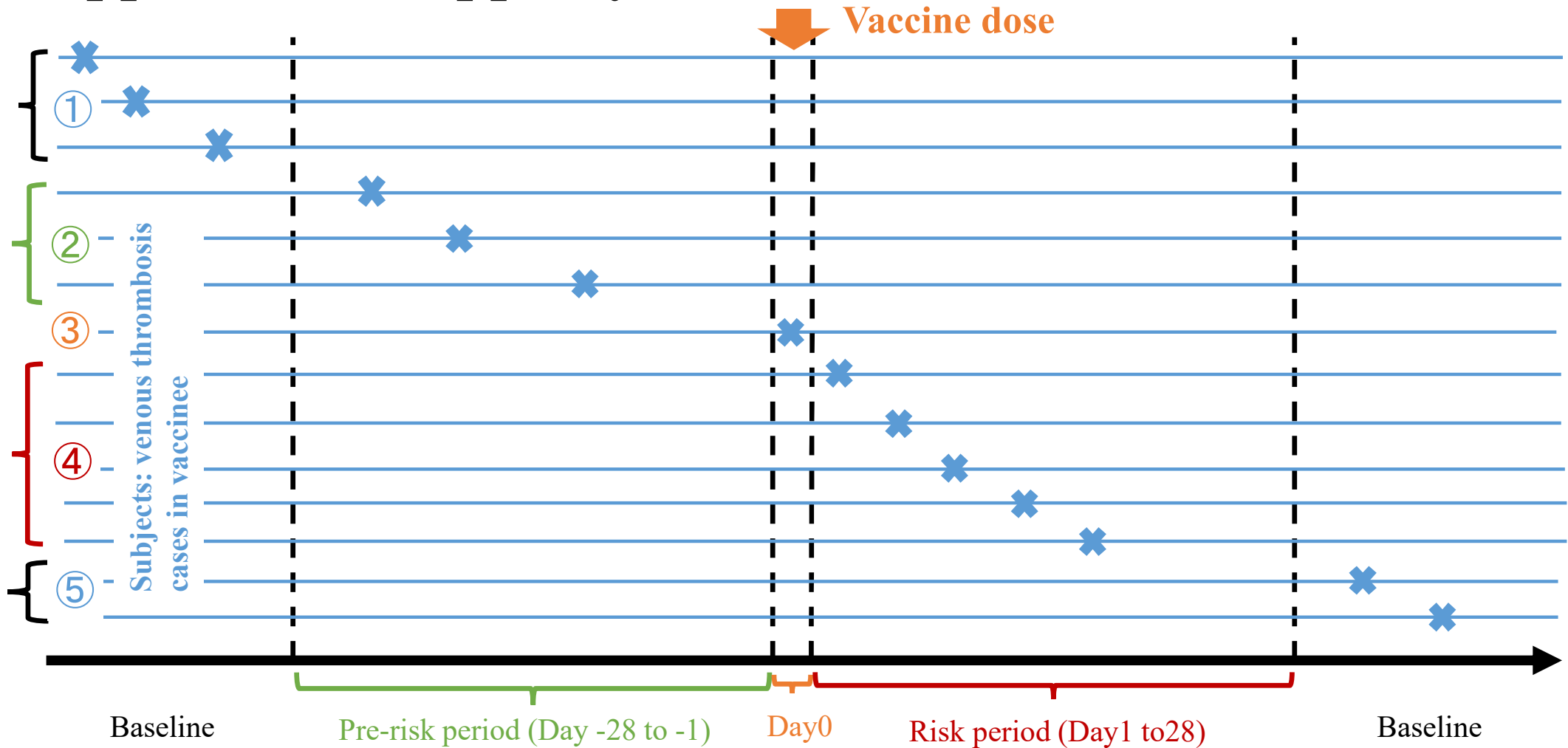
Sensitivity analysis-2



Abbreviations

MRR: mortality rate ratio, 95%CI: 95% confidence interval, SMR: standardized mortality ratio

Appendix 10: Hippisley-Cox's research methods



①,⑤ baseline period incidence rate:1.00

②Pre-risk period (Day -28 to -1) IRR: 0.64(0.60-0.68) (Pfizer) or 0.69 (0.66-0.73) (AstraZeneca)

③Day 0 IRR: 0.35 (0.24-0.52) (Pfizer) or 0.46 (0.35-0.60) (AstraZeneca)

④Risk period(Day 1 to 28)meta summary IRR:0.93(0.89-0.98)

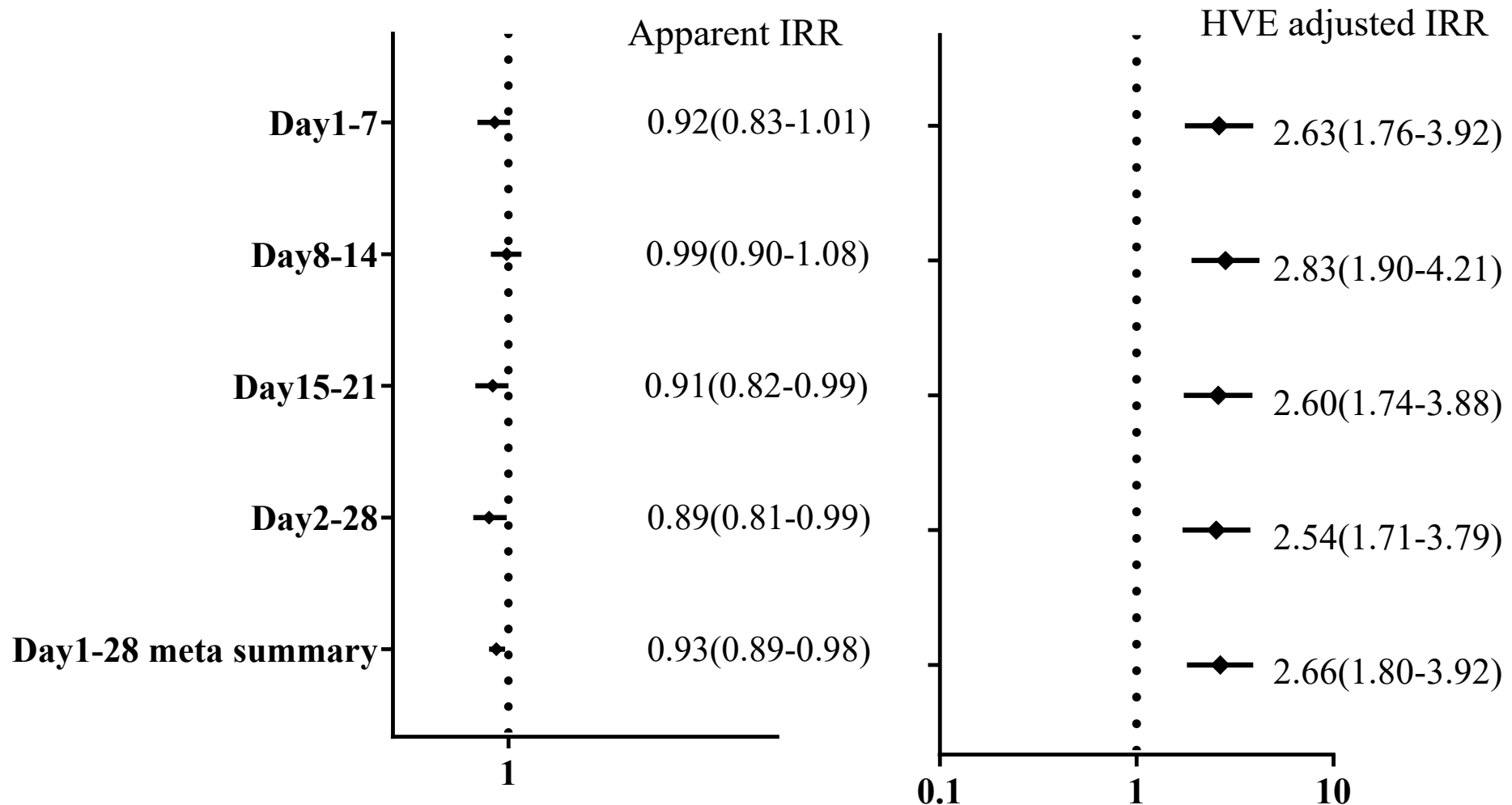
X Onset of venous thrombosis

- **Abbreviation** IRR: incidence rate ratio (95% confidence interval)

- Self-controlled case series is a method where the sum of the blue line areas for each period is the respective observed person-years.

- People who develop venous thrombosis on the day of planned vaccination avoid vaccination. This is the reason incidence is lowest on the day 0.

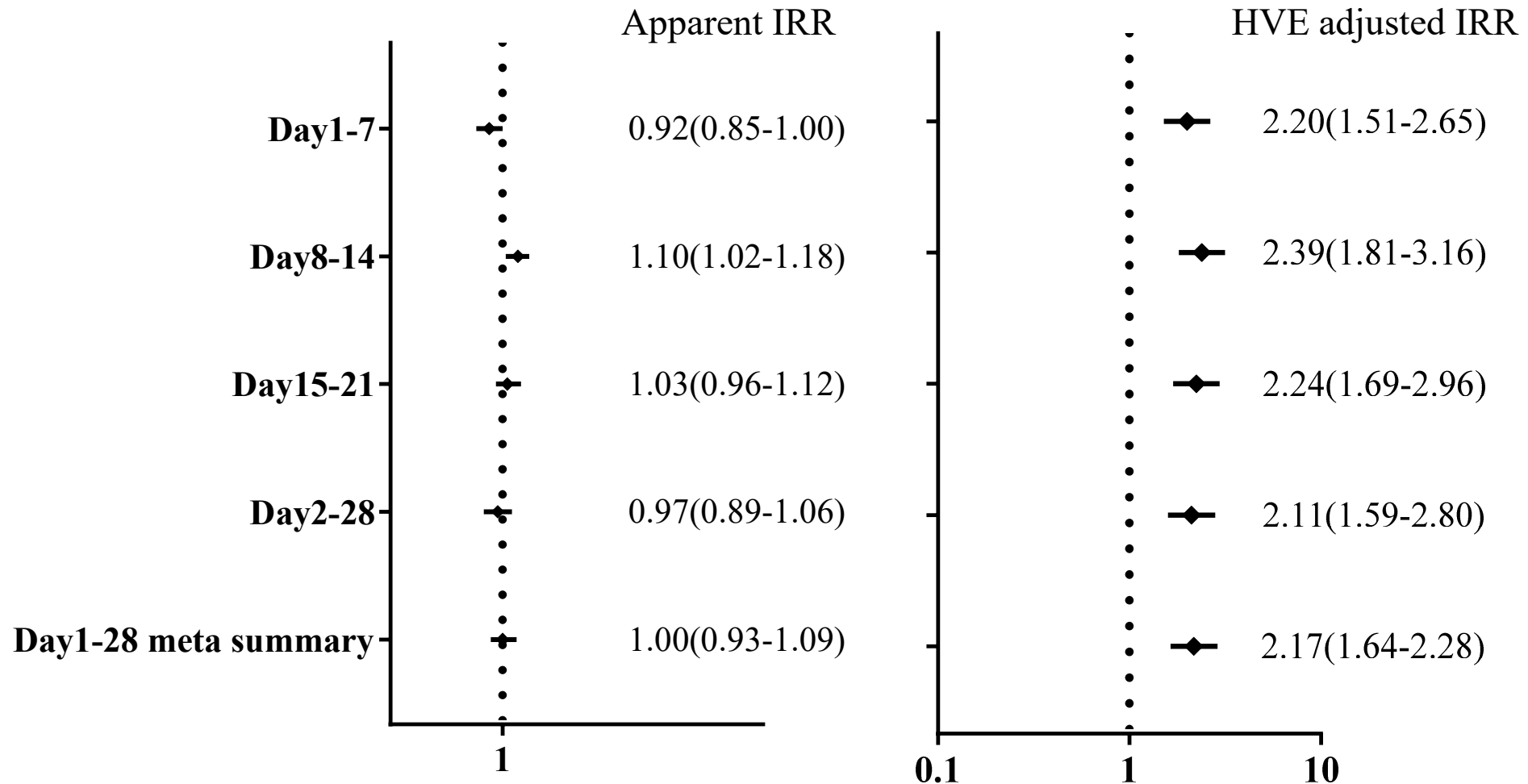
Appendix 11-1: Incidence rate ratio for venous thrombosis following Pfizer's vaccine



Abbreviations HVE: healthy-vaccinee effect, IRR: Incidence rate ratio

The apparent risk of developing venous thrombosis is below 1 (Apparent IRR), due to HVE ('all who were able to be vaccinated', 'healthy persons with the lowest frequency of venous thrombosis immediately before vaccination'). A comparison correcting for this bias (incidence on the day of vaccination: 0.38, HVE adjusted IRR) shows an increased venous thrombosis after vaccination

Appendix 11-2: Incidence rate ratio for venous thrombosis following AstraZeneca's vaccine



Abbreviations HVE: healthy-vaccinee effect, IRR: Incidence rate ratio

The apparent risk of developing venous thrombosis is below 1 (Apparent IRR), due to HVE ('all who were able to be vaccinated', 'healthy persons with the lowest frequency of venous thrombosis immediately before vaccination'). A comparison correcting for this bias (incidence on the day of vaccination: 0.46, HVE adjusted IRR) shows an increased venous thrombosis after vaccination