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Clinical outcomes of myocarditis after SARS-CoV-2 mRNA vaccination in four Nordic countries: population based cohort study

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ABSTRACT

OBJECTIVE To investigate the clinical outcomes of myocarditis associated with mRNA vaccines against the SARS-CoV-2 virus compared with other types of myocarditis.

DESIGN Population based cohort study.

SETTING Nationwide register data from four Nordic countries (Denmark, Finland, Norway, and Sweden), from 1 January 2018 to the latest date of follow-up in 2022.

PARTICIPANTS The Nordic myocarditis cohort; 7292 individuals aged ≥12 years who had an incident diagnosis of myocarditis as a main or secondary diagnosis, in a population of 23 million individuals in Denmark, Finland, Norway, and Sweden.

MAIN OUTCOME MEASURES Heart failure, or death from any cause within 90 days of admission to hospital for new onset myocarditis, and hospital readmission within 90 days of discharge to hospital for new onset myocarditis. Clinical outcomes of myocarditis associated with SARS-CoV-2 mRNA vaccination, covid-19 disease, and conventional myocarditis were compared.

RESULTS In 2018-22, 7292 patients were admitted to hospital with new onset myocarditis, with 530 (7.3%) categorised as having myocarditis associated with SARS-CoV-2 mRNA vaccination, 109 (1.5%) with myocarditis associated with covid-19 disease, and 6653 (91.2%) with conventional myocarditis. At the 90 day follow-up, 62, nine, and 988 patients had been readmitted to hospital in each group (vaccination, covid-19, and conventional myocarditis groups, respectively), corresponding to a relative risk of readmission of 0.79 (95% confidence interval 0.62 to 1.00) and 0.55 (0.30 to 1.04) for the vaccination type and covid-19 type myocarditis groups, respectively, compared with the conventional myocarditis group. At the 90 day follow-up, 27, 18, and 616 patients had a diagnosis of heart failure or died in the vaccination type, covid-19 type, and conventional myocarditis groups, respectively. The relative risk of heart failure within 90 days was 0.56 (95% confidence interval 0.37 to 0.85) and 1.48 (0.86 to 2.54) for myocarditis associated with vaccination and covid-19 disease, respectively, compared with conventional myocarditis; the relative risk of death was 0.48 (0.21 to 1.09) and 2.35 (1.06 to 5.19), respectively. Among patients aged 12-39 years with no predisposing comorbidities, the relative risk of heart failure or death was markedly higher for myocarditis associated with covid-19 disease than for myocarditis associated with vaccination (relative risk 5.78, 1.84 to 18.20).

CONCLUSIONS Compared with myocarditis associated with covid-19 disease and conventional myocarditis, myocarditis after vaccination with SARS-CoV-2 mRNA vaccines was associated with better clinical outcomes within 90 days of admission to hospital.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Myocarditis is a known adverse event associated with mRNA vaccines against the SARS-CoV-2 virus, but the clinical outcomes are not well described at the population level

⇒ How the clinical outcomes of myocarditis associated with vaccination compare with outcomes after myocarditis associated with covid-19 infection and conventional myocarditis is unclear

WHAT THIS STUDY ADDS

⇒ In a population based study covering 23 million individuals, myocarditis after SARS-CoV-2 mRNA vaccination was associated with a lower risk of heart failure within 90 days of admission to hospital compared with myocarditis associated with covid-19 disease and conventional myocarditis

⇒ Among younger individuals with no predisposing comorbidities, myocarditis related to covid-19 disease was associated with a markedly higher risk of heart failure or death within 90 days of admission to hospital compared with myocarditis associated with vaccination

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ These findings suggest that the clinical outcomes of myocarditis associated with SARS-CoV-2 mRNA vaccination are less severe than the outcomes of other types of myocarditis, which is relevant for doctors, their patients, and the public when considering vaccination policy

Introduction

Myocarditis is a rare adverse event after vaccination with the two mRNA vaccines, tozinameran (BNT162b2) and elasomeran (mRNA-1273), against the SARS-CoV-2 virus. The risk seems to be highest in younger age groups, in men, and after the second dose of vaccine,[1–10] with the number of excess patients with myocarditis per 100 000 men aged 16-24 years after a second dose of a SARS-CoV-2 mRNA vaccine estimated at 5.6 per 100 000 for tozinameran and 18.4 per 100 000 for elasomeran. How the clinical outcomes of myocarditis after vaccination with

SARS-CoV-2 mRNA vaccines compare with outcomes after other types of myocarditis, such as myocarditis associated with covid-19 disease and myocarditis not related to covid-19 or vaccination (ie, conventional myocarditis) is unclear.

The clinical outcomes of myocarditis range from no sequelae to chronic heart failure or death.[11] Hence a large scale evaluation of the clinical outcomes of these two new types of myocarditis compared with conventional myocarditis is needed to better evaluate the risks and benefits of vaccination, especially in younger individuals. Based on nationwide data on all incident admissions to hospital for myocarditis in 2018-22, sourced from a population of 23 million individuals in Denmark, Finland, Norway, and Sweden, we compared the clinical outcomes of myocarditis associated with vaccination, myocarditis associated with covid-19 disease, and conventional myocarditis, with respect to readmission to hospital, heart failure, and death.

Methods

Nordic myocarditis cohort

We conducted a population based multi-country study of nationwide register data from four Nordic countries (Denmark, Finland, Norway, and Sweden), as defined in a prespecified common protocol (online supplemental material 1). Our Nordic myocarditis cohort included all individuals aged ≥12 years who had an incident diagnosis of myocarditis as a main or secondary diagnosis (defined by ICD-10 (international classification of diseases and related health problems, 10th revision) codes I40.0, I40.1, I40.8, I40.9, I41.1, I41.8, or I51.4) at discharge (alive or dead) from inpatient hospital care, from 1 January 2018 to the latest date of follow-up in 2022, which was specific for each country (online supplemental table S1).

In Denmark, inpatient hospital care was defined as a hospital stay of ≥24 hours because duration of hospital contacts coding has replaced inpatient hospital care coding in current Danish patient registries. Patients with a pre-existing diagnosis of myocarditis (defined by ICD-10 codes) or heart failure (ICD-10 codes defined in online supplemental table S2) were excluded from the study. Online supplemental table S1 describes the washout periods for pre-existing diagnoses in the different countries. Only patients with a potential 90 days of follow-up in the register data were included in the study. Information on clinical diagnoses and length of hospital stay was sourced from national registries (online supplemental table S3).

Individuals admitted to hospital for myocarditis within 28 days of vaccination with a SARS-CoV-2 mRNA vaccine (any dose) were categorised as having myocarditis associated with vaccination; individuals admitted to hospital for myocarditis within 28 days of a positive polymerase chain reaction (PCR) test result for the SARS-CoV-2 virus were categorised as having myocarditis associated with covid-19 disease. The remaining patients who were admitted to hospital for myocarditis were categorised as conventional myocarditis. If an individual had received an mRNA vaccine and had a positive PCR test result for SARS-CoV-2 infection within 28 days, the latest exposure defined the type of myocarditis. Information on mRNA vaccinations for the SARS-CoV-2 virus were obtained from national vaccination registries in each country, and information on positive PCR test results were taken from national infectious disease surveillance registries (online supplemental table S3).

Length of stay after admission to hospital for new onset myocarditis was calculated as day of discharge minus day of admission + 1. If a patient with incident myocarditis had a subsequent admission to hospital within 24 hours of discharge, the subsequent admission to hospital was counted as part of the original admission to hospital for new onset myocarditis.

Cohort stratification

To evaluate the role of predisposing comorbidity, we included information on pre-existing diagnoses (in the two years before admission to hospital for new onset myocarditis) of malignancy, cardiovascular disease, or autoimmune diseases (ICD-10 codes defined in online supplemental table S2), from main or secondary diagnoses recorded in inpatient or specialist outpatient care. Also, we recorded whether the admission for new onset myocarditis was on or after 1 January 2020, to separate patients with myocarditis occurring before or during the covid-19 pandemic.

Outcomes

The clinical outcomes investigated were a new onset diagnosis of heart failure within 90 days of admission to hospital for new onset myocarditis; death from any cause within 90 days of admission to hospital for new onset myocarditis; and readmission to inpatient hospital care for any cause within 90 days of discharge from hospital for new onset myocarditis. If new onset heart failure was diagnosed in the same admission period as new onset myocarditis, new onset heart failure was categorised as occurring on the day after admission to hospital for myocarditis.

Statistical analysis

Cumulative 90 day relative risks of heart failure and death by type of myocarditis type for all four countries were estimated, with conventional myocarditis as the reference category. In subgroup analyses, we used a combined outcome of heart failure or death within 90 days of myocarditis, to preserve the statistical power to describe differences between the myocarditis groups. Subgroup analyses were performed by

age group (12-39 years and ≥40 years), sex, and in those admitted to hospital for new onset myocarditis on or after 1 January 2020 (reference was those admitted to hospital for new onset myocarditis before the pandemic). To investigate outcomes in healthy younger individuals with myocarditis, we conducted another analysis in those aged <40 years with no pre-existing diagnoses of malignancy, cardiovascular disease, or autoimmune disease. Similarly, subgroup analyses of cumulative 90 day relative risks of readmission after discharge from hospital for new onset myocarditis were performed by age group, sex, and in those admitted to hospital for new onset myocarditis on or after 1 January 2020 (reference was those admitted to hospital for new onset myocarditis before the pandemic), in these younger individuals with no pre-existing diagnoses of malignancy, cardiovascular disease, or autoimmune disease.

Cumulative incidences of heart failure and death by country for conventional myocarditis and myocarditis associated with vaccination, as a function of time from admission to hospital for myocarditis, were estimated with the Kaplan-Meier estimator (calculated as 1−Kaplan-Meier estimates). Cumulative incidence of readmission by country was also estimated with the Kaplan-Meier estimator but with time from discharge from hospital as the underlying time scale. Also, Kaplan-Meier estimates in multiples of 10 days of follow-up, by country, were combined with a random effects meta-analysis implemented with the mixmeta package[12] of R.[13] As input to the meta-analyses, log odds of estimates specific to each country were used as estimates, and the difference between log odds of confidence limits specific to each country were divided by 2×1.96 as standard errors. If at least one of the country estimates was zero, then the sum of events divided by the total number of patients with myocarditis was used to obtain results combined across countries. Cumulative incidences by country were not estimated for myocarditis associated with covid-19 disease because of limited statistical power.

Patient and public involvement

No patients or members of the public were directly involved in the design, analysis, or writing up of the study, owing to insufficient funds and time. The study was conducted by national public health institutions in Denmark, Finland, Norway, and Sweden, who have a legal obligation to investigate potential health hazards to the public.

Results

Characteristics of the Nordic myocarditis cohort

Our cohort included 7292 patients with a diagnosis of myocarditis; 530 (7.3%) were categorised as having myocarditis associated with vaccination, 109 (1.5%) were associated with covid-19 disease, and 6653 (91.2%) had conventional myocarditis (table 1). Patients were predominantly men (5304 (72.7%) overall) and 3715 (50.9%) were aged <40 years. Online supplemental table S4 shows median (interquartile range) age by type of myocarditis, age group, and country. Eighty five (16.0%), 54 (49.5%), and 1893 (28.5%) patients were admitted to hospital for ≥7 days in the vaccination type, covid-19 type, and conventional myocarditis groups, respectively. Only 11 of 639 patients with non-conventional myocarditis had received a SARS-CoV-2 mRNA vaccine and had covid-19 disease within 28 days of admission to hospital for myocarditis.

Absolute and relative risk of heart failure and death

At 90 days of follow-up for new onset myocarditis, heart failure was diagnosed in 22 (4.5 %), 12 (11.0 %), and 496 (7.5 %) patients with myocarditis associated with vaccination, myocarditis associated with covid-19 disease, and conventional myocarditis, respectively. We found that patients with myocarditis after vaccination had a significantly decreased risk of heart failure at 90 days after admission to hospital for myocarditis (relative risk 0.56, 95% confidence interval 0.37 to 0.85, P=0.006) compared with those with conventional myocarditis (table 2). Conversely, we found a non-significant increased risk of heart failure at 90 days in patients with myocarditis associated with covid-19 disease (1.48, 0.86 to 2.54) compared with conventional myocarditis. Death was rare during the 90 days of follow-up, with six (1.1%), six (5.5%), and 156 (2.3%) patients dying of any cause within 90 days of admission to hospital in the vaccination, covid-19, and conventional myocarditis groups, respectively. The relative risk of death over 90 days of follow-up was 0.48 (0.21 to 1.09) for patients with myocarditis associated with vaccination and 2.35 (1.06 to 5.19) for patients with myocarditis associated with covid-19 disease, compared with conventional myocarditis (table 2).

For estimates of the risk of heart failure in individual countries, we found similar patterns for myocarditis associated with vaccination and conventional myocarditis across the Nordics countries (online supplemental figure S1); limited statistical power did not allow calculation of risk estimates for myocarditis associated with covid-19 disease. We found no indication of differences between the Nordic countries for the risk of death for patients with vaccination type myocarditis within 90 days of follow-up, although statistical power was limited because of few deaths (online supplemental figure S2). In combined meta-analyses, we found that estimates of risk for both heart failure and death were lower for patients with myocarditis associated with vaccination compared with conventional myocarditis for all time points during follow-up (figure 1).

Table 1 | Characteristics of 7292 individuals with new onset myocarditis (myocarditis associated with SARS-CoV-2 mRNA vaccination, myocarditis associated with covid-19 disease, and conventional myocarditis), in Denmark, Finland, Norway, and Sweden, 2018-22 (Nordic myocarditis cohort)

	Type of myocarditis		
Characteristics	Vaccination	Covid-19	Conventional
Total No of patients	530 (100.0)	109 (100.0)	6653 (100.0)
No of patients by country:			
Denmark	98 (18.5)	8 (7.3)	695 (10.4)
Finland	140 (26.4)	25 (22.9)	2059 (30.9)
Norway	109 (20.6)	18 (16.5)	1161 (17.5)
Sweden	183 (34.5)	58 (53.2)	2738 (41.2)
Time period:			
2018-19	0	0	3820 (57.4)
2020-22	530 (100.0)	109 (100)	2833 (42.6)
Age group (years):			
12-24	202 (38.1)	19 (17.4)	1620 (24.3)
25-39	138 (26.0)	29 (26.6)	1707 (25.7)
≥40	190 (35.8)	61 (56.0)	3326 (50.0)
Sex:			
Women	117 (22.1)	33 (30.3)	1838 (27.6)
Men	413 (77.9)	76 (69.7)	4815 (72.4)
Length of initial admission to hospital (days):			
≤3	154 (29.1)	21 (19.3)	2069 (31.1)
4-6	291 (54.9)	34 (31.2)	2691 (40.4)
≥7	85 (16.0)	54 (49.5)	1893 (28.5)
Predisposing comorbidity:			
Any*	71 (13.4)	12 (11.0)	1100 (16.5)
None	459 (86.6)	97 (89.0)	5553 (83.5)

Values are numbers (percentages).
*Diagnosis of malignancy, cardiovascular disease, or autoimmune disease before admission to hospital for new onset myocarditis.

Absolute and relative risk of readmission

At 90 days of follow-up from discharge for new onset myocarditis, 62 (11.7%), nine (8.3%), and 988 (14.9%) patients were readmitted to hospital in the vaccination type, covid-19 type, and conventional myocarditis groups, respectively. The relative risk of readmission between types of myocarditis within 90 days of discharge from hospital, with conventional myocarditis as the reference, was 0.79 (95% confidence interval 0.62 to 1.00) for patients with myocarditis associated with vaccination and 0.55 (0.30 to 1.04) for patients with myocarditis associated with covid-19 disease (table 3). Online supplemental figure S3 presents the risk of readmission in the vaccination and conventional myocarditis groups in 10 day periods for each country. In a combined Nordic analysis, we found that the estimated risk of readmission to hospital was numerically lower for patients with myocarditis associated with vaccination compared with those with conventional myocarditis at all periods during follow-up (online supplemental figure S4).

Subgroup analyses

In subgroup analyses, we found similar patterns to the main analyses in younger patients, older patients, and in men and women, with a lower risk of the combined outcome of heart failure and death by 90 days of follow-up for patients with

Table 2 | Relative risk of incident heart failure or death within 90 days of follow-up from admission to hospital for new onset myocarditis in individuals with myocarditis associated with SARS-CoV-2 mRNA vaccination, myocarditis associated with covid-19 disease, and conventional myocarditis (Nordic myocarditis cohort)

Type of myocarditis	Diagnosis of heart failure (No of patients)	Death from any cause (No of patients)	Total No of patients	Relative risk (95% CI) of heart failure	Relative risk (95% CI) of death
Vaccination	22	6	530	0.56 (0.37 to 0.85)	0.48 (0.21 to 1.09)
Covid-19	12	6	109	1.48 (0.86 to 2.54)	2.35 (1.06 to 5.19)
Conventional	496	156	6653	1 (reference)	1 (reference)

CI=confidence interval.

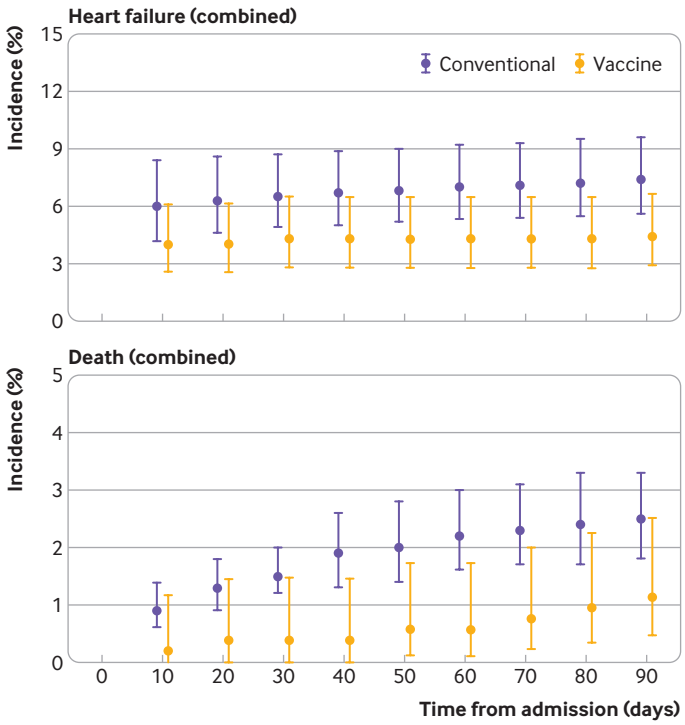

Figure 1 | Cumulative incidences of heart failure and death, combined from all countries, during follow-up (at multiples of 10 days) in the Nordic myocarditis cohort, for patients with myocarditis associated with SARS-CoV-2 mRNA vaccination and patients with conventional myocarditis

myocarditis associated with vaccination compared with those with conventional myocarditis or myocarditis associated with covid-19 disease (online supplemental table S4). Among men and when the analysis was restricted to patients admitted on or after 1 January 2020, we found a significantly lower risk of heart failure or death for patients with myocarditis associated with SARS-CoV-2 mRNA vaccination compared with the two other types of myocarditis (P=0.005 and P=0.002, compared with convential myocarditis, respectively, and both P<0.001 compared with covid-19 type myocarditis, respectively; online supplemental table S5). We found no significant differences in the risk of readmission in younger patients and in women for the three myocarditis groups (online supplemental table S6), but a significantly reduced risk of readmission was found for men and those admitted on or after 1 January 2020 in the vaccination type myocarditis group compared with the conventional myocarditis group (P=0.03 and P=0.03, respectively). We also found a significantly reduced risk of readmission among older patients in the covid-19 type myocarditis group compared with the conventional myocarditis group (P=0.02, online supplemental table S6). Sensitivity analyses of patients with conventional myocarditis admitted to hospital before 1 January 2020 (ie, before the pandemic) as reference were comparable with the results of the main analyses (online supplemental table S7).

Finally, we performed an analysis restricted to patients aged 12-39 years with no pre-existing registered diagnoses of malignancy, heart disease, or autoimmune disease (table 4). We found that myocarditis after SARS-CoV-2 mRNA vaccination was associated with a non-significant reduced relative risk of heart failure or death at 90 days of follow-up compared with conventional myocarditis (relative risk 0.50, 95% confidence interval 0.22 to 1.12). In this subgroup, we also found that myocarditis after covid-19 disease was associated

Table 3 | Relative risk of readmission to hospital for any cause within 90 days of follow-up from discharge for new onset myocarditis in individuals with myocarditis associated with SARS-CoV-2 mRNA vaccination, myocarditis associated with covid-19 disease, and conventional myocarditis (Nordic myocarditis cohort)

Type of myocarditis	Readmission to hospital for any cause (No of patients)	Total No of patients	Relative risk (95% CI) of readmission
Vaccination	62	530	0.79 (0.62 to 1.00)
Covid-19	9	109	0.55 (0.30 to 1.04)
Conventional	988	6638	1 (reference)

CI=confidence interval.

Table 4 | Relative risk of incident heart failure or death, as a combined outcome, within 90 days of follow-up from admission to hospital for new onset myocarditis in individuals aged 12-39 years, with no predisposing comorbidities, and with myocarditis associated with SARS-CoV-2 mRNA vaccination, myocarditis associated with covid-19 disease, or conventional myocarditis

Type of myocarditis	Diagnosis of heart failure or death (No of patients)	Total No of individuals	Relative risk (95% CI) of diagnosis of heart failure or death
Vaccination	6	326	0.50 (0.22 to 1.12)
Covid-19	5	47	2.87 (1.23 to 6.70)
Conventional	114	3077	1 (ref.)

CI=confidence interval.

with an increased risk of heart failure or death within 90 days of admission (relative risk 5.78, 1.84 to 18.20) compared with myocarditis associated with vaccination. We found no differences in the risk of readmission between the types of myocarditis for patients aged <40 years with no diagnoses of malignancy, heart disease, or autoimmune disease (online supplemental table S6).

Discussion

Principal findings

In a population based study of 23 million individuals in Denmark, Finland, Norway, and Sweden, we found that myocarditis after vaccination with SARS-CoV-2 mRNA vaccines was associated with a significantly lower risk of heart failure within 90 days of admission compared with conventional myocarditis and myocarditis after covid-19 disease (P=0.006 and P=0.005, respectively). Also, among younger patients with no potentially predisposing comorbidities for developing myocarditis, we found that myocarditis after covid-19 disease was associated with a substantially higher risk of heart failure or death at 90 days of follow-up compared with myocarditis after vaccination. Taken together, our findings suggested that the outcomes of myocarditis after vaccination were less severe than other types of myocarditis during the first 90 days after the onset of myocarditis.

Strengths and limitations

Our study was based on nationwide health registers in four Nordic countries, covering all patients with myocarditis admitted to hospital aged ≥12 years. Also, the register data on SARS-CoV-2 mRNA vaccination, PCR test results for SARS-CoV-2 infection, admissions to hospital for myocarditis, and outcomes after myocarditis were collected prospectively as part of routine clinical and administrative practices, thereby eliminating potential recall bias.

A limitation of our study was that we did not have information on paraclinical evaluations of the severity of myocarditis (eg, electrocardiography, echocardiography, or cardiac magnetic resonance imaging (MRI)). Our prespecified outcome of a diagnosis of heart failure by a hospital physician, however, has previously been associated with high validity in the non-geriatric population.[14] Also, compared with only radiographic findings, a diagnosis of heart failure is likely to reflect clinically relevant impairment. A second limitation of the study was that patients with myocarditis not related to vaccination or covid-19 disease were combined into one category, with some incidences of myocarditis caused by drug treatment for an underlying condition (eg, myocarditis induced by cancer chemotherapy), which inherently could result in a higher risk of readmission to hospital, heart failure, and death. In our sensitivity analysis restricted to younger individuals without predisposing comorbidities, however, our findings were similar to the main analysis.

A third limitation of the study was the potential for misclassification of the cause of myocarditis for patients with myocarditis associated with vaccination and covid-19 disease. This potential bias is difficult to avoid in large scale studies, however, and most likely is non-differential. Furthermore, in our sensitivity analyses with those admitted to hospital for new onset myocarditis before the pandemic as reference, we found similar findings to our main analyses, suggesting no strong bias from misdiagnosed cases during the pandemic period. A fourth limitation was the slight heterogeneity in the definition of myocarditis, because for patients in Denmark, admission to hospital was defined as ≥24 hours because of a current lack of distinction between inpatents and outpatients in Danish registries. A fifth limitation was no examination of medical prescriptions before diagnosis, which could have indicated the cause of myocarditis for a small subset of patients. Finally, because of current regulations on data privacy, we could not adjust the combined Nordic cohort for individual level covariates, and therefore we conducted subgroups analyses.

Comparison with other studies

Our results are compatible with the findings of smaller cohort studies in individual clinical centres,[15 16] which found that myocarditis associated with SARS-CoV-2 mRNA vaccination was associated mainly with mild clinical outcomes. Nevertheless, six patients with myocarditis after vaccination died within 90 days of admission to

hospital. Establishing causality given the rarity of death is difficult (1.1% of patients with myocarditis associated with vaccination), however, because these deaths could have been from other causes or from conventional myocarditis occurring by chance within 28 days of vaccination. Schauer et al, in their study covering three to eight months after the first admission to hospital for myocarditis associated with vaccination, reported that resolution of cardiac MRI abnormalities were not complete in all patients.[15] Because the clinical significance of these abnormalities is not yet known, continued surveillance of this patient group to detect possible developing cardiomuscular disease is warranted. The overall findings on outcomes of myocarditis associated with vaccination by us and others are reassuring, however, and should be considered when weighing the benefits and potential risks of mRNA vaccines against the SARS-CoV-2 virus at the individual and population levels.

Although our study consistently suggested that the outcomes of myocarditis after vaccination were less severe than for other types of myocarditis, we found only minimal differences in the relative risk of readmission to hospital within 90 days by type of myocarditis. This finding could reflect increased clinical interest in patients with myocarditis associated with vaccination, however, which could have resulted in increased rates of readmission for further clinical evaluation. Also, the higher risk of death among patients with myocarditis after covid-19 disease could potentially bias the risk of readmission downward for this patient group.

Compared with myocarditis associated with vaccination, myocarditis after covid-19 disease had substantially worse clinical outcomes, with a longer stay for the initial admission to hospital and increased risk of heart failure or death among younger individuals with no predisposing comorbidities. The difference in clinical outcomes for the two types of myocarditis could indicate differences in cause rather than a similar exposure to the SARS-CoV-2 spike protein, which is expressed during both mRNA vaccination and SARS-CoV-2 infection. The absolute risk of covid-19 myocarditis in the four Nordic countries was low during the study period,[7] however, despite high testing rates for the SARS-CoV-2 virus and high seroprevalence of SARS-CoV-2 nucleocapsid antibodies.[17]

Our population based study provides new prognostic information on myocarditis associated with vaccination. The low cumulative incidence of heart failure or death by 90 days for patients developing myocarditis after vaccination is reassuring. We previously found that the incidence of myocarditis after a second dose of mRNA vaccine was higher than after a positive test result for SARS-CoV-2 infection among younger patients.[7] In this study, however, our findings strongly suggested that the clinical outcomes were substantially worse for myocarditis associated with covid-19 disease. Among younger patients with no predisposing comorbidities, we found that the risk of heart failure or death within 90 days of new onset myocarditis was about six times higher for patients with myocarditis associated with covid-19 disease than for those with myocarditis after vaccination. Also, comparing the incidence of myocarditis after vaccination versus after covid-19 disease might not be meaningful when determining recommendations for the use of mRNA vaccines against the SARS-CoV-2 virus. Vaccination with mRNA vaccines has many well described beneficial properties, including protection against severe forms of covid-19 disease[18 19] and death.[18 20]

Future studies of patients who developed myocarditis after SARS-CoV-2 mRNA vaccination should aim for an extended follow-up period of at least one year. Also, longitudinal evaluation of changes in paraclinical parameters, such as measurement of systolic and diastolic cardiac dysfunction, scarring on cardiac MRI, assessment of heart arrhythmia, and biological markers will be valuable for determining the natural history of myocarditis after vaccination with mRNA vaccines.

Conclusions

We found that myocarditis after vaccination with SARS-CoV-2 mRNA vaccines was associated with a lower risk of heart failure within 90 days of admission to hospital compared with conventional myocarditis and myocarditis after covid-19 disease. Less severe outcomes of myocarditis after vaccination were found in different subgroups, including younger patients with no predisposing comorbidities, and in both men and women. Our results suggested that the outcome of myocarditis associated with SARS-CoV-2 mRNA vaccination was less severe than for other types of myocarditis.

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Contributors AHu, HLG, PH, OK, RL, and AHu contributed to the concept and design of the study; AHu, HLG, PH, JVH, NP, NG, TH, JD, OK, and RL, contributed to the acquisition and analysis of the data; JVH, NP, NG, TH, and OK performed the statistical analysis; all authors contributed to critical revision of the manuscript for important intellectual content. The guarantor (AHu) accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Ethics approval The cohort study was carried out according to the legal and ethical regulations in each participating country, as previously described in detail.[21] Denmark: the study was conducted with administrative register data. According to Danish law, ethics approval is not required for such research. Finland: the study was a part of vaccine surveillance work, one of the duties of the Finnish Institute for Health and Welfare (THL). For this work, the institute is obliged to use all available data, including register data, to investigate potential harmful effects of the vaccines. Consent to participate was not applicable as this was a register based study. Norway: the study was approved by the Norwegian Regional Committee for Health Research Ethics South East (REK Sør-Øst A, reference 122745), and has conformed to the principles embodied in the Declaration of Helsinki. The emergency preparedness register was established according to the Health Preparedness Act §2-4. Consent to participate was not applicable as this was a register based study. Sweden: the study was approved by the Swedish Ethical Review Authority (2020-06859, 2021-02186) and has conformed to the principles embodied in the Declaration of Helsinki. Consent to participate was not applicable as this was a register based study. exempted this study. For all four participating countries (Denmark, Finland, Norway, and Sweden), consent to participate was not applicable in this register based study.

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Data availability statement Data may be obtained from a third party and are not publicly available. Individual level data underlying the country specific analyses were only available within each Nordic country. The data do not belong to the authors and they are not permitted to share these data, except as presented in this manuscript.

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PROTOCOL V.1.6: Clinical Outcomes after Myocarditis – a Nordic population-based cohort study

Background

Myocarditis is a rare adverse event following vaccination with the two available SARS-CoV-2 mRNA vaccines BNT162b2 and mRNA-1273. The association appears to be strongest in the younger age groups below the age of 40 years and after the second dose. The severity of clinical outcomes after myocarditis is nevertheless wide-ranging, from no sequelae to chronic heart failure or death. It is therefore important to characterize the outcome severity of myocarditis following SARS-CoV-2 mRNA vaccination compared with myocarditis not occurring immediately following vaccination and myocarditis following SARS-CoV-2 infection.

Objectives

To describe the risk of re-admission, heart failure, and death within 90-days of incident myocarditis diagnosis (occurring within 28 days of SARS-CoV-2 mRNA vaccination, occurring within 28 days of RT-PCR positive test for SARS-CoV-2, or unrelated to vaccination and infection).

Methods

Nordic Myocarditis Cohort

We will conduct a multi-country evaluation taking advantage of nationwide register data available in the Nordic countries (Denmark, Finland, Norway, and Sweden). Our study cohort will comprise all individuals aged 12 years or older who were first-time diagnosed with myocarditis as a main or secondary diagnosis (ICD-10 codes, I40.0, I40.1, I40.8, I40.9, I41.1, I41.8, or I51.4) at discharge from inpatient hospital care from January 1, 2018 to latest possible date of follow-up. Patients with any (in-patient or out-patient, main or secondary) pre-existing diagnosis of myocarditis (defined as above) or heart failure (defined as ICD-10 codes I11.0, I13.0, I13.2, I42.0, I42.7, I43.0, I50, I50.0, I50.1, I50.2, I50.3, I50.4, I50.8, I50.9,) will be excluded from the study (3 years of wash-out prior to the day of first-time myocarditis admission[1]). To avoid potential duplicate case during 2018-2022, all individuals with matching person-specific variables will be removed from the cohort if appearing again after a first-time myocarditis diagnosis. All cases admitted for a myocarditis hospitalization within 28 days of vaccination with a SARS-CoV-2 mRNA vaccination are categorized as '*SARS-CoV-2 mRNA vaccine-associated myocarditis*', while all cases admitted for a myocarditis hospitalization within 28 days of a positive SARS-CoV-2 PCR test are categorized as '*SARS-CoV-2 infection-associated myocarditis*'. If both SARS-CoV-2 mRNA vaccinated and PCR test positive within 28 days, the latest exposure counts. Remaining cases will be categorized as '*regular myocarditis*'.

Only cases that were discharged (dead or alive) prior to 90 days before the end of the country-specific follow-up, and therefore having potential 90 days of follow-up, will be included in the study.

Outcomes

[1] For Norway, washout was only possible from January 1, 2017 onwards.

Outcomes following first-time myocarditis admission will be; a) a first-time diagnosis of heart failure (in-patient or out-patient, primary or secondary diagnosis during 90 days following *admission* for a first-time diagnosis of myocarditis, b) death during 90 days following *admission* for a first-time diagnosis of myocarditis, in addition to c) re-admission (in-patient hospitalization of any cause), during 90 days following *discharge* for a first-time diagnosis of myocarditis.

If a first-time heart failure diagnosis is diagnosed during the same hospitalization as a first-time myocarditis diagnosis, heart failure will be categorized as occurring at day 0, the day of the myocarditis in-patient admission.

Length-of-stay for a first-time myocarditis hospitalization will be estimated as 'day-of-discharge' minus 'day-of-admission' + 1. If a patient with first-time myocarditis has a subsequent in-patient hospitalization within on the day of discharge or the day after, then this hospitalization will be counted as a part of the initial first-time myocarditis hospitalization.

Cohort stratification

For comorbidity stratification will use a 'comorbidity' boolean variable which is '1' if the case has any pre-existing diagnoses (defined as 2 years prior to first-time myocarditis admission) of malignancy (ICD-10: C00-C97), cardiovascular disease (ICD-10: I00-I99), or autoimmune disease (ICD-10: K50.x, K51.x, M32.x, M05.x-M06.x, E05.0, E06.3, G35.x, L40.x, E27.1, E27.2, G12.2, M45.x, M08.1, K90.0, M33.x, L52.x, G61.0, D59.0-D59.1, D69.0, D69.3, M08.x, L93.x, G70.0, D51.0, L12.x, M31.3, M30.0, K74.3, I00.x-01.x, D86.x, M34.x, M31.5-M31.6, L80.x, M35.x), (in-patient or out-patient, main or secondary diagnoses), and otherwise '0'.

For length-of-stay stratification we will stratify length-of-stay in groups of ≤3 days, 4-6 days, and ≥ 7 days.

In addition, a stratification boolean variable will specify whether the admission of first-time myocarditis was on or after January 1, 2020 ('1') or prior this date ('0').

Statistical analysis

Outcomes by myocarditis group, given by time since myocarditis diagnosis will be compared by country-specific Kaplan-Meier plots and combined tables of 90-day relative risk and 90-day risk difference between myocarditis groups.

Country-specific cumulative incidences will be calculated for readmission (as a function of days from discharge) and heart failure and death (as a function of days from admission) as one minus the Kaplan-Meier estimate. Emigration will be a censoring event and death a censoring event for readmission and heart failure. If a first-time heart failure is diagnosed during the same hospitalization as the first-time myocarditis, the heart failure will be coded as occurring on day 1, the day after the myocarditis admission. Cumulative incidences at 10, 20, … and 90 days follow-up will be presented in figures.

In the combined aggregate tables there will not be censoring for emigration or death. Sensitivity analyses of combined numbers will be performed by age group (categorized as 12-39 years, and 40 years or older) and among women. As additional sensitivity analyses, we will restrict the cohort to individuals younger than 40 years without pre-existing diagnoses of malignancy, cardiovascular disease, or autoimmune disease.

Results

We will present a Table 1 with country-specific descriptive data on the age and sex distribution of myocarditis cases by myocarditis group, age group, and sex (cell counts between 1 and 5 will be described as '*'). In addition, we will present length-of-stay during the initial myocarditis admission, by myocarditis group. Tables 2-4 will present combined cumulative 90-day relative risk and combined cumulative 90-day risk difference between myocarditis groups of respectively heart failure, death, and readmission, with regular myocarditis as reference.

Figure 1A-D and 2A-D will present country-specific Kaplan-Meier estimates of heart failure and death, respectively, during 90-days of follow-up following diagnosis by myocarditis type, with day-of-admission as day 0 (with 10-day resolution, as described above). Figure 3A-D will present country-specific Kaplan-Meier estimates of re-admission (in-hospital of any cause), with day-of-discharge as day 0 (with 10-day resolution).

SUPPLEMENTARY MATERIALS

Clinical Outcomes Following SARS-CoV-2 mRNA Vaccine Myocarditis

Contents

Table S1. Country-specific wash-out and follow-up periods.

Country	Wash-out period	Follow-up period
Denmark	Three years prior to the date of admission (with Jan 1, 2015 as earliest date of potential wash-out)	Jan 1, 2018 – Apr 30, 2022
Finland	Three years prior to the date of admission (with Jan 1, 2015 as earliest date of potential wash-out)	Jan 1, 2018 – March 13, 2022
Norway	One year prior to the date of admission (with January 1, 2017, as the earliest date of potential wash-out)	Jan 1, 2018 -– April 27, 2022
Sweden	Three years prior to the date of admission (with Jan 1, 2015 as earliest date of potential wash-out)	Jan 1, 2018 – Jan 31, 2022

Table S2. ICD-10 codes used for defining heart failure and comorbidity.

Disease category	ICD-10 codes
Heart failure	I11.0, I13.0, I13.2, I42.0, I42.7, I43.0, I50, I50.0, I50.1, I50.2, I50.3, I50.4, I50.8, I50.9
Autoimmune disease	K50.x, K51.x, M32.x, M05.x-M06.x, E05.0, E06.3, G35.x, L40.x, E27.1, E27.2, G12.2, M45.x, M08.1, K90.0, M33.x, L52.x, G61.0, D59.0-D59.1, D69.0, D69.3, M08.x, L93.x, G70.0, D51.0, L12.x, M31.3, M30.0, K74.3, I00.x-01.x, D86.x, M34.x, M31.5-M31.6, L80.x, M35.x
Cardiovascular disease	I00-I99
Malignancy	C00-C97

Table S3. National registries used for obtaining clinical information, information on vaccinations, and information on tests for infectious diseases*.

Country	Clinical information registries	Vaccination information registries	Infectious disease registries
Denmark	The Danish National Patient Register[1]	The Danish Vaccination Register[2]	The Danish Microbiology Database[3]
Finland	National Care Register for Health Care[4]	The National Vaccination Register[5]	National Infectious Diseases Register[6]
Norway	The Norwegian Patient Registry[7]	The Norwegian Immunisation Register[8]	Norwegian Surveillance System for Communicable Diseases
Sweden	The Swedish Patient Register[9]	The National Vaccination Register in Sweden[10]	Register on Surveillance of Notifiable Communicable Diseases[11]

* Information on linkage between individual national registries has been described previously[12]. Furthermore, the cohort study was carried out according to legal and ethical regulations within each participating country, as previously described in detail[13].

Table S4. Country-specific medians and interquartile ranges (IQR) of age by myocarditis type, age group, and country.

	All myocarditis cases (median, IQR)			Cases aged 12-39 years (median, IQR)		
Country	Vaccine	COVID-19	Conventional	Vaccine	COVID-19	Conventional
Denmark	31 (20-48)	51 (41-61)	37 (24-58)	23 (19-30)	-*	24 (19-30)
Finland	30 (18-48)	30 (17-46)	40 (26-57)	22 (17-30)	18 (17-28)	25 (20-32)
Norway	33 (23-57)	52 (36-66)	44 (27-60)	24 (20-29)	23 (19-36)	26 (21-32)
Sweden	28 (20-51)	45 (30-59)	37 (24-58)	21 (18-27)	29 (25-33)	24 (20-30)

*Five or fewer cases.

Table S5. Relative risk of incident heart failure or death, as a combined outcome, within 90 days of follow-up since admission for new-onset myocarditis, by subgroup.

Myocarditis type by subgroup	Heart failure diagnosis or death within 90 days of admission	Total number of individuals	Relative risk of heart failure diagnosis or death within 90 days since admission
12–39 year olds			
Vaccine myocarditis	8	340	0.61 (0.30–1.24)
COVID-19 myocarditis	5	48	2.71 (1.16–6.31)
Conventional myocarditis	128	3,327	1 (ref.)
≥ 40 year olds			
Vaccine myocarditis	19	190	0.68 (0.44–1.05)
COVID-19 myocarditis	13	61	1.45 (0.89–2.37)
Conventional myocarditis	488	3,326	1 (ref.)
Men			
Vaccine myocarditis	16	413	0.49 (0.30–0.81)
COVID-19 myocarditis	12	76	2.01 (1.19–3.41)
Conventional myocarditis	378	4,815	1 (ref.)
Women			
Vaccine myocarditis	11	117	0.73 (0.41–1.29)
COVID-19 myocarditis	6	33	1.40 (0.67–2.92)
Conventional myocarditis	238	1,838	1 (ref.)
Admitted on January 1, 2020 or later			
Vaccine myocarditis	27	530	0.54 (0.37–0.80)
COVID-19 myocarditis	18	109	1.77 (1.14–2.73)
Conventional myocarditis	265	2,833	1 (ref.)

Table S6. Relative risk of readmission within 90 days of follow-up since discharge for new-onset myocarditis, by subgroup.

Myocarditis type by subgroup	Readmission within 90 days of discharge	Total number of individuals	Relative risk of Readmission within 90 days since discharge
12–39 year olds			
Vaccine myocarditis	26	340	0.77 (0.52–1.12)
COVID-19 myocarditis	5	48	1.04 (0.45–2.41)
Conventional myocarditis	332	3,326	1 (ref.)
≥ 40 year olds			
Vaccine myocarditis	36	190	0.96 (0.71–1.29)
COVID-19 myocarditis	4	61	0.33 (0.13–0.86)
Conventional myocarditis	656	3,312	1 (ref.)
Men			
Vaccine myocarditis	39	413	0.72 (0.53–0.98)
COVID-19 myocarditis	5	76	0.50 (0.21–1.17)
Conventional myocarditis	633	4,807	1 (ref.)
Women			
Vaccine myocarditis	23	117	1.01 (0.69–1.48)
COVID-19 myocarditis	4	33	0.63 (0.25–1.57)
Conventional myocarditis	355	1,831	1 (ref.)
Admitted on January 1, 2020 or later			
Vaccine myocarditis	62	530	0.76 (0.59–0.98)
COVID-19 myocarditis	9	109	0.49 (0.29–1.01)
Conventional myocarditis	434	2,823	1 (ref.)
12–39 year olds without predisposing comorbidity			
Vaccine myocarditis	24	326	0.82 (0.55–1.22)
COVID-19 myocarditis	5	47	1.18 (0.51–2.73)
Conventional myocarditis	277	3,076	1 (ref.)

Table S7. Relative risk of readmission within 90 days of follow-up since discharge for new-onset myocarditis and relative risk of heart failure or death within 90 days of follow-up since admission for new-onset myocarditis, by myocarditis subgroup using only pre-pandemic cases as reference.

Myocarditis type	Readmission within 90 days of discharge	Total number of individuals	Relative risk of readmission within 90 days since discharge
Vaccine myocarditis	62	530	0.81 (0.63–1.03)
COVID-19 myocarditis	9	109	1.04 (0.30–1.07)
Conventional myocarditis (pre-2020 only)	554	3,815	1 (ref.)
Myocarditis type	Heart failure diagnosis or death within 90 days of admission	Total number of individuals	Relative risk of heart failure diagnosis or death within 90 days since admission
Vaccine myocarditis	27	530	0.55 (0.38–0.81)
COVID-19 myocarditis	18	109	1.80 (1.16–2.77)
Conventional myocarditis (pre-2020 only)	351	3,820	1 (ref.)

Figure S1. Country-specific cumulative incidences of heart failure during follow-up.

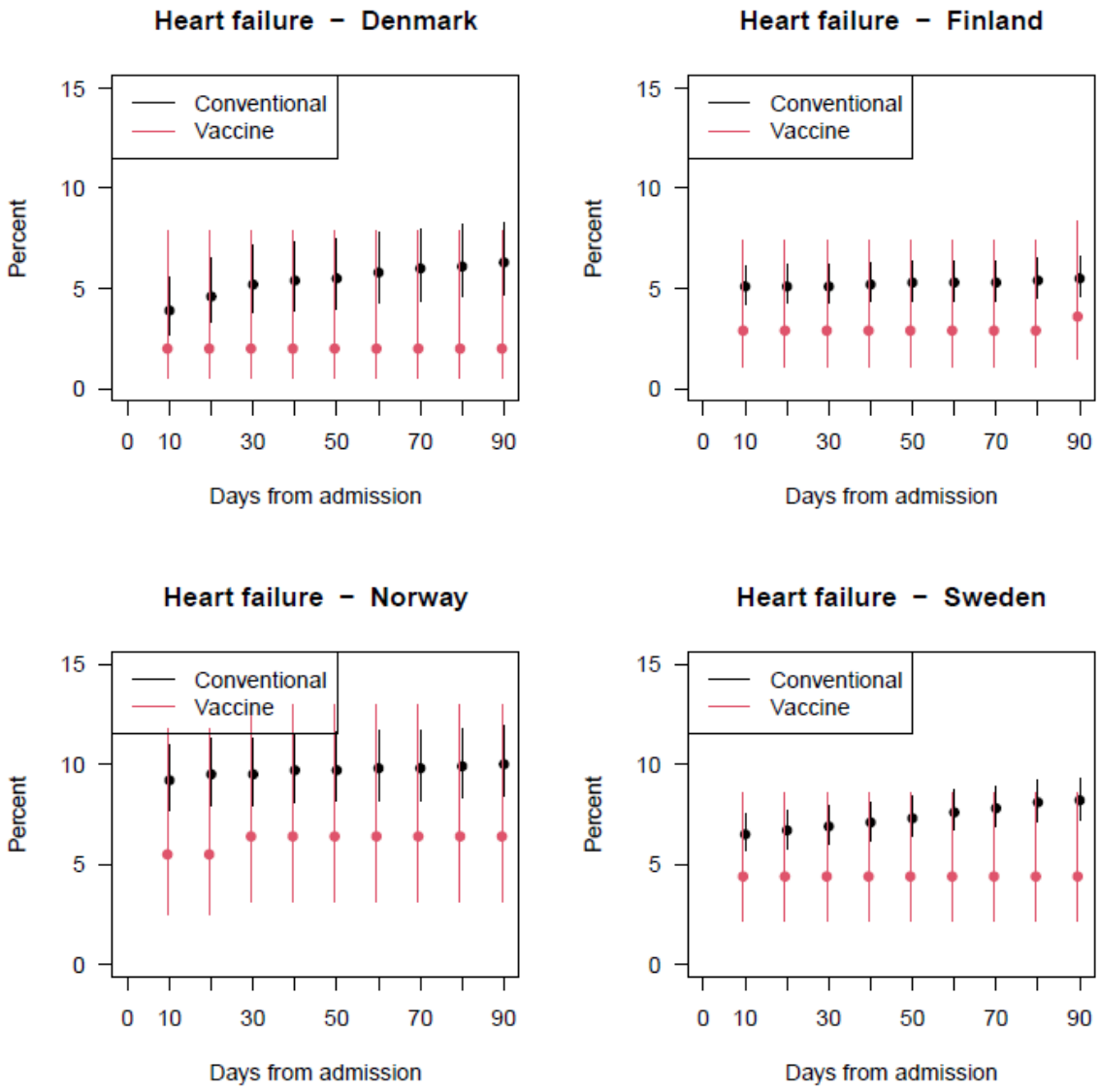


Figure S2. Country-specific cumulative incidences of death during follow-up.

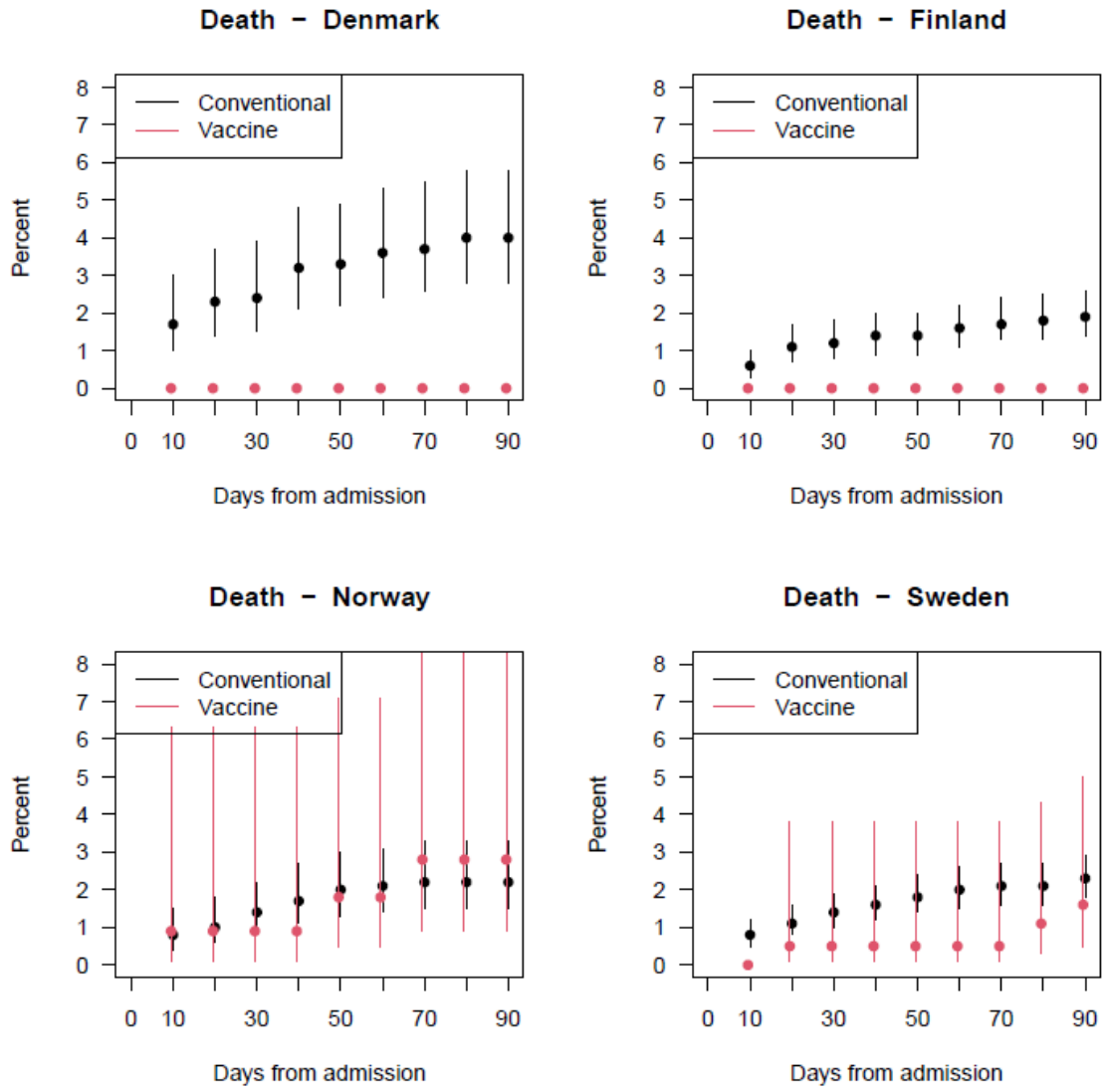


Figure S3. Country-specific cumulative incidences of readmission during follow-up.

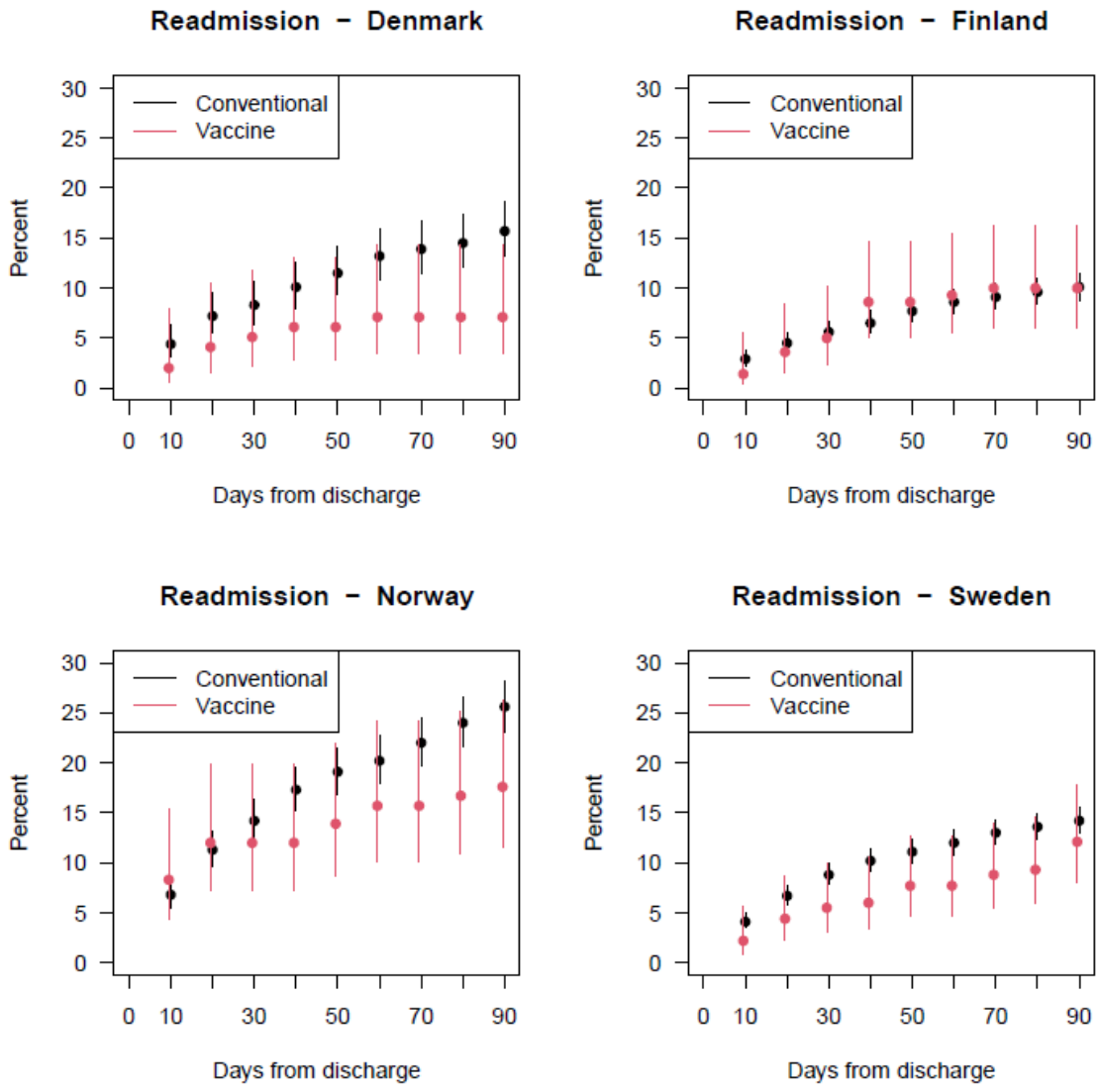
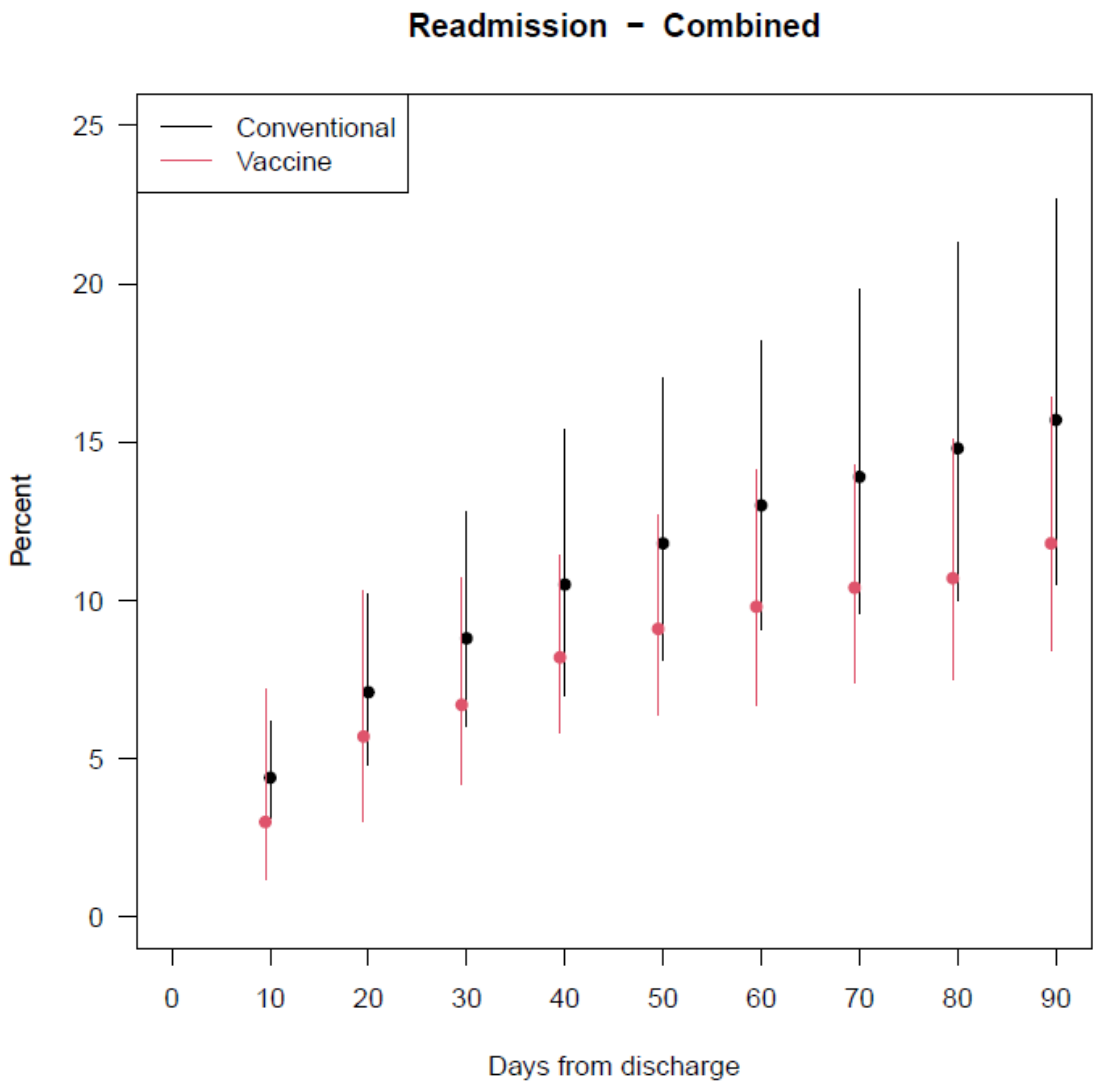


Figure S4. Cumulative incidence of readmission, combined from all countries, during follow-up.



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