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Overview of pericarditis and myocarditis associated with COVID-19 vaccines

Introduction

Pericarditis and myocarditis have recently been recognized as adverse drug reactions (ADRs) of the mRNA vaccines against COVID-19, manufactured by Pfizer/BioNTech (Comirnaty) and Moderna (Spikevax). The updated Summaries of Product Characteristics (SmPC) of both vaccines mention that very rare cases of myocarditis and pericarditis have been observed following vaccination [1, 2].

Pericarditis is an inflammation of the membrane lining that surrounds the heart. It can be caused by viral infections and non-infectious conditions, such as systemic inflammatory diseases (like rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis), hypothyroidism, radiation, trauma and following myocardial infarction. Pericarditis is a common pericardial disease and a relatively common cause of chest pain [3]. The incidence of pericarditis is not exactly known, since the condition is often self-limiting and does not always require diagnostic testing, since that does not influence management of the disease [4, 5].
Myocarditis is an inflammatory condition of the heart muscle with damage to cardiac cells. Myocarditis can be caused by various infections, auto-immune disorders and exogenous agents. Genetic and environmental factor predispose susceptible people. The incidence of myocarditis is about 10-20 per 100,000 person-years. Young males are at increased risk [6]. In The Netherlands in 2019 pericarditis and myocarditis were registered in various healthcare data systems 19.4 and 2.9 per 100,000 person-years respectively [7]. In figure 2 these Dutch background rates are visualised in more detail [7].

This overview describes reported cases of pericarditis and myocarditis reported in The Netherlands following vaccination against Sars-CoV-2 infection with mRNA vaccines as well as adenovector vaccines of AstraZeneca (Vaxzevria) and Janssen.

Reports

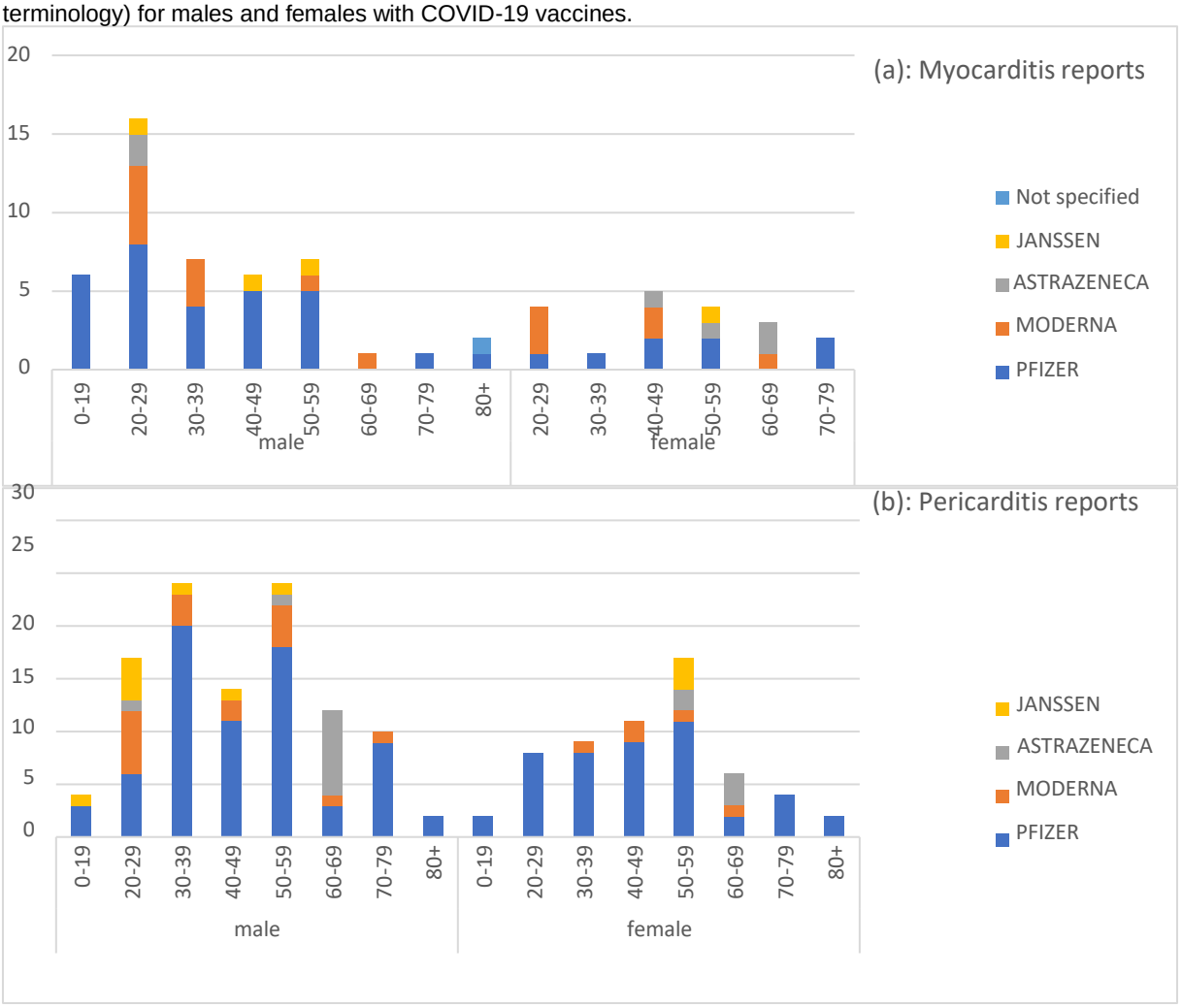
Until October, 19th 2021 The Netherlands Pharmacovigilance Centre Lareb received 231 unique individual case safety reports of pericarditis (166) and myocarditis (65) following vaccination with all available COVID-19 vaccines in total. In table 1, characteristics of the reports are summarized.

The majority of the events is reported with Comirnaty (Pfizer/BioNTech), which is the most commonly used vaccine in The Netherlands.
A relatively large part of the reports (36%) has been reported by healthcare professionals. Overall, over 95% of ADR reports with COVID-19 vaccines have reported by patients themselves. About 57% of the reports were considered serious, of which 109 patients (47%) had to be admitted to hospital, 23 (10%) had a possible life-threatening situation and 4 patients died (1.7%). Another two reports mention that the patient died from another cause after having had pericarditis following vaccination. However, 60-70% of the patients had recovered or were recovering at time of reporting.
For both pericarditis and myocarditis about two-third of the reports concerns males. The age distribution is visualized in figure 1, showing the greatest number of myocarditis reports in males aged 20-29 years, whereas pericarditis was more equally reported in multiple age-groups of men and women.
Pericarditis as well as myocarditis were reported in almost equal proportions following the first and second vaccination moments. The times-to-onset vary widely from less than one day to 3 months. Remarkably, the mean time-to-onset of myocarditis following the first vaccination of an mRNA vaccine was shorter than with the other vaccines. The number of reports with a maximum time-to-onset of 30 days for pericarditis is 80 (89%) and 57 (77%), for the first and second vaccination moment respectively. And 27 (79%) and 22 (71%) for myocarditis following the first and second vaccination moment.
Seven people who developed pericarditis or myocarditis following the second vaccination dose also had pericarditis (4) or myocarditis like symptoms (3) after the first dose.

	Total		Pfizer (Comirnaty)		Moderna (Spikevax)		AstraZeneca (Vaxzevria)		Janssen		Not specified
Reports (N, %)											
- Pericarditis	166	71,9%	118	75,6%	22	57,9%	15	71,4%	11	73,3%	0
- Myocarditis	65	28,1%	38	24,4%	16	42,1%	6	28,6%	4	26,7%	1
- Total	231		156		38		21		15		1
Reported by (N, %)											
- Healthcare professionals	83	35,9%	54	34,6%	14	36,8%	8	38,1%	6	40,0%	1
- Consumers	148	64,1%	102	65,4%	24	63,2%	13	61,9%	9	60,0%	0
Seriousness (N, %)											
- Serious	132	57,1%	87	55,8%	20	52,6%	16	76,2%	8	53,3%	1
- Non-serious	99	42,9%	69	44,2%	18	47,4%	5	23,8%	7	46,7%	0
Age and gender (N,%)											
- Pericarditis											
- - Male	107	64,5%	72	61,0%	17	77,3%	10	66,7%	8	72,7%	0
- - Female	59	35,5%	46	39,0%	5	22,7%	5	33,3%	3	27,3%	0
- - Mean age (male)(range)	45,5	(14-86)	46,5	(14-86)	41,6	(22-71)	57,7	(25-68)	29,8	(19-53)	0
- - Mean age (female) (range)	48,2	(18-81)	46,0	(18-81)	51,2	(36-66)	61,0	(56-66)	55,0	(52-59)	0
- Myocarditis											
- - Male	46	70,8%	30	78,9%	10	62,5%	2	33,3%	3	75,0%	1
- - Female	19	29,2%	8	21,1%	6	37,5%	4	66,7%	1	25,0%	0
- - Mean age (male) (range)	36,6	(20-72)	35,9	(17-80)	34,8	(24-66)	25,5	(24-27)	40,0	(21-54)	90
- - Mean age (female) (range)	47,9	(17-90)	50,3	(22-72)	39,3	(20-66)	55,3	(42-62)	51,0	(51)	-
Vaccination moment (N,%)											
- Pericarditis											
- - First vaccination	92	55,4%	61	51,7%	12	54,5%	8	53,3%	11	100%	0
- - Second vaccination	74	44,6%	57	48,3%	10	45,5%	7	46,7%			0
- Myocarditis											
- - First vaccination	34	52,3%	17	44,7%	8	50,0%	4	66,7%	4	100%	1
- - Second vaccination	31	47,7%	21	55,3%	8	50,0%	2	33,3%			0
Time to onset (mean, days/range)											
- Pericarditis											
- - First vaccination	14,0	(0-80)	10,9	(1-39)	15,3	(0-42)	29,4	(2-60)	18,1	(1-80)	
- - Second vaccination	20,1	(0-106)	20,4	(0-106)	19,6	(1-57)	18,3	(4-56)			
- Myocarditis											
- - First vaccination	11,8	(0-91)	8,3	(0-32)	4,4	(0-19)	16,0	(3-50)	38,1	(2-91)	10,0
- - Second vaccination	17,3	(0-92)	17,0	(0-92)	18,4	(1-46)	15,0	-15,0			
Outcome (N, %)											
- Pericarditis											
- - Recovered/recovering	117	70,5	78	66,1	18	81,8	13	86,7	8	72,7	
- - Not recovered/Unknown**	48	28,9	39	33,1	4	18,2	2	13,3	3	27,3	
- - Fatal	1	0,6	1	0,8	0	0,0	0	0,0	0	0,0	
- Myocarditis											
- - Recovered/recovering	40	61,5	27	71,1	11	68,8	1	0,0	1	25,0	
- - Not recovered/Unknown**	22	33,8	10	26,3	5	31,3	5	83,3	1	25,0	1
- - Fatal	3	4,6	1	2,6	0	0,0	0	0,0	2	50,0	

Table 1: Report characteristics of pericarditis and myocarditis associated with COVID-19 vaccines in The Netherlands. These are based on MedDRA terminology including the Preferred Terms (PT) Myocarditis (including LLTs perimyocarditis / myopericarditis), Pericarditis, Viral myocarditis, Viral pericarditis, Eosinophilic myocarditis. * Vaccination numbers were obtained from RIVM (CIMS), date: 7-10-2021. ** At time of reporting, the outcome is not always reported or the patient had not recovered at that moment.

Figure 1. Age distribution of all myocarditis (a) and pericarditis (b) reports (according to MedDRA coding terminology) for males and females with COVID-19 vaccines.



Diagnostics

In case of 90% of the reports there was some degree of diagnostic certainty, based on being reported by a physician (148) or the presence of diagnostic tests such as ECG (163), MRI (26), CT scan (14), ultrasound (86) or blood tests (143). In 21 reports diagnostic information was not available, but which were also counted as pericarditis or myocarditis cases, just as was reported. Reports without a reported diagnosis of myocarditis or pericarditis and limited to characteristic symptoms only (such as chest pain, palpitations, dyspnea) were not taken into account in this overview.

Other causes

In 20% of the reports of myocarditis and in 11% of the reports of pericarditis, the patient had had COVID-19 the past (at least one month before vaccination). Two had a very recent or current COVID-19 infection while developing pericarditis.

Eighteen people had other kinds of infections shortly before developing pericarditis or myocarditis, which could have contributed to the disease. However, 60 people denied having had a recent infection when they were asked in a follow up question ‘did you have an infection or other illness recently’.

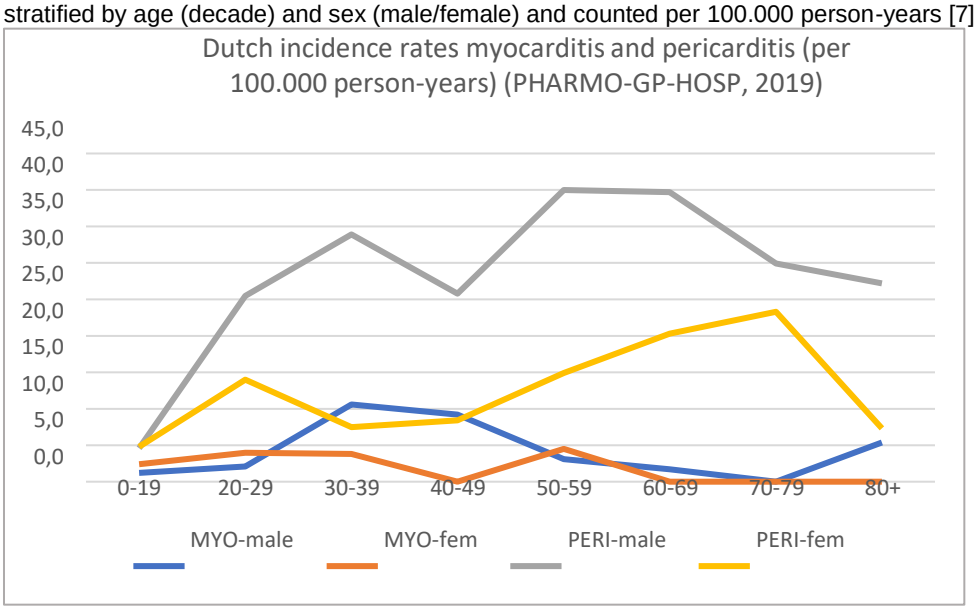
Fourteen people had pericarditis or myocarditis in the past due to various causes, such as COVID-19 (1), auto-immune disease (1), cardiac disease (2) or unspecified cause (10).

In total, 7 people had concurrent (or recent) cardiac diseases (myocardial infarction (5), arrhythmia (2)) and 5 had auto-immune diseases while developing myocarditis or pericarditis.

Comparison with background incidence

For comparison of the reported number of cases of myocarditis and pericarditis following vaccination with COVID-19 vaccines with background incidence rates, data were obtained from Dutch hospital and general practitioner registries based on ICD-10 coding selected by PHARMO institute. In figure 2 incidence rates of pericarditis and myocarditis from 2019 are shown.

Figure 2: Background incidence rates of myocarditis and pericarditis in The Netherlands, in 2019. Data are stratified by age (decade) and sex (male/female) and counted per 100.000 person-years [7].



The observed-over-expected ratio's (OE) are calculated by dividing the number of reported cases (as a proxy for 'observed') by the number of 'expected' cases. To define this numerator, vaccine exposure data were obtained from RIVM (CIMS database) and the expected number of cases was calculated by the formula: $N_{Expected}$ = ($N_{vaccine\_exposure}$ * (At risk period / 365) * 1/100,000) * Incidence rate. Since the mechanism of myocarditis following vaccinations is unknown, a plausible risk-window or time-to-onset is hard to define. In literature, the majority of cases occurred within one or two weeks following vaccination. In some studies, 4 weeks or one month were taken into account and with smallpox vaccination, the risk window for myocarditis was set on 30 days [22]. Therefore, the at-risk-period was set on 30 days after the first or second vaccination moment. Reports with time-to-onset of 30 days or less (n=186) were included in the calculations.

In figure 3 the observed-over-expected ratios (OE) are shown for myocarditis and pericarditis with each vaccine. Within each plot, numbers are stratified for sex, age and vaccination moment (dose). If OE is > 1, more cases were observed (reported) than expected based on background incidence rates of 2019 within a risk window of 30 days following vaccination. A complete table of results can be found in appendix 2.

For pericarditis, in most groups OE is not greater than 1, meaning that the number of reports is not greater than expected. In a number of groups with OE > 1, this is not statistically significant if the 95% confidence interval contains 1. Some exceptions are men, aged 20-39 years following the second dose of Moderna and AstraZeneca and women, aged 40-59 following Janssen vaccine (one dose). Of note, the rate of underreporting is not known. True incidence of pericarditis following vaccination is therefore likely to be higher.

For myocarditis, OE is greater than 1 in multiple groups. Following the second dose of Pfizer vaccine, the number of reported cases in younger men (0-19) was significantly greater than expected. For other groups with Pfizer vaccine, the outcomes are less clear, since confidence intervals are broad. With Moderna, OE > 1 for men 20-39 years after both doses and for women 20-39 years after dose 1. With the AstraZeneca vaccine myocarditis was reported more frequently than expected in males 20-39 after the first dose and in females aged 40-59 after the first dose. With the Janssen vaccine, in men the number of reports is about what can be expected.

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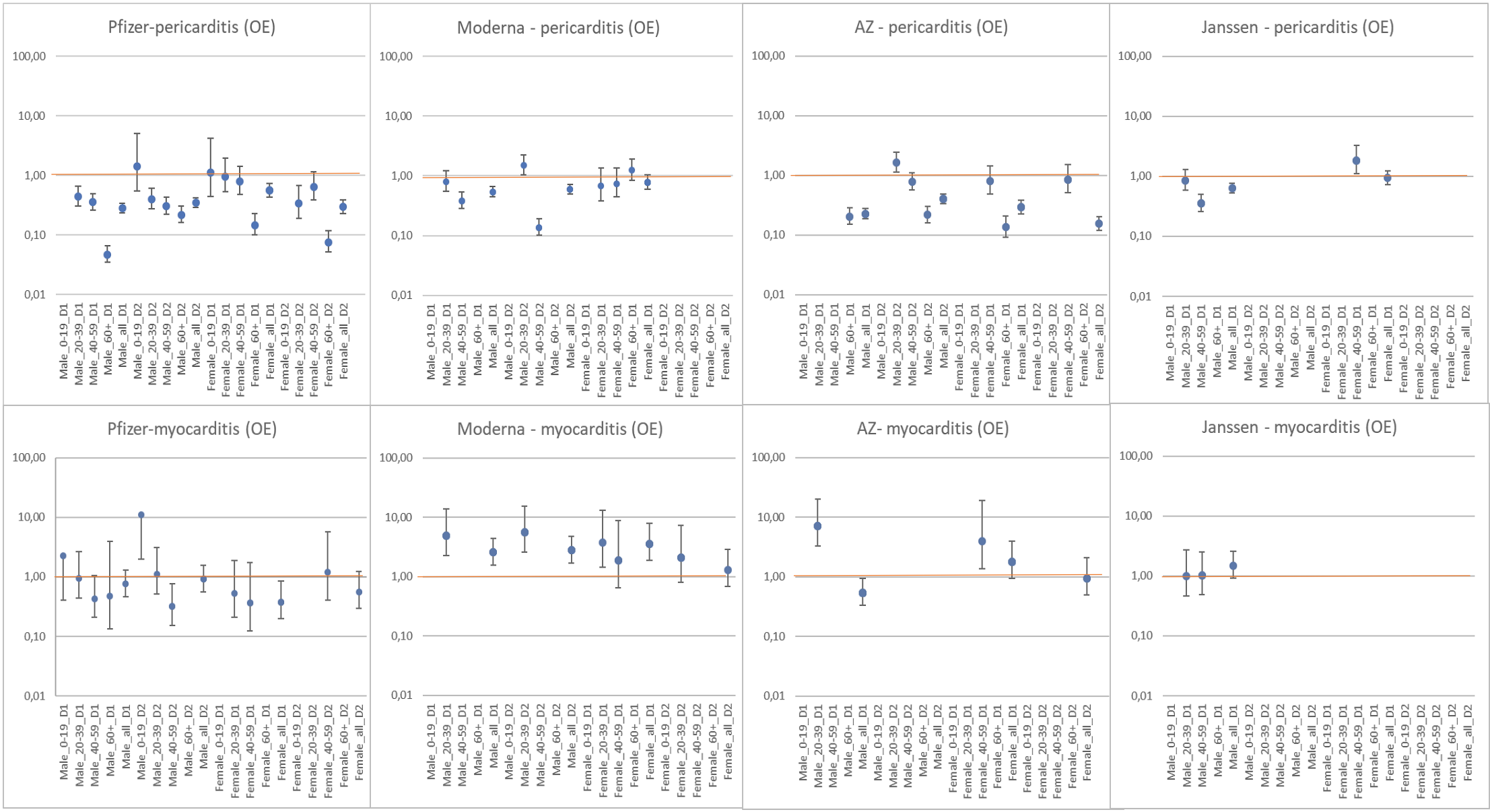
Figure 3: Observed-over-Expected ratios (OE) of myocarditis and pericarditis reports per COVID-19 vaccine, stratified for men and women, in age groups and per dose. The scale is semi-logarithmic. If there are no cases in a subgroup, OE = 0. If OE ratio > 1, the number of reported cases exceeds the expected number based on background incidence. The error bars show the range of the lower and upper limits of the 95%confidence intervals; when the background incidence rates are 0.0, expected is 0 and would be OE endless (not shown); this is the case in: 1) Myocarditis, male 0-19 with background rate 1.2 [0.0-6.5] where upper limits cannot be calculated; 2) Myocarditis, female 60+ background rate 0.0 [0.0-2.8] where OE is not shown, of not O=1 with second dose Pfizer, O=1 with first and second dose AstraZeneca. More details are available in appendix 2.



Other sources of information

Literature

Many case-reports have been published about myocarditis and pericarditis with mRNA vaccines, especially in younger males. Few case-reports describe myocarditis or pericarditis in females, other age groups and with vector-based vaccines such as Janssen. [10]
The incidence of myocarditis following vaccination in Israel (Pfizer) studied in a healthcare registry was 2.13 (95% CI 1.56-2.70) per 100.000 persons who had at least one dose and was highest in males 16-29 years with 10.69 (6.93-14.46) per 100.000 persons [11]. In military personnel (Israel, Pfizer), 5.07 per 100.000 people developed myocarditis within 1 week following the second dose [12]. Mevorach found an increase of incidence rates of 5.34 (4.48 to 6.40) up to 13.60 (9.30 to 19.20) for myocarditis following vaccination (Pfizer, both doses) in males aged 16-19 years [13]. The course of the disease was mild to moderate in the majority of affected patients [11-13].
In the United States of America, the mean monthly number of cases of myocarditis in 40 hospitals during the pre-vaccine period was 16.9 per 100.000 (95% CI, 15.3-18.6) compared to 27.3 (95% CI, 22.4-32.9) during the vaccine period. The mean numbers of cases of pericarditis were 49.1 (95% CI, 46.4-51.9) and 78.8 (95% CI, 70.3-87.9), per 100.000 respectively. Differences were statistically significant. Myocarditis developed rapidly in younger patients, mostly after the second vaccination. Pericarditis affected older patients later, after either the first or second dose of Pfizer, Moderna or Janssen vaccines [14].
In Scandinavian countries an excess rate of myocarditis and pericarditis patients was seen in a nationwide healthcare registry system, mainly following the second dose of Moderna in the general population and in men aged 18-39 years. With the Pfizer vaccine, the excess rate was less increased and the absolute numbers were low. They also found that Sars-CoV-2 infection was associated with myocarditis, more strongly in people over 40 years [9].

Databases

Spontaneous reporting databases from the UK (Yellow Card), USA (VAERS) and Europe (Eudravigilance) were recently reviewed on pericarditis and myocarditis following mRNA COVID-19 vaccines. The numbers of reports are summarized in table 2.
In the USA, the majority (60-69%) of cases occurred following the second dose. A higher frequency was also seen in males and younger age groups (< 40 years) for both vaccines. In Europe, 53-71% of the cases was reported in males. In cases from Europe and the UK, a total of 17 reported a fatal outcome (14 Pfizer, 3 Moderna) [4].

	Pfizer/BioNTech		**Moderna**	
	N reports	Reporting rate per million vaccinated persons*	N reports	Reporting rate per million vaccinated persons
Pericarditis				
○ **UK**	140	6.73	25	1.79
○ **USA**	759	3.53	342	2.69
○ **Europe**	650	2.87	117	3.84
Myocarditis				
○ **UK**	165	7.93	29	2.07
○ **USA**	968	6.47	461	3.65
○ **Europe**	957	4.23	228	6.15

Table 2. Reports of pericarditis and myocarditis from the UK, USA and Europe, reviewed by Lane and Shakir. [4]
** In UK and Europe: vaccinees with at least one dose; USA: fully vaccinated people (two doses)*

VigiBase, WHO's global database of suspected adverse reactions to medicinal products, developed and maintained by Uppsala Monitoring Centre, collected over 8500 reports of myocarditis and pericarditis with COVID-19 vaccines. Both pericarditis and myocarditis were mainly reported in male adults (18-45 years), with a higher number of reports of myocarditis compared to pericarditis. For all vaccines except AstraZeneca, the number of reported cases was disproportionate, indicating a potential signal for an adverse reaction following vaccination. This statistic approach does not correct for background incidence and vaccine exposure data. A summary of these reports is shown in table 3 [15].

	Total	Pfizer/BioNTech	Moderna	AstraZeneca	Janssen
Pericarditis					
Number (total)	8516	6 455	1 369	512	155
- male (%)	4801 (56%)	3585 (56%)	845 (62%)	254 (50%)	106 (68%)
- female (%)	3668 (43%)	2836 (44%)	518 (38%)	252 (50%)	48 (31%)
Disproportionality					
- ROR (ROR_{025})	13.1 (12.7)	17.2 (16.7)	6.1 (5.7)	1.5 (1.4)	2.8 (2.4)
- IC (IC_{025})	2.7 (2.7)	3.4 (3.3)	2.5 (2.4)	0.6 (0.4)	1.5 (1.2)
Myocarditis					
Number (total)	11382	8 130	2 687	353	185
- male (%)	8397 (74%)	5889 (73%)	2165 (81%)	189 (54%)	138 (75%)
- female (%)	2916 (26%)	2190 (27%)	511 (19%)	159 (45%)	47 (25%)
Disproportionality					
- ROR (ROR_{025})	13.9 (13.5)	16.3 (15.8)	9.6 (9.2)	0.8 (0.7)	2.5 (2.2)
- IC (IC_{025})	2.7 (2.7)	3.3 (3.3)	3.1 (3.0)	-0.4 (-0.5)	1.3 (1.1)

Table 3. Reports of pericarditis and myocarditis from VigiBase. [15] For disproportionality ROR (and ROR_{025}) > 1 and IC (and IC_{025}) > 0 indicate disproportionate reporting. Note that the number of reports also depends on the vaccines administered, of which the numbers are not exactly known.

Mechanism

In literature, some hypotheses for the pathophysiologic mechanism of myocarditis or pericarditis following immunization are described.
Vaccine associated myopericarditis has been described following smallpox vaccination [16, 17]. An immune inflammatory mechanism of myocardial injury was proposed, since cases showed lymphocytic infiltration with eosinophil degranulation in areas of myocardial necrosis in autopsy. On the contrary, in viral myocarditis a direct viral infection of the myocardium is involved. The mechanisms between viral infection and immunization as a cause for myocarditis may therefore be different [18].
For mRNA vaccines, modified RNA is suggested to act as an antigen, as has been described for RNA (not modified) which is highly reactogenic [19, 20]. A genetic predisposition might explain sensitivity for a stronger innate and acquired immune response against mRNA particles resulting in activation of proinflammatory cascades and immunologic pathways. In myocarditis, also heart-reactive auto-antibodies have been described, indicating a predisposition for immune mediated cardiac inflammation [20].
The higher prevalence of myocarditis in younger men (in general and following immunization) is poorly understood. It is suggested that elevated testosterone contributes to viral binding to myocytes, inhibition of anti-inflammatory responses and upregulation of cardiac fibrotic remodeling genes [21]. Estrogen, on the other hand, could have a protective role by balancing regulatory and pro-inflammatory T-cells [21].

Discussion

In literature, many publications show that myocarditis and pericarditis are mainly associated with the second dose of mRNA vaccines in younger males with short time-to-onset and a relatively mild course of disease. In our reports, myocarditis and pericarditis were reported with any dose of mRNA and vector based COVID-19 vaccines, more in men than in women and among all age groups. The majority has recovered or was recovering at time of reporting. In four reports, myocarditis (3) and pericarditis (1) had a fatal outcome. Another two reports mention that the patient died from another cause after having had pericarditis following vaccination. It should be noted that a causal relationship could not be confirmed with certainty in all non-fatal and fatal cases. Although pericarditis and myocarditis are now known ADRs with mRNA vaccines, it is impossible to exclude any other cause in every single report.

Other causes

The most common causes for myocarditis and pericarditis are a recent infection and auto-immune diseases [23]. In our reports, a quarter excluded infection as other possible cause but a minority had known concurrent causes such as recent infection or existing cardiac or auto-immune diseases.
Sars-CoV-2 (COVID-19) infection is also associated with myocarditis and pericarditis [9,10]. An Israeli study showed an 18 times increased risk for myocarditis after Sars-CoV-2 infection compared to healthy controls, whereas following vaccination the risk was 3 times increased [24]. In our reports, 11-20% of the patients had COVID-19 in medical history, which is similar to all reports with COVID-19 vaccines in general (about 18%). However, undiagnosed COVID-19 cannot be excluded. Only two people had a confirmed Sars-CoV-2 infection shortly before pericarditis.

Frequency
Based on spontaneous reporting, frequencies or incidence cannot be calculated. From ADR database studies reporting rates of 2-7 per one million vaccinated persons for pericarditis and 3-8 per million for myocarditis were observed with mRNA vaccines [4]. In the Netherlands, the reporting rate for pericarditis varies from 2-20 per one million vaccinated persons, and for myocarditis from 0-11 per one million vaccinated persons. The highest reporting rates were found for pericarditis as well as myocarditis following both doses of Moderna in males. For details, see appendix 2.
In health care registry studies, the frequency of myocarditis following vaccination varies from 2 to 27 per 100.000 vaccinated persons and for pericarditis the frequency is about 49 per 100.000 persons [11-13].

Limitations OE method
An observed-over-expected ratio (OE) can correct for background incidence and vaccine exposure. In our OE method, reported cases are considered as observed cases. Underreporting is a common feature of voluntary reporting systems. Since the extent of underreporting is unknown, the number of observed cases can be underestimated. Media attention however may have increased awareness and diagnosing of pericarditis and myocarditis, as well as willingness to report these conditions following vaccination with COVID-19 vaccines. This might have led to a reduction in underreporting. On the other hand, background incidence rates based on previous periods may be lower compared to current attention to pericarditis and myocarditis.
Since the Dutch background incidence rates were based on 2019, the effect of Sars-CoV-2 infections during the COVID-19 pandemic, which is associated with myocarditis and pericarditis as well, was not taken into account.
To compare Dutch reports with other outcomes of studies in literature, the data were stratified for vaccine, dose, sex and four age groups for myocarditis and pericarditis separately. As a consequence, absolute numbers in stratified group were small and calculated ratios can be inaccurate.
Although in few strata OE ratios (including the lower limit confidence intervals) were greater than 1, a potential risk in other groups cannot be ruled out. We compare an ‘observed’ number based on spontaneous reporting with ‘expected’ from healthcare registries. The ‘observed’ number is likely to be underestimated. Therefore, OE ratios reaching 1 should give rise to be alert as well. Of note, only reports with high diagnostic certainty (reported diagnosis) were taken into account in our analysis. Reports with only symptoms but without a clear diagnose and in which one of both diagnoses were not explicitly mentioned were not counted. Initial symptoms of pericarditis and myocarditis do not always require diagnosis and these conditions are often self-limiting and can be underrecognized and underdiagnosed. Therefore, the real number of pericarditis and myocarditis cases may be higher than observed.

Conclusion

Lareb received 194 reports of myocarditis and pericarditis with mRNA-vaccines in men and women and among all age-groups, of which 159 had a plausible time-to-onset up to 30 days following the first or second dose of vaccination. An excess of observed cases compared to expected cases was seen for myocarditis with the second dose of Pfizer and Moderna in boys aged 12-19, with both the first and second dose of Moderna in males aged 20-39 and with the first dose of Moderna in females aged 20-39 years. More than expected cases were also seen for pericarditis in males aged 20-39 years receiving the second dose of Moderna.
With the viral vector vaccines, 36 reports of myocarditis and pericarditis were received, of which 26 had a plausible time-to-onset up to 30 days following vaccination. Although absolute numbers are small, an excess of observed cases compared to expected cases was seen for pericarditis in men aged 20-39 following the second dose of AstraZeneca and for women aged 40-59 following a single dose of Janssen. For myocarditis, in males aged 20-39 and females aged 40-59 an excess of cases was seen following the first dose of AstraZeneca as well as in adult men in general who received the Janssen vaccine.

In part, the Dutch reports are consistent with literature, with a known risk of myocarditis and pericarditis with mRNA vaccines, mainly following the second dose and in younger men. However, this overview shows that myocarditis and pericarditis have also been reported in other age groups and in women and with viral vector vaccines.

It is not possible to quantify the exact risk of myocarditis and pericarditis following COVID-19 vaccination for the Dutch population based on the number of spontaneously reported cases. Additional research is needed to quantify this risk and to specify people at risk with mRNA vaccines. This also counts for a possible association with the viral vector vaccines.

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This signal has been raised on November 26, 2021. It is possible that in the meantime other information became available. For the latest information, including the official SmPC’s, please refer to website of the MEB www.cbg-meb.nl

Appendix 1: Summary of Brighton Collaboration Case definitions of pericarditis and myocarditis

	Pericarditis	Myocarditis
Diagnostics		
Biopsy / Autopsy	Pericardial inflammation	Myocardial inflammation
Physical examination	Pericardial friction rub*	
ECG*/#	Concave-upward ST segment elevation ST segment depression in aVR PR depression throughout leads	Arrythmia AV node / intraventricular conduction delay Frequent ectopy
Imaging*	*Ultrasound, MRI or CT*: Pericardial fluid collection or inflammation	*MRI cardiac*[#]: Patchy oedema, gadolinium enhancement *Cardiac ultrasound*[#/##]: New ventricular function Segmental wall abnormalities Systolic/diastolic function depressed Ventricular dilatation Wall thickness change Intracavitary thrombi
Blood test		Troponin T, Troponin I increased[##] CK-MB increased[##] Inflammation marker increased (CRP, BSE, D-dimer)
Symptoms		
Specific**	Chest pain Palpitations Dyspnoea Sweating Sudden death	Chest pain Palpitations Dyspnoes Sweating Sudden death
Non specific	Fever Shouder/upper back pain Cough Oedema Cyanosis Weakness Fatigue Altered mental status Nausea, vomiting, diarrhoea	Fatigue Abdominal pain Dizziness Fainting Oedema Cough

According to Brighton Collaboration case definition for pericarditis and myocarditis (for people > 2 years), a definitive case (level 1) is confirmed by biopsy or autopsy, or when 2 out 3 items (*) are present for pericarditis and when Troponin is increased and one specific abnormality is shown by imaging[#]. A probable case for pericarditis has at least one specific symptom (**) and 1 out 3 items (*) are present and alternative explanations are excluded. A probable case for myocarditis has 1 out of 3 items (##) present and alternative explanations are excluded. A possible case for pericarditis has at least 1 non-specific symptom and 1 of the first three mentioned specific symptoms and non-specific ECG changers or radiography showing an enlarged heart and alternative explanations are excluded. A possible case for myocarditis has at least one elevated inflammation biomarker and at least one non-specific ECG abnormality and alternative explanations are excluded. Source: https://brightoncollaboration.us/myocarditis-case-definition-update/

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Appendix 2. Observed over expected ratio calculation. LL = lower limit 95% confidence interval, UL = upper limit 95% confidence interval.

Vaccine Reaction Male/ Female	Age group	N reports (1st dose)	N reports (2nd dose)	N (TTO 30 d) first dose	N (TTO 30 d) second dose	First dose (vaccinations)	Second dose (vaccinations)	Reporting rate per million vaccinations (all TTO, 1st dose)	Reporting rate per million vaccinations (all TTO, 2nd dose)	IR (PHARMO)	[95% CI]	Expect-ed risk period 30 days (first dose)	CI_LL	CI_UL	Expect-ed risk period 30 days (second dose)	CI_LL	CI_UL	O/E (first dose)	CI_LL	CI_UL	O/E (2nd dose)	CI_LL	CI_UL
Pfizer																							
Pericarditis																							
Female	0-19	2	0	2	0	451676	360037	4,4	0,0	4,8	[1.3-12.3]	1,8	0,5	4,6	1,4	0,4	3,6	1,1	0,4	4,1	0,0	0,0	0,0
	20-39	10	6	10	3	1186863	1017791	8,4	5,9	10,7	[5.3-19.1]	10,4	5,2	18,6	8,9	4,4	16,0	1,0	0,5	1,9	0,3	0,2	0,7
	40-59	11	9	11	8	1413384	1289099	7,8	7,0	11,9	[6.6-19.6]	13,8	7,7	22,8	12,6	7,0	20,8	0,8	0,5	1,4	0,6	0,4	1,1
	60+	5	3	4	2	1769998	1711804	2,8	1,8	18,7	[12.1-27.6]	27,2	17,6	40,2	26,3	17,0	38,8	0,1	0,1	0,2	0,1	0,1	0,1
	all	28	18	27	13	4822939	4379510	5,8	4,1	12,3	[9.3-16.0]	48,8	36,9	63,4	44,3	33,5	57,6	0,6	0,4	0,7	0,3	0,2	0,4
Male	0-19	1	2	0	2	464639	373564	2,2	5,4	4,6	[1.3-11.9]	1,8	0,5	4,5	1,4	0,4	3,7	0,0	0,0	0,0	1,4	0,5	5,0
	20-39	13	13	13	10	1206728	1030125	10,8	12,6	29,7	[19.7-42.9]	29,5	19,5	42,5	25,1	16,7	36,3	0,4	0,3	0,7	0,4	0,3	0,6
	40-59	16	13	14	11	1437801	1310704	11,1	9,9	33,5	[24.0-45.7]	39,6	28,4	54,0	36,1	25,9	49,2	0,4	0,3	0,5	0,3	0,2	0,4
	60+	3	11	2	9	1523175	1470578	2,0	7,5	34,2	[24.5-46.4]	42,8	30,7	58,1	41,3	29,6	56,1	0,0	0,0	0,1	0,2	0,2	0,3
	all	33	39	29	32	4633554	4185902	7,1	9,3	26,9	[22.2-32.4]	102,4	84,5	123,4	92,5	76,4	111,5	0,3	0,2	0,3	0,3	0,3	0,4
Myocarditis																							
female	0-19	0	0	0	0	451676	360037	0,0	0,0	2,4	[0.3-8.7]	0,9	0,1	3,2	0,7	0,1	2,6	0,0	0,0	0,0	0,0	0,0	0,0
	20-39	2	0	2	0	1186863	1017791	1,7	0,0	3,9	[1.1-9.9]	3,8	1,1	9,7	3,2	0,9	8,3	0,5	0,2	1,9	0,0	0,0	0,0
	40-59	1	3	1	3	1413384	1289099	0,7	2,3	2,4	[0.5-6.9]	2,8	0,6	8,0	2,5	0,5	7,3	0,4	0,1	1,7	1,2	0,4	5,7
	60+	0	2	0	1	1769998	1711804	0,0	1,2	0,0	[0.0-2.8]	0,0	0,0	4,1	0,0	0,0	3,9		0,0			0,3	
	all	3	5	3	4	4822939	4379510	0,6	1,1	2,0	[0.9-3.8]	7,9	3,6	15,1	7,2	3,2	13,7	0,4	0,2	0,8	0,6	0,3	1,2
male	0-19	1	5	1	4	464639	373564	2,2	13,4	1,2	[0.0-6.5]	0,4	0,0	2,5	0,4	0,0	2,0	2,3	0,4		11,2	2,0	
	20-39	6	6	6	6	1206728	1030125	5,0	5,8	6,4	[2.3-13.8]	6,3	2,3	13,7	5,4	1,9	11,7	1,0	0,4	2,6	1,1	0,5	3,1
	40-59	6	4	3	2	1437801	1310704	4,2	3,1	5,9	[2.4-12.1]	6,9	2,8	14,3	6,3	2,6	13,0	0,4	0,2	1,1	0,3	0,2	0,8
	60+	1	1	1	0	1523175	1470578	0,7	0,7	1,7	[0.2-6.0]	2,1	0,3	7,5	2,0	0,2	7,3	0,5	0,1	4,0	0,0	0,0	0,0
	all	14	16	11	12	4633554	4185902	3,0	3,8	3,8	[2.2-6.2]	14,5	8,4	23,6	13,1	7,6	21,3	0,8	0,5	1,3	0,9	0,6	1,6

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Moderna																						
Pericarditis																						
female	0-19	0	0	0	0	12787	10768	0,0	0,0	4,8	[1.3-12.3]	0,1	0,0	0,1	0,0	0,0	0,1	0,0	0,0	0,0	0,0	0,0
	20-39	1	0	1	0	168720	151582	5,9	0,0	10,7	[5.3-19.1]	1,5	0,7	2,6	1,3	0,7	2,4	0,7	0,4	1,4	0,0	0,0	0,0
	40-59	2	1	2	0	275516	255117	7,3	3,9	11,9	[6.6-19.6]	2,7	1,5	4,4	2,5	1,4	4,1	0,7	0,5	1,3	0,0	0,0	0,0
	60+	1	0	1	0	52701	48331	19,0	0,0	18,7	[12.1-27.6]	0,8	0,5	1,2	0,7	0,5	1,1	1,2	0,8	1,9	0,0	0,0	0,0
	all	4	1	4	0	509819	465866	7,8	2,1	12,3	[9.3-16.0]	5,2	3,9	6,7	4,7	3,6	6,1	0,8	0,6	1,0	0,0	0,0	0,0
male	0-19	0	0	0	0	12590	10444	0,0	0,0	4,6	[1.3-11.9]	0,0	0,0	0,1	0,0	0,0	0,1	0,0	0,0	0,0	0,0	0,0	0,0
	20-39	4	5	3	5	153914	136692	26,0	36,6	29,7	[19.7-42.9]	3,8	2,5	5,4	3,3	2,2	4,8	0,8	0,6	1,2	1,5	1,0	2,3
	40-59	4	2	3	1	284339	264548	14,1	7,6	33,5	[24.0-45.7]	7,8	5,6	10,7	7,3	5,2	9,9	0,4	0,3	0,5	0,1	0,1	0,2
	60+	0	2	0	0	49958	46595	0,0	42,9	34,2	[24.5-46.4]	1,4	1,0	1,9	1,3	0,9	1,8	0,0	0,0	0,0	0,0	0,0	0,0
	all	8	9	6	6	500937	458370	16,0	19,6	26,9	[22.2-32.4]	11,1	9,1	13,3	10,1	8,4	12,2	0,5	0,4	0,7	0,6	0,5	0,7
Myocarditis																						
female	0-19	0	0	0	0	12787	10768	0,0	0,0	2,4	[0.3-8.7]	0,0	0,0	0,1	0,0	0,0	0,1	0,0	0,0	0,0	0,0	0,0	0,0
	20-39	2	1	2	1	168720	151582	11,9	6,6	3,9	[1.1-9.9]	0,5	0,2	1,4	0,5	0,1	1,2	3,7	1,5	13,1	2,1	0,8	7,3
	40-59	1	1	1	0	275516	255117	3,6	3,9	2,4	[0.5-6.9]	0,5	0,1	1,6	0,5	0,1	1,4	1,9	0,6	8,8	0,0	0,0	0,0
	60+	0	1	0	0	52701	48331	0,0	20,7	0,0	[0.0-2.8]	0,0	0,0	0,1	0,0	0,0	0,1	0,0	0,0		0,0	0,0	
	all	3	3	3	1	509819	465866	5,9	6,4	2,0	[0.9-3.8]	0,8	0,4	1,6	0,8	0,3	1,5	3,6	1,9	8,0	1,3	0,7	2,9
male	0-19	0	0	0	0	12590	10444	0,0	0,0	1,2	[0.0-6.5]	0,0	0,0	0,1	0,0	0,0	0,1	0,0	0,0		0,0	0,0	
	20-39	4	4	4	4	153914	136692	26,0	29,3	6,4	[2.3-13.8]	0,8	0,3	1,7	0,7	0,3	1,6	5,0	2,3	13,7	5,6	2,6	15,5
	40-59	1	0	0	0	284339	264548	3,5	0,0	5,9	[2.4-12.1]	1,4	0,6	2,8	1,3	0,5	2,6	0,0	0,0	0,0	0,0	0,0	0,0
	60+	0	1	0	0	49958	46595	0,0	21,5	1,7	[0.2-6.0]	0,1	0,0	0,0	0,1	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
	all	5	5	4	4	500937	458370	10,0	10,9	3,8	[2.2-6.2]	1,6	0,9	2,6	1,4	0,8	2,3	2,6	1,6	4,4	2,8	1,7	4,8
AstraZeneca																						
Pericarditis																						
female	0-19	0	0	0	0	3328	3164	0,0	0,0	4,8	[1.3-12.3]	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
	20-39	0	0	0	0	69812	65429	0,0	0,0	10,7	[5.3-19.1]	0,6	0,3	1,1	0,6	0,3	1,0	0,0	0,0	0,0	0,0	0,0	0,0
	40-59	1	1	1	1	128238	120443	7,8	8,3	11,9	[6.6-19.6]	1,3	0,7	2,1	1,2	0,7	1,9	0,8	0,5	1,4	0,9	0,5	1,5
	60+	3	0	1	0	476716	451083	6,3	0,0	18,7	[12.1-27.6]	7,3	4,7	10,8	6,9	4,5	10,2	0,1	0,1	0,2	0,0	0,0	0,0
	all	4	1	2	1	678099	640123	5,9	1,6	12,3	[9.3-16.0]	6,9	5,2	8,9	6,5	4,9	8,4	0,3	0,2	0,4	0,2	0,1	0,2
male	0-19	0	0	0	0	1297	1194	0,0	0,0	4,6	[1.3-11.9]	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
	20-39	0	1	0	1	26512	25068	0,0	39,9	29,7	[19.7-42.9]	0,6	0,4	0,9	0,6	0,4	0,9	0,0	0,0	0,0	1,6	1,1	2,5
	40-59	0	1	0	1	48281	46000	0,0	21,7	33,5	[24.0-45.7]	1,3	1,0	1,8	1,3	0,9	1,7	0,0	0,0	0,0	0,8	0,6	1,1
	60+	4	4	3	3	516905	489921	7,7	8,2	34,2	[24.5-46.4]	14,5	10,4	19,7	13,8	9,9	18,7	0,2	0,2	0,3	0,2	0,2	0,3
	all	4	6	3	5	593003	562190	6,7	10,7	26,9	[22.2-32.4]	13,1	10,8	15,8	12,4	10,3	15,0	0,2	0,2	0,3	0,4	0,3	0,5
Myocarditis																						
female	0-19	0	0	0	0	3328	3164	0,0	0,0	2,4	[0.3-8.7]	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
	20-39	0	0	0	0	69812	65429	0,0	0,0	3,9	[1.1-9.9]	0,2	0,1	0,6	0,2	0,1	0,5	0,0	0,0	0,0	0,0	0,0	0,0

	40-59	1	1	1	0	128238	120443	7,8	8,3	2,4	[0.5-6.9]	0,3	0,1	0,7	0,2	0,0	0,7	4,0	1,4	19,0	0,0	0,0	0,0
	60+	1	1	1	1	476716	451083	2,1	2,2	0,0	[0.0-2.8]	0,0	0,0	1,1	0,0	0,0	1,0		0,9			1,0	
	all	2	2	2	1	678099	640123	2,9	3,1	2,0	[0.9-3.8]	1,1	0,5	2,1	1,1	0,5	2,0	1,8	0,9	4,0	1,0	0,5	2,1
male	0-19	0	0	0	0	1297	1194	0,0	0,0	1,2	[0.0-6.5]	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0		0,0	0,0	
	20-39	2	0	1	0	26512	25068	75,4	0,0	6,4	[2.3-13.8]	0,1	0,1	0,3	0,1	0,0	0,3	7,2	3,3	20,0	0,0	0,0	0,0
	40-59	0	0	0	0	48281	46000	0,0	0,0	5,9	[2.4-12.1]	0,2	0,1	0,5	0,2	0,1	0,5	0,0	0,0	0,0	0,0	0,0	0,0
	60+	0	0	0	0	516905	489921	0,0	0,0	1,7	[0.2-6.0]	0,7	0,1	0,1	0,7	0,1	0,1	0,0	0,0	0,0	0,0	0,0	0,0
	all	2	0	1	0	593003	562190	3,4	0,0	3,8	[2.2-6.2]	1,9	1,1	3,0	1,8	1,0	2,9	0,5	0,3	0,9	0,0	0,0	0,0
Janssen																							
Pericarditis																							
female	0-19	0		0		16095		0,0		4,8	[1.3-12.3]	0,1	0,0	0,2	0,0	0,0	0,0	0,0	0,0	0,0			
	20-39	0		0		121834		0,0		10,7	[5.3-19.1]	1,1	0,5	1,9	0,0	0,0	0,0	0,0	0,0	0,0			
	40-59	3		3		170003		17,6		11,9	[6.6-19.6]	1,7	0,9	2,7	0,0	0,0	0,0	1,8	1,1	3,3			
	60+	0		0		6525		0,0		18,7	[12.1-27.6]	0,1	0,1	0,1	0,0	0,0	0,0	0,0	0,0	0,0			
	all	3		3		314478		9,5		12,3	[9.3-16.0]	3,2	2,4	4,1	0,0	0,0	0,0	0,9	0,7	1,2			
male	0-19	1		0		24807		40,3		4,6	[1.3-11.9]	0,1	0,0	0,2	0,0	0,0	0,0	0,0	0,0	0,0			
	20-39	5		4		191707		26,1		29,7	[19.7-42.9]	4,7	3,1	6,8	0,0	0,0	0,0	0,9	0,6	1,3			
	40-59	2		2		203997		9,8		33,5	[24.0-45.7]	5,6	4,0	7,7	0,0	0,0	0,0	0,4	0,3	0,5			
	60+	0		0		7332		0,0		34,2	[24.5-46.4]	0,2	0,1	0,3	0,0	0,0	0,0	0,0	0,0	0,0			
	all	8		6		427902		18,7		26,9	[22.2-32.4]	9,5	7,8	11,4	0,0	0,0	0,0	0,6	0,5	0,8			
Myocarditis																							
female	0-19	0		0		16095		0,0		2,4	[0.3-8.7]	0,0	0,0	0,1	0,0	0,0	0,0	0,0	0,0	0,0			
	20-39	0		0		121834		0,0		3,9	[1.1-9.9]	0,4	0,1	1,0	0,0	0,0	0,0	0,0	0,0	0,0			
	40-59	1		0		170003		5,9		2,4	[0.5-6.9]	0,3	0,1	1,0	0,0	0,0	0,0	0,0	0,0	0,0			
	60+	0		0		6525		0,0		0,0	[0.0-2.8]	0,0	0,0	0,0	0,0	0,0	0,0		0,0				
	all	1		0		314478		3,2		2,0	[0.9-3.8]	0,5	0,2	1,0	0,0	0,0	0,0	0,0	0,0	0,0			
male	0-19	0		0		24807		0,0		1,2	[0.0-6.5]	0,0	0,0	0,1	0,0	0,0	0,0	0,0	0,0				
	20-39	1		1		191707		5,2		6,4	[2.3-13.8]	1,0	0,4	2,2	0,0	0,0	0,0	1,0	0,5	2,8			
	40-59	2		1		203997		9,8		5,9	[2.4-12.1]	1,0	0,4	2,0	0,0	0,0	0,0	1,0	0,5	2,5			
	60+	0		0		7332		0,0		1,7	[0.2-6.0]	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0			
	all	3		2		427902		7,0		3,8	[2.2-6.2]	1,3	0,8	2,2	0,0	0,0	0,0	1,5	0,9	2,6			