NON-INTERVENTIONAL INTERIM STUDY REPORT ABSTRACT

Title: Post-Authorisation Active Surveillance Study of Myocarditis and Pericarditis Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

Date: 18 September 2023

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Keywords: Pfizer-BioNTech COVID-19 vaccine; database study; active surveillance study; post-conditional approval safety study; non-interventional study; myocarditis.

Rationale and background:
The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has resulted in a global pandemic. The Pfizer-BioNTech COVID-19 vaccine, Comirnaty® (tozinameran), a novel mRNA-based vaccine, has been authorised for use in the European Union (EU) for the prevention of COVID-19. Efficient and timely monitoring of the safety of the vaccine is needed in European countries. The safety of the Pfizer-BioNTech COVID-19 vaccine is being investigated in clinical and epidemiological studies conducted worldwide.

The Centers for Disease Control and Prevention (CDC) in the United States (US) issued a statement indicating a possible link between vaccination to prevent COVID-19 and myocarditis for both the Pfizer-BioNTech COVID-19 vaccine and the mRNA-1273 vaccine (Spikevax®) produced by Moderna. Several researchers have reported an increase in risk of myocarditis or pericarditis within 42 days of receiving the vaccination, compared with the risk among unvaccinated persons, particularly after the second dose and among young male recipients. European Medicines Agency (EMA)'s safety committee (Pharmacovigilance Risk Assessment Committee [PRAC]) has assessed recent data on the known risk of myocarditis and pericarditis following vaccination with Comirnaty and Spikevax. The outcome of the review confirmed the risk of myocarditis and pericarditis, which is already reflected in the product information for these two vaccines.

To further examine the risk of myocarditis and pericarditis with the Pfizer-BioNTech COVID-19 vaccine, Pfizer and Vaccine monitoring Collaboration for Europe (VAC4EU) are conducting this study. This is a study carried out in parallel with the EUPAS41623 cohort study, titled *Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine*, which estimates the incidence rates of prespecified adverse events of special interest (AESIs) in five European countries among individuals who received at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among unvaccinated matched individuals.

Research question and objectives:

This study will address the following research question: "What is the natural history of myocarditis and pericarditis cases after being vaccinated with the Pfizer-BioNTech COVID-19 vaccine in European countries?"

Primary study objective

- To describe the natural history (treatment, survival, hospitalisations, long-term cardiac outcomes) of myocarditis or pericarditis among individuals diagnosed with myocarditis and/or pericarditis after receiving at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination, using a cohort study design.

Secondary study objective

- To examine and identify potential risk factors for myocarditis and pericarditis, such as age, sex, Pfizer-BioNTech COVID-19 vaccination status, vaccine doses received (e.g., first, second, third, and booster doses), and history of COVID-19, using a cohort study design

Study design:
This cohort study is carried out in parallel with the ongoing retrospective cohort study (EUPAS41623) titled '*Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine'*, which includes individuals across five European countries who have received at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine, as well as individuals who have not received a COVID-19 vaccine.

For the primary objective (natural history), the study design is a cohort of cases of myocarditis and of pericarditis, with at least 12 months data look-back, who are followed from date of diagnosis to end of follow-up (death, last data update, disenrollment). Individuals were excluded if they had a history of vaccination with a non-Pfizer-BioNTech COVID-19 vaccine before diagnosis or if they had a diagnosis of myocarditis or pericarditis in the year prior to diagnosis.

For the secondary objective a cohort study was conducted, and three dose-specific analysis populations were created. Individuals vaccinated with dose 1, dose 2, and dose 3 of the Pfizer-BioNTech COVID-19 vaccine were each matched 1:1 with unvaccinated individuals on calendar time of vaccination, age, sex, history of COVID-19, place of residence, history

of influenza vaccination, pregnancy status, immunocompromised status, presence of pre-existing medical conditions, and socioeconomic status/education level.

For the final analysis all cases should be validated. For the current interim report, case validation has not been conducted.

Setting:

Five data access providers (DAPs) have contributed data from electronic healthcare data sources in Europe for the objectives of this interim report: Pedianet, IT; PHARMO Institute for Drug Outcomes Research (PHARMO), NL; University of Oslo - Norwegian Health Registries (NHR), NO; EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute (EpiChron), ES; Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària (SIDIAP), ES.

Subjects and study size, including dropouts
The source population was all individuals registered in the healthcare data sources listed above. The current study period included data from the following calendar time:

- Pedianet between 31 May 2021 and 31 August 2022;
- PHARMO between 6 January 2021 and 30 June 2022;
- NHR between 1 January 2021 and 31 December 2021;
- EpiChron between 27 December 2020 and 31 July 2022;
- SIDIAP between 1 January 2021 and 30 June 2022.

Variables and data sources:

Exposure to vaccine was based on recorded prescription, dispensing, or administration of the Pfizer-BioNTech COVID-19 vaccine. The number of vaccine doses was categorised by distance since last dose for the primary objective. COVID-19 was identified by diagnosis code or COVID-19 PCR, or antigen test. Myocarditis and pericarditis were identified by diagnosis codes, tagged narrow by the VAC4EU code lists task force, across different vocabularies. Validation has not yet been conducted. Diagnostic tests for the diagnosis of myocarditis or pericarditis are typically conducted in the hospital, and cannot be retrieved in an automated fashion; these will be collected in the case review and validation. Treatments for myocarditis after discharge, were included from the pharmacy records or prescribing records. For myocarditis these included paracetamol, antivirals, antibiotics, immunosuppressant agents as well as heart failure therapy (beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, or angiotensin-II-receptor blockers, aldosterone antagonists, cardiac glycosides, calcium channel blockers and anti-arrhythmics). Procedural treatments, could not be extracted from the records and will be included during case review and validation. Pharmacological treatments for pericarditis included antibiotics, NSAIDs and

colchicine. Procedures conducted in hospital will be extracted from during case review and validation.

Outcomes during follow-up were identified in the databases from day zero, with algorithms based on codes for diagnoses)and included hospitalisation, death (all cause), sudden cardiac death, heart failure, cardiogenic shock, fulminant myocarditis, chronic myocarditis, inflammatory cardiomyopathy, heart transplant, arrhythmia, chronic pericarditis, restrictive pericarditis, recurrent myocarditis, recurrent pericarditis. Confirmation of these outcomes will be collected during case review and validation, but are not included in this interim report.

Vaccination after myocarditis or pericarditis diagnosis was described by platform (mRNA or non-mRNA platform vaccine).

Covariates were assessed at time zero (diagnosis of myocarditis or pericarditis for primary objective, and time of vaccination dose for secondary objective) and include: age, sex, pregnancy status, geographic region, socioeconomic status (if available), residency in long-term care facility (if available), Healthcare worker status (if available), COVID-19 history, smoking status, body mass index, comorbidities: anaphylaxis, allergies, diabetes mellitus, hypertension, cardiovascular disease, myocardial infarction, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic respiratory disease, chronic kidney disease, moderate or severe kidney disease, chronic liver disease, moderate or severe liver disease, any cancer (and subtypes for Charlson index), auto-immune disorders, influenza or respiratory tract infection HIV/AIDs, Sickle cell disease, connective tissue disease. Composite scores were Charlson index and CDC at risk group for severe COVID-19. Comedications in year prior time zero included: analgesics, antibiotics, antivirals, corticosteroids, NSAIDs, statins, psychotropics, warfarin, novel anticoagulants. Healthcare utilisation was measured in year prior to diagnosis and in 2 weeks prior to diagnosis and included number of hospitalisations, number of emergency department visits (if available), long term care facility/nursing facility, primary care visits, cancer screening attendance, other preventative health services, and any COVID-19 tests. Data about other vaccinations, including influenza, pneumococcal, DTP, MMR, Hib, hepatitis B, varicella, HPV, meningitis and rotavirus vaccines (if recorded) at any time previously were collected. Many surrogates of frailty were considered, but not always easy to operationalise without chart review: wheelchair use, home hospital bed, paralysis, hemiplegia, Parkinson's disease, skin ulcer, weakness, stroke, ambulance transport, dementia, difficulty walking, home oxygen, rehabilitation care, psychiatric illness, sepsis, heart failure, podiatric care, bladder incontinence, diabetes complications, arthritis, coagulation deficiencies, vertigo, and lipid abnormalities.

Results:

This interim study report is based on data from five data sources, Italy (Pedianet, children only), The Netherlands (PHARMO), Norway (NHR), and Spain (EpiChron and SIDIAP) for both the primary and secondary objectives.

Results for the primary objectives

The source population captured 15.6 million persons. From this population 1,643 persons were diagnosed with myocarditis and 3,889 with pericarditis. After application of exclusion criteria the cohort of myocarditis patients comprised 1,127 persons and the cohort of pericarditis cases 2,727 persons. PHARMO, EpiChron and SIDIAP had 1.5 years of observation period to identify myocarditis and pericarditis in the population, in Norway this was one year and in Pedianet it was 15 months.

Follow-up time after the diagnosis of myocarditis or pericarditis was limited with median follow-up times of between 5 and 11 months for myocarditis and 8 and 12 months for pericarditis. A total of 525 myocarditis cases (46.6% of those included) had been vaccinated with the Pfizer-BioNTech COVID-19 vaccine prior to diagnosis and 1,420 pericarditis cases (52.1% of those included). Most vaccinated cases occurred more than 14 days after the last dose (>80%) for both myocarditis and pericarditis, and the majority occurred after dose 2, with very few cases after dose 3 during the study period. In persons who received two doses, most myocarditis and pericarditis events occurred more than 22 days after the last dose.

The median age of myocarditis cases varied between data sources, ranging from 37 to 55 years in vaccinated cohorts and from 38 to 48 years for unvaccinated cohorts (most cases were between 18 and 60 years of age), prevalence of females varied from 0% to 37% in vaccinated cases and from 22.86% to 66.67% in unvaccinated cases, and was comparable between vaccinated and unvaccinated within data sources. Very few women were pregnant at diagnosis.

The median age for pericarditis cases was higher than for myocarditis cases and ranged from 54 to 68 years, consistent with the known epidemiology. The prevalence of females ranged from 24% to 54% in pericarditis cases, which is higher than for myocarditis and consistent with known epidemiology. Pregnancy prevalence rates were even lower than for myocarditis, which is explained by higher age.

Healthcare utilisation was high, with the large majority of myocarditis and pericarditis cases having at least one hospitalisation in the year prior to diagnosis (in NHR, EpiChron and SIDIAP data sources where this could be assessed), and 5 to 11% were hospitalised in the 2 weeks prior to diagnosis. primary care visits were also very frequent, with low percentages of myocarditis cases having no primary carer visit in the year prior to diagnosis, and this was even lower in pericarditis cases. In addition, the majority also had a primary care visit in the two weeks prior to diagnosis. Emergency department visits were observed only in EpiChron. Recorded COVID-19 tests were not very frequent in the year prior to diagnosis, and varied between the data sources, which is a data quality issue that is being further investigated. Surrogates of frailty, which were use of support aids, were difficult to assess in most data sources, because of the lack of recording of wheelchair use, ambulance use, etc. Surrogate frailty indicators such as psychiatric illness, heart failure and arthritis could be measured and were the most frequent indicators of frailty. Prevalence of these conditions was consistently

higher in vaccinated cases, which might be explained by the targetting of the first available COVID-19 vaccines to more frail persons. In terms of comorbidities beyond surrogates of frailty, cardiovascular disease was frequent (>50%) in both myocarditis and pericarditis cohorts, across all data sources, and was higher in vaccinated cohorts than in unvaccinated cohorts. The CDC score for risk of severe COVID-19 disease showed than the majority of myocarditis and pericarditis cases had two or more risk conditions for severe COVID-19. Analgesics, antibiotics, NSAIDs, psychotropics, statins and novel anticoagulants were frequently used in the year prior to diagnosis, with inconsistent patterns between vaccinated and unvaccinated cases across data sources.

Many of the myocarditis and pericarditis cases were (re)-vaccinated after the diagnosis of myocarditis or pericarditis in both vaccinated and unvaccinated cohorts, with either Pfizer-BioNTech COVID-19 vaccine or another COVID-19 vaccine. Patterns of pharmacological treatment of myocarditis in the 365 days after diagnosis were similar between vaccinated and unvaccinated cases. Following myocarditis diagnosis cardiovascular medications as well as NSAIDs, analgesics and immunosuppressants were frequently administered. Non-pharmacological interventional treatments could not be identified from the discharge records and we aim to collect these during the case review and validation. Patterns of pharmacological treatment of pericarditis in the 90 days after diagnosis were also similar between vaccinated and unvaccinated cases, NSAIDs and analgesics were frequently used. Non-pharmacological interventional treatments in the hospital could not be identified from the discharge records and may be obtained during case review and validation which will be done for the final report.

Outcomes of myocarditis and pericarditis

Outcomes were identified using only diagnostic codes and algorithms in this interim report. For the final report the outcomes will be validated during the case review and validation. Subgroup analyses by age and gender could not be reported because of the small numbers.

Hospitalisation

The overall 12-month risk of hospitalisation was high in each of the data sources, from day 0. This is because most cases were identified in hospital. To investigate the risk of hospitalisation after the first episode, a lag time of, for example, 30 days should be included from t_0; this will be discussed and the protocol will be amended, in necessary.

Death

The overall 9- and 12-month risk of death was low for myocarditis cases, with overlapping confidence intervals between vaccinated and unvaccinated cases, although the crude risk of death was consistently higher in vaccinated than unvaccinated. No deaths occurred in Pedianet. The 9-month risks of death (which could be assessed in most data sources) in the myocarditis cohorts were 2.71% (95% CI: 0.0-6.34) and 0% in the vaccinated and

unvaccinated cohorts in PHARMO, 17.15% (95% CI: 6.2-26.8) and 7.0 % (95% CI: 3.1-10.8) in the vaccinated and unvaccinated cohorts in NHR, 10.0% (95% CI%: 0.03-19.0) and 5.80 % (95% CI: 2.2-8.9) in the vaccinated and unvaccinated cohorts in EpiChron and 9.85% (95% CI: 3.7-15.6) and 8.58% (95% CI: 4.4-12.6) in the vaccinated and unvaccinated cohorts in SIDIAP.

In pericarditis cases the overall 9-month risk of death was 13.85% (95% CI: 0-30) and 21.6% (95% CI: 2.8-36.7) in the vaccinated and unvaccinated cohorts in PHARMO (selected group identified in hospital only), 3.41% and 2.05% in vaccinated and unvaccinated in NHR, 5.61% and 3.58% vaccinated and unvaccinated in EpiChron, and 6.91% and 4.49% in vaccinated and unvaccinated in SIDIAP) all with overlapping confidence intervals between vaccinated and unvaccinated.

Inflammatory cardiomyopathy

The 9-month risk of inflammatory cardiomyopathy after myocarditis was very low without cases in Pedianet, PHARMO and NHR. Nine-month risks were 2.27% and 2.86% in vaccinated and unvaccinated in myocarditis cases in EpiChron and 1.12% and 3.43 % in vaccinated and unvaccinated myocarditis cases in SIDIAP.

No cases were observed in Pedianet, PHARMO, NHR and EpiChron in pericarditis cases. In SIDIAP the 9-month risk was 0% and 0.28% in vaccinated and unvaccinated in SIDIAP.

Chronic myocarditis

In cases of myocarditis, the 9-month risk of chronic myocarditis was 11.4% in and 22.86% in the vaccinated and unvaccinated cohorts in EpiChron. In SIDIAP the 9-month risk was 26.3% and 29.4% in the vaccinated and unvaccinated cohorts. This outcome may be misclassified and will be improved after validation of cases in the final report.

Chronic pericarditis

No cases of chronic pericarditis were identified in the pericarditis cohort in Pedianet, PHARMO and NHR. In EpiChron the 9-month risk of chronic pericarditis was 0% and 1.74% in the vaccinated and unvaccinated cohorts. In SIDIAP the 9-month risk of chronic pericarditis was 0.68% and 1.02% in the vaccinated and unvaccinated cohorts in SIDIAP, without differences between vaccinated and unvaccinated.

Heart transplant

Only a few heart transplants were identified. Identification of heart transplants will be improved during the case review and validation.

Cardiogenic shock

Cardiogenic shock were not identified in Pedianet and NHR. In PHARMO the 9-month risks in myocarditis cases were 0% and 0.55% in the vaccinated and unvaccinated cohorts. In EpiChron there were no cases in the myocarditis cohort. In SIDIAP the 9-month risks of cardiogenic shock were 3.30% and 5.92% in the vaccinated and unvaccinated cohorts.

In the pericarditis cohorts, the 9-month risks were 0% and 4.2% in the vaccinated and unvaccinated cohorts in PHARMO. In EpiChron, the 9-month risks were 1.64% and 0.87% in the vaccinated and unvaccinated cohorts. In SIDIAP the 9-month risks were 1.30% and 0.99% in the vaccinated and unvaccinated cohorts. Risks were comparable between the vaccinated and unvaccinated cohorts.

Heart failure

The 12-months risks of heart failure in the myocarditis cohorts were 2.61% in PHARMO, 14.5% in NHR, 15.2% in EpiChron and 14.8% in SIDIAP. Although risks were higher in the vaccinated cohorts, the 95% CIs for the vaccinated and unvaccinated cohorts overlapped.

In pericarditis cases, the 12-month risks of heart failure were 15.7% in PHARMO, 9.4% in NHR, 14.6% in EpiChron and 15.6% in SIDIAP. In all data sources the risk of heart failure was higher in the vaccinated cohorts than unvaccinated, but confidence intervals overlapped except in SIDIAP, where the crude risks were 20.6% (95% CI: 17.3-23.8) and 11.2 (95%CI: 8.9-13.5) in the vaccinated and unvaccinated cohorts.

Subgroup analyses by age and gender could not be reported because of the small numbers.

Fulminant myocarditis

Fulminant myocarditis is a rare condition, was found in all data sources since it was included in the myocarditis diagnosis as an outcome. The algorithm is being improved for the final report.

Arrhythmia

The risk of arrhythmia increased immediately at diagnosis and could be a secondary diagnosis at presentation. We recommend the introduction of a lag time to assess the prognosis of myocarditis and pericarditis to differentiate from outcomes present at diagnoses and those that are part of the natural history.

Restrictive pericarditis

The 9-month risk of restrictive pericarditis in pericarditis cases was 0% in vaccinated and 1.74% in unvaccinated in Epichron. In SIDIAP the risk of restrictive pericarditis was 0.50% in vaccinated and 0.87% in unvaccinated.

Results secondary objectives

Data sources

The same data sources contributed data for the secondary objective as for the primary objective.

Study population

The study population comprised three matched cohorts based on the number of doses of the Pfizer-BioNTech COVID-19 vaccine received. The dose 1 matched cohort included 8,269,984 vaccinated individuals and the same number of matched unvaccinated individuals. The dose 2 matched cohort included 6,418,241 matched vaccinated and unvaccinated individuals, and the dose 3 matched cohort included 1,375,296 vaccinated and the same number of unvaccinated matched individuals. Vaccinated individuals were matched with unvaccinated individuals using age, sex, history of COVID-19, region, history of influenza vaccination, pregnancy status, immunocompromised status and the CDC at-risk for severe COVID-19 score.

Risk window and censoring

Primary results focused on a 14-day risk window after each dose, with sensitivity analyses for 7 and 21 days. Most individuals were censored in follow-up because of the end of the 14-day risk window, or because the unvaccinated individual was vaccinated, which ended follow-up for the pair.

Characteristics of the different matched dose cohorts

Due to matching, the vaccinated and unvaccinated dose cohorts had a similar distribution of comorbidity, but the patterns of age and co-morbidity differed between the different dose cohorts across data sources. This may be strongly influenced by the different available observation periods in the data sources (see table above) and booster vaccination roll out strategies across age groups in the countries. In Pedianet, third doses of Pfizer-BioNTech COVID-19 vaccine were only available for 12–17-year-old children during the observation period, whereas dose 1 and 2 cohorts comprised also 5–11-year-old children. In PHARMO the median age of the first dose Pfizer-BioNTech COVID-19 vaccine cohort was 49 but was 45 years in the second dose cohort and 34 in the third dose, in which most persons vaccinated with Pfizer-BioNTech COVID-19 vaccine were between 18 and 60 years of age. In NHR, which only had an observation period until December 2021, the median age was 47 years in the first dose cohort, 53 in the second and 68 in the third dose cohort since the elderly were boosted in the fall of 2021. In this third dose cohort the majority was over 65 years of age. In EpiChron the observation period was until July 2022, when most persons had had an opportunity to receive booster vaccines. The median age for the first dose cohort was 48 years, with a relative high percentage (>20%) of those aged ≥70 years in the Pfizer-BioNTech COVID-19 vaccinated group, median age was 44 years for the second dose

cohort, with fewer 70+ receiving Pfizer-BioNTech COVID-19 vaccine (10%), the third dose cohort median age was 48 years, still with lower percentage of 70+ in the Pfizer-BioNTech COVID-19 vaccinated group (12%), but also hardly any children (only 1% of under 18). In SIDIAP the observation period was until June 2022, when most persons had had an opportunity to receive booster vaccines. The median age for the first dose cohort was 45 years, with a relative high percentage (>20%) of 70+ receiving the Pfizer-BioNTech COVID-19 vaccine, median age was 46 years for the second dose cohort, with more than 20% of 70+ receiving Pfizer-BioNTech COVID-19 vaccine, the third dose cohort median age was 77 years, with a very high percentage of 70+ in the Pfizer-BioNTech COVID-19 vaccinated (70%), and hardly any children (only 1% of under 18).

In each data source the prevalence of history of any cardiovascular disease or use of cardiovascular medicines was highest in each of the dose cohorts and based on the age distribution of the different dose cohorts, the prevalence varied across the dose cohorts. Among surrogates of frailty, psychiatric illness, weakness and arthritis were most prevalent. Vaccination with vaccines other than COVID-19 vaccines was only identified in Pedianet and NHR. The most frequent medications used in the year prior to t_0 were antibiotics, analgesics, NSAIDs and psychotropics, general with a slightly higher rate in vaccinated cohorts compared with unvaccinated cohorts, which varied across the dose cohorts, because of the differences in age, as discussed above.

Risk factors for myocarditis in the 14-day risk window

For this interim analysis univariate associations were estimated between the different risk factors and the occurrence of myocarditis in the 14-day risk window after t_0, in the matched cohorts. Due to the limited number of myocarditis cases in some of the data sources (e.g. Pedianet, PHARMO, EpiChron) we could not estimate the association at all or only for risk factors that have a relatively high prevalence. In NHR and SIDIAP we had enough myocarditis cases to assess risk factors in the first dose and second dose cohorts, in the third dose cohorts we could not estimate many risk factors. Table 1 below summarises the key univariate associations in the 14-day risk window.

No dose of the vaccine appeared to be clearly associated with the development of myocarditis in any of the data sources.in the 14 days after vaccination. It is coherent that a history of cardiovascular disease as well as other underlying chronic conditions (as observed in Charlson score and CDC risk score) were associated with an increased risk of myocarditis. Across multiple data sources use of corticosteroids was associated with an increased risk of myocarditis, which might point to a higher risk of an infectious agent in the presence of immunocompromised conditions. In the univariate analysis, vaccination with Pfizer-BioNTech COVID-19 vaccine was not significantly associated with myocarditis in the dose 1 or 2 cohorts, based on the 14-day risk window. COVID-19 was also not identified as risk factor, which is likely explained by the incomplete capture of the diagnosis in these interim analyses.

Risk factors for pericarditis in the 14-day risk window

The risk factors that were found to be associated with pericarditis in the 14-day risk window analysed for this interim report are summarised in Table 2.

Risk factors for pericarditis included increasing age, male gender, more comorbidity (CDC score), respiratory infections, SARS-CoV-2 infection, pneumococcal vaccine, corticosteroids, immunocompromised conditions and several other medicines, which is consistent with the literature. According to the European Society for Cardiology (ESC) viruses are considered the most common infective agents for pericarditis, and include coxsackieviruses A and B, echovirus, adenoviruses, parvovirus B19, HIV, influenza as well as multiple herpes viruses such as EBV and CMV. Less commonly, other forms of bacteria can cause pericarditis including Coxiella burnetii, Meningococcus, Pneumococcus, Staphylococcus and Streptococcus. Non-infectious causes are numerous and include malignancy (often secondary to metastatic disease), connective tissue disease (such as systemic lupus erythematosus, rheumatoid arthritis, and Behçet's disease), and metabolic etiologies.

Table 1. Summary of results from univariate analyses to identify risk factors for myocarditis

	Pedianet		PHARMO		NHR		EpiChron		SIDIAP	
Dose	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**
Pfizer-BioNTech COVID-19 Vaccination	NE	NE	0.50 (NS)	3.0 (NS)	0.87 (NS)	0.58 (NS)	NE	NE	1.20 (NS)	1.57 (NS)
Age	NE	NE	NS	NS	NS	0.98 (0.97-1.0)	NS	0.91 (0.86-0.97)	NS	0.97 (0.94-1.0)
Male gender	NE	NE	NS	NS	NS	3.9 (1.24-12.3)	NE	NE	NS	NS
Cardiovascular disease	NE	NE	NS	NS	21.1 (5.0-89) esp. heart failure and myocardial infarctions	8.0 (2.4-27) esp. heart failure and myocardial infarctions	NE	NE	5.5 (1.4-21.6) esp. heart failure and myocardial infarctions	1.2 (0.3-5.8)
Diabetes	NE	NE	NE	NE	NS	NS	NE	NE	8.9 (2.4-33)	NS
Respiratory disease	NE	NE	NE	NE	NS	NS	NE	NE	5.4 (1.5-19.5)	NS
Liver disease	NE	NE	NE	NE	NE	NE	NE	NE	19.7 (4.8-81)	NS
Kidney disease	NE	NE	NE	NE	NE	NE	NE	NE	5.0 (1.1-24)	NS
CDC score	NE	NE	NS	NE	2 or more: 13.0 (3.0-56)	2 or more: 6.6 (1.8-24)	NE	NE	NE	NS
Charlson score	NE	NE	NE	NE	3 or more: 5.4 (2.2-13.2)	NS	NE	NE	2: 6.1 (1.2-30.4) 3 or more: 17.4 (3.8-81)	NE
Resp. Infections	NE	NE	NE	NE	4.2 (1.8-10)	NS	NE	NE	NS	NS
Immunocompromised conditions	NE	NE	NS	NE	NS	NS	NE	NE	NS	NS
Frailty indicators	NE	NE	NS	NE	Stroke	Weakness	NE	NE	diabetes complications	diabetes complications
Medications	NE	NE	NS	NE	Analgesics, antibiotics, corticosteroids, NSAIDs and novel oral anticoagulants	Corticosteroids	NE	NE	Corticosteroids	NS/NE
Other vaccines	NE	NE	NA	NA	Pneumococcal TPV	NS or NE	NE	NE	NA	NA

NS: not statistically significant, NA: risk factor not assessed, NE: not estimable

Table 2. Summary of results from univariate analyses to identify risk factors for pericarditis

	Pedianet		PHARMO		NHR			EpiChron		SIDIAP		
Dose	**1**	**2**	**1**	**2**	**1**	**2**	**3**	**1**	**2**	**1**	**2**	**3**
Pfizer-BioNTech COVID-19 vaccination	NE	NE	NA	NA	0.98 (NS)	0.68 (NS)	0.24 (NS)	0.86 (NS)	NE	1.3 (NS)	1.14 (NS)	0.60 (NS)
Age	NE	NE	NA	NA	1.02 (1.0-1.03)	NS	1.05 (1.0-1.11)	NS	0.95 (0.9-1.0)	1.02 (1.01-1.03)	NS	1.03 (1.01-1.06)
Male gender	NE	NE	NA	NA	1.65 (1.0-2.6)	NS	6.9 (1.2-40)	NS	NE	NS	3.3 (1.6-6.7)	NS
Cardiovascular disease	NE	NE	NA	NA	8.9 (5.4-14.7) esp. AMI & HF	9.7 (4.9-19) esp. AMI	NS	HF:15.7 (3.1-79)	NE	2.5 (1.5-4.4) esp.HF	NS. AMI: 24.2 (5.7-103)	NS
Diabetes	NE	NE	NA	NA	NS	NS	NS	6.4 (1.6-25)	NE	NS	NS	NS
Respiratory disease	NE	NE	NA	NA	2.0 (1.2-3.3)	NS	NS	NS	NE	NS	NS	NS
Liver disease	NE	NE	NA	NA	4.4 (1.0-19)	NE	NE	NE	NE	2.8 (1.1-7.0)	NS	NE
Kidney disease	NE	NE	NA	NA				NE	NE	7.1 (2.6-20)	NS	NE
Malignancies	NE	NE	NA	NA	2.9 (12.3-5.7)	NS	NS	NE	NE	NE	NE	NE
Auto-immune disorders	NE	NE	NA	NA	2.4 (1.5-4.0)	NS	NS	NE	NE	3.3 (1.1-10)	NS	NE
Connective tissue disease	NE	NE	NA	NA	2.7 (1.5-4.8)	NS	NS	NS	9.0 (1.8-44)	3.7 (1.6-8.5)	NS	NS
CDC score	NE	NE	NA	NA	2: 9.9 (5.4-18.3)	NS	9.9 (1.3-76)	NE	NE	2: 2.2 (1.2-4.0)	NS	NE
Charlson score	NE	NE	NA	NA	3 or more: 4.2 (2.4-7.4)	NS	NS	NE	NE	2 and 3 2.9 (1.4-5.9)	NS	NE
Resp. Infections	NE	NE	NA	NA	4.6 (2.9-7.5)	2.4 (1.1-5.0)	NS	5.9 (1.7-20)	NE	2.2 (1.2-3.8)	NS	NE
COVID-19 diagnosis	NE	NE	NA	NA	15.1 (3.8-61)	NE	NE	NS	NE	NS	NS	NE
Immunocompromised conditions	NE	NE	NA	NA	4.9 (3.3-7.5)	2.3 (1.0-5.3)	19 (3.4-104)	NS	NE	NS	NS	NS
Frailty indicators	NE	NE	NA	NA	Stroke Arthritis	NS	NS	Lipid abnormality	NE	Parkinson Sepsis Incontinence Lipids	NS	NE
Medications	NE	NE	NA	NA	Analgesics antibiotics Corticosteroids NSAIDs Psychotropics Statins NOAC	Corticosteroids NSAIDs Statins NOAC	Corticosteroids NSAIDs Psychotropics	statins	NE	Analgesics Antibiotics NOAC	NS	NS
Other vaccines	NE	NE	NA	NA	pneumococcal	pneumococcal	NE	NA	NA	NA	NA	NA

NS: not statistically significant, NA: risk factor not assessed, NE: not estimable; NOAC: novel oral anticoagulants; HF: heart failure; AMI: acute myocardial infarction

Limitations

Limitations of the data sources

Only five of the eight data sources could provide data for this interim report, and those that provided data, could not provide data from all types of healthcare settings, which limits assessment of healthcare utilisation and may affect rates of outcomes. ARS continues to discuss with the authorities about access to the regional data. CPRD has obtained a new data extraction and these data will be included in the final study report. HSD is unlikely to participate since COVID-19 vaccination recording is still incomplete and not fit for purpose for this study. For all other data sources, we compared the vaccination rates in our study with those from the COVID-19 vaccine tracker from the European Centre for Disease Prevention and Control (ECDC) and they were compatible.

For PHARMO we will link primary care data with hospital data for individuals for the analyses in the final report. This will improve the distinction between myocarditis and pericarditis, and the detection of other outcomes. The ICPC vocabulary used in the PHARMO and NHR is not sufficiently granular to allow myocarditis and pericariditis to be differentiated. For NHR, we plan to obtain an update of the data including full ICD10 codes for all databases.

In this interim report the myocarditis and pericarditis cases were not validated, and misclassification may differ between data sources, depending on the healthcare setting from which they originate. Moreover, assessment of several outcomes in the primary objective was sub-optimal, either because they overlapped in time with the index episode (e.g. hospitalisation, arrhythmia), or because the codes used cannot distinguish between recurring and chronic events. During the case review and validation this information will be extracted manually. Some variables, mostly those that are not systematically captured, were not assessable for this interim report, but investigations are underway to understand how and where they are captured in an unstructured manner and how they can be captured. This work is ongoing and will be improved for the final study report.

Data on interventions and treatments in hospital are not typically captured in discharge records, and payment details, charts or discharge letters may need to be used to retrieve this information; we are exploring how this might be possible within the various data sources.

Limitations of the script

The two study objectives are complex, and quality control of the scripts was conducted by independent double programming. Despite the extensive QC, there are still some problems with the outputs that could not be corrected prior to submission of this report. These are undergoing investigation and will be improved for the final study report. This includes variables with unstructured values or measurements, e.g., smoking, SES, BMI, COVID-19 and variables that do not get systematically captured: cancer screening, other preventative measures, support aids indicating frailty, non-pharmacological treatments, algorithm for fulminant myocarditis, other vaccines. Pregnancy was used in the primary objective, but could not be used in the secondary objective. We aim to improve this for the final report.

Limitations of the methods

The results for all the analyses reported here are descriptive. No multivariate analysis was conducted, and no causal inference can be made. Several of the outcomes that were to be measured as outcomes (e.g. chronic myocarditis, chronic pericarditis, hospitalisation, arrhythmia) seem to have been captured at diagnosis and not during the natural history. We propose that a window should be used for assessment, e.g., 30 days after diagnosis. This will be discussed and the protocol and SAP amended, if necessary.

The primary analysis for the secondary analysis was based on a 14-days risk window, but in the primary objective we noted that most cases of myocarditis and pericarditis occurred after 14 days. To have more power in the secondary objective, it may be better to use a 21-day risk window for the secondary objective. For the final study report we will conduct full statistical analyses, including full comparative analyses of the vaccinated and unvaccinated cohorts of myocarditis and pericarditis cases.

The available lookback period differed between the data sources, which may have resulted in differences in the estimates for prevalence of comorbidities.

Interpretation

This results in this interim report show that myocarditis and pericarditis occur infrequently in the source population, consistent with known epidemiology. Myocarditis cases were younger than pericarditis cases, and they were more often male, also consistent with known epidemiology. Cases had a high prevalence of comorbidity, especially cardiovascular disease, and had frequent healthcare and medications use, which were also found to be risk factors in the secondary objective. A large proportion of individuals with myocarditis and pericarditis was (re)-vaccinated after diagnosis. During the case review and validation that will be carried out for the final report we will be able to assess whether this led to a recurrence of myocarditis or pericarditis.

The overall 9 and 12-month risk of death was low for myocarditis cases, with overlapping confidence intervals between vaccinated and unvaccinated cases, although the crude risk of death was consistently higher in vaccinated cohorts than in unvaccinated cohorts. No deaths occurred in Pedianet, 9-month risks of death (which could be assessed in most data sources) in myocarditis cases in PHARMO were 2.71% and 0% in the vaccinated and unvaccinated cohorts, 17.15% and 7.0 % in NHR in vaccinated and unvaccinated cohorts, 10.0% and 5.80 % in EpiChron in vaccinated and unvaccinated cohorts and 9.85% in vaccinated and 8.58% in SIDIAP in vaccinated and unvaccinated cohorts.

In pericarditis cohorts the overall 9-month risks of death were 13.85% and 21.6% in PHARMO (for a subgroup who had hospital available) in the vaccinated and unvaccinated cohorts, 3.41% and 2.05% in NHR in the vaccinated and unvaccinated cohorts, 5.61% and 3.58% in EpiChron in the vaccinated and unvaccinated cohorts, and 6.91% and 4.49% in

SIDIAP in the vaccinated and unvaccinated cohorts with overlapping 95% CIs between the vaccinated and unvaccinated cohorts.

Vaccination with the Pfizer-BioNTech COVID-19 vaccine was not a significant univariate risk factor in the overall population in this interim analysis. This is inconsistent with prior studies that showed an increased risk of myocarditis after the second dose of the Pfizer-BioNTech vaccine,. However, we used a 14-day risk window in our analyses, whereas most other studies used 21- or 28-day risk windows.

CONCLUSIONS

The results for the primary objective of this study showed that myocarditis and pericarditis occurred infrequently in both vaccinated and unvaccinated cohorts, myocarditis cases were younger than pericarditis cases and were more often male, which is consistent with known epidemiology. There was a high prevalence of cardiovascular disease, healthcare and medication use in the myocarditis and pericarditis cohorts. Pharmacological treatments and non-pharmacological interventions were frequent. In the analyses for the secondary objective these factors were often identified as risk factors, in both the first dose and second dose cohorts. Disease progression could not be well assessed without case review and validation, except for the outcomes death and heart failure. Crude risk estimates were consistently higher in the vaccinated cohorts compared with unvaccinated cohorts, but the 95% CIs overlapped. These analyses were only descriptive, without any control for confounding.

Vaccination with the Pfizer-BioNTech COVID-19 vaccine was not a significant univariate risk factor in the overall population in this interim analysis. Future analyses of risk factors will include variation of the risk window after vaccination, validation of the cases according to Brighton Collaboration criteria, multivariate analysis of risk factors and improved data management.

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