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Systematic review of spontaneous reports of myocarditis and pericarditis in transplant recipients and immunocompromised patients following COVID-19 mRNA vaccination

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ABSTRACT

Objectives To determine whether spontaneous reporting rates of myocarditis and pericarditis differed in immunocompromised patients compared with the whole population overall, and in terms of demographics, vaccine dose and time-to-onset.

Design Systematic review of spontaneously reported data from the European Union/European Economic Area (EU/EEA), the USA and the UK.

Data sources EudraVigilance (EU/EEA), Vaccine Adverse Event Reporting System (VAERS; USA) and the Medicines and Healthcare products Regulatory Agency (UK) spontaneous reporting databases were searched from date of vaccine launch to 1 December 2021.

Eligibility criteria Publicly available spontaneous reporting data for 'myocarditis' and 'pericarditis' from EU/EEA and USA following COVID-19 messenger RNA vaccines. Reports with comorbidities or concurrent medication indicative of transplantation, HIV infection or cancer ('immunocompromised' population) were compared with each overall database population.

Data extraction and synthesis Two researchers extracted data. Spontaneously reported events of myocarditis and pericarditis were presented for immunocompromised populations for each data source, stratified by age, sex, dose and time-to-onset (where available). Seriousness of each event was determined according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline E2A definition. Proportional reporting ratio (PRR) was calculated.

Results There were 178 reports of myocarditis and pericarditis among immunocompromised individuals overall. Seriousness was comparable between the immunocompromised and overall populations in both databases. No trends in age or sex were observed among immunocompromised individuals. Most reports followed a second vaccine dose and occurred within 14 days. The frequency of reporting was similar to the wider population (PRR=1.36 (95% CI=0.89 to 1.82) for VAERS population).

Conclusions Myocarditis and pericarditis following COVID-19 vaccination are very rare, and benefits of COVID-19 vaccination continue to outweigh any perceived risks. Reporting rates of myocarditis and pericarditis were similar in immunocompromised individuals, however defining characteristics differed compared with the whole population; therefore, continued monitoring of adverse events following vaccination remains vital to understand differences between population subgroups.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to bring together spontaneous reporting data from three regions (Europe, the USA and the UK) comparing immunocompromised and immunocompetent populations adverse reactions following COVID-19 messenger RNA vaccination.
⇒ Spontaneously reported adverse drug reaction data are known to be subject to under-reporting and missing information, including information on co-morbidities and concomitant medications.
⇒ Further biases that may have influenced results, include differences in vaccination strategies between the three regions examined, differences in data collected via spontaneous reporting systems and the fact that serious events are more likely to be reported.
⇒ It is not possible to estimate incidence rates using spontaneous reporting data due to a lack of precise denominator data, that is, the number of people who received the vaccine in the corresponding period.

INTRODUCTION

The COVID-19 messenger RNA (mRNA) vaccines developed by Pfizer/BioNTech and Moderna were the first mRNA vaccines approved for use and have been successfully implemented in the fight against the COVID-19 pandemic.[1–3] They are successful both in terms of efficacy of the vaccines to elicit a protective immune response as well as the speed of development; this methodology for vaccination likely enables rapid modifications to fight any potential variants that may evade the current vaccinations in the future. This success does not come without concerns

though, and careful monitoring in real-world studies are essential to ensure these new mRNA vaccinations are safe across the whole population. It is also important to determine whether multiple dosing has any adverse effects, especially if modified mRNA vaccinations may be used in the future to fight new COVID-19 variants or other viral infections.

Spontaneous reporting of adverse events enables a snapshot of real-world responses to be assessed, with the caveat that there is often under-reporting and missing data within these reports.[4 5] Reported adverse events have been reported across the world in response to COVID-19 mRNA vaccinations and several have been recognised within the product information guidance, including myocarditis, pericarditis and myopericarditis.[6 7] Myocarditis and pericarditis are caused by inflammation of the myocardium pericardium leading to chest pain, shortness of breath, palpitations, cardiac failure or abnormal heart rhythms.[8 9] In Europe, myocarditis and pericarditis have been reported at an excess of 26–57 events per million within 1 week of COVID-19 mRNA vaccination, while in the USA it has been estimated that these events are reported at a rate of between 1 and 40.6 cases per million second doses of COVID-19 mRNA vaccines administered.[10 11] Within these populations, reporting rates were dependent on sex and age, with males under 30 years of age reporting myocarditis and pericarditis following COVID-19 mRNA vaccines at a higher rate than females under 30 years and people aged 30 years and over.[10 11] The incidence of myocarditis and pericarditis following COVID-19 mRNA vaccination is likely to be higher considering the well-known under-reporting of spontaneous adverse reactions.

Due to potential differences in the immune response to vaccination between immunocompromised and 'healthy' individuals, we hypothesised that immunocompromised individuals might experience myocarditis or pericarditis at a higher frequency, that characteristics (age and sex) of immunocompromised patients reporting these events may differ, that clinical course may be more severe and that duration of symptoms may be longer compared with immunocompetent individuals. We therefore aimed to determine the number of reports of myocarditis or pericarditis submitted by immunocompromised patient subgroups and whether these reports follow a similar reporting trend, in terms of age, sex, time-to-onset and vaccine dose, compared with the total population following mRNA vaccination.

MATERIALS AND METHODS

Systematic searches of spontaneous reporting outputs of the European Union/European Economic Area (EU/EEA; EudraVigilance) and the USA (Vaccine Adverse Event Reporting System (VAERS) via CDC Wonder tool) were conducted to obtain data on reported events of 'myocarditis' and 'pericarditis' among immunocompromised individuals following COVID-19 mRNA vaccination (COVID-19 Vaccines Pfizer/BioNTech (Comirnaty) and Moderna (Spikevax)). Searches of the VAERS and EudraVigilance databases covered the period from the date of vaccine launch until 30 November 2021.

Meanwhile, systematic searches were carried out in the UK's Yellow Card scheme's database of spontaneous reports to attain reports of 'myocarditis' and 'pericarditis' following mRNA vaccination for immunocompromised individuals. These searches were carried out by Medicines and Healthcare Regulatory Agency (MHRA) staff and supplied to us for analysis. The datalock point was 1 December 2021. Counts of overall reports of myocarditis and pericarditis were obtained within a personal communication from the MHRA. Further details regarding the overall population fatalities were obtained from the 'Coronavirus vaccine—weekly summary of Yellow Card reporting'.[12] The datalock point for these data was 8 December 2021. Immunocompromised individuals were defined as patients who were: transplant recipients, patients with HIV/AIDS or patients with cancer using chemotherapies. Counts of myocarditis and pericarditis reports were tabulated for each immunocompromised subgroup.

Full details of these searches are provided in the online supplemental file.

The level of detail within reports differs between spontaneous reporting databases depending on data collection forms used. In the VAERS database, it is possible to search for comorbidities, while in EudraVigilance it is necessary to use concomitant immunosuppressive treatments as a surrogate for immunosuppression. Therefore, in the VAERS database we searched for reports of myocarditis or pericarditis following at least one dose of COVID-19 mRNA vaccine (COVID-19 Vaccine Pfizer/BioNTech (Comirnaty) or COVID-19 Moderna (Spikevax)), where a history of transplantation was reported. To align the data analysis both databases were searched for medications which could be used as a surrogate marker for transplantation, HIV/AIDS or cancer; these medications included antirejection treatments, steroids, HIV/AIDS treatments and anticancer therapeutics approved in the USA and EU.[13–15] A full list of these medications is provided in the online supplemental file. Methotrexate was included as a medication proxy for auto-immune conditions and cancer; however, due to its wide use in autoimmune disease methotrexate was treated as a separate category. Age group and sex were obtained from each report and presented in a flow chart. Where reported, time-to-onset and vaccine dose were extracted and tabulated. Seriousness was obtained for each case, as defined in ICH Topic E2A: Clinical Safety Data Management, namely myocarditis and pericarditis events which were fatal, caused or prolonged hospitalisation (including surgery, where specified) or were life-threatening.[16] Two researchers independently searched the spontaneous reporting databases and extracted data.

It is not possible to estimate incidence using spontaneously reported data due to inherent limitations of

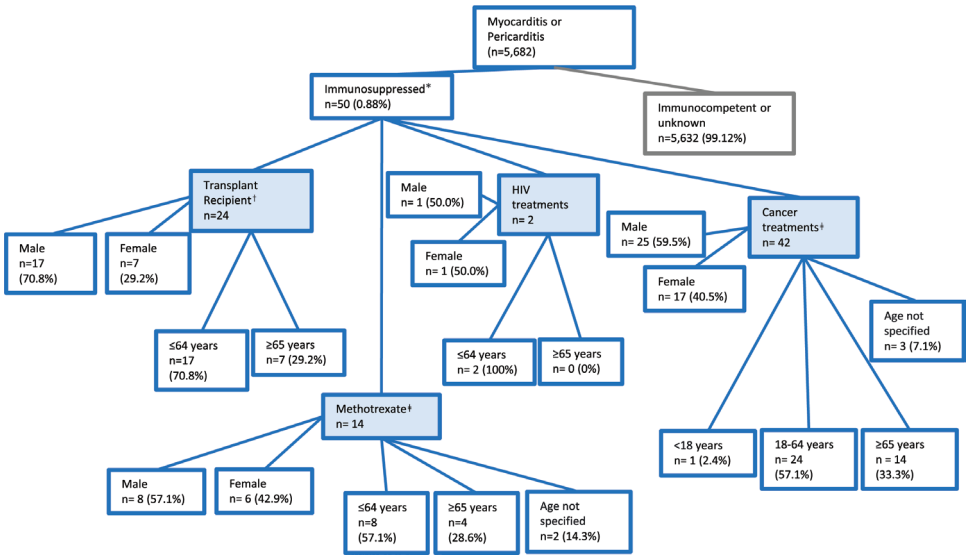

Figure 1 Tree diagram detailing the characteristics of vaccinees submitting spontaneous reports of myocarditis and pericarditis to EudraVigilance for European Union and European Economic Area only, following COVID-19 messenger RNA (mRNA) vaccines in immunocompromised individuals. Reports of myocarditis or pericarditis were searched in the EudraVigilance database following COVID-19 mRNA vaccines, either Moderna (Spikevax) or Pfizer/BioNTech (Comirnaty) (n=50 reports). The resultant reports were further assessed for individuals that were likely to be immunosuppressed based on the following search terms (transplant medications*, HIV/AIDS treatments, EU-approved cancer therapies). Concomitant medications were used as a proxy for disease status. *Counts are not mutually exclusive; one report may contain multiple concomitant medications from different categories. †Where tacrolimus, mycophenolate mofetil, ciclosporin or prednisolone were reported as concomitant medications. ‡Methotrexate was included as a potential transplant medication, however due to its wide use in autoimmune disease this was listed independently of the treatments used as a proxy for transplantation.

spontaneous reporting systems (under-reporting of events and the lack of a denominator in the database). Instead, proportional reporting rates (PRR) were calculated using the method described by Evans *et al*.[17] Unlike incidence rates which evaluates the number of events relative to the total population exposed, PRR uses the total number of Adverse Drug Reactions (ADRs) reported following exposure to the vaccine in each subgroup as the denominator. A ratio of reports of myocarditis and pericarditis from immunocompromised subgroups is then compared with the total myocarditis and pericarditis reports from all vaccinees following any dose of COVID-19 mRNA vaccination. PRR was calculated for the VAERS population only, due to limitations of the search functions available for the EudraVigilance dataset.

Patient and public involvement

Patients and the public were not consulted during this study due to the data source used. No identifiable information is included within the outputs of spontaneous reporting systems.

RESULTS

European Union/European Economic Area

There were 50 individual cases of myocarditis or pericarditis submitted to EudraVigilance up to 30 November 2021 with EU/EEA origin, among patients with immunosuppression as suggested by concomitant medications. Myocarditis was detailed in 19 (38.0%) of the 50 total reports, while pericarditis was reported for 29 (58.0%) cases. There were two reports (4.0%) where both myocarditis and pericarditis were described. Most reports were from patients in the 18–64 years age group (59.5% of 50 reports); 92.0% of reports concerned adults aged 18 years or older (figure 1). Twenty-nine of the 50 reports involved a male patient (58.0%; figure 1). In total, 82 medications of interest were reported within the 50 cases submitted to EudraVigilance up to 30 November 2021 (table 1). Of all concomitant medications investigated, cancer treatments were most commonly reported (n=50 of 82 medications, 61.0%; table 1). Ciclosporin was least frequently reported (n=1, 1.2%; table 1).

Of the 50 reports from immunocompromised individuals, 38 (76.0%) met the criteria for a 'serious' event (defined as: event caused or prolonged hospitalisation, was life-threatening or had a fatal outcome; table 2). None of the myocarditis or pericarditis events reported in immunocompromised subgroups of interest up to 30 November 2021 had a fatal outcome. In contrast, 75.78% of myocarditis or pericarditis events reported to EudraVigilance in the population overall met the criteria for a serious case (n=4309 of 5681 cases reported following a COVID-19 mRNA vaccine, overall). Of these 5681 cases, 156 (2.7%) reported a fatal outcome.

The USA

Meanwhile in the VAERS spontaneous reporting system, there was a total of 3062 reports of myocarditis

Table 1 Concomitant medications within spontaneous reports of myocarditis and pericarditis submitted to EudraVigilance for the European Union and European Economic Area only, following COVID-19 mRNA vaccines

	Tacrolimus	Mycophenolate mofetil	Methotrexate	Ciclosporin	Prednisolone	HIV treatments	Cancer treatments*	Total†
Comirnaty								
Myocarditis	1	2	5	0	6	1	14	**29**
Pericarditis	0	2	7	1	8	1	25	**44**
Myopericarditis	0	0	0	0	0	0	2	**2**
Spikevax								
Myocarditis	1	2	1	0	0	0	0	**4**
Pericarditis	0	0	1	0	1	0	1	**3**
Myopericarditis	0	0	0	0	0	0	0	**0**
Total*†	2	6	14	1	15	2	42	**82**

Reports of myocarditis or pericarditis were searched in the EudraVigilance database following COVID-19 mRNA vaccines, either COVID-19 Vaccine Moderna (Spikevax) or Pfizer/BioNTech (Comirnaty). Medications were used as a proxy for immunocompromised subgroups: transplant recipients (tacrolimus, mycophenolate mofetil, methotrexate, prednisolone, ciclosporin and steroids (including prednisolone)), HIV infection and patients undergoing cancer treatment.
Numbers in bold font represent totals.
*Hydrocortisone excluded as no indications given within reports and the drug is commonly used to treat other conditions .
†Reports may contain more than one concomitant medication and/or more than one event.
mRNA, messenger RNA.

or pericarditis following mRNA vaccination (Pfizer or Moderna), of which 1.83% (n=57; figure 2) were from immunocompromised individuals. These spontaneous reports of myocarditis or pericarditis in immunocompromised individuals differed in their gender and age distribution compared with the whole population with myocarditis or pericarditis.[18] The whole population had a bias of younger males experiencing myocarditis or pericarditis following COVID-19 mRNA vaccinations,[18] whereas from the immunocompromised population 52.6% of these events occurred in males and 50.9% were under 60 years of age. Thus, this could indicate a broadening in those susceptible to myocarditis or pericarditis in immunocompromised individuals. Splitting the analysis of immunocompromised individuals into transplant recipients, medically induced immunosuppression using methotrexate, HIV and cancer is indicated in figure 2. Within these four subsets. we investigated whether there were patterns in time-to-onset or vaccination dose for reported myocarditis or pericarditis events (table 3). Predominately, events were reported after the second mRNA vaccination (mean 51.8%; range 33.3%–61.3% within immunocompromised subgroups), while 8.9% of events (range 0%–16.1% within immunocompromised subgroups) were reported following the third vaccination dose (table 3). Approximately 70% of reported events

Table 2 Breakdown of serious myocarditis and pericarditis events reported via EudraVigilance and VAERS

	Serious events EudraVigilance*			Serious events VAERS			Total		
Immunocompromised characteristic	N	%† (95% CI)	Total reported in subgroup	N	%† (95% CI)	Total reported in subgroup	N	%† (95% CI)	Total reported in subgroup
Transplant	22	91.7 (73.0 to 99.0)	**24**	2	20.0 (2.5 to 55.6)	**10**	24	70.5 (52.5 to 84.9)	**34**
Methotrexate-treated patients	11	78.6 (49.2 to 95.3)	**14**	5	55.6 (21.2 to 86.3)	**9**	16	69.6 (47.1 to 86.8)	**23**
HIV	2	100	**2**	3	42.9 (9.9 to 81.6)	**7**	5	55.5 (21.2 to 86.3)	**9**
Cancer therapeutics	32	65.3 (50.4 to 78.3)	**49**	13	41.9 (24.5 to 60.9)	**31**	45	56.3 (44.7 to 67.3)	**80**

Reports of myocarditis, pericarditis or myopericarditis were searched in the VAERS database following COVID-19 messenger RNA vaccines, either Moderna or Pfizer/BioNTech. The resultant reports were further assessed for individuals that were likely to be immunocompromised based on the following search terms (transplant, medicinal immunosuppressant drugs; tacrolimus, mycophenolate mofetil, methotrexate, prednisolone, ciclosporin and steroids, HIV or approved cancer therapeutics). Serious events were determined as required hospitalisation, surgery or fatality as detailed in the comments box. Values indicate the events recorded and the percentage of the total events in each of the four characteristic categories with a 95% CI. Serious event defined as: event caused or prolonged hospitalisation, required surgery, was life-threatening or was fatal.
Numbers in bold font represent totals.
*Counts not mutually exclusive, multiple medications could be reported in the same case.
†Percentage of total reports within the EudraVigilance or VAERS database for that subgroup.
VAERS, Vaccine Adverse Event Reporting System.

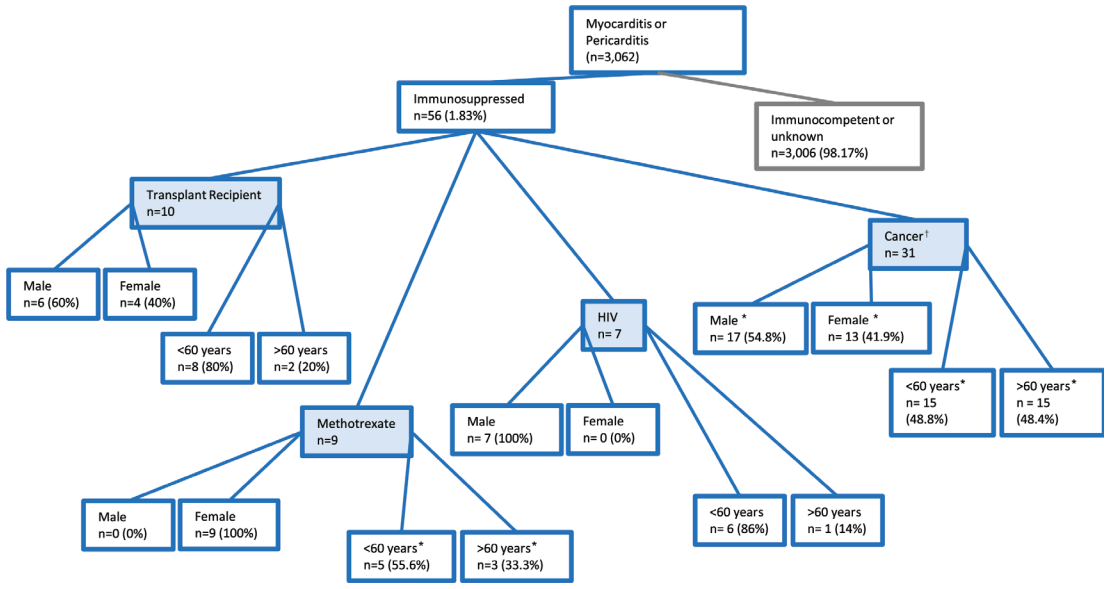

Figure 2 Tree diagram detailing the characteristics of spontaneous reports of myocarditis and pericarditis on the Vaccine Adverse Event Reporting System (VAERS) database following COVID-19 messenger RNA (mRNA) vaccines in immunocompromised individuals. Reports of myocarditis, pericarditis or myopericarditis were searched in the VAERS database following COVID-19 mRNA vaccines, either Moderna or Pfizer BioNTech. The resultant reports were further assessed for individuals that were likely to be immunocompromised based on the following search terms (transplant, tacrolimus, mycophenolate mofetil, methotrexate, prednisolone, ciclosporin). Transplant recipients were assessed separately to immunocompromised individuals that received medication, independent of disease setting. *Unspecified category, †cancer defined by use of cancer-approved medicines.

occurred within 14 days of vaccination (n=39; range 44.4%–100% within immunocompromised subgroups; table 3). Therefore, this is suggestive of a potential causal effect due to the rapid onset of symptoms following exposure to a COVID-19 mRNA vaccine. The seriousness of each event (resulting in hospitalisation, surgery or fatality) was assessed and recorded in table 2, with 41.1% (n=23) of the 56 reports of myocarditis or pericarditis from immunocompromised subgroups meeting the criteria for 'serious'. Surgery was required for three individuals, and one fatality was recorded. The fatal event occurred in a female undergoing cancer therapy, 8 days after receiving the first dose of COVID-19 vaccine Moderna. Cause of death was not specified within the report, however an autopsy demonstrated systemic inflammatory reaction, which affected primarily the small blood vessels of the brain with leptomeninges, heart, lungs and liver also affected. Generalised systemic tissue inflammation caused diffuse intravascular inflammatory microthrombi and haemorrhagic myocarditis. In comparison, for all myocarditis and pericarditis reports 63.4% were classified as serious, this includes immunocompromised as well as immunocompetent individuals.

To determine whether these events were reported at higher levels in immunocompromised compared with immunocompetent (or unspecified) individuals, a PRR was calculated. This was only possible in the VAERS dataset, due to data limitations in the EudraVigilance and Yellow Card datasets. In the VAERS population, the reporting rate of myocarditis and pericarditis was slightly higher for immunocompromised patients (transplant recipients, patients with HIV/AIDS and patients with cancer) compared with immunocompetent individuals (PRR=1.36 (95% CI: 0.89 to 1.82)). However, no statistical differences were observed. It should be noted that PRR are not the same as incidence rates. Data on duration of symptoms were not available for either database examined.

The UK

In total, 1009 reports of myocarditis and pericarditis following either COVID-19 mRNA vaccination had been submitted to the Yellow Card scheme up to 1 December 2021.[12] As of 8 December 2021, there had been three reported fatal outcomes; all three fatal events were in people who had received Pfizer/BioNTech.[12] The reporting rate for Pfizer/BioNTech was 11 cases of myocarditis reported per million, and 8 cases of pericarditis reported per million first or second vaccine doses. For Moderna, there were 39 reports of myocarditis doses and 22 reports of pericarditis per million first and second doses of the vaccine administered.[12] Reporting rates were highest for the 19–29 years age group for both COVID-19 mRNA vaccines, with a trend for decreased reporting in older age groups in the population overall.[12]

Among immunocompromised individuals overall, there were 72 cases of myocarditis, pericarditis or myopericarditis reported to the Yellow Card scheme up to 1 December 2021 (figure 3). Therefore, of all myocarditis or pericarditis reports recorded in the UK, 7.1% were from immunocompromised individuals. The majority of myocarditis and pericarditis events were from people

Table 3 Spontaneous reports of myocarditis and pericarditis on the VAERS database following COVID-19 mRNA vaccines in immunocompromised individuals subdivided into time to onset and vaccine dosage

Reports to VAERS															
	Outcome			Vaccine dose								Time to onset of symptoms			
				Dose 1		Dose 2		Dose 3		Unknown dose		<14 **days**		>14 **days**	
Immunocompromised characteristic		N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Transplant	Myocarditis	1	11.1 (0.3 to 48.2)	0	0.00	2	22.2 (2.8 to 60.0)	0	0.0	0	0.0	0	0.0	2	22.2 (2.8 to 60.0)
	Pericarditis	5	55.6 (21.2 to 86.3)	1	11.1 (0.3 to 48.2)	2	22.2 (2.8 to 60.0)	0	0.0	3	33.3	4	44.4 (13.7 to 78.8)	2	22.2 (2.8 to 60.0)
	Myopericarditis	3	33.3 (7.5 to 70.1)	1	11.1 (0.3 to 48.2)	1	11.1 (0.3 to 48.2)	0	0.0	0	0.0	1	11.1 (0.3 to 48.2)	1	11.1 (0.3 to 48.2)
	Total	9	100.0	3	33.3 (7.5 to 70.7)	3	33.3 (7.5 to 70.7)	0	0.0	3	33.3 (7.5 to 70.7)	4	44.4 (13.7 to 78.8)	5	55.6 (21.2 to 86.3)
Methotrexate	Myocarditis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Pericarditis	8	88.9 (51.8 to 99.7)	4	44.4 (13.7 to 78.8)	4	44.4 (13.7 to 78.8)	0	0.0	0	0.0	6	66.7 (29.9 to 92.5)	1	11.1 (0.3 to 48.2)
	Myopericarditis	1	11.1 (0.3 to 48.2)	0	0.0	0	0.0	0	0.0	1	11.1 (0.3 to 48.2)	1	11.1 (0.3 to 48.2)	0	0.0
	Total	9	100.0	4	44.4 (13.7 to 78.8)	4	44.4 (13.7 to 78.8)	0	0.0	1	11.1 (0.3 to 48.2)	7	77.8 (40.0 to 97.2)	1	11.1 (0.3 to 48.2)
HIV	Myocarditis	2	28.6 (3.7 to 71.0)	1	14.3 (0.4 to 57.9)	1	14.3 (0.4 to 57.9)	0	0.0	0	0.0	2	28.6	0	0.0
	Pericarditis	4	57.1 (18.4 to 90.1)	3	42.9 (9.9 to 81.6)	1	14.3 (0.4 to 57.9)	0	0.0	0	0.0	4	57.1 (18.4 to 90.1)	0	0.0
	Myopericarditis	1	14.3 (0.4 to 57.9)	0	0.0	1	14.3 (0.4 to 57.9)	0	0.0	0	0.0	1	14.3 (0.4 to 57.9)	0	0.0
	Total	7	100.0	4	57.1 (18.4 to 90.1)	3	42.9 (9.9 to 81.6)	0	0.0	0	0.0	7	100.0	0	0.0
Cancer therapeutics	Myocarditis	10	32.3 (16.7 to 51.4)	2	6.5 (0.8 to 21.4)	6	19.4 (7.5 to 37.5)	1	3.2 (0.1 to 16.7)	1	3.2 (0.1 to 16.7)	8	25.8 (11.9 to 44.6)	2	6.5 (0.8 to 21.4)
	Pericarditis	17	54.8 (36.0 to 72.7)	4†	12.9 (3.6 to 29.8)	11	35.5 (19.2 to 54.6)	2	6.5 (0.8 to 21.4)	0	0.0	10†	32.3 (16.7 to 51.4)	7	22.6 (9.6 to 41.1)
	Myopericarditis	4	12.9 (3.6 to 29.8)	0	0.0	2	6.5 (0.8 to 21.4)	2	6.5 (0.8 to 21.4)	0	0.0	3	9.7 (2.0 to 25.8)	0	0.0
	Total	31	100.0	6	19.4 (7.5 to 37.5)	19	61.3 (42.2 to 78.2)	5	16.1 (5.5 to 33.7)	1	3.2 (0.1 to 16.7)	21*	67.7 (48.6 to 83.3)	9*	29.0 (14.2 to 48.0)
All	Total	56	100.0	17	28.1 (18.8 to 44.1)	31	55.4 (41.5 to 68.7)	5	8.9 (3.0 to 19.6)	5	8.9 (3.0 to 19.6)	39	69.6 (55.9 to 81.2)	15	26.8 (15.8 to 40.3)

Reports of myocarditis, pericarditis or myopericarditis were searched in the VAERS database following COVID-19 mRNA vaccines, either Moderna or Pfizer/BioNTech. The resultant reports were further assessed for individuals that were likely to be immunocompromised based on the following search terms (transplant, immunosuppressant drugs; tacrolimus, mycophenolate mofetil, methotrexate, prednisolone, ciclosporin and steroids, HIV or approved cancer therapeutics: https://www.cancer.gov/about-cancer/treatment/drugs). Values indicate the events recorded and as a percentage of the total in each of the four characteristic categories with 95% CIs.
*n=1, unspecified time to onset.
†n=1, fatality.
mRNA, messenger RNA; VAERS, Vaccine Adverse Event Reporting System.

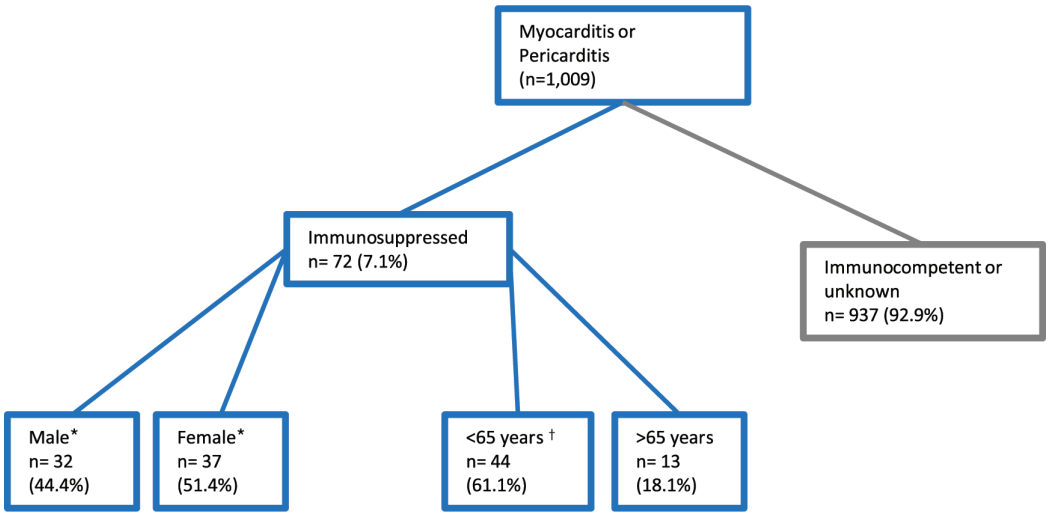

Figure 3 Tree diagram detailing the characteristics of spontaneous reports of myocarditis and pericarditis on the Yellow Card database following COVID-19 messenger RNA (mRNA) vaccines in immunocompromised individuals (Yellow Card, UK). Reports of myocarditis, pericarditis or myopericarditis from immunocompromised individuals were searched in the Yellow Card scheme following COVID-19 mRNA vaccines, either Moderna or Pfizer BioNTech. Data provided by Medicines and Healthcare products Regulatory Agency, datalock 1 December 2021. *n=3 unspecified, †n=2 under 18 years. For age category n=5 unknown.

aged <65 years, similar to the overall population who had reported events in the UK, whereas the male dominance of events seen in the whole population (74.9% of myocarditis and pericarditis were from male population)[18] was not seen in the immunocompromised, here 51.4% of reports were from female population (n=37; figure 3). Further classification of these events reported in the UK are detailed in table 4. One event was excluded from the analysis as it was not classified as myocarditis or pericarditis, rather it described general cardiac issues following COVID-19 mRNA vaccination.

Myocarditis and pericarditis may occur more often in patients with cancer following Pfizer mRNA vaccination

Next, we determined whether myocarditis and pericarditis in the immunocompromised subgroups, categorised as: transplant recipients, methotrexate-treated patients, HIV patients or individuals on approved cancer therapeutics (see online supplemental file for full medication lists) differed with the vaccines manufacturer used. This analysis was undertaken using the EudraVigilance and VAERS datasets only, due to how the information was reported from these systems allowed for stratification in this manner. Of the reports in these two datasets Pfizer/BioNTech had a higher number of reports, although details on total vaccines, and from which manufacturer, given in these discrete immunocompromised populations is unknown, which may have impacted the higher number of reports following Pfizer/BioNTech vaccine administration compared with Moderna. Vaccine roll out, vaccine interval period and demographics of recipients of

Table 4 Spontaneous reports of myocarditis and pericarditis submitted to the Yellow Card Scheme in the UK following COVID-19 mRNA vaccines in immunocompromised individuals

Reports to Yellow Card (UK)														
			Vaccine dose								Time to onset of symptoms			
Outcome			Dose 1		Dose 2		Dose 3		Unknown		<14 days		>14 days	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Myocarditis	30	42.3 (30.6 to 54.6)	13	18.3 (10.1 to 29.3)	11	15.5 (8.0 to 26.0)	5	7.0 (2.3 to 15.7)	1	1.4 (0.0 to 7.6)	19	26.8 (16.9 to 38.6)	8	11.3 (5.0 to 21.0)
Pericarditis	38	53.5 (41.3 to 65.5)	9	12.7 (6.0 to 22.7)	14	19.7 (11.2 to 30.9)	12	16.9 (9.0 to 27.7)	3	4.2 (0.9 to 11.9)	24	33.8 (23.0 to 46.0)	13	18.3 (10.1 to 29.3)
Myopericarditis	3	4.2 (0.9 to 11.9)	0	0	3	4.2 (0.9 to 11.9)	0	0	0	0	2	2.8 (0.3 to 9.8)	1	1.4 (0.0 to 7.6)
Total	71†*	100	22	31.0 (20.5 to 43.1)	28	39.4 (28.0 to 51.7)	17	23.9 (14.6 to 35.5)	4	5.6 (1.6 to 13.8)	45*	63.4 (51.1 to 74.5)	22*	31.0 (20.5 to 43.1)

Reports of myocarditis or pericarditis were searched in the Yellow Card scheme following COVID-19 mRNA vaccines, either COVID-19 Vaccine Moderna (Spikevax) or Pfizer/BioNTech (Comirnaty). Events were classified by vaccination dose and time to onset of symptoms
*n=4 missing information on time to onset.
†n=1 excluded due to no classification by myocarditis, pericarditis or myopericarditis.
mRNA, messenger RNA.

Table 5 Myocarditis and pericarditis adverse events reported following Moderna or Pfizer/BioNTech mRNA vaccination stratified by immunocompromised subgroups

Immunocompromised characteristic	EudraVigilance		VAERS		Total			
					Pfizer/BioNTech		Moderna	
	Pfizer/BioNTech	Moderna	Pfizer/BioNTech	Moderna	N	% (95% CI)	N	% (95% CI)
Transplant	20	4	7	2	27	24.77 (17.00 to 33.96)	6	20.69 (7.99 to 39.72)
Methotrexate-treated patients	12	2	1	8	13	11.93 (6.51 to 19.53)	10	34.48 (17.94 to 54.33)
HIV	2	0	4	3	6	5.5 (2.05 to 11.60)	3	10.34 (2.19 to 27.35)
Cancer therapeutics	41	1	22	9	63	57.8 (47.96 to 67.20)	10	34.48 (17.94 to 54.33)
Total	75	7	34	22	109	100	29	100

Reports of myocarditis, pericarditis or myopericarditis were searched in the EudraVigilance and VAERS database following COVID-19 mRNA vaccines, either Moderna or Pfizer/BioNTech. The resultant reports were further assessed for individuals that were likely to be immunocompromised based on the following search terms (transplant, immunosuppressant drugs; tacrolimus, mycophenolate mofetil, methotrexate, prednisolone, ciclosporin and steroids, HIV or approved cancer therapeutics: https://www.cancer.gov/about-cancer/treatment/drugs). Values indicate the events reported from each vaccine manufacture within each immunocompromised category. Percentage of the total reports for each manufacture are calculated for each of the characteristic categories.
mRNA, messenger RNA; VAERS, Vaccine Adverse Event Reporting System.

each vaccine in each region were unknown and may have differed, which may have led to higher reports following Pfizer/BioNTech administration compared with Moderna. This is inconsistent with the overall reporting population where higher reporting rates from Moderna were seen, potentially due to higher amounts of mRNA contained with Moderna vaccines compared with Pfizer/BioNTech (100 µg vs 30 µg, respectively).[19 20] To determine whether the number of reports from each immunocompromised subgroup differed following each vaccine type, the percentage of reports was calculated using the total number of myocarditis and pericarditis reports from each vaccine type as the denominator. Following Pfizer/BioNTech vaccine administration, 57.8% of reports of myocarditis and pericarditis were received from individuals on cancer therapeutics, whereas a lower percentage of reports was received following Moderna vaccination (table 5). These data suggest that potentially different immunocompromised conditions may require careful consideration as to the type of mRNA COVID-19 vaccines given.

Myocarditis and pericarditis events are not restricted to mRNA-based COVID-19 vaccines

Vaccine-associated myocarditis and pericarditis following COVID-19 vaccination is not only restricted to the use of mRNA-based vaccinations. Reports of myocarditis and pericarditis have been reported following adenovirus vector COVID-19 vaccines, suggesting it may not be the mRNA component of vaccines which trigger this response but the immune response or elements of SARS-CoV-2 itself. In the UK, 385 events of myocarditis and pericarditis had been reported via the Yellow Card scheme following administration of the AstraZeneca adenovirus vector COVID-19 vaccine, up to 15 December 2021,[12] which includes immunocompromised as well as immunocompetent populations. Meanwhile, a total of 348 events have been reported to EudraVigilance following vaccination with AstraZeneca or Janssen COVID-19 vaccines (table 6) and 141 events following Janssen vaccination have been reported to VAERS (table 6). We were able to stratify the events reported to EudraVigilance and VAERS into those reported by immunocompromised individuals and

Table 6 Comparison of the number of myocarditis and pericarditis adverse events following the different COVID-19 vaccination types

		mRNA vaccines		Adenovirus vector vaccines	
		Events (n)	% (95% CI)*	Events (n)	% (95% CI)*
EudraVigilance	Immunocompromised	50	0.9 (0.7 to 1.2)	5	1.43 (0.47 to 3.32)
	Immunocompetent or unknown	5632	99.1 (98.8 to 99.3)	343	98.56 (96.68 to 99.53)
	Total	**5682**	100.0	**348**	100.0
VAERS	Immunocompromised	57	1.86 (1.41 to 2.40)	3	2.13 (0.44 to 6.09)
	Immunocompetent or unknown	3006	98.14 (97.60 to 98.59)	138	97.87 (93.91 to 99.56)
	Total	**3063**	100.0	**141**	100.0

Reports of myocarditis, pericarditis or myopericarditis were searched in the EudraVigilance and VAERS database following COVID-19 mRNA vaccines, either Moderna or Pfizer/BioNTech, and adenovirus vector vaccines (AstraZeneca or Janssen). Comparison was made between the immunocompromised group identified in our analysis and the overall reporting population to the EudraVigilance and VAERS databases for these vaccines.
*Percentage of total.
mRNA, messenger RNA; VAERS, Vaccine Adverse Event Reporting System.

immunocompetent and calculated the percentage of total events from each dataset that were associated with these two population groups (table 6). The number of myocarditis and pericarditis events is much lower following viral vector vaccines, although direct comparison is not advisable due to differing total number of vaccinees receiving each type of vaccine. Percentages of reports from immunocompromised individuals are comparable for mRNA-based vaccines and adenovirus vector vaccines, with 95% CIs which overlap (table 6).

Mechanisms of myocarditis and pericarditis following mRNA COVID-19 vaccination

The mechanisms for myocarditis or pericarditis following COVID-19 mRNA vaccination are not yet fully understood. It has not yet been determined whether it is the mRNA element itself or the 'self' generated COVID-19 spike protein from the mRNA message within the vaccines or the resultant immune response, which cardiac tissues are sensitive to.

Following infection or vaccination, the adaptive immune system is activated. Adaptive immunity involves lymphocytes, particularly B cells and certain T cells, that bind and recognise the foreign antigen. On first infection, or vaccination, the pathogen is bound by naïve B cells via the B cell receptor (BCR) or processed by antigen-presenting cells (APCs) into smaller fragments, known as antigens. In order to mount an appropriate immune response, B cells will undergo differentiation and maturation within the lymph nodes in the germinal centre reaction (figure 4). The germinal centre reaction results in the generation of high affinity, high avidity BCRs for the antigen and leads to the production of antibody producing/secreting plasma B cells and memory B cells (figure 4). Memory B cells will retain the ability to recognise this antigen after the infection has been cleared from the body and is able to rapidly produce plasma B cells and antibodies should the body encounter the pathogen again, rapidly eliminating a second challenge of infection. Simultaneously, T cells will undergo maturation in the thymus in the presence of foreign antigen presented by APCs and through the process of positive and negative selection results in deletion of T cells that bind with high avidity to 'self' molecules and promotes expansion of T cells that bind to the foreign antigen. This process of positive and negative selection also gives rise to immune tolerance where there is some cross-over in recognition of self-antigens.[21] This immune-tolerance process may give rise to T cells that are reactive to self-antigens, in particular heart auto-reactivity,[22] which could lead to myocarditis and pericarditis.

There are multiple hypotheses suggested by Das *et al*[23] that may explain the mechanism of myocarditis and pericarditis in response to the COVID-19 mRNA vaccines, including:

1. mRNA vaccines might generate very high antibody response producing a response similar to multisystem inflammatory syndrome in children that is associated with COVID-19 infection.
2. Induction of anti-idiotype cross-reactive antibody-mediated cytokine expression in the myocardium, resulting in aberrant apoptosis and inflammation.
3. mRNA vaccines can induce a non-specific innate immune response or a molecular mimicry mechanism may occur.
4. The mRNA itself may be a potent immunogen producing an adjuvant effect.

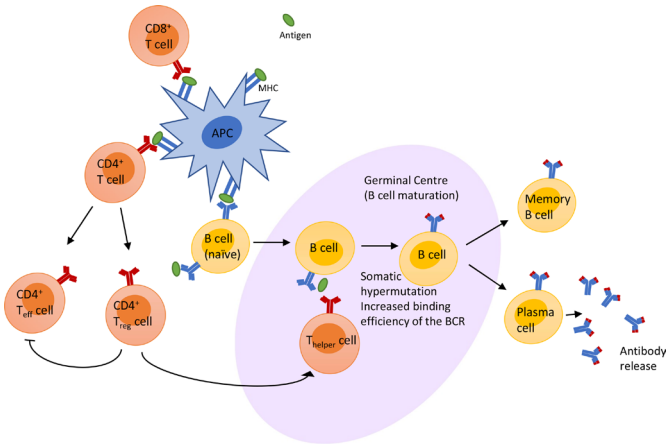

Figure 4 Schematic of the immune response to antigen. Antigen is part of a foreign/non-self pathogen and is presented by an antigen-presenting cell (APC) either following viral protein digestion and presentation on the major histocompatibility complex (MHC) or via messenger RNA (mRNA) translation of the protein within the APC then the protein is presented on the MHC. The non-self protein presented on the MHC is recognised by B and T cells. This triggers a cascade of intracellular signalling responses and leads to the maturation of the B cells, within the germinal centre of a lymph node. The germinal centre reaction involves interactions with B cells, antigen and T cells; leading to somatic hypermutation of the B cell receptor (BCR), generating a BCR that is better adapted to recognise the antigen. The B cell then differentiates into memory B cells and plasma B cells to release the antibodies into the general circulation to clear the body of the infection.

The advantage of mRNA vaccines is their ability to elicit a greater memory response compared with adenovirus vector vaccines.[24] The longevity of mRNA vaccines (as evidenced by the persistence of the mRNA and mRNA translation APCs/dendritic cells at the injection site and draining lymph nodes) for up to 10 days may enable fine-tuning of the immune responses due to somatic hypermutation, increasing the affinity of the BCR to the immunogen, as well as enabling memory B cell maturation[25] (figure 4). The ability of mRNA vaccines to produce the immunogen of interest via mRNA translation from within APCs was thought to mimic viral infection, which would elicit a $CD8^+$ cytotoxic T cell response but this is not seen with the COVID-19 mRNA vaccines or in mRNA vaccine trials against rabies virus glycoprotein (RABV-G) or influenza (H1N1).[25] These mRNA vaccines

have demonstrated that, in non-human primates, $CD4^+$ helper T cell responses are elicited.[26 27]

The role of $CD4^+$ T cells in myocarditis has been reviewed by Vdovenko and Eriksson that indicates that $CD4^+$ T cells are the main drivers of heart-specific autoimmunity.[22] Therefore, the $CD4^+$ T cell response following mRNA vaccines may trigger myocarditis. $CD4^+$ T cells differentiate into effector or regulatory T cells (T_{eff} or T_{reg}, respectively). T_{regs} are vital in immune tolerance to suppress autoimmune T_{eff} cells. Gender differences in circulating T_{regs} has been linked with gender differences in myocarditis.[22] Thus, the involvement in $CD4^+$ T cells in myocarditis development may indicate that autoimmune responses may occur following mRNA vaccination, via induction of $CD4^+$ T cell expression and may point to the observed differences in myocarditis incidence between male and female population following vaccination.[18]

Whether the mRNA within the vaccine itself is immunogenic will likely depend on multiple variables within the mRNA sequence. The COVID-19 mRNA vaccines deliver a single-stranded mRNA (ssRNA) encoding the spike protein, with modified nucleotides. The modified N^1-methyl-psuedouridine are known to dampen innate immune responses, while increasing the efficiency of translation in vivo.[27] As ssRNA is produced by all cells within the body, ssRNA would be recognised as 'self' and would not trigger an immune response. Double-stranded RNA (dsRNA) is generally recognised by the cell as viral or is triggered for degradation via the RNA-induced silencing complex, the cells' innate ability to modify protein expression by degradation of mRNA.[28] Thus, the sequence of the ssRNA in the mRNA vaccine will determine the likelihood of complementarity (to itself, other mRNAs or microRNAs) to generate dsRNA which could then trigger immune responses via toll-like receptors[29] as well as alter mRNA translation mechanisms.[28] Further investigation is needed to determine whether the mRNA sequence is complementary to any 'self' mRNA or microRNAs, as this could provide a greater understanding on why certain organs may be preferentially targeted in response to COVID-19 mRNA vaccination. The ability for mRNA vaccines to produce binding and neutralising antibodies in all participants in phase I/II trials[24] demonstrates the ability for these vaccines to activate the immune system similar to viral infection but with high antibody titres.[30] Although it should be noted that immunocompromised individuals elicit a reduced antibody response following vaccination.[31 32] Thus, these highly immunogenic mRNA vaccines are activating the B and T lymphocytes, with the potential that heart-specific autoreactive $CD4^+$ T cells may also be activated (or not adequately suppressed correctly via immune-tolerance interactions of T_{regs} with T_{eff} cells) potentially leading to reporting of myocarditis and pericarditis.[4 12 33]

DISCUSSION AND CONCLUSIONS

Based on the results of spontaneous reporting analyses, there was limited evidence supporting our hypothesis that frequency or seriousness of the myocarditis and pericarditis events reported to spontaneous reporting systems was substantially different for immunocompromised people compared with the reporting population as a whole. In the overall database populations, myocarditis and pericarditis seemed to more frequently affect younger male population, however the characteristics of those susceptible may have broadened in the immunocompromised population in terms of age and sex; therefore, risk factors for these events are less clear within the immunocompromised population.

Recent reporting of myocarditis and pericarditis in immunocompromised individuals (people on immunosuppressant medications following transplantation, treatment of cancer or people with HIV infection) raises an important question into how the immune system is responding to mRNA vaccination in these individuals, and whether alternative COVID-19 vaccinations should be considered. Given the current understanding that COVID-19 mRNA vaccines elicit a $CD4^+$ T cell response and the fact that immunocompromised patients have inhibited B and T lymphocyte activity, immune suppression could be a factor which increases the risk of adverse events following COVID-19 mRNA vaccination. In particular, myocarditis and pericarditis following COVID-19 mRNA vaccination may be due to the involvement of $CD4^+$ T cells. Although patients with HIV have demonstrated a similar immune response to vaccination compared with healthy adults, other immunocompromised patient subgroups, including those with solid or haematological cancers, solid organ or bone marrow transplantation, and other immunosuppressive conditions, have been shown to generate a lower immune response to COVID-19 vaccination compared with healthy controls.[34–37] Therefore, it is possible that immunosuppression due to medication or a medical condition may have an impact on the safety and efficacy of mRNA vaccines against SARS-CoV-2 and other conditions.

Our analysis has not demonstrated a higher frequency of reports of myocarditis and pericarditis among the immunocompromised patient subgroups examined (PRR for the VAERS population=1.36 (95% CI: 0.89 to 1.82)), although the clinical course may be different for these patients compared with immunocompetent individuals and requires further monitoring. When the signal first emerged, myocarditis and pericarditis following COVID-19 mRNA vaccination were considered mild conditions of short duration which mostly affected younger males.[18 38–41] Our analysis of reports from immunocompromised individuals resulted in this sex distribution being less apparent for immunocompromised individuals compared with that seen in the general population.[18 39 40] Among immunocompromised individuals, males accounted for 52.6% of reported events of myocarditis and pericarditis submitted to all three datasets combined, thus a slight decrease in male predominance for this effect. Overall,

59.7% cases of myocarditis and pericarditis reported from immunocompromised individuals were under the age of 64 years. Furthermore, many of the reported events submitted to EudraVigilance and VAERS among immunocompromised subgroups met the criteria for a serious case (77.6% of 49 reports submitted to EudraVigilance and 68.4% of 57 reports to VAERS). Meanwhile, 76.8% of myocarditis or pericarditis cases reported after COVID-19 mRNA vaccines to EudraVigilance from the population as a whole met the criteria for a serious case, while 63.4% of all cases reported to VAERS were serious in nature. For the VAERS population, time to onset was consistent with previous suggestions that these events occur within 14 days of vaccination, with approximately 70% of events reported to occur within 14 days of receiving a COVID-19 mRNA vaccine.[38 42] Consistencies in the frequency of events reported and the seriousness of cases for immunocompromised people within the data sources used suggests results may be generalisable to other populations in which mRNA vaccines are used. Interestingly, in comparison to the US data which demonstrated that 50% of events in immunocompromised occurred following the second dose of an mRNA vaccination, the UK data demonstrate a less apparent separation between doses 1 and 2 (31% vs 39.4%), while 23.9% of events occurred following the third dose.

Spontaneous adverse events reported to the Yellow Card scheme in the UK following a COVID-19 mRNA vaccination resulted in higher reporting of myocarditis and pericarditis in immunocompromised individuals as a proportion of the total myocarditis and pericarditis reports compared with immunocompromised individuals in the EU and US databases (7.1% vs 0.84% and 1.86%, respectively). There are many potential reasons for these differences including different reporting systems that may allow for better collection of comorbidities or concomitant medication. Spontaneously reported data from the population as a whole indicated myocarditis and pericarditis occurred predominately in young male population. Results from the UK are consistent with those from the EU and the USA, where data demonstrated a broadening of these susceptible characteristics in immunocompromised individuals. Up to 15 December 2021, 38.4% of reports of myocarditis and pericarditis following COVID-19 mRNA vaccination were from female population in the UK; therefore in the immunocompromised population there had been a 1.37-fold higher frequency of myocarditis and pericarditis reports from immunocompromised female population.[12] The majority of reports occurred following the second dose (39.4%) in the UK, which was consistent with reports from the USA (54.4% reported following a second dose), although this interpretation should be taken with caution given that the third dose (booster) programme is still ongoing in the UK, with more data likely to be reported in the coming weeks and months. However, immunocompromised people were prioritised to receive their third (booster) dose when the UK booster vaccination programme started in September 2021, therefore it is expected that the majority of people within this subpopulation would have received their third dose by the datalock point of 1 December 2021.[43 44]

The use of spontaneous reporting systems has some limitations which are important to recognise, including the possibility that these data are underestimated due to underreporting of events and missing information on comorbidities and concurrent medications within individual case reports.[5 45 46] Additionally, concomitant medication was not commonly reported; medications for cancer and HIV/AIDS may be used for other conditions and may therefore inaccurately represent the number of immunocompromised patients within the dataset. However, for the EudraVigilance population, the use of a proxy measure was the only method for identifying reports from people in these patient subgroups. Furthermore, not all immunosuppressive treatments were examined in this analysis, but a comprehensive list of immunosuppressants should be included in future studies. It will therefore become increasingly important to monitor the occurrence and clinical course of myocarditis and pericarditis among immunocompromised patients as booster vaccination programmes progress. While COVID-19 vaccination programmes continue to progress to widespread roll-out of third and subsequent booster doses, more immunocompromised individuals will become exposed to COVID-19 mRNA vaccines and some for the first time, particularly in countries where adenovirus vector COVID-19 vaccines were preferentially given to older members of the population and those at higher clinical risk of severe COVID-19 outcomes (many of whom were immunocompromised) for their first two doses. Current data indicate that three doses of mRNA vaccines are safe, which included immunocompromised individuals in the population cohort.[47] Consideration should be given to the risk of myocarditis and pericarditis in vaccine recipients who demonstrate low response or non-response to COVID-19 vaccination where additional vaccine doses are warranted; while immunocompromised patient subgroups have generally been shown to elicit sufficient immune response to COVID-19 vaccination, many of those who do respond poorly may be immunocompromised, including patients with cancer or transplant recipients.[48] Further studies are required to better understand the occurrence of myocarditis and pericarditis following additional mRNA COVID-19 vaccine doses in immunocompromised individuals and for those who have demonstrated limited response to vaccination.

It should also be noted that undiagnosed COVID-19 infection may be an underlying risk factor for myocarditis or pericarditis rather than the vaccine. In the USA, it has been demonstrated that risk of cardiac complications is higher following SARS-CoV-2 infection than mRNA vaccination in all age groups for both male and female population.[49] In the UK, SARS-CoV-2 infection has been found to increase risk of hospitalisation or death from cardiac complications, including myocarditis and pericarditis, and produce a higher number of excess events due to exposure compared with mRNA vaccination.[50] Epidemiological studies are warranted to determine whether a similar pattern is seen among immunocompromised individuals. Within the data analysed

from spontaneous reporting systems for the immunocompromised group, only one case of pericarditis following Pfizer vaccination was identified as also being infected with COVID-19. As immunocompromised individuals accounted for <10% of all reports of myocarditis and pericarditis in response to vaccination across the three regions analysed, detecting cases where COVID-19 infection may also have contributed to the reaction will be a small proportion of this limited number of reports. Thus, levels of detecting in this method of analysis may be unable to identify these potentially rare events in this population. It is worth noting that immunocompromised individuals may also be less likely to become infected if they are shielding or maintaining stricter social distancing measures. This raises the very interesting question of whether vaccination-associated myocarditis and pericarditis is a consequence of the immune response elicited to generate a robust response that also occurs following infection. Therefore, is vaccination preventing these individuals suffering or reducing the severity of myocarditis and pericarditis if they were exposed to the SARS-CoV-2 virus?

Based on current data, immunocompromised individuals reporting myocarditis or pericarditis differed in gender and age distribution compared with the whole population. As risk factors for myocarditis and pericarditis are less clear in the immunocompromised population, it will be important to continue monitoring the occurrence and clinical course of myocarditis and pericarditis in immunocompromised individuals following COVID-19 mRNA vaccines. Further monitoring of events in immunocompromised patients will be of particular importance if mRNA treatments and vaccines continue to be pursued for these conditions. If mRNA vaccines, and potentially other mRNA-based therapeutics, are linked with adverse events in immunocompromised individuals, this may alter their therapeutic potential, may alter treatment regimes or may stratify patients into different treatment options. It is worth noting that autoimmune disorders, such as arthritis and systemic lupus, have been linked to pericarditis as well as some immunosuppressive medications, including methotrexate.[51] Thus, careful evaluation needs to be undertaken, taking into consideration the baseline characteristics of this population to accurately determine the reporting rates related to mRNA vaccination.

It should be noted that our results are based on the best available, although limited, information. Results should be confirmed by quantitative data from formal pharmacoepidemiological studies, to allow accurate calculation of incident risk of myocarditis and pericarditis among immunocompromised patients compared with immunocompetent individuals. Further ongoing monitoring is needed to formally characterise the clinical course of myocarditis and pericarditis following mRNA vaccination among immunocompromised patients. It is important to stress that events of myocarditis and pericarditis following COVID-19 vaccination are very rare and the benefits of COVID-19 vaccination continue to outweigh any perceived risks.

In conclusion, myocarditis and pericarditis are very rare events following COVID-19 mRNA vaccination in immunocompromised individuals, and risk factors such as age and sex are less clear in immunocompromised individuals compared with the total population. Slight differences were observed in reporting frequency of these adverse events between the different immunocompromised populations and vaccines, thus continued monitoring may enhance stratification of patients in the future for the most appropriate vaccine type to use.

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Competing interests All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: The Drug Safety Research Unit (DSRU) is a registered independent charity (No. 327206) associated with the University of Portsmouth. The DSRU receives donations and grants from pharmaceutical companies; however, the companies have no control over the conduct or publication of its studies. The DSRU has received grants to conduct unconditional studies on the Oxford/AstraZeneca COVID-19 vaccine and is in negotiations to receiving grants for conducting CPRD studies for Pfizer, Moderna and Janssen COVID-19 vaccines. The DSRU has conducted benefit-risk studies on products for COVID-19, including remdesivir, lopinavir/ritonavir, chloroquine and hydroxychloroquine, and convalescent plasma. SS is the principal investigator for an active surveillance study for the Oxford/AstraZeneca vaccine, but this assessment is unrelated to this study. SS has been a member of Data Safety Monitoring Boards for Ipsen, Biogen and Diurnal. None of these companies have any involvement with COVID-19 vaccines. SS was invited by AstraZeneca to advise on the events of thrombosis with thrombocytopenia with the COVID-19 vaccine and to be a member of an advisory committee on a safety study of the Oxford/AstraZeneca vaccine in Europe. SL and AY have no conflicts of interest regarding this study.

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Supplementary File to accompany the manuscript entitled "*Systematic review of spontaneous reports of myocarditis and pericarditis in transplant recipients and immunocompromised patients following COVID-19 mRNA vaccination*" by Lane et al.

Search Strategies used:

EudraVigilance:

Searches were conducted within the EudraVigilance online system (https://www.adrreports.eu/). Searches were conducted for each mRNA COVID-19 vaccine individually to provide a line listing of reported myocarditis and pericarditis events for the overall population.

Symptom terms: "Myocarditis" and "Pericarditis"

Restrictions: European Economic Area geographic origin only

Returned records were then filtered by reported concomitant medications to use as a proxy for immunosuppression, these search terms were identical to those used in the VAERS medications at time of vaccination, please see below. Where both myocarditis and pericarditis were reported by the same case, this was counted as "Myopericarditis."

MHRA Yellow Card scheme:

Searches of MHRA Yellow Card records were conducted by MHRA and provided to the research team for further analysis.

Reaction terms (MedDRA PT): Acute endocarditis, Atypical mycobacterium pericarditis, Autoimmune myocarditis, Autoimmune pericarditis, Bacterial pericarditis, Camptodactyly-arthropathy-coxa vara-pericarditis syndrome, Carditis, Coxsackie carditis, Coxsackie endocarditis, Coxsackie myocarditis, Coxsackie pericarditis, Cytomegalovirus myocarditis, Cytomegalovirus pericarditis, Endocarditis, Endocarditis Q fever, Endocarditis bacterial, Endocarditis candida, Endocarditis enterococcal, Endocarditis fibroplastica, Endocarditis gonococcal, Endocarditis haemophilus, Endocarditis helminthic, Endocarditis histoplasma, Endocarditis meningococcal, Endocarditis noninfective, Endocarditis prophylaxis, Endocarditis pseudomonal, Endocarditis rheumatic, Endocarditis staphylococcal, Endocarditis syphilitic, Endocarditis viral, Enterovirus myocarditis, Eosinophilic myocarditis, Fungal endocarditis, Giant cell myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis, Lupus endocarditis, Lupus myocarditis, Lyme carditis, Malarial myocarditis, Meningococcal carditis, Myocarditis, Myocarditis bacterial, Myocarditis helminthic, Myocarditis infectious, Myocarditis meningococcal, Myocarditis mycotic, Myocarditis post infection, Myocarditis septic, Myocarditis syphilitic, Myocarditis toxoplasmal, Pericarditis, Pericarditis adhesive, Pericarditis amoebic, Pericarditis constrictive, Pericarditis fungal, Pericarditis gonococcal, Pericarditis helminthic, Pericarditis histoplasma, Pericarditis infective, Pericarditis lupus, Pericarditis malignant, Pericarditis meningococcal, Pericarditis mycoplasmal, Pericarditis rheumatic, Pericarditis syphilitic, Pericarditis tuberculous, Pericarditis uraemic, Pleuropericarditis, Purulent pericarditis, Radiation myocarditis, Radiation pericarditis, Streptococcal endocarditis, Subacute endocarditis, Syphilitic endocarditis of heart valve, Viral myocarditis, Viral pericarditis

Medical History and indication of suspect or other drugs: Transplant, cancer, neoplasm, HIV, AIDs, Immunodeficiency, Immune system disorder, lymphoma, steroid therapy, splenectomy, Systemic

lupus erythematosus, Rheumatoid arthritis, Inflammatory bowel disease, Crohn's disease, Ulcerative Colitis

Drugs searched: The data was also reviewed to identify co-suspects or other drugs which were Anti-rejection drugs, Monoclonal anti-bodies and steroids

VAERS:

Search terms used for all VAERS searches include the following split into the subheadings available on the VAERS cdc wonder site:

Symptom terms: "Myocarditis" and "Pericarditis"

Vaccine Characteristics: "COVID19 (COVID19 VACCINE)", which was limited to vaccine manufacturer: "MODERNA" and "PFIZER\BIONTECH" with "All Doses"

Location, age and gender: "The United State/Territories/Unknown", Age "All ages" and Sex: "All Genders"

We did not restrict on event characteristics or reporting dates – these fields were unrestricted to include "All".

To identify Transplant recipients, we searched the text fields under the heading of History/Allergies using the terms: "transplant"

To identify Methotrexate treated individuals, we searched the text fields under the heading of Medications at time of vaccination using the term: "methotrexate"

To identify HIV patients, we searched the text fields under the heading of Medications at the time of vaccination using the following approved HIV medications: "abacavir, Ziagen, Emtriva, Epivir, Viread, Retrovir, doravirine, Pifeltro, Sustiva, Intelence, Viramune, Edurant, atazanavir, Reyataz, Prezista, Lexiva, Invirase, Aptivus, enfuvirtide, Fuzeon, maraviroc, Selzentry, cabotegravir, Vocabria, Tivicay, Isentress, fostemsavir, Rukobia, ibalizumab-uiyk, Trogarzo, cobicistat, Tybost, abacavir and lamivudine, Epzicom, Triumeq, Trizivir, Evotaz, Biktarvy, Cabenuva, Prezcobix, Symtuza, Dovato, Juluca, Delstrigo, Atripla, Symfi, Symfi Lo, Genvoya, Stribild, Odefsey, Complera, Descovy, Truvada, Cimduo, Combivir, Kaletra"

To identify Cancer patients, we searched the text fields under the heading of Medications at the time of vaccination using the following approved Cancer medications:

Abecma (Idecabtagene Vicleucel)
Abemaciclib
Abiraterone Acetate
Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation)
ABVD
ABVE
ABVE-PC
AC
Acalabrutinib
AC-T
Actemra (Tocilizumab)
Adcetris (Brentuximab Vedotin)
ADE
Ado-Trastuzumab Emtansine
Adriamycin (Doxorubicin Hydrochloride)
Afatinib Dimaleate

Afinitor (Everolimus)

Akynzeo (Netupitant and Palonosetron Hydrochloride)

Aldara (Imiquimod)

Aldesleukin

Alecensa (Alectinib)

Alectinib

Alemtuzumab

Alimta (Pemetrexed Disodium)

Aliqopa (Copanlisib Hydrochloride)

Alkeran for Injection (Melphalan Hydrochloride)

Alkeran Tablets (Melphalan)

Aloxi (Palonosetron Hydrochloride)

Alpelisib

Alunbrig (Brigatinib)

Ameluz (Aminolevulinic Acid Hydrochloride)

Amifostine

Aminolevulinic Acid Hydrochloride

Amivantamab-vmjw

Anastrozole

Apalutamide

Aprepitant

Aranesp (Darbepoetin Alfa)

Aredia (Pamidronate Disodium)

Arimidex (Anastrozole)

Aromasin (Exemestane)

Arranon (Nelarabine)

Arsenic Trioxide

Arzerra (Ofatumumab)

Asparaginase Erwinia Chrysanthemi

Asparaginase Erwinia Chrysanthemi (Recombinant)-rywn

Asparlas (Calaspargase Pegol-mknl)

Atezolizumab

Avapritinib

Avastin (Bevacizumab)

Avelumab

Axicabtagene Ciloleucel

Axitinib

Ayvakit (Avapritinib)

Azacitidine

Azedra (Iobenguane I 131)

Balversa (Erdafitinib)

Bavencio (Avelumab)

BEACOPP

Belantamab Mafodotin-blmf

Beleodaq (Belinostat)

Belinostat

Belzutifan

Bendamustine Hydrochloride

Bendeka (Bendamustine Hydrochloride)

BEP

Besponsa (Inotuzumab Ozogamicin)

Bevacizumab

Bexarotene

Bicalutamide

BiCNU (Carmustine)

Binimetinib

Blenrep (Belantamab Mafodotin-blmf)

Bleomycin Sulfate

Blinatumomab

Blincyto (Blinatumomab)

Bortezomib

Bosulif (Bosutinib)

Bosutinib

Braftovi (Encorafenib)

Brentuximab Vedotin

Brexucabtagene Autoleucel

Breyanzi (Lisocabtagene Maraleucel)

Brigatinib

Brukinsa (Zanubrutinib)

BuMel

Busulfan

Busulfex (Busulfan)

Cabazitaxel

Cablivi (Caplacizumab-yhdp)

Cabometyx (Cabozantinib-S-Malate)

Cabozantinib-S-Malate

CAF

Calaspargase Pegol-mknl

Calquence (Acalabrutinib)

Campath (Alemtuzumab)

Camptosar (Irinotecan Hydrochloride)

Capecitabine

Caplacizumab-yhdp

Capmatinib Hydrochloride

CAPOX

Carac (Fluorouracil--Topical)

Carboplatin

CARBOPLATIN-TAXOL

Carfilzomib

Carmustine

Carmustine Implant

Casodex (Bicalutamide)

CEM

Cemiplimab-rwlc

Ceritinib

Cerubidine (Daunorubicin Hydrochloride)

Cervarix (Recombinant HPV Bivalent Vaccine)

Cetuximab

CEV

Chlorambucil

CHLORAMBUCIL-PREDNISONE

CHOP

Cisplatin

Cladribine

Clofarabine

Clolar (Clofarabine)

CMF

Cobimetinib Fumarate

Cometriq (Cabozantinib-S-Malate)

Copanlisib Hydrochloride

COPDAC

Copiktra (Duvelisib)

COPP

COPP-ABV

Cosmegen (Dactinomycin)

Cotellic (Cobimetinib Fumarate)

Crizotinib

CVP

Cyclophosphamide

Cyramza (Ramucirumab)

Cytarabine

Dabrafenib Mesylate

Dacarbazine

Dacogen (Decitabine)

Dacomitinib

Dactinomycin

Danyelza (Naxitamab-gqgk)

Daratumumab

Daratumumab and Hyaluronidase-fihj

Darbepoetin Alfa

Darolutamide

Darzalex (Daratumumab)

Darzalex Faspro (Daratumumab and Hyaluronidase-fihj)

Dasatinib

Daunorubicin Hydrochloride

Daunorubicin Hydrochloride and Cytarabine Liposome

Daurismo (Glasdegib Maleate)

Decitabine

Decitabine and Cedazuridine

Defibrotide Sodium

Defitelio (Defibrotide Sodium)

Degarelix

Denileukin Diftitox

Denosumab

Dexamethasone

Dexrazoxane Hydrochloride

Dinutuximab

Docetaxel

Dostarlimab-gxly

Doxil (Doxorubicin Hydrochloride Liposome)

Doxorubicin Hydrochloride

Doxorubicin Hydrochloride Liposome

Durvalumab

Duvelisib

Efudex (Fluorouracil--Topical)

Eligard (Leuprolide Acetate)

Elitek (Rasburicase)

Ellence (Epirubicin Hydrochloride)

Elotuzumab

Eloxatin (Oxaliplatin)

Eltrombopag Olamine

Elzonris (Tagraxofusp-erzs)

Emapalumab-lzsg

Emend (Aprepitant)

Empliciti (Elotuzumab)

Enasidenib Mesylate

Encorafenib

Enfortumab Vedotin-ejfv

Enhertu (Fam-Trastuzumab Deruxtecan-nxki)

Entrectinib

Enzalutamide

Epirubicin Hydrochloride

EPOCH

Epoetin Alfa

Epogen (Epoetin Alfa)

Erbitux (Cetuximab)

Erdafitinib

Eribulin Mesylate

Erivedge (Vismodegib)

Erleada (Apalutamide)

Erlotinib Hydrochloride

Erwinaze (Asparaginase Erwinia chrysanthemi)

Ethyol (Amifostine)

Etopophos (Etoposide Phosphate)

Etoposide

Etoposide Phosphate

Everolimus

Evista (Raloxifene Hydrochloride)

Evomela (Melphalan Hydrochloride)

Exemestane

Exkivity (Mobocertinib Succinate)

5-FU (Fluorouracil Injection)

5-FU (Fluorouracil--Topical)

Fam-Trastuzumab Deruxtecan-nxki

Fareston (Toremifene)

Farydak (Panobinostat Lactate)

Faslodex (Fulvestrant)

FEC

Fedratinib Hydrochloride

Femara (Letrozole)

Filgrastim

Firmagon (Degarelix)

Fludarabine Phosphate

Fluoroplex (Fluorouracil--Topical)

Fluorouracil Injection

Fluorouracil--Topical

Flutamide

FOLFIRI

FOLFIRI-BEVACIZUMAB

FOLFIRI-CETUXIMAB

FOLFIRINOX

FOLFOX

Folotyn (Pralatrexate)

Fostamatinib Disodium

Fotivda (Tivozanib Hydrochloride)

Fulphila (Pegfilgrastim)

FU-LV

Fulvestrant

Gamifant (Emapalumab-lzsg)

Gardasil (Recombinant HPV Quadrivalent Vaccine)

Gardasil 9 (Recombinant HPV Nonavalent Vaccine)

Gavreto (Pralsetinib)

Gazyva (Obinutuzumab)

Gefitinib

Gemcitabine Hydrochloride

GEMCITABINE-CISPLATIN

GEMCITABINE-OXALIPLATIN

Gemtuzumab Ozogamicin

Gemzar (Gemcitabine Hydrochloride)

Gilotrif (Afatinib Dimaleate)

Gilteritinib Fumarate

Glasdegib Maleate

Gleevec (Imatinib Mesylate)

Gliadel Wafer (Carmustine Implant)

Glucarpidase

Goserelin Acetate

Granisetron

Granisetron Hydrochloride

Granix (Filgrastim)

Halaven (Eribulin Mesylate)

Hemangeol (Propranolol Hydrochloride)

Herceptin Hylecta (Trastuzumab and Hyaluronidase-oysk)

Herceptin (Trastuzumab)

HPV Bivalent Vaccine, Recombinant

HPV Nonavalent Vaccine, Recombinant

HPV Quadrivalent Vaccine, Recombinant

Hycamtin (Topotecan Hydrochloride)

Hydrea (Hydroxyurea)

Hydroxyurea

Hyper-CVAD

Ibrance (Palbociclib)

Ibritumomab Tiuxetan

Ibrutinib

ICE

Iclusig (Ponatinib Hydrochloride)

Idamycin PFS (Idarubicin Hydrochloride)

Idarubicin Hydrochloride

Idecabtagene Vicleucel

Idelalisib

Idhifa (Enasidenib Mesylate)

Ifex (Ifosfamide)

Ifosfamide

IL-2 (Aldesleukin)

Imatinib Mesylate

Imbruvica (Ibrutinib)

Imfinzi (Durvalumab)

Imiquimod

Imlygic (Talimogene Laherparepvec)

Infigratinib Phosphate

Infugem (Gemcitabine Hydrochloride)

Inlyta (Axitinib)

Inotuzumab Ozogamicin

Inqovi (Decitabine and Cedazuridine)

Inrebic (Fedratinib Hydrochloride)

Interferon Alfa-2b, Recombinant

Interleukin-2 (Aldesleukin)

Intron A (Recombinant Interferon Alfa-2b)

Iobenguane I 131

Ipilimumab

Iressa (Gefitinib)

Irinotecan Hydrochloride

Irinotecan Hydrochloride Liposome

Isatuximab-irfc

Istodax (Romidepsin)

Ivosidenib

Ixabepilone

Ixazomib Citrate

Ixempra (Ixabepilone)

Jakafi (Ruxolitinib Phosphate)

JEB

Jelmyto (Mitomycin)

Jemperli (Dostarlimab-gxly)

Jevtana (Cabazitaxel)

Kadcyla (Ado-Trastuzumab Emtansine)

Kepivance (Palifermin)

Keytruda (Pembrolizumab)

Kisqali (Ribociclib)

Koselugo (Selumetinib Sulfate)

Kymriah (Tisagenlecleucel)

Kyprolis (Carfilzomib)

Lanreotide Acetate

Lapatinib Ditosylate

Larotrectinib Sulfate

Lenalidomide

Lenvatinib Mesylate

Lenvima (Lenvatinib Mesylate)

Letrozole

Leucovorin Calcium

Leukeran (Chlorambucil)

Leuprolide Acetate

Levulan Kerastik (Aminolevulinic Acid Hydrochloride)

Libtayo (Cemiplimab-rwlc)

Lisocabtagene Maraleucel

Lomustine

Loncastuximab Tesirine-lpyl

Lonsurf (Trifluridine and Tipiracil Hydrochloride)

Lorbrena (Lorlatinib)

Lorlatinib

Lumakras (Sotorasib)

Lumoxiti (Moxetumomab Pasudotox-tdfk)

Lupron Depot (Leuprolide Acetate)

Lurbinectedin

Luspatercept-aamt

Lutathera (Lutetium Lu 177-Dotatate)

Lutetium (Lu 177-Dotatate)

Lynparza (Olaparib)

Margenza (Margetuximab-cmkb)

Margetuximab-cmkb

Marqibo (Vincristine Sulfate Liposome)

Matulane (Procarbazine Hydrochloride)

Mechlorethamine Hydrochloride

Megestrol Acetate

Mekinist (Trametinib Dimethyl Sulfoxide)

Mektovi (Binimetinib)

Melphalan

Melphalan Hydrochloride

Mercaptopurine

Mesna

Mesnex (Mesna)

Methotrexate Sodium

Methylnaltrexone Bromide

Midostaurin

Mitomycin

Mitoxantrone Hydrochloride

Mobocertinib Succinate

Mogamulizumab-kpkc

Monjuvi (Tafasitamab-cxix)

Moxetumomab Pasudotox-tdfk

Mozobil (Plerixafor)

MVAC

Mvasi (Bevacizumab)

Myleran (Busulfan)

Mylotarg (Gemtuzumab Ozogamicin)

Nanoparticle Paclitaxel (Paclitaxel Albumin-stabilized Nanoparticle Formulation)

Naxitamab-gqgk

Necitumumab

Nelarabine

Neratinib Maleate

Nerlynx (Neratinib Maleate)

Netupitant and Palonosetron Hydrochloride

Neulasta (Pegfilgrastim)

Neupogen (Filgrastim)

Nexavar (Sorafenib Tosylate)

Nilandron (Nilutamide)

Nilotinib

Nilutamide

Ninlaro (Ixazomib Citrate)

Niraparib Tosylate Monohydrate

Nivestym (Filgrastim)

Nivolumab

Nplate (Romiplostim)

Nubeqa (Darolutamide)

Nyvepria (Pegfilgrastim)

Obinutuzumab

Odomzo (Sonidegib)

OEPA

Ofatumumab

OFF

Olaparib

Omacetaxine Mepesuccinate

Oncaspar (Pegaspargase)

Ondansetron Hydrochloride

Onivyde (Irinotecan Hydrochloride Liposome)

Ontak (Denileukin Diftitox)

Onureg (Azacitidine)

Opdivo (Nivolumab)

OPPA

Orgovyx (Relugolix)

Osimertinib Mesylate

Oxaliplatin

Paclitaxel

Paclitaxel Albumin-stabilized Nanoparticle Formulation

PAD

Padcev (Enfortumab Vedotin-ejfv)

Palbociclib

Palifermin

Palonosetron Hydrochloride

Palonosetron Hydrochloride and Netupitant

Pamidronate Disodium

Panitumumab

Panobinostat Lactate

Paraplatin (Carboplatin)

Pazopanib Hydrochloride

PCV

PEB

Pegaspargase

Pegfilgrastim

Peginterferon Alfa-2b

PEG-Intron (Peginterferon Alfa-2b)

Pemazyre (Pemigatinib)

Pembrolizumab

Pemetrexed Disodium

Pemigatinib

Perjeta (Pertuzumab)

Pertuzumab

Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf

Pexidartinib Hydrochloride

Phesgo (Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf)

Piqray (Alpelisib)

Plerixafor

Polatuzumab Vedotin-piiq

Polivy (Polatuzumab Vedotin-piiq)

Pomalidomide

Pomalyst (Pomalidomide)

Ponatinib Hydrochloride

Portrazza (Necitumumab)

Poteligeo (Mogamulizumab-kpkc)

Pralatrexate

Pralsetinib

Prednisone

Procarbazine Hydrochloride

Procrit (Epoetin Alfa)

Proleukin (Aldesleukin)

Prolia (Denosumab)

Promacta (Eltrombopag Olamine)

Propranolol Hydrochloride

Provenge (Sipuleucel-T)

Purinethol (Mercaptopurine)

Purixan (Mercaptopurine)

Qinlock (Ripretinib)

Radium 223 Dichloride

Raloxifene Hydrochloride

Ramucirumab

Rasburicase

Ravulizumab-cwvz

Reblozyl (Luspatercept-aamt)

R-CHOP

R-CVP

Recombinant Human Papillomavirus (HPV) Bivalent Vaccine

Recombinant Human Papillomavirus (HPV) Nonavalent Vaccine

Recombinant Human Papillomavirus (HPV) Quadrivalent Vaccine

Recombinant Interferon Alfa-2b

Regorafenib

Relistor (Methylnaltrexone Bromide)

Relugolix

R-EPOCH

Retacrit (Epoetin Alfa)

Retevmo (Selpercatinib)

Revlimid (Lenalidomide)

Ribociclib

R-ICE

Ripretinib

Rituxan (Rituximab)

Rituxan Hycela (Rituximab and Hyaluronidase Human)

Rituximab

Rituximab and Hyaluronidase Human

Rolapitant Hydrochloride

Romidepsin

Romiplostim

Rozlytrek (Entrectinib)

Rubidomycin (Daunorubicin Hydrochloride)

Rubraca (Rucaparib Camsylate)

Rucaparib Camsylate

Ruxolitinib Phosphate

Rybrevant (Amivantamab-vmjw)

Rydapt (Midostaurin)

Rylaze (Asparaginase Erwinia Chrysanthemi [Recombinant]-rywn)

Sacituzumab Govitecan-hziy

Sancuso (Granisetron)

Sarclisa (Isatuximab-irfc)

Sclerosol Intrapleural Aerosol (Talc)

Selinexor

Selpercatinib

Selumetinib Sulfate

Siltuximab

Sipuleucel-T

Soltamox (Tamoxifen Citrate)

Somatuline Depot (Lanreotide Acetate)

Sonidegib

Sorafenib Tosylate

Sotorasib

Sprycel (Dasatinib)

STANFORD V

Sterile Talc Powder (Talc)

Steritalc (Talc)

Stivarga (Regorafenib)

Sunitinib Malate

Sustol (Granisetron)

Sutent (Sunitinib Malate)

Sylatron (Peginterferon Alfa-2b)

Sylvant (Siltuximab)

Synribo (Omacetaxine Mepesuccinate)

Tabloid (Thioguanine)

Tabrecta (Capmatinib Hydrochloride)

TAC

Tafasitamab-cxix

Tafinlar (Dabrafenib Mesylate)

Tagraxofusp-erzs

Tagrisso (Osimertinib Mesylate)

Talazoparib Tosylate

Talc

Talimogene Laherparepvec

Talzenna (Talazoparib Tosylate)

Tamoxifen Citrate

Tarceva (Erlotinib Hydrochloride)

Targretin (Bexarotene)

Tasigna (Nilotinib)

Tavalisse (Fostamatinib Disodium)

Taxotere (Docetaxel)

Tazemetostat Hydrobromide

Tazverik (Tazemetostat Hydrobromide)

Tecartus (Brexucabtagene Autoleucel)

Tecentriq (Atezolizumab)

Temodar (Temozolomide)

Temozolomide

Temsirolimus

Tepadina (Thiotepa)

Tepmetko (Tepotinib Hydrochloride)

Tepotinib Hydrochloride

Thalidomide

Thalomid (Thalidomide)

Thioguanine

Thiotepa

Tibsovo (Ivosidenib)

Tisagenlecleucel

Tivozanib Hydrochloride

Tocilizumab

Tolak (Fluorouracil--Topical)

Topotecan Hydrochloride

Toremifene

Torisel (Temsirolimus)

Totect (Dexrazoxane Hydrochloride)

TPF

Trabectedin

Trametinib Dimethyl Sulfoxide

Trastuzumab

Trastuzumab and Hyaluronidase-oysk

Treanda (Bendamustine Hydrochloride)

Trexall (Methotrexate Sodium)

Trifluridine and Tipiracil Hydrochloride

Trisenox (Arsenic Trioxide)

Trodelvy (Sacituzumab Govitecan-hziy)

Truseltiq (Infigratinib Phosphate)

Truxima (Rituximab)

Tucatinib

Tukysa (Tucatinib)

Turalio (Pexidartinib Hydrochloride)

Tykerb (Lapatinib Ditosylate)

Ukoniq (Umbralisib Tosylate)

Ultomiris (Ravulizumab-cwvz)

Umbralisib Tosylate

Undencyca (Pegfilgrastim)

Unituxin (Dinutuximab)

Uridine Triacetate

VAC

Valrubicin

Valstar (Valrubicin)

Vandetanib

VAMP

Varubi (Rolapitant Hydrochloride)

Vectibix (Panitumumab)

VeIP

Velcade (Bortezomib)

Vemurafenib

Venclexta (Venetoclax)

Venetoclax

Verzenio (Abemaciclib)

Vidaza (Azacitidine)

Vinblastine Sulfate

Vincristine Sulfate

Vincristine Sulfate Liposome

Vinorelbine Tartrate

VIP

Vismodegib

Vistogard (Uridine Triacetate)

Vitrakvi (Larotrectinib Sulfate)

Vizimpro (Dacomitinib)

Voraxaze (Glucarpidase)

Vorinostat

Votrient (Pazopanib Hydrochloride)

Vyxeos (Daunorubicin Hydrochloride and Cytarabine Liposome)

Welireg (Belzutifan)

Xalkori (Crizotinib)

Xatmep (Methotrexate Sodium)

Xeloda (Capecitabine)

XELIRI

XELOX

Xgeva (Denosumab)

Xofigo (Radium 223 Dichloride)

Xospata (Gilteritinib Fumarate)

Xpovio (Selinexor)

Xtandi (Enzalutamide)

Yervoy (Ipilimumab)

Yescarta (Axicabtagene Ciloleucel)

Yondelis (Trabectedin)

Yonsa (Abiraterone Acetate)

Zaltrap (Ziv-Aflibercept)

Zanubrutinib

Zarxio (Filgrastim)

Zejula (Niraparib Tosylate Monohydrate)

Zelboraf (Vemurafenib)

Zepzelca (Lurbinectedin)

Zevalin (Ibritumomab Tiuxetan)

Ziextenzo (Pegfilgrastim)

Zinecard (Dexrazoxane Hydrochloride)

Zirabev (Bevcizumab)

Ziv-Aflibercept

Zofran (Ondansetron Hydrochloride)

Zoladex (Goserelin Acetate)

Zoledronic Acid

Zolinza (Vorinostat)

Zometa (Zoledronic Acid)

Zyclara (Imiquimod)

Zydelig (Idelalisib)

Zykadia (Ceritinib)

Zynlonta (Loncastuximab Tesirine-lpyl)

Zytiga (Abiraterone Acetate)