Autoimmune conditions following mRNA (BNT162b2) and inactivated (CoronaVac) COVID-19 vaccination: A descriptive cohort study among 1.1 million vaccinated people in Hong Kong

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A R T I C L E I N F O

A B S T R A C T

Background: Concerns regarding the autoimmune safety of COVID-19 vaccines may negatively impact vaccine uptake. We aimed to describe the incidence of autoimmune conditions following BNT162b2 and CoronaVac vaccination and compare these with age-standardized incidence rates in non-vaccinated individuals.
Methods: This is a descriptive cohort study conducted in public healthcare service settings. Territory-wide longitudinal electronic medical records of Hong Kong Hospital Authority users (≥16 years) were linked with COVID-19 vaccination records between February 23, 2021 and June 30, 2021. We classified participants into first/second dose BNT162b2 groups, first/second dose CoronaVac groups and non-vaccinated individuals for incidence comparison. The study outcomes include hospitalized autoimmune diseases (16 types of immune-mediated diseases across six body systems) within 28 days after first and second dose of vaccination. Age-standardized incidence rate ratios (IRRs) with exact 95% confidence intervals (CIs) were estimated using Poisson distribution.
Results: This study included around 3.9 million Hong Kong residents, of which 1,122,793 received at least one dose of vaccine (BNT162b2: 579,998; CoronaVac: 542,795), and 721,588 completed two doses (BNT162b2: 388,881; CoronaVac: 332,707). Within 28 days following vaccination, cumulative incidences for all autoimmune conditions were below 9 per 100,000 persons, for both vaccines and both doses. None of the age-standardized incidence rates were significantly higher than the non-vaccinated individuals, except for an observed increased incidence of hypersomnia following the first dose of BNT162b2 (standardized IRR: 1.47; 95% CI: 1.10–1.94).
Conclusions: Autoimmune conditions requiring hospital care are rare following mRNA and inactivated COVID-19 vaccination with similar incidence to non-vaccinated individuals. The association between first dose BNT162b2 vaccination and immune-related sleeping disorders requires further research. Population-based robust safety surveillance is essential to detect rare and unexpected vaccine safety events.

1. Introduction

There has been a long-standing debate about vaccination and its potential to trigger autoimmune diseases (AID). For example, the influenza vaccine and Guillain-Barré syndrome [1], the Measles-Mumps-Rubella vaccine and thrombocytopenic purpura [2]. Although causality is not fully established, the fear of new onset or recurrence of AID may contribute to vaccine hesitancy and negatively impact vaccine uptake [3]. Currently, several vaccines using different technology platforms (mRNA, inactivated virus, protein subunit and viral vector) have been developed and authorized for emergency use against COVID-19 worldwide [4]. The characteristics of these vaccine platforms could result in different levels of neutralizing antibodies, T-cell response, and avoidance/occurrence of immune-mediated diseases.

Autoimmune safety events reported in Phase II/III trials, such as Bell's Palsy in mRNA vaccine (Moderna) [5] and transverse myelitis in viral vector vaccine (AstraZeneca (ChAdOx1)) [6], were uncommon and have been labeled in the prescribing information. However, since the launch of global vaccination against COVID-19, several case reports and analyses have described autoimmune conditions following vaccination. In a prospective cohort analysis, Simpson et al. implied an association between viral vector vaccine (AstraZeneca (ChAdOx1)) and the development of immune thrombocytopenia [7]. Wan et al. suggested the safety signal of Bell's palsy with inactivated vaccine (CoronaVac) in a nested case-control and case series study [8]. Case reports or case series of Guillain-Barré syndrome [9–12], cutaneous vasculitis [13], reactive arthritis [14] and immune-medicated disease flare [14] from both mRNA and inactivated virus platforms are continuously emerging, and the list is not exclusive. Given the ongoing COVID-19 pandemic and the likelihood of routine vaccination for infection control, it is of timely importance to assess the autoimmune safety of COVID-19 vaccines in real-world settings.

Hong Kong (HK) is among the few jurisdictions in the world that have approved the emergency use of COVID-19 vaccines from two different technology platforms: inactivated virus vaccine, CoronaVac, from Sinovac Biotech (HK) Limited and mRNA vaccine, BNT162b2, from Fosun-BioNTech (equivalent to Pfizer-BioNTech). The rollout of the public-funded mass vaccination program began with CoronaVac on February 23, 2021 and was closely followed by BNT162b2 on March 12, 2021. By June 30, 2021, more than 3.73 million doses of COVID-19 vaccine had been administered alongside the implementation of population-based surveillance program for safety monitoring. In this study, we analyzed the territory-wide electronic medical records (EMRs) database and summarized the incidence of AID across the predefined disease spectrum among CoronaVac and BNT162b2 recipients in HK. We assessed the population-level risk of AID following mRNA and inactivated virus COVID-19 vaccination to inform vaccination decisions.

2. Methods

2.1. Data sources

We obtained population-based EMRs from the Hospital Authority (HA) and vaccination records from the Department of Health (DH) of HK Government to conduct this study. The HA manages all public hospitals and clinics in HK and provides publicly funded health services to all eligible HK residents (>7 million). The EMRs database managed by HA is centralized from the territory-wide clinical management system of 42 public hospitals with high population coverage, representativeness, and coding accuracy [15–18]. DH, the government health adviser and agency that executes health-related policies and statutory functions, manages COVID-19 vaccination records of all HK residents. EMRs from the HA were linked with the DH vaccination records using de-identified non-reversible pseudo-ID to protect patient privacy. The database has been used for several COVID-19 vaccine safety assessment in HK [8,

19–29].

2.2. Study design and population

This was a population-based descriptive cohort study. The study population consisted of all Hong Kong residents ≥16 years who had ever used the HA service (emergency admission, general or specialist outpatient clinic visit, or hospital admission) between January 1, 2018 and June 30, 2021. DH vaccination records between February 23 and June 30, 2021 were linked to the HA database to confirm vaccination status. Following the vaccination record linkage, we generated pseudo index dates for the non-vaccinated individuals to facilitate cohort follow-up. Within each age and sex group, we matched each vaccine recipient with non-vaccinated individuals at maximum ratio (the number of vaccine recipients divided by the number of non-vaccinated individuals in each age-sex strata) and assigned the vaccination date as the pseudo index date for the non-vaccinated individuals. We treated first dose and second dose as independent episodes and conducted the non-vaccinated group matching separately.

We followed up these individuals from the index date (date of first dose vaccination, date of second dose vaccination, or age-sex matched pseudo index date for non-vaccinated individuals) to the date of event of interest, date of registered death, 28 days after index date, or the end date of data availability (June 30, 2021), whichever was earlier. To differentiate whether the event was completely related to the first dose, in the first dose analysis, we also censored the follow-up one day before the second dose, if any. The record linkage, matching procedure and cohort follow-up is illustrated in Supplementary Fig. 1.

2.3. Outcome measures

We assessed the incidence of hospital admission related to a spectrum of 16 pre-specified AID, grouped by body systems including: 1) immune-mediated cardiovascular diseases (Kawasaki disease, single organ cutaneous vasculitis); 2) organ specific immune-mediated endocrine disorder (subacute thyroiditis); 3) immune-mediated hematological diseases (anti-phospholipid antibody syndrome, idiopathic thrombocytopenia); 4) immune-mediated multisystem diseases (Sjogren syndrome, systemic lupus erythematosus); 5) immune-mediated musculoskeletal diseases (acute aseptic arthritis, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, spondyloarthritis); and 6) immune-mediated neurological disorders (acute disseminated encephalomyelitis, Guillain-Barré syndrome, narcolepsy and related disorders, and transverse myelitis). We used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for outcomes identification (Supplementary Table 1). The selection of autoimmune conditions was based on 1) the list of adverse events of special interests (AESI) according to the World Health Organization's Global Advisory Committee on Vaccine Safety (GACVS) [30]; 2) Brighton Collaboration Safety Platform for Emergency vACcines (SPEAC) [31]; 3) consultation with a local immunologist about the other immune-related AESI that might be of concern. All these diseases were pre-defined before analysis without the influence of the availability of ICD-9-CM diagnostic codes. We defined each individual outcome as an incident case if this was the patient's first relevant diagnosis (primary diagnosis) in the inpatient setting during the 28 days of follow-up. Patients with a diagnosis history within 365 days before the index date were excluded from the study cohort. The same procedure was conducted for first dose, second dose and non-vaccinated groups.

2.4. Main analysis

We reported two age-standardized health situation measurements as the main outcome of this study. First, we described the 28-day cumulative incidence (per 100,000 persons) of each condition, using 5-year age band weightings (16–19, 20–24, 25–29, 30–34, 35–39, 40–44,

Table 1
Baseline characteristics and pre-existing comorbidities of study cohorts.

	First dose				Second dose			
	None	BNT162b2	CoronaVac	SMD	None	BNT162b2	CoronaVac	SMD
N	2816133	579998	542795	–	1892783	388881	332707	–
Male (%)	1183236 (42.0)	275965 (47.6)	266681 (49.1)	0.095	831868 (43.9)	190562 (49.0)	175487 (52.7)	0.118
Age (mean (SD))	55.67 (19.17)	46.72 (15.06)	54.01 (13.85)	0.374	56.81 (19.27)	47.49 (14.88)	54.67 (13.97)	0.389
Charlson Comorbidity Index (mean (SD))	0.35 (0.91)	0.10 (0.41)	0.15 (0.49)	0.250	0.37 (0.93)	0.10 (0.41)	0.15 (0.49)	0.263
Myocardial infarction (%)	16935 (0.6)	617 (0.1)	891 (0.2)	0.057	12229 (0.6)	418 (0.1)	548 (0.2)	0.060
Congestive Heart Failure (%)	32695 (1.2)	425 (0.1)	912 (0.2)	0.096	24414 (1.3)	302 (0.1)	581 (0.2)	0.102
Peripheral vascular disease (%)	7525 (0.3)	249 (0.0)	362 (0.1)	0.039	5631 (0.3)	175 (0.0)	240 (0.1)	0.042
Cerebrovascular disease (%)	111165 (3.9)	4309 (0.7)	7350 (1.4)	0.145	80569 (4.3)	2964 (0.8)	4611 (1.4)	0.153
Stroke or systemic embolism (%)	37828 (1.3)	1226 (0.2)	2197 (0.4)	0.088	27494 (1.5)	852 (0.2)	1360 (0.4)	0.093
Asthma (%)	27317 (1.0)	3665 (0.6)	3309 (0.6)	0.027	18798 (1.0)	2468 (0.6)	2043 (0.6)	0.028
Chronic obstructive pulmonary disease (%)	58132 (2.1)	4778 (0.8)	5343 (1.0)	0.070	41664 (2.2)	3244 (0.8)	3365 (1.0)	0.075
Dementia (%)	11122 (0.4)	103 (0.0)	149 (0.0)	0.057	8477 (0.4)	69 (0.0)	105 (0.0)	0.061
Diabetes without chronic complication (%)	351241 (12.5)	27787 (4.8)	41633 (7.7)	0.185	245849 (13.0)	18561 (4.8)	25251 (7.6)	0.196
Diabetes with chronic complication (%)	20940 (0.7)	871 (0.2)	1302 (0.2)	0.060	14766 (0.8)	594 (0.2)	795 (0.2)	0.063
Chronic renal failure (%)	38702 (1.4)	1155 (0.2)	2048 (0.4)	0.091	28288 (1.5)	778 (0.2)	1297 (0.4)	0.097
Mild liver disease (%)	4056 (0.1)	231 (0.0)	324 (0.1)	0.023	2846 (0.2)	158 (0.0)	188 (0.1)	0.024
Moderate-severe liver disease (%)	2871 (0.1)	141 (0.0)	188 (0.0)	0.021	1980 (0.1)	95 (0.0)	108 (0.0)	0.021
Rheumatoid arthritis and other inflammatory polyarthropathies (%)	10584 (0.4)	813 (0.1)	873 (0.2)	0.031	7010 (0.4)	479 (0.1)	456 (0.1)	0.033
Malignancy (%)	75657 (2.7)	4682 (0.8)	5220 (1.0)	0.096	52132 (2.8)	3054 (0.8)	3107 (0.9)	0.100
Metastatic solid tumor (%)	14757 (0.5)	348 (0.1)	418 (0.1)	0.058	10256 (0.5)	226 (0.1)	234 (0.1)	0.060

Note: P-values for vaccinated and non-vaccinated groups comparison all <0.001. Abbreviation: SMD, standard mean difference (defined as the average of SMD among unvaccinated, CoronaVac and BNT162b2).

45–49, 50–54, 55–59,60–64, 65–69, 70–74, 75–79, 80–84 and ≥ 85 years) based on the HK 2021 mid-year population census. Second, to account for the follow-up time differences among groups, we reported the age-standardized incidence rate (per 100,000 person-years) using the indirect standardization method. We treated the non-vaccinated group as an internal reference group and calculated the proportion of follow-up time (in person-years) in each age strata (16–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84 and ≥ 85 years) for incidence standardization. For each condition, we used observed number of cases, the follow-up time and proportion of person-years in each age strata to calculate age-specific crude incidence rate and aggregated the age-standardized incidence rate. We further estimated the expected cases in each group and calculated the standardized incidence rate ratios (IRRs) with exact 95% confidence intervals (CIs) using Poisson distribution [32,33].

2.5. Additional analyses

We conducted several additional analyses. First, in order to exclude the possibility that the autoimmune conditions were related to SARS-CoV-2 infection, we removed individuals who had positive SARS-CoV-2 PCR tests prior to June 30, 2021 and replicated the main analysis. Until Omicron variant began to spread in HK, PCR test was the gold standard for official diagnosis of COVID-19 and all suspected cases were required to undergo PCR test to be a confirmed case. Second, considering that some of the autoimmune manifestations, e.g., Guillain-Barré syndrome, may take longer than 28 days to develop, we removed the 28-day follow-up requirement in the second dose analysis and extended the observation period to the end date of data availability. Third, for the estimation of standardized IRRs, we further extended the case definition using both primary and secondary diagnoses at discharge, in consideration of potential different coding practices by clinicians. Fourth, given autoimmune diseases are more prevalent in females, we conducted the sex-stratified analysis to investigate the potential disease incidence differences between males and females. In addition, we conducted an ecological study to complement the main analysis. We assumed that the COVID-19 vaccination program (implemented from March to June

2021) will not impact the natural occurrence of AID at the population level and the incidence would be stable over the years within the study cohort. Hence, we illustrated a four-month (March–June) cumulative incidence trend for each AID between 2018 and 2021. The observed number of incident cases were divided by the total number of HA active patients (≥16 years) in the corresponding year to calculate the cumulative incidence. Age-standardization was also conducted based on the HK 2021 mid-year population census. All analyses were conducted using R 4.0.3 and cross-checked by two authors (LG and XT).

2.6. Ethics

Ethical approval for this study was granted by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 21–149 and UW 21–138); and the Department of Health Ethics Committee (LM 21/2021). Patient identification was anonymized from HA and DH databases and patient consent was not required.

3. Results

We obtained the EMRs of 3,946,550 HA active patients with affirmed vaccination status. After age-sex matching with the non-vaccinated group, 1,122,793 vaccine recipients (BNT162b2: 579,998; CoronaVac: 542,795) were included in the first dose analysis, and 721,588 vaccine recipients (BNT162b2: 388,881; CoronaVac: 332,707) were included in the second dose analysis with follow-up until censoring (Supplementary Fig. 1). 63.0% in the first dose analysis and 71.9% in the second dose analysis had the injection on or before June 3, 2021 with the full 28 days observation from vaccination date to the study end date (June 30, 2021). Compared with non-vaccinated individuals, vaccine recipients were younger, more likely to be males, and less likely to have pre-existing chronic diseases. Detailed baseline characteristics of the study cohorts are summarized in Table 1.
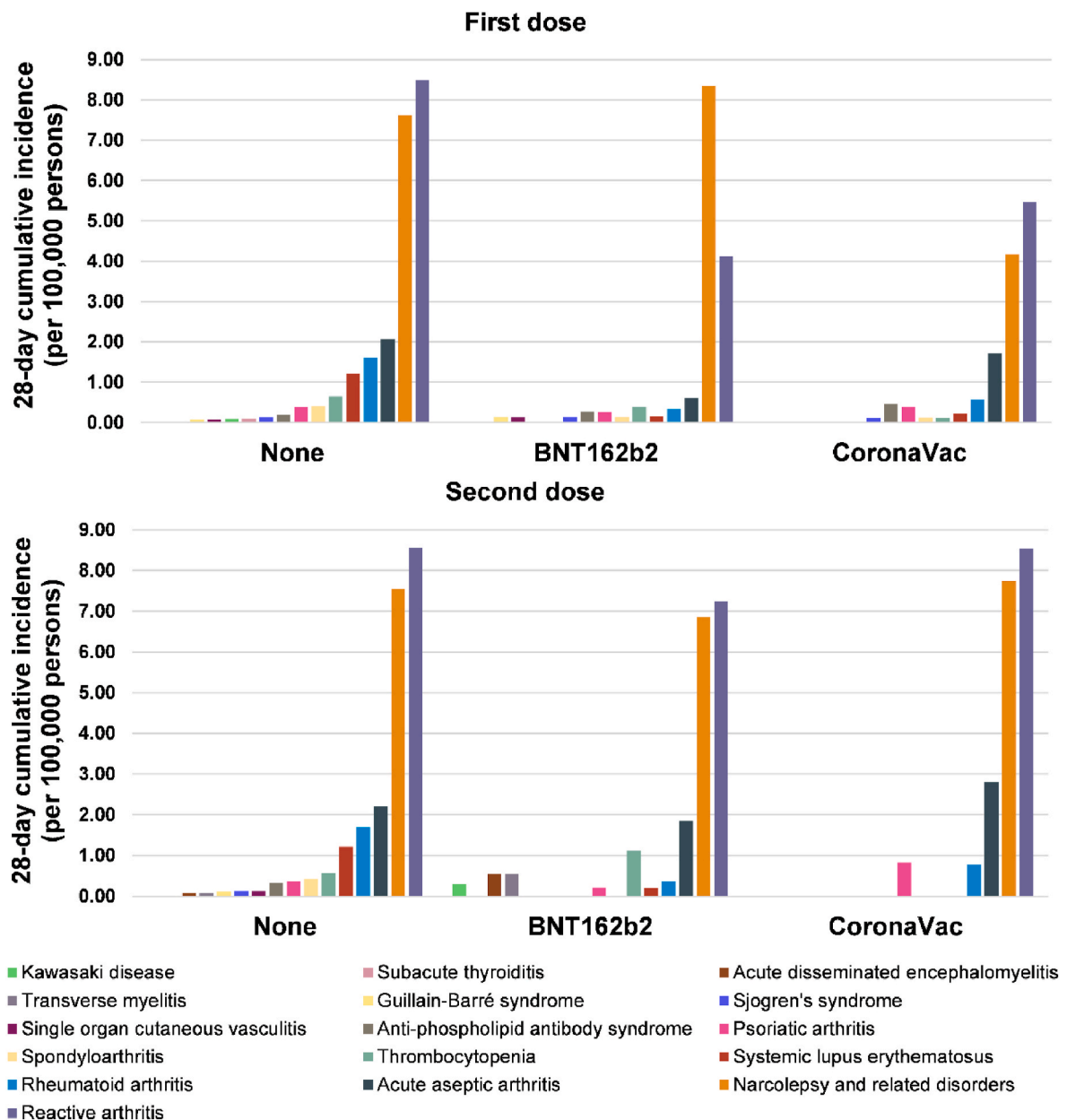
Fig. 1. Cumulative incidence of hospitalized autoimmune diseases among vaccine recipients and non-vaccinated individuals.

3.1. Main analysis

Within 28 days after the index date, autoimmune conditions requiring hospitalization were generally rare (cumulative incidence all below 9 per 100,000 persons) among vaccine recipients and non-vaccinated individuals (Fig. 1). After the first dose, most of the analyzed immune-mediated cardiovascular, endocrine, hematological, nervous, and multisystem diseases had a cumulative incidence lower than 1 per 100,000 persons for both BNT162b2 and CoronaVac recipients, translating to fewer than 10 cases per 1 million of first dose administration (Table 2). Several autoimmune conditions following immunization are extremely rare and zero cases were recorded in our database for acute disseminated encephalomyelitis, Kawasaki disease, subacute thyroiditis, and transverse myelitis for BNT162b2 and CoronaVac and also Guillain-Barré syndrome, single organ cutaneous vasculitis for CoronaVac. The incidence of reactive arthritis and narcolepsy-related disorders were relatively higher compared to other AIDs, with cumulative incidence ranging between 4.12 and 8.35 per

100,000 persons among first dose vaccine recipients (Table 2). Similarly, the majority of the autoimmune conditions following the second dose also had a 28-day cumulative incidence of less than 1 per 100,000 persons (Fig. 1). Reactive arthritis, narcolepsy-related disorders and thrombocytopenia appeared to have a numerically higher incidence than the corresponding incidence reported after the first dose.

When considering age and follow-up time into the measurement of disease occurrence using standardized incidence rate, we did not detect a significantly increased incidence rate of all the interested autoimmune conditions among the vaccine recipients (Fig. 2 first dose analysis; Fig. 3 second dose analysis), except narcolepsy and related disorders among first dose BNT162b2 recipients (standardized incidence: 220.56 versus 136.29 per 100,000 person-years; standardized IRR: 1.47; 95% CI: 1.10–1.94). The age-standardized all-cause mortality was considerably lower in the vaccine groups, suggesting that individuals who received the vaccine might be healthier than the non-vaccinated.

Table 2

28-day cumulative incidence (per 100,000 persons) of autoimmune conditions among vaccine recipients and non-vaccinated individuals.

Body system	Disease	First dose			Second dose		
		None	BNT162b2	CoronaVac	None	BNT162b2	CoronaVac
Cardiovascular system	Kawasaki disease	0.080	0.00	0.00	0.00	0.29	0.00
	Single organ cutaneous vasculitis	0.066	0.13	0.00	0.12	0.00	0.00
Endocrine system	Subacute thyroiditis	0.090	0.00	0.00	0.00	0.00	0.00
Hematological system	Anti-phospholipid antibody syndrome	0.19	0.27	0.46	0.32	0.00	0.00
	Thrombocytopenia	0.64	0.39	0.11	0.57	1.11	0.00
Multisystem	Sjogren's syndrome	0.13	0.14	0.11	0.12	0.00	0.00
	Systemic lupus erythematosus	1.21	0.15	0.22	1.21	0.20	0.00
Musculoskeletal system	Acute aseptic arthritis	2.07	0.61	1.71	2.21	1.85	2.80
	Reactive arthritis	8.49	4.12	5.46	8.56	7.24	8.53
	Rheumatoid arthritis	1.60	0.34	0.57	1.69	0.36	0.77
	Psoriatic arthritis	0.38	0.26	0.39	0.37	0.20	0.82
	Spondyloarthritis	0.40	0.14	0.12	0.42	0.00	0.00
Nervous system	Acute disseminated encephalomyelitis	0.00	0.00	0.00	0.071	0.55	0.00
	Guillain-Barré syndrome	0.062	0.14	0.00	0.10	0.00	0.00
	Narcolepsy and related disorders	7.62	8.35	4.17	7.55	6.86	7.74
	Transverse myelitis	0.00	0.00	0.00	0.07	0.55	0.00
All-cause death	Death	60.47	3.29	4.54	63.18	6.83	3.98

3.2. Additional analyses

In total, we removed 10,185 individuals who had previous SARS-CoV-2 infection before our study end date, and the results were consistent with the main analysis (Supplementary Figs. 2 and 3). After removing the 28-day follow-up time restriction in the second dose analysis, there were more autoimmune conditions with non-significant IRRs greater than one, including Sjogren's syndrome, acute disseminated encephalomyelitis, and transverse myelitis in both BNT162b2 and CoronaVac groups, psoriatic arthritis in CoronaVac group, and narcolepsy and related disorders in the BNT162b2 group (Supplementary Fig. 4). When using both primary and secondary diagnoses for case definition, the standardized IRRs for all disease groups yielded consistent results as the main analysis (Supplementary Figs. 5 and 6). The tendency for increased risk of narcolepsy and related disorder among first dose BNT162b2 recipients remained but became non-significant (standardized incidence: 242.26 versus 197.88 per 100,000 person-years standardized IRR: 1.23; 95% CI: 0.95–1.58). In general, we did not find significant differences between males and females (Supplementary Table 2 and Supplementary Table 3), but the observed tendency of increased incidence of thrombocytopenia after the second dose of BNT162b2 in the main analysis became prominent in females. In the ecological analysis of 3.9 million HA active patients, we observed a relatively stable trend of a four-month cumulative incidence between 2018 and 2021 for all autoimmune conditions analyzed (Supplementary Fig. 7).

4. Discussion

HK is among the ten jurisdictions in the world implementing both mRNA and inactivated virus vaccines for emergency use, which allows us to analyze the autoimmune safety performance of the two technology platforms in one population cohort. In this territory-wide descriptive cohort study following more than 1 million people with BNT162b2 and CoronaVac vaccination in HK, we found that autoimmune conditions that need inpatient management are rare, with a comparable incidence rate with non-vaccinated individuals. Under the circumstance of emerging case reports on autoimmune conditions following COVID-19 vaccination, this study provides population-level perspectives on autoimmune safety, with the potential to enhance vaccine confidence among the public.

Among the autoimmune conditions analyzed in this study, published case reports focused mainly on Guillain-Barré syndrome, immune thrombocytopenia, and cutaneous vasculitis [7,9–13,34]. Because of the low incidence, the observed number of these three conditions are all less

than 5 among our 1.1 million vaccine recipient records. Within 28 days after vaccination, most of the standardized incidence rates were not significantly higher than in non-vaccinated individuals, and we were unable to detect major safety signals for these conditions for both vaccines. In the additional analysis that removed the requirement of 28 days follow-up, we observed more diseases with an IRR greater than one although they did not reach significant levels. This might suggest that some autoimmune manifestations may take longer than 28 days to develop and the risk window for vaccine safety monitoring needs thoughtful adjustment. The natural rarity of autoimmune diseases with or without the vaccination proposes a huge challenge for signal detection and association evaluation. The World Health Organization has called for pharmacovigilance preparedness for COVID-19 vaccines in all countries [35]. Our study highlights that, for rare safety events monitoring, it is particularly imperative to establish a population-based, real-time surveillance system through multiple stakeholder collaboration and capacity building. In addition, in line with the existing literature [23,36], we observed a tendency of increased incidence of thrombocytopenia following the second dose of BNT162b2; and the safety signal prominent in females as shown in the age-stratified analysis. A similar observation was reported in the safety study on ChAdOx1-S (Oxford-AstraZeneca COVID-19 vaccine) [37]. The potential sex-specific effect of vaccine-associated thrombocytopenia warrants further investigation.

Similar to the observations from other COVID-19 vaccine safety studies, individuals who received the vaccines are generally healthier with fewer comorbidities than the general population [37,38]. In HK, the rollout of the COVID-19 vaccination program prioritized healthcare workers, personnel maintaining critical public services and care home residents at the initial stage [39]. Four months after the program commencement, 44% of the eligible HK population had already received the first vaccine dose while the uptake in care home residents was only 5%. This possibly explains the significantly lower incidence of systemic lupus erythematosus, reactive arthritis, and rheumatoid arthritis, and most pronouncedly, all-cause mortality, among vaccine recipients found in this study. In addition, Hong Kong maintained a very low mortality rate due to COVID-19 before the recent circulation and pandemic of Omicron. Up to June 30, 2021 (the study end date), the cumulative number of death due to COVID-19 is only 212 out of 11,937 confirmed cases [40], therefore, we anticipate the attribution of death from COVID-19 on the all-cause mortality is minimal. The current mortality analysis mainly indicated the 'healthy-cohort' effect from the vaccinated group.

Notably, this observation should not be misinterpreted as the vaccine lowers the risk of these diseases or prevents death. Due to the limited
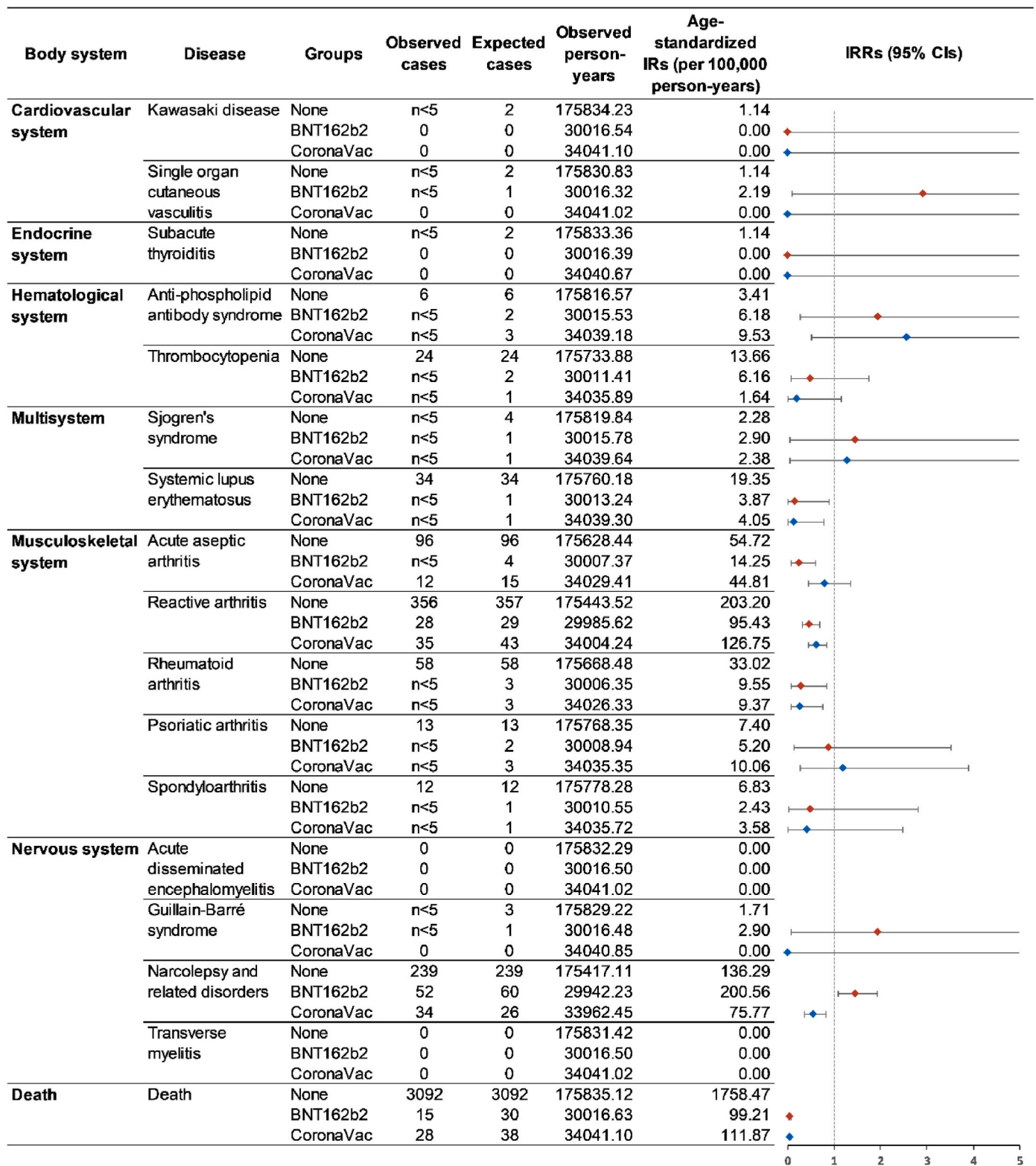
Body system	Disease	Groups	Observed cases	Expected cases	Observed person-years	Age-standardized IRs (per 100,000 person-years)	IRRs (95% CIs)
Cardiovascular system	Kawasaki disease	None	n<5	2	175834.23	1.14	
		BNT162b2	0	0	30016.54	0.00	
		CoronaVac	0	0	34041.10	0.00	
	Single organ cutaneous vasculitis	None	n<5	2	175830.83	1.14	
		BNT162b2	n<5	1	30016.32	2.19	
		CoronaVac	0	0	34041.02	0.00	
Endocrine system	Subacute thyroiditis	None	n<5	2	175833.36	1.14	
		BNT162b2	0	0	30016.39	0.00	
		CoronaVac	0	0	34040.67	0.00	
Hematological system	Anti-phospholipid antibody syndrome	None	6	6	175816.57	3.41	
		BNT162b2	n<5	2	30015.53	6.18	
		CoronaVac	n<5	3	34039.18	9.53	
	Thrombocytopenia	None	24	24	175733.88	13.66	
		BNT162b2	n<5	2	30011.41	6.16	
		CoronaVac	n<5	1	34035.89	1.64	
Multisystem	Sjogren's syndrome	None	n<5	4	175819.84	2.28	
		BNT162b2	n<5	1	30015.78	2.90	
		CoronaVac	n<5	1	34039.64	2.38	
	Systemic lupus erythematosus	None	34	34	175760.18	19.35	
		BNT162b2	n<5	1	30013.24	3.87	
		CoronaVac	n<5	1	34039.30	4.05	
Musculoskeletal system	Acute aseptic arthritis	None	96	96	175628.44	54.72	
		BNT162b2	n<5	4	30007.37	14.25	
		CoronaVac	12	15	34029.41	44.81	
	Reactive arthritis	None	356	357	175443.52	203.20	
		BNT162b2	28	29	29985.62	95.43	
		CoronaVac	35	43	34004.24	126.75	
	Rheumatoid arthritis	None	58	58	175668.48	33.02	
		BNT162b2	n<5	3	30006.35	9.55	
		CoronaVac	n<5	3	34026.33	9.37	
	Psoriatic arthritis	None	13	13	175768.35	7.40	
		BNT162b2	n<5	2	30008.94	5.20	
		CoronaVac	n<5	3	34035.35	10.06	
	Spondyloarthritis	None	12	12	175778.28	6.83	
		BNT162b2	n<5	1	30010.55	2.43	
		CoronaVac	n<5	1	34035.72	3.58	
Nervous system	Acute disseminated encephalomyelitis	None	0	0	175832.29	0.00	
		BNT162b2	0	0	30016.50	0.00	
		CoronaVac	0	0	34041.02	0.00	
	Guillain-Barré syndrome	None	n<5	3	175829.22	1.71	
		BNT162b2	n<5	1	30016.48	2.90	
		CoronaVac	0	0	34040.85	0.00	
	Narcolepsy and related disorders	None	239	239	175417.11	136.29	
		BNT162b2	52	60	29942.23	200.56	
		CoronaVac	34	26	33962.45	75.77	
	Transverse myelitis	None	0	0	175831.42	0.00	
		BNT162b2	0	0	30016.50	0.00	
		CoronaVac	0	0	34041.02	0.00	
Death	Death	None	3092	3092	175835.12	1758.47	
		BNT162b2	15	30	30016.63	99.21	
		CoronaVac	28	38	34041.10	111.87	

Fig. 2. Standardized incidence rates of autoimmune conditions among first dose vaccine recipients and non-vaccinated individuals.

case numbers of each disease in this descriptive cohort study, we considered only age and follow-up time, not other confounding factors, when assessing autoimmune safety following COVID-19 vaccination. It is anticipated that more individuals with well-controlled chronic conditions, including the elderly, will be vaccinated given the government's commitment to achieve optimal vaccine uptake and herd immunity. The number of rare safety outcomes could possibly accumulate, and further

analytical epidemiological studies are highly encouraged to evaluate the association with comprehensive covariate adjustment.

With great interest, we observed a potential safety signal of narcolepsy and related disorders following the first dose of BNT162b2. The initial motivation for including narcolepsy in the list of interested AIDs was due to the widely reported increased risk of narcolepsy among Pandemrix (AS03 adjuvanted pandemic A/H1N1 influenza vaccine)
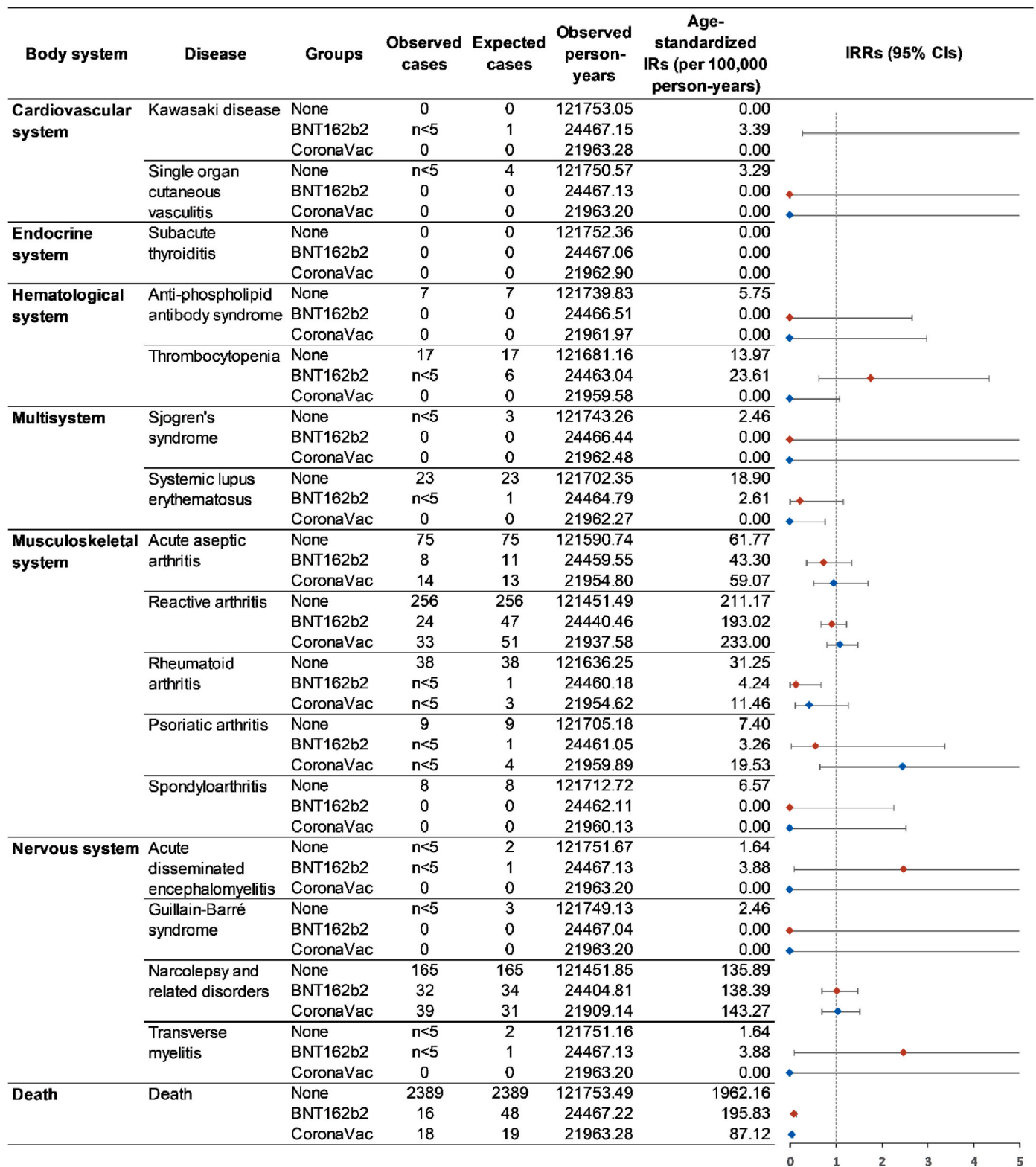
Body system	Disease	Groups	Observed cases	Expected cases	Observed person-years	Age-standardized IRs (per 100,000 person-years)	IRRs (95% CIs)
Cardiovascular system	Kawasaki disease	None	0	0	121753.05	0.00	
		BNT162b2	n<5	1	24467.15	3.39	
		CoronaVac	0	0	21963.28	0.00	
	Single organ cutaneous vasculitis	None	n<5	4	121750.57	3.29	
		BNT162b2	0	0	24467.13	0.00	
		CoronaVac	0	0	21963.20	0.00	
Endocrine system	Subacute thyroiditis	None	0	0	121752.36	0.00	
		BNT162b2	0	0	24467.06	0.00	
		CoronaVac	0	0	21962.90	0.00	
Hematological system	Anti-phospholipid antibody syndrome	None	7	7	121739.83	5.75	
		BNT162b2	0	0	24466.51	0.00	
		CoronaVac	0	0	21961.97	0.00	
	Thrombocytopenia	None	17	17	121681.16	13.97	
		BNT162b2	n<5	6	24463.04	23.61	
		CoronaVac	0	0	21959.58	0.00	
Multisystem	Sjogren's syndrome	None	n<5	3	121743.26	2.46	
		BNT162b2	0	0	24466.44	0.00	
		CoronaVac	0	0	21962.48	0.00	
	Systemic lupus erythematosus	None	23	23	121702.35	18.90	
		BNT162b2	n<5	1	24464.79	2.61	
		CoronaVac	0	0	21962.27	0.00	
Musculoskeletal system	Acute aseptic arthritis	None	75	75	121590.74	61.77	
		BNT162b2	8	11	24459.55	43.30	
		CoronaVac	14	13	21954.80	59.07	
	Reactive arthritis	None	256	256	121451.49	211.17	
		BNT162b2	24	47	24440.46	193.02	
		CoronaVac	33	51	21937.58	233.00	
	Rheumatoid arthritis	None	38	38	121636.25	31.25	
		BNT162b2	n<5	1	24460.18	4.24	
		CoronaVac	n<5	3	21954.62	11.46	
	Psoriatic arthritis	None	9	9	121705.18	7.40	
		BNT162b2	n<5	1	24461.05	3.26	
		CoronaVac	n<5	4	21959.89	19.53	
	Spondyloarthritis	None	8	8	121712.72	6.57	
		BNT162b2	0	0	24462.11	0.00	
		CoronaVac	0	0	21960.13	0.00	
Nervous system	Acute disseminated encephalomyelitis	None	n<5	2	121751.67	1.64	
		BNT162b2	n<5	1	24467.13	3.88	
		CoronaVac	0	0	21963.20	0.00	
	Guillain-Barré syndrome	None	n<5	3	121749.13	2.46	
		BNT162b2	0	0	24467.04	0.00	
		CoronaVac	0	0	21963.20	0.00	
	Narcolepsy and related disorders	None	165	165	121451.85	135.89	
		BNT162b2	32	34	24404.81	138.39	
		CoronaVac	39	31	21909.14	143.27	
	Transverse myelitis	None	n<5	2	121751.16	1.64	
		BNT162b2	n<5	1	24467.13	3.88	
		CoronaVac	0	0	21963.20	0.00	
Death	Death	None	2389	2389	121753.49	1962.16	
		BNT162b2	16	48	24467.22	195.83	
		CoronaVac	18	19	21963.28	87.12	

Fig. 3. Standardized incidence rates of autoimmune conditions among second dose vaccine recipients and non-vaccinated individuals.

recipients in European countries and Canada during the 2009H1N1 pandemic [41–46], which could contribute to vaccine hesitancy against COVID-19 [47,48]. Considering the potential delay and miscoded diagnosis of narcolepsy from inpatient settings [49],we used a series of ICD-9-CM codes (307.4x, 347.xx and 780.5x, Supplementary Table 1) to investigate a broader range of relevant sleeping disorders according to ACCESS - a project funded by the EMA for the safety monitoring of

COVID-19 vaccines [50]. When breaking down the ICD-9-CM codes, we found that hypersomnia (ICD-9-CM: 780.53) was predominately coded but no case was coded as narcolepsy (ICD-9-CM: 347). Therefore, the increased incidence may not be attributed to narcolepsy, but mainly associated with hypersomnia, a likely manifestation of fatigue and increased sleep duration commonly reported after the COVID-19 vaccination [38,51,52]. To date, no narcolepsy-related disorder case

report is related to COVID-19 vaccination. There is a recent proof-of-concept study using wearable devices found an increased sleeping duration up to four days post-BNT162b2 vaccination [53]. The sleeping signal detected in this study encourages further investigation on the immunogenicity, mechanism and association between mRNA vaccine and sleeping disorders.

With the availability of territory-wide longitudinal EMRs, this study systematically reported the incidence of autoimmune conditions among vaccine recipients and non-vaccinated controls in the same period and within the same health system. This would avoid reporting bias from enhanced surveillance when using the historical background incidence as the control. There are also limitations in this study. Due to limited data sources, our case definition was restricted to autoimmune conditions that were severe enough to warrant hospitalization and inpatient care. Mild, self-limiting autoimmune conditions not requiring inpatient treatment are beyond the scope of this study. Similarly, our EMRs database does not include health information from the private sector, and information on other vaccination which may cause such diseases. Finally, case identification largely depended on ICD-9-CM diagnosis codes, which could cast some uncertainty on coding practices and affirmative diagnosis. However, previous studies using the EMRs database from the HA showed high coding accuracy [15–18] and our additional analyses using both primary and secondary diagnosis would minimize this risk.

5. Conclusions

Within 28 days after BNT162b2 and CoronaVac vaccination, autoimmune conditions requiring hospitalization are rare and similar to disease occurrence among the non-vaccinated population. The association between first dose BNT162b2 vaccination and immune-related sleeping disorders requires further research. Population-based active safety surveillance is essential to detect rare and unexpected adverse events and serves as a useful tool for future hypothesis testing epidemiology studies.

Author statements

Xue Li: Conceptualization, Methodology, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project administration. Le Gao: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Project administration. Xinning Tong: Methodology, Software, Formal analysis, Validation, Writing - Review & Editing. Vivien K.Y. Chan: Formal analysis, Writing - Review & Editing, Project administration. Celine S.L. Chui: Conceptualization, Resources, Data Curation, Writing - Review & Editing, Project administration. Francisco T.T. Lai: Conceptualization, Resources, Data Curation, Writing - Review & Editing, Project administration. Carlos K.H. Wong: Conceptualization, Resources, Data Curation, Writing - Review & Editing, Project administration. Eric Y.F. Wan: Conceptualization, Resources, Data Curation, Writing - Review & Editing, Project administration. Esther W. Y. Chan: Conceptualization, Resources, Data Curation, Writing - Review & Editing. Kui Kai Lau: Investigation, Writing - Review & Editing. Chak Sing Lau: Conceptualization, Methodology, Writing - Review & Editing. Ian C.K. Wong: Conceptualization, Methodology, Resources, Data Curation, Writing - Review & Editing, Supervision, Funding acquisition.

Declaration of competing interest

Data availability

The authors do not have permission to share data.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2022.102830.

References

[1] C. Vellozzi, S. Iqbal, K. Broder, Guillain-Barre syndrome, influenza, and influenza vaccination: the epidemiologic evidence, Clin. Infect. Dis. 58 (2014) 1149–1155, https://doi.org/10.1093/cid/ciu005.

[2] N. Andrews, J. Stowe, E. Miller, H. Svanström, K. Johansen, J. Bonhoeffer, et al., A collaborative approach to investigating the risk of thrombocytopenic purpura after measles-mumps-rubella vaccination in England and Denmark, Vaccine 30 (2012) 3042–3046, https://doi.org/10.1016/j.vaccine.2011.06.009.

[3] E. Dubé, M. Vivion, N.E. MacDonald, Vaccine hesitancy, vaccine refusal and the anti-vaccine movement: influence, impact and implications, Expert Rev. Vaccines 14 (2015) 99–117, https://doi.org/10.1586/14760584.2015.964212.

[4] C.B. Creech, S.C. Walker, R.J. Samuels, SARS-CoV-2 vaccines, JAMA 325 (2021) 1318–1320, https://doi.org/10.1001/jama.2021.3199.

[5] L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, et al., Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine, N. Engl. J. Med. 384 (2021) 403–416, https://doi.org/10.1056/NEJMoa2035389.

[6] M. Voysey, S.A.C. Clemens, S.A. Madhi, L.Y. Weckx, P.M. Folegatti, P.K. Aley, et al., Safety and efficacy of the ChAdOx1 nCov-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK, Lancet 397 (2021) 99–111, https://doi.org/10.1016/S0140-6736(20)32661-1.

[7] C.R. Simpson, T. Shi, E. Vasileiou, S.V. Katikireddi, S. Kerr, E. Moore, et al., First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland, Nat. Med. 27 (2021) 1290–1297, https://doi.org/10.1038/s41591-021-01408-4.

[8] E.Y.F. Wan, C.S.L. Chui, F.T.T. Lai, E.W.Y. Chan, X. Li, V.K.C. Yan, et al., Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study, Lancet Infect. Dis. 22 (2022) 64–72, https://doi.org/10.1016/S1473-3099(21)00451-5.

[9] T. Hasan, M. Khan, F. Khan, G. Hamza, Case of Guillain-Barré syndrome following COVID-19 vaccine, BMJ Case Rep. 14 (2021), e243629, https://doi.org/10.1136/bcr-2021-243629.

[10] B.V. Maramattom, P. Krishnan, R. Paul, S. Padmanabhan, S. Cherukudal Vishnu Nampoothiri, A.A. Syed, et al., Guillain-barre syndrome following ChAdOx1-S/nCoV-19 vaccine, Ann. Neurol. 90 (2021) 312–314, https://doi.org/10.1002/ana.26143.

[11] O. Ogbebor, H. Seth, Z. Min, N. Bhanot, Guillain-Barré syndrome following the first dose of SARS-CoV-2 vaccine: a temporal occurrence, not a causal association, IDCases 24 (2021), e01143, https://doi.org/10.1016/j.idcr.2021.e01143.

[12] J. Finsterer, Exacerbating guillain–barré syndrome eight days after vector-based COVID-19 vaccination, Case Rep Infect Dis 2021 (2021) 3619131, https://doi.org/10.1155/2021/3619131.

[13] D.E. McMahon, E. Amerson, M. Rosenbach, J.B. Lipoff, D. Moustafa, A. Tyagi, et al., Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases, J. Am. Acad. Dermatol. 85 (2021) 46–55, https://doi.org/10.1016/j.jaad.2021.03.092.

[14] A. Watad, G. De Marco, H. Mahajna, A. Druyan, M. Eltity, N. Hijazi, et al., Immune-mediated disease flares or new-onset disease in 27 subjects following mRNA/DNA SARS-CoV-2 vaccination, Vaccines 9 (2021) 435, https://doi.org/10.3390/vaccines9050435.

[15] E.W. Chan, W.C.Y. Lau, W.K. Leung, M.T.C. Mok, Y. He, T.S.M. Tong, et al., Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a population-based study, Gastroenterology 149 (2015) 586–595, https://doi.org/10.1053/j.gastro.2015.05.002, e3.

[16] W.C.Y. Lau, E.W. Chan, C.-L. Cheung, C.W. Sing, K.K.C. Man, G.Y.H. Lip, et al., Association between dabigatran vs warfarin and risk of osteoporotic fractures among patients with nonvalvular atrial fibrillation, JAMA 317 (2017) 1151–1158, https://doi.org/10.1001/jama.2017.1363.

[17] K.K.C. Man, D. Coghill, E.W. Chan, W.C.Y. Lau, C. Hollis, E. Liddle, et al., Association of risk of suicide attempts with methylphenidate treatment, JAMA Psychiatry. 74 (2017) 1048–1055, https://doi.org/10.1001/jamapsychiatry.2017.2183.

[18] A.Y.S. Wong, A. Root, I.J. Douglas, C.S.L. Chui, E.W. Chan, Y. Ghebremichael-Weldeselassie, et al., Cardiovascular outcomes associated with use of clarithromycin: population based study, BMJ 352 (2016) h6926, https://doi.org/10.1136/bmj.h6926.

[19] X. Li, X. Tong, I.C.K. Wong, K. Peng, C.S.L. Chui, F.T.T. Lai, et al., Lack of inflammatory bowel disease flare-up following two-dose BNT162b2 vaccine: a population-based cohort study, Gut (2022), https://doi.org/10.1136/gutjnl-2021-326860. Published Online First: 08 February 2022:gutjnl-2021-326860.

[20] F.T.T. Lai, X. Li, K. Peng, L. Huang, P. Ip, X. Tong, et al., Carditis after COVID-19 vaccination with a messenger rna vaccine and an inactivated virus vaccine : a case-control study, Ann. Intern. Med. 175 (3) (2022) 362–370, https://doi.org/10.7326/M21-3700.

[21] X. Li, X. Tong, W.W.Y. Yeung, P. Kuan, S.H.H. Yum, C.S.L. Chui, et al., Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong, Ann. Rheum. Dis. 81 (4) (2021) 564–568, https://doi.org/10.1136/annrheumdis-2021-221571.

[22] G.T. Chua, M.Y.W. Kwan, C.S.L. Chui, R.D. Smith, E.C. Cheung, T. Tian, et al., Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents following comirnaty vaccination, Clin. Infect. Dis. (2021), https://doi.org/10.1093/cid/ciab989.

[23] C.W. Sing, C.T.L. Tang, C.S.L. Chui, M. Fan, F.T.T. Lai, X. Li, et al., COVID-19 vaccines and risks of hematological abnormalities: nested case-control and self-controlled case series study, Am. J. Hematol. 97 (4) (2022) 470–480, https://doi.org/10.1002/ajh.26478.

[24] F.T.T. Lai, L. Huang, K. Peng, X. Li, C.S.L. Chui, E.Y.F. Wan, et al., Post-Covid-19-vaccination adverse events and healthcare utilization among individuals with or without previous SARS-CoV-2 infection, J. Intern. Med. (2022), https://doi.org/10.1111/joim.13453.

[25] E.Y.F. Wan, C.S.L. Chui, Y. Wang, V.W.S. Ng, V.K.C. Yan, F.T.T. Lai, et al., Herpes zoster related hospitalization after inactivated (CoronaVac) and mRNA (BNT162b2) SARS-CoV-2 vaccination: a self-controlled case series and nested case-

[26] control study, Lancet Reg Health West Pac 21 (2022) 100393, https://doi.org/10.1016/j.lanwpc.2022.100393.

[26] X. Xiong, C.K.H. Wong, I.C.H. Au, F.T.T. Lai, X. Li, E.Y.F. Wan, et al., Safety of inactivated and mRNA COVID-19 vaccination among patients treated for hypothyroidism: a population-based cohort study, Thyroid (2022), https://doi.org/10.1089/thy.2021.0684.

[27] X. Li, F.T.T. Lai, G.T. Chua, M.Y.W. Kwan, Y.L. Lau, P. Ip, et al., Myocarditis following COVID-19 BNT162b2 vaccination among adolescents in Hong Kong, JAMA Pediatr. (2022), https://doi.org/10.1001/jamapediatrics.2022.0101.

[28] F.T.T. Lai, G.T. Chua, E.W.W. Chan, L. Huang, M.Y.W. Kwan, T. Ma, et al., Adverse events of special interest following the use of BNT162b2 in adolescents: a population-based retrospective cohort study, Emerg. Microb. Infect. 11 (2022) 885–893, https://doi.org/10.1080/22221751.2022.2050952.

[29] C.K.H. Wong, X. Xiong, K.T.K. Lau, C.S.L. Chui, F.T.T. Lai, X. Li, et al., Impact of a delayed second dose of mRNA vaccine (BNT162b2) and inactivated SARS-CoV-2 vaccine (CoronaVac) on risks of all-cause mortality, emergency department visit, and unscheduled hospitalization, BMC Med. 20 (2022) 119, https://doi.org/10.1186/s12916-022-02321-4.

[30] World Health Organization, Background Paper on Covid-19 Disease and Vaccines: Prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines, 22 December 2020. https://apps.who.int/iris/handle/10665/338095, World Health Organization, 2020.

[31] B. Law, SO2-D2. 1.2 Priority List of COVID-19 Adverse Events of Special Interest: Quarterly Update December 2020, Safety Platform for Emergency vACcines (SPEAC), 2021. https://brightoncollaboration.us/wp-content/uploads/2020/12/SO2_D2.1.2_V1.2_COVID-19_AESI-update-23Dec2020.pdf. (Accessed 28 March 2022).

[32] G.R. Cohen, S.Y. Yang, Mid-P confidence intervals for the Poisson expectation, Stat. Med. 13 (1994) 2189–2203, https://doi.org/10.1002/sim.4780132102.

[33] M.P. Fay, Two-sided exact tests and matching confidence intervals for discrete data, The R Journal 2 (1) (2010) 53–58.

[34] V. Kharkar, T. Vishwanath, S. Mahajan, R. Joshi, P. Gole, Asymmetric cutaneous vasculitis following COVID-19 vaccination with unusual eosinophil preponderance, Clin. Exp. Dermatol. (2021), https://doi.org/10.1111/ced.14797.

[35] The World Health Organization, Covid-19 Vaccines: Safety Surveillance Manual, 2020. https://www.who.int/publications/i/item/10665338400. (Accessed 25 July 2021).

[36] J. Hippisley-Cox, M. Patone, X.W. Mei, D. Saatci, S. Dixon, K. Khunti, et al., Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study, BMJ 374 (2021) n1931, https://doi.org/10.1136/bmj.n1931.

[37] A. Pottegård, L.C. Lund, Ø. Karlstad, J. Dahl, M. Andersen, J. Hallas, et al., Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study, BMJ 373 (2021) n1114, https://doi.org/10.1136/bmj.n1114.

[38] C. Menni, K. Klaser, A. May, L. Polidori, J. Capdevila, P. Louca, et al., Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study, Lancet Infect. Dis. 21 (2021) 939–949, https://doi.org/10.1016/S1473-3099(21)00224-3.

[39] The Government of the Hong Kong Special Administrative Region, Vaccination Priority Groups to Be Expanded to Cover People Aged 30 or above, 2021. https://www.info.gov.hk/gia/general/202103/15/P2021031500626.htm. (Accessed 25 July 2021).

[40] Centre for Health Protection | Department of Health | The Government of the Hong Kong Special Administrative Region. Latest local situation of COVID-19 (Details of previous cases). https://www.chp.gov.hk/files/xls/previous_cases_covid19_en.xlsx. (accessed 28 March, 2022).

[41] K. Gadroen, S. Straus, A. Pacurariu, D. Weibel, X. Kurz, M. Sturkenboom, Patterns of spontaneous reports on narcolepsy following administration of pandemic influenza vaccine; a case series of individual case safety reports in Eudravigilance, Vaccine 34 (2016) 4892–4897, https://doi.org/10.1016/j.vaccine.2016.08.062.

[42] F. Granath, R. Gedeborg, H. Smedje, N. Feltelius, Change in risk for narcolepsy over time and impact of definition of onset date following vaccination with AS03 adjuvanted pandemic A/H1N1 influenza vaccine (Pandemrix) during the 2009 H1N1 influenza pandemic, Pharmacoepidemiol. Drug Saf. 28 (2019) 1045–1053, https://doi.org/10.1002/pds.4788.

[43] J. Montplaisir, D. Petit, M.J. Quinn, M. Ouakki, G. Deceuninck, A. Desautels, et al., Risk of narcolepsy associated with inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine in Quebec, PLoS One 9 (2014), e108489, https://doi.org/10.1371/journal.pone.0108489.

[44] D. O'Flanagan, A.S. Barret, M. Foley, S. Cotter, C. Bonner, C. Crowe, et al., Investigation of an association between onset of narcolepsy and vaccination with pandemic influenza vaccine, Ireland April 2009-December 2010, Euro Surveill. 19 (2014) 15–25.

[45] J. Stowe, N. Andrews, C. Kosky, G. Dennis, S. Eriksson, A. Hall, et al., Risk of narcolepsy after AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine in adults: a case-coverage study in England, Sleep 39 (2016) 1051–1057, https://doi.org/10.5665/sleep.5752.

[46] A.M. Winstone, L. Stellitano, C. Verity, N. Andrews, E. Miller, J. Stowe, et al., Clinical features of narcolepsy in children vaccinated with AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine in England, Dev. Med. Child Neurol. 56 (2014) 1117–1123, https://doi.org/10.1111/dmcn.12522.

[47] Narcolepsy fiasco spurs Covid vaccine fears in Sweden. 2020; https://medicalxpress.com/news/2020-11-narcolepsy-fiasco-spurs-covid-vaccine.html. (accessed 22 July, 2021).

[48] J. Silberner, Overcoming vaccine hesitancy: five minutes with Heidi Larson, BMJ 364 (2019) l1259, https://doi.org/10.1136/bmj.l1259.

[49] Y.T. Wei, P.Y. Lee, C.Y. Lin, H.J. Chen, C.C. Lin, J.S. Wu, et al., Non-alcoholic fatty liver disease among patients with sleep disorders: a Nationwide study of Taiwan, BMC Gastroenterol. 20 (2020) 32, https://doi.org/10.1186/s12876-020-1178-7.

[50] VAC4EU COVID-19 vaccine monitoring. 2021; https://vac4eu.org/covid-19-vaccine-monitoring/. (accessed 28 July, 2021).

[51] F.T.T. Lai, M.T.Y. Leung, E.W.W. Chan, L. Huang, L.K.W. Lau, K. Peng, et al., Self-reported reactogenicity of CoronaVac (Sinovac) compared with Comirnaty (Pfizer-BioNTech): a prospective cohort study with intensive monitoring, Vaccine 40 (2022) 1390–1396, https://doi.org/10.1016/j.vaccine.2022.01.062.

[52] E.W.W. Chan, M.T.Y. Leung, L.K.W. Lau, J. Leung, D. Lum, R.S. Wong, et al., Comparing self-reported reactogenicity between adolescents and adults following the use of BNT162b2 (Pfizer-BioNTech) messenger RNA COVID-19 vaccine: a prospective cohort study, Int. J. Infect. Dis. 116 (2022) 47–50, https://doi.org/10.1016/j.ijid.2021.12.354.

[53] A.G. Hajduczok, K.M. DiJoseph, B. Bent, A.K. Thorp, J.B. Mullholand, S.A. MacKay, et al., Physiologic response to the pfizer-BioNTech COVID-19 vaccine measured using wearable devices: a prospective observational study, JMIR Form Res (2021), https://doi.org/10.2196/28568.