

MedCheck in English No.27

COVID-19 Information

SARS-CoV-2 vaccine increases arrhythmia mortality

Supplementary appendix

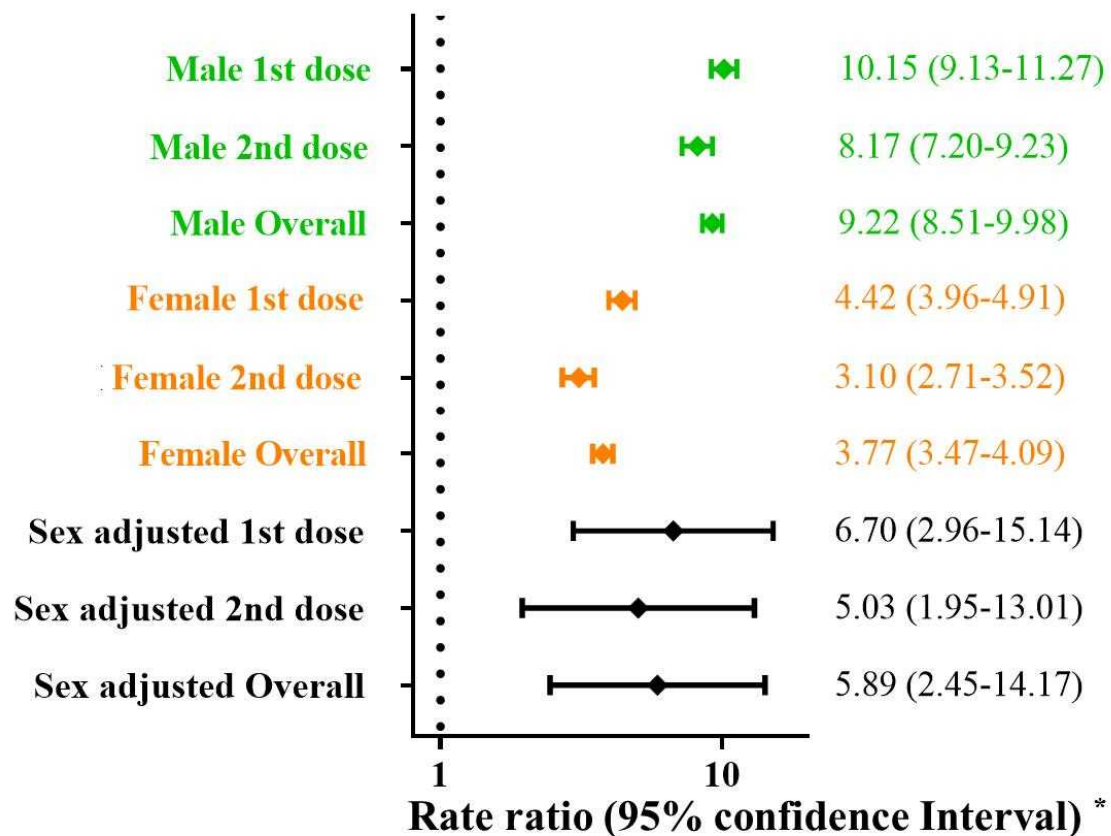
2023-9-15

MedCheck Editorial team

Table. Mortality risk from arrhythmia after Pfizer's SARS-CoV-2 vaccine compared with general population in England.

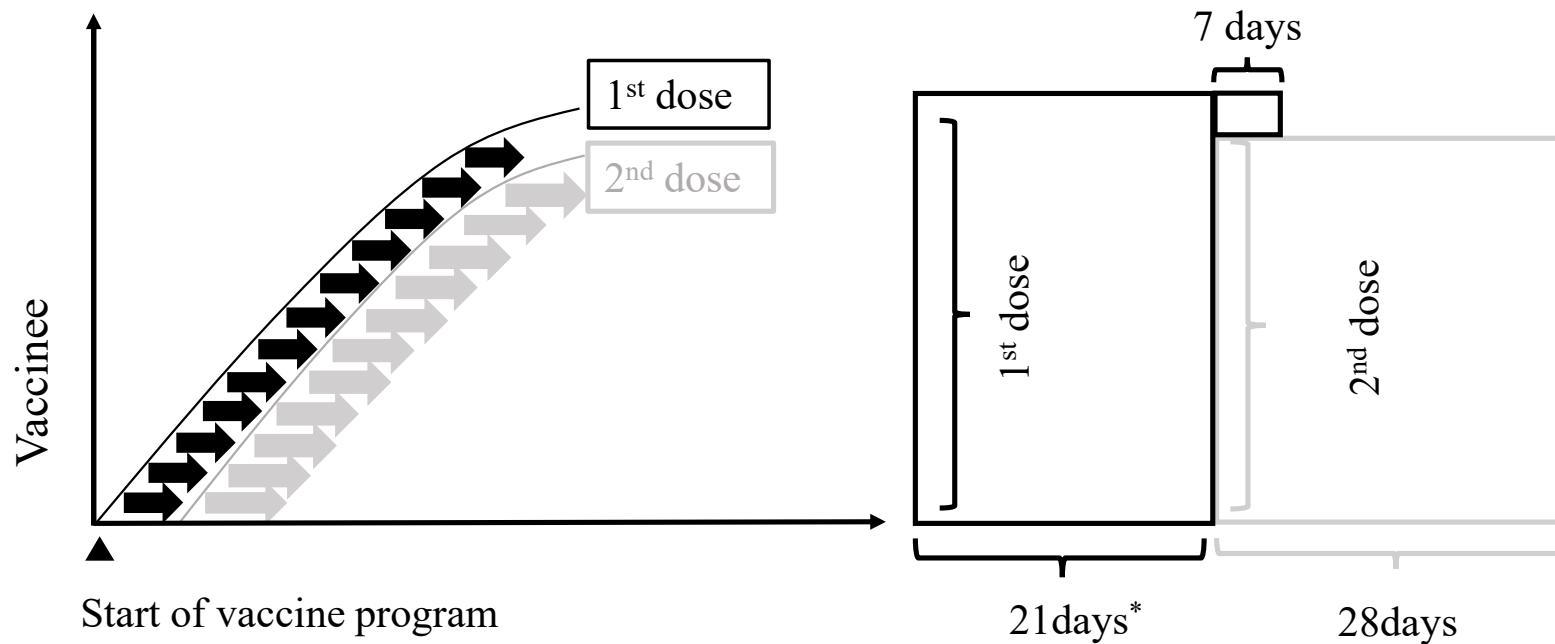
General population 2017-19 (reference)				Vaccinated population (Pfizer)					Mortality rate ratio (Vaccinated/reference)	
Sex	Arrhythmia deaths (N)	Population total (N)	Mortality rate (/100,000 pys)	dose	Arrhythmia deaths (N)	Vaccinated population (N)	Person-years (pys)*	Mortality rate (/100,000 pys)	Crude (95% CI)	Sex adjusted (95% CI)
Male	7,627	67,405,353	11.32	1st	390	5,401,842	339,466	114.89	10.15 (9.13-11.27)	
				2nd	277	3,906,666	299,689	92.43	8.17 (7.20-9.23)	
				Overall	667	5,401,842	639,155	104.36	9.22 (8.51-9.98)	
Female	12,792	70,093,050	18.25	1st	360	7,233,091	446,501	80.63	4.42 (3.96-4.91)	
				2nd	245	5,650,542	433,466	56.52	3.10 (2.71-3.52)	
				Overall	605	7,233,091	879,967	68.75	3.77 (3.47-4.09)	
Total	20,419	137,498,403	14.85	1st	755	16,993,389	1,073,988	70.30	4.73 (4.39-5.10)	6.70 (2.96-15.14)
				2nd	524	11,972,733	918,456	57.05	3.84 (3.51-4.19)	5.03 (1.95-13.01)
				Overall	1,279	16,993,389	1,992,444	64.19	4.32 (4.08-4.57)	5.89 (2.45-14.17)

*Calculations were shown in Appendix 2-1.



*Arrhythmia mortality rate in the general population is higher in female than that in male and crude mortality rate ratios in female were far lower than in male. Therefore mortality rate ratios for both sexes were calculated adjusting sex as a confounding factor. Sex adjusted pooled mortality rate ratios were shown using a random-effects model, because the I^2 values were over 90% (very different mortality rate ratio by sex).

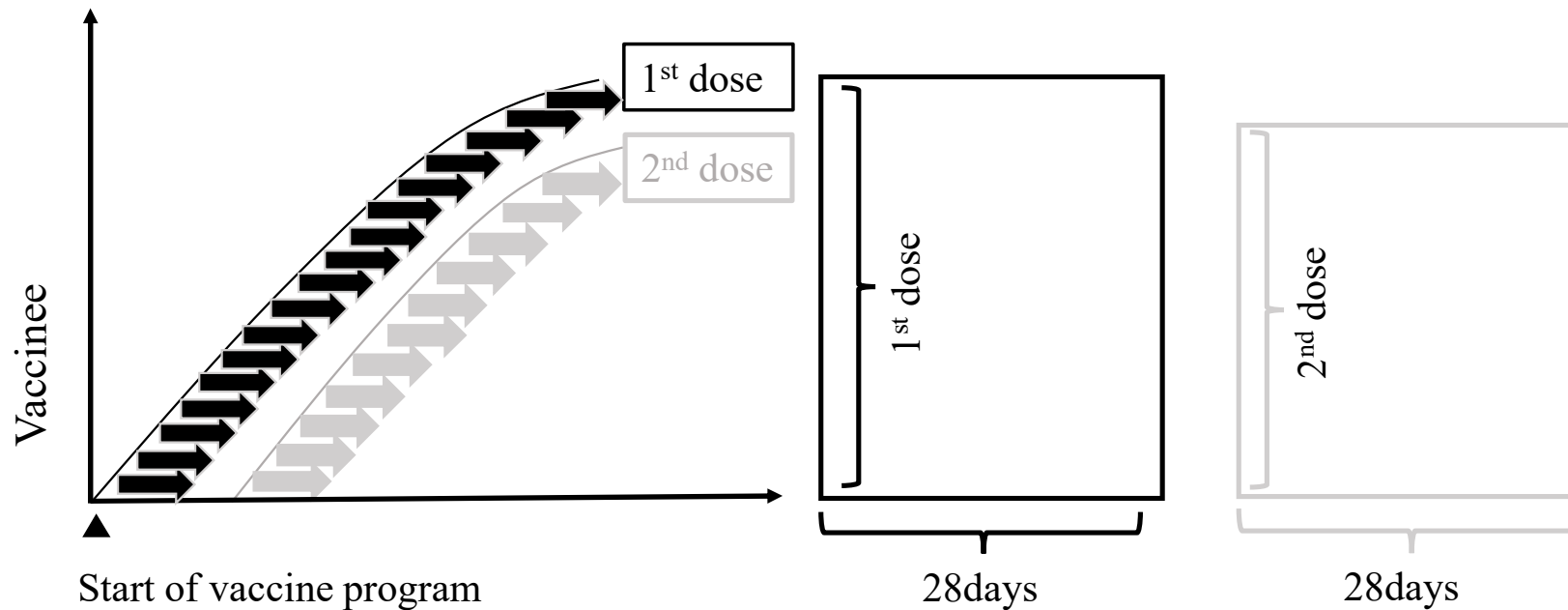
Figure. Sex adjusted arrhythmia mortality rate ratio for Pfizer's SARS-CoV-2 vaccine



Black arrows indicate the observation period for 1st vaccinee; the area enclosed by the black rectangle indicates the person-times for the entire 1st vaccinee. *According to the Pfizer Vaccine's package insert, the interval between the 1st and 2nd dose is approximately 21 days.

Grey arrows indicate the observation period for 2nd vaccinee; the area enclosed by the grey rectangle indicates the person-times for the entire 2nd vaccinee.

Appendix 1-1: Concept of person-years calculation for Pfizer's SARS-CoV-2 vaccinee



Black arrows indicate the observation period for 1st vaccinee; the area enclosed by the black rectangle indicates the person-times for the entire 1st vaccinee. * According to the Astra Zeneca Vaccine's package insert, the interval between the 1st and 2nd dose is 28 to 84 days.

Grey arrows indicate the observation period for 2nd vaccinee; the area enclosed by the grey rectangle indicates the person-times for the entire 2nd vaccinee.

Appendix 1-2: Concept of person-years calculation for AstraZeneca's SARS-CoV-2 vaccinee

Appendix 2-1 : Calculations of person-time for Pfizer's SARS-CoV-2 vaccinee

First Dose

Sex	1 st Vaccinated (N)	Interval from 1 st dose to 2 nd dose (days)	Person-time from 1 st dose to 2 nd dose (Person-years)	Vaccinees (Only 1 st dose) (N)	Observation period (Only 1 st dose) (days)	Person-time (Only 1 st dose) (Person-years)	Person-time for 1 st dose (Person-years)
	A	B	$C=A \times B/365$	D	$E=(28-B)$	$F=(D \times E/365)$	$G=(C+F)$
Male	5,401,842	21	310,791	1,495,176	7	28,675	339,466
Female	7,233,091	21	416,150	1,582,549	7	30,350	446,501
Total*	16,993,389	21	977,702	5,020,656	7	96,287	1,073,988

Second Dose

Sex	2 nd Vaccinated (N)	Observation period (2 nd dose) (days)	Person-time for 2 nd dose (Person-years)
	H	I	$J=H \times I/365$
Male	3,906,666	28	299,689
Female	5,650,542	28	433,466
Total*	11,972,733	28	918,456

Upper row: 1st vaccinated, Bottom row: 2nd vaccinated, * includes sex unspecified

Appendix 2-2 : Calculations of person-time for AstraZeneca's SARS-CoV-2 vaccinee

First Dose

Sex	1 st vaccinated (N)	Observation period (1 st dose) (days)	Person-time for 1 st dose (Person-years)
	A	B	$C=A \times B/365$
Male	7,191,428	28	551,671
Female	8,918,403	28	684,151
Total*	20,615,911	28	1,581,495

Second Dose

Sex	2 nd vaccinated (N)	Observation period (2 nd dose) (days)	Person-time for 2 nd dose (Person-years)
	H	I	$J=H \times I/365$
Male	6,900,964	28	529,389
Female	8,559,325	28	656,606
Total*	19,754,224	28	1,515,393

* includes sex unspecified

Appendix 3 : Arrhythmia mortality in the general population (2017-2019) aged 15 years and over in England

Sex	Age group (years)	Arrhythmia deaths in 2017-2019 (N)	Population total 2017-2019 (N)	Arrhythmia mortality (/100,000 person-years)
Male	15-29	83	15,995,481	0.52
	30-39	78	11,172,599	0.70
	≥40	7,466	40,237,273	18.55
	Male total	7,627	67,405,353	11.32
Female	15-29	49	15,287,671	0.32
	30-39	44	11,274,120	0.39
	≥40	12,699	43,531,259	29.17
	Female total	12,792	70,093,050	18.25
Total	15-29	132	31,283,152	0.42
	30-39	122	22,446,719	0.54
	≥40	20,165	83,768,532	24.07
	Total	20,419	137,498,403	14.85

Appendix 4. Mortality risk from arrhythmia after AstraZeneca's SARS-CoV-2 vaccine compared with general population in England.

General population 2017-19 (reference)				Vaccinated population (AstraZeneca)					Mortality rate ratio (Vaccinated/reference)	
Sex	Arrhythmia deaths	Population total (N)	Mortality rate (/100,000)	dose	Arrhythmia deaths (N)	Vaccinated population (N)	Person-years (pys)*	Mortality rate (/100,000)	Crude (95% CI)	Sex adjusted (95% CI)
Male	7,627	67,405,353	11.32	1st	410	7,191,428	551,671	74.32	6.57 (5.93-7.26)	
				2nd	218	6,900,964	529,389	41.18	3.64 (3.17-4.16)	
				Overall	628	7,191,428	1,081,060	58.09	5.13 (4.73-5.57)	
Female	12,792	70,093,050	18.25	1st	489	8,918,403	684,151	71.48	3.92 (3.57-4.29)	
				2nd	256	8,559,325	656,606	38.99	2.14 (1.88-2.42)	
				Overall	745	8,918,403	1,340,757	55.57	3.04 (2.82-3.28)	
Total	20,419	137,498,403	14.85	1st	904	20,615,911	1,581,495	57.16	3.85 (3.59-4.12)	5.07 (3.05-8.41)
				2nd	478	19,754,224	1,515,393	31.54	2.12 (1.93-2.33)	2.78 (1.65-4.70)
				Overall	1,382	20,615,911	3,096,887	44.63	3.01 (2.84-3.17)	3.95 (2.37-6.60)

*a: Calculations were shown in Appendix 2-2.

*b: Arrhythmia mortality rate in the general population is higher in female than that in male and crude mortality rate ratios in female were far lower than in male. Therefore mortality rate ratios for both sexes were calculated adjusting sex as a confounding factor. Sex adjusted pooled mortality rate ratios were shown using a random-effects model, because the I^2 values were over 90% (very different mortality rate ratio by sex).

Appendix 5-1: Percent coverage of Pfizer's SARS-CoV-2 vaccine by age group.

Age group (years)	Population in 2021 (N)	1st dose (N)	1st dose coverage (%)	2nd dose (N)	2nd dose coverage (%)
16-29	10,324,377	4,285,600	41.5%	1,244,710	12.1%
30-39	7,753,274	3,945,405	50.9%	2,475,091	31.9%
≥40	28,640,319	8,762,384	30.6%	8,252,932	28.8%
Total	46,717,970	16,993,389	36.4%	11,972,733	25.6%

Appendix 5-2: Percent coverage of AstraZeneca's SARS-CoV-2 vaccine by age group.

Age group (years)	Population in 2021 (N)	1st dose (N)	1st dose coverage (%)	2nd dose (N)	2nd dose coverage (%)
16-29	10,324,377	1,064,443	10.3%	988,291	9.6%
30-39	7,753,274	1,598,406	20.6%	1,494,285	19.3%
≥40	28,640,319	17,953,062	62.7%	1,494,285	5.2%
Total	46,717,970	20,615,911	44.1%	19,754,224	42.3%

Appendix 6-1: Person-time calculations for Pfizer's SARS-CoV-2 vaccinee by age group.

First Dose

Age group (years)	1 st vaccinated (N)	Interval from 1 st dose to 2 nd dose (days)	Person-time from 1 st dose to 2 nd dose (Person-years)	Vaccinee (Only 1 st dose) (N)	Observation period (Only 1 st dose) (days)	Person-time (Only 1 st dose) (Person-years)	Person-time for 1 st dose (Person-years)
	A	B	$C=(A \times B/365)$	D	$E=(28-B)$	$F=(D \times E/365)$	$G=(C+F)$
16-29	4,285,600	21	246,569	3,040,890	7	58,318	304,887
30-39	3,945,405	21	226,996	1,470,314	7	28,198	255,194
≥ 40	8,762,384	21	504,137	509,452	7	9,770	513,907

Second Dose

Age group (years)	2 nd vaccinated (N)	Observation period (2 nd dose) (days)	Person-time for 2 nd dose (Person-years)
	H	I	$J=H \times I/365$
16-29	1,244,710	28	95,485
30-39	2,475,091	28	189,870
≥ 40	8,252,932	28	633,102

Appendix 6-2: Person-time calculations for AstraZeneca’s SARS-CoV-2 vaccinee by age group.

First Dose

Age group (years)	1 st vaccinated (N)	Observation period (1 st dose) (days)	Person-time for 1 st dose (Person-years)
	A	B	$C=A \times B/365$
16-29	1,064,443	28	81,656
30-39	1,064,443	28	81,656
≥ 40	17,953,062	28	1,377,221

Second Dose

Age group (years)	2 nd vaccinated (N)	Observation period (2 nd dose) (days)	Person-time for 2 nd dose (Person-years)
	H	I	$J=H \times I/365$
16-29	988,291	28	75,814
30-39	1,494,285	28	114,630
≥ 40	17,271,648	28	1,324,948

Appendix 7a: Sensitivity analysis-1

Age group (years)	Arrhythmia cases after vaccination ^{*1} (N)	Expected arrhythmia 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	c_1	$C_1 = T \times c_1 / t_1$
Total	$t_1 = (a_1 + b_1 + c_1)$	T

^{*1} $a_1, b_1,$ and c_1 were listed in Supplementary table 3b in reference [4].

^{*2}T was listed in Supplementary table 1 in reference [4].

Appendix 7b-1: Sensitivity analysis-1 for Pfizer's SARS-CoV-2 vaccine

Age group (years)	Vaccine dose	Arrhythmia cases after vaccination (N)	Proportion of arrhythmia cases to total (all ages) (%)	Expected arrhythmia deaths by age groups* (N)
16-29	1 st	810	4.4%	33
	2 nd	315	1.5%	8
30-39	1 st	829	4.5%	34
	2 nd	487	2.3%	12
≥ 40	1 st	16,720	91.1%	688
	2 nd	20,145	96.2%	504
Total	1 st	18,359	100%	755
	2 nd	20,947	100%	524

* Assuming a proportional relationship between post-vaccination arrhythmia incidence and arrhythmia mortality by age group

Appendix 7b-2: Sensitivity analysis-1 for AstraZeneca's SARS-CoV-2 vaccine

Age group (years)	Vaccine dose	Arrhythmia cases after vaccination (N)	Proportion of arrhythmia cases to total (all ages) (%)	Expected arrhythmia deaths by age groups* (N)
16-29	1 st	498	2.1%	19
	2 nd	416	1.8%	9
30-39	1 st	674	2.8%	25
	2 nd	574	2.5%	12
≥ 40	1 st	23,053	95.2%	860
	2 nd	22,029	95.7%	457
Total	1 st	24,225	100%	904
	2 nd	23,019	100%	478

*Assuming a proportional relationship between post-vaccination arrhythmia incidence and arrhythmia mortality by age group

Appendix7c : Results for sensitivity analysis-1

Age group (years)	Arrhythmia MRR (95% CI), for Pfizer's SARS-CoV-2 vaccine		
	1st dose	2nd dose	Overall
16-29	25.89(16.54-39.85)	19.56(8.05-41.02)	24.38(16.75-34.83)
30-39	24.58(15.67-37.98)	11.81(5.82-22.06)	19.13(13.33-27.04)
≥ 40	5.56(5.14-6.01)	3.31(3.02-3.62)	4.32(4.07-4.58)
SMR	5.80(5.39-6.25)	3.46(3.17-3.79)	4.53(4.28-4.80)

Age group (years)	Arrhythmia MRR (95% CI), for AstraZeneca's SARS-CoV-2 vaccine		
	1st dose	2nd dose	Overall
16-29	55.14(31.25-93.01)	28.13(12.32-56.71)	42.14(26.97-63.73)
30-39	56.33(33.88-91.08)	19.26(9.44-36.13)	34.68(23.33-50.47)
≥ 40	2.59(2.42-2.78)	1.43(1.30-1.57)	2.02(1.91-2.14)
SMR	3.25(2.99-3.54)	1.71(1.53-1.91)	2.48(2.32-2.65)

MRR: mortality rate ratio

Appendix 8a: Sensitivity analysis-2

Age group (years)	Arrhythmia death in general population ^{*1} (N)	Expected arrhythmia deaths in vaccinated Population ^{*2} (N)
15-29	a_2	$A_2 = T \times a_2 / t_2$
30-39	b_2	$B_2 = T \times b_2 / t_2$
≥ 40	c_2	$C_2 = T \times c_2 / t_2$
Total	$t_2 = (a_2 + b_2 + c_2)$	T

^{*1} $a_2, b_2,$ and c_2 were calculated from data in the Mortality Statistics for England [24].

^{*2}T (total arrhythmia death in vaccinated population) was listed in Supplementary table 1 in ref. [4].

Appendix 8b-1: Sensitivity analysis-2 for Pfizer's SARS-CoV-2 vaccine

Age group (years)	Vaccine dose	Arrhythmia deaths in general population (N)	Proportion of arrhythmia deaths in general population by age group (%)	Expected arrhythmia deaths in vaccinated Population* (N)
16-29	1 st	132	0.6%	5
	2 nd	132	0.6%	3
30-39	1 st	122	0.6%	5
	2 nd	122	0.6%	3
≥ 40	1 st	20,165	98.8%	746
	2 nd	20,165	98.8%	517
Total	1 st	20,419	100%	755
	2 nd	20,419	100%	524

*Assumed to be proportional to the proportion of arrhythmia deaths in the general population

Appendix 8b-2: Sensitivity analysis-2 for AstraZeneca's SARS-CoV-2 vaccine

Age group (years)	Vaccine dose	Arrhythmia deaths in general population (N)	Proportion of arrhythmia deaths in general population by age group (%)	Expected arrhythmia deaths in vaccinated Population * (N)
16-29	1 st	132	0.6%	6
	2 nd	132	0.6%	3
30-39	1 st	122	0.6%	5
	2 nd	122	0.6%	3
≥ 40	1 st	20,165	98.8%	893
	2 nd	20,165	98.8%	472
Total	1 st	20,419	100%	904
	2 nd	20,419	100%	478

*Assumed to be proportional to the proportion of arrhythmia deaths in the general population

Appendix 8c : Results of sensitivity analysis-2

Age group (years)	Arrhythmia MRR (95% CI) for Pfizer's SARS-CoV-2 vaccine		
	1st dose	2nd dose	Overall
16-29	3.79(1.17-9.40)	8.41(1.91-24.26)	4.89(2.10-9.83)
30-39	3.25(0.95-8.34)	3.03(0.64-9.11)	3.16(1.30-6.52)
≥ 40	6.03(5.59-6.49)	3.40(3.10-3.71)	4.57(4.32-4.84)
SMR	6.00(5.57-6.46)	3.43(3.14-3.74)	4.57(4.32-4.83)

Age group (years)	Arrhythmia MRR (95% CI), for AstraZeneca's SARS-CoV-2 vaccine		
	1st dose	2nd dose	Overall
16-29	17.41(6.17-39.96)	9.38(1.89-28.63)	13.55(6.06-26.50)
30-39	11.27(3.53-27.76)	4.82(0.97-14.75)	7.50(3.17-15.25)
≥ 40	2.69(2.51-2.88)	1.48(1.35-1.62)	2.10(1.99-2.22)
SMR	2.84(2.64-3.06)	1.55(1.40-1.71)	2.20(2.08-2.34)

MRR: mortality rate ratio