Manuscript Title: Adverse Events of Special Interest and mortality following the mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines

Analytic plan:

To compare the incidences of various adverse events of special interest (AESI) and all-cause mortality between CoronaVac (inactivated vaccine) and BNT162b2 (mRNA-based vaccine) following the first and second doses.

## Design

Retrospective cohort study among people aged 18 or above with electronic medical records who were previously received at least one dose of CoronaVac or BNT162b2 in Hong Kong from 23rd February to 9th September 2021.

## Cohort selection – Inverse probability of treatment weighting (IPTW)

## First, we will include all vaccinated people aged 18 or above and exclude those who received mixed doses. Second, we identify two study cohorts and define observation periods. a) First dose recipients cohort. All vaccinated people will be included. We set the date of the first dose as the start of the observation period and followed them until death, second dose vaccination, 21 days after the first dose, or censored on the data cutoff date (30th September 2021). b) Second dose recipients cohort. People who completed the vaccine series will be included in this cohort. We set the date of the second dose as the start of the observation period and follow them until death, 21 days after the first dose, or censored on the data cutoff date (30th September 2021). Third, propensity score models will be performed based on age, sex, any previous SARS-CoV-2 infection, pre-existing comorbidities, medication use, venue for vaccination, and dosing interval. Fourth, we will apply IPTW using the propensity scores and truncate the 1st and 99th percentiles of observed PS weighting distribution to account for extreme weights. Standardized mean differences of <0.1 in the variables are considered an indication of balance.

## Exposure

Vaccination with CoronaVac (reference) or BNT162b2.

## Outcome

## Overall AESI and individual AESI are the primary outcomes, and all-cause mortality is the secondary outcome. We will use the list of AESI, which are advocated by the WHO Global Advisory Committee on Vaccine Safety. AESI outcomes include Guillain-Barré syndrome, acute disseminated encephalomyelitis, sleeping disturbance or disorder, acute aseptic arthritis, type 1 diabetes, thrombocytopenia, subacute thyroiditis, microangiopathy, heart failure, stress cardiomyopathy, arrhythmia, carditis, thromboembolism, coronary artery disease, myocardial infarction, venous thromboembolism, arterial thromboembolism, hemorrhagic disease, single organ cutaneous vasculitis, acute liver injury, acute kidney injury, acute pancreatitis, generalized convulsion, meningoencephalitis, transverse myelitis, bell’s palsy, acute respiratory distress syndrome, erythema multiforme, chilblain - like lesions, anosmia and ageusia, anaphylaxis, multisystem inflammatory syndrome in children, sudden death, rhabdomyolysis. The list of AESI is defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Diagnosis and Procedure codes, and laboratory parameters (Table 1).

## Analysis

Cohort characteristics will be tabulated. Cumulative incidence and crude incidence rate of each outcome by first and second dose will be calculated. The incidence rate ratio will be estimated to show the differences in the risks of AESI and all-cause mortality between brands of the vaccines.

IPTW-weighted Poisson regression models with person-years as an offset term will be fitted to estimate the incidence rate ratios. Sensitivity analysis will be conducted to exclude people with previous SARS-CoV-2 infections who might have an increased risk of various disease diagnoses associated with SARS-CoV-2 infection.

Table 1 Definitions of adverse events of special interest (AESI)

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| --- | --- |
| **AESI** | **ICD-9-CM diagnosis and procedure codes, and laboratory parameters.** |
| Guillain-Barré Syndrome | 357.0 Acute infective polyneuritis 357.8x Other inflammatory and toxic neuropathy 357.9 Inflammatory/toxic neuropathy, unspecified |
| Acute disseminated encephalomyelitis (ADEM) | 323.6x Postinfectious encephalitis, myelitis, and encephalomyelitis 323.8x Other causes of encephalitis, myelitis and encephalomyelitis |
| Sleeping disturbance or disorder | 347.xx Cataplexy and narcolepsy 307.4 (Nonorganic sleep disorder, unspecified), 780.5 (unspecified sleep disturbance) [Procedure codes: 89.17 Polysomnography 89.18 Multiple sleep latency] |
| Acute aseptic arthritis | 274.0x Gouty arthropathy 696.0 Psoriatic arthropathy 716.5x Unspecified polyarthropathy or polyarthritis 716.6x Unspecified monoarthritis 716.9x Unspecified arthropathy 712.xx Crystal arthropathies 711.5x Arthropathy associated with other viral diseases |
| Type 1 Diabetes | 250.01 Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled 250.03 Diabetes mellitus without mention of complication, type I [juvenile type], uncontrolled 250.11 Diabetes with ketoacidosis, type I [juvenile], not stated as uncontrolled 250.13 Diabetes with ketoacidosis, type I [juvenile], uncontrolled 250.21 Diabetes with hyperosmolarity, type I [juvenile], not stated as uncontrolled 250.23 Diabetes with hyperosmolarity, type I [juvenile], uncontrolled 250.31 Diabetes with other coma, type I [juvenile], not stated as uncontrolled 250.33 Diabetes with other coma, type I [juvenile], uncontrolled 250.41 Diabetes with renal manifestations, type I [juvenile], not stated as uncontrolled 250.43 Diabetes with renal manifestations, type I [juvenile], uncontrolled 250.51 Diabetes with ophthalmic manifestations, type I [juvenile], not stated as uncontrolled 250.53 Diabetes with ophthalmic manifestations, type I [juvenile], uncontrolled 250.61 Diabetes with neurological manifestations, type I [juvenile], not stated as uncontrolled 250.63 Diabetes with neurological manifestations, type I [juvenile], uncontrolled 250.71 Diabetes with peripheral circulatory disorders, type I [juvenile], not stated as uncontrolled 250.73 Diabetes with peripheral circulatory disorders, type I [juvenile], uncontrolled 250.81 Diabetes with other specified manifestations, type I [juvenile], not stated as uncontrolled 250.83 Diabetes with other specified manifestations, type I [juvenile], uncontrolled 250.91 Diabetes with unspecified complications, type I [juvenile], not stated as uncontrolled 250.93 Diabetes with unspecified complications, type I [juvenile], uncontrolled |
| (Idiopathic) Thrombocytopenia | 287.3x Primary thrombocytopenia 287.4x Secondary thrombocytopenia 287.5 Thrombocytopenia, unspecified 279.1x Deficiency of cell-mediated immunity 283.1x Non-autoimmune hemolytic anemias 284.1x Drug-induced bone marrow suppression 446.6 Thrombotic microangiopathy 776.1 Transient neonatal thrombocytopia |
| Subacute thyroiditis | 245.1 Subacute thyroiditis |
| Acute cardiovascular injury including: | |
| Microangiopathy | 446.6 Thrombotic microangiopathy |
| Heart failure | 428.x Heart failure 398.9x Other and unspecified rheumatic heart diseases 402.xx Hypertensive heart disease (with or without heart failure) 404.xx Hypertensive heart and chronic kidney disease (with or without heart failure) |
| Stress cardiomyopathy | 429.8x Other ill-defined heart diseases |
| Arrhythmia | 427.xx Cardiac dysrhythmias 426.7 Anomalous atrioventricular excitation 794.3x Nonspecific abnormal results of function study of cardiovascular system 785.0 Tachycardia, unspecified |
| Carditis | 420.9 Pericarditis 422.xx Acute myocarditis 423.9 Unspecified disease of pericardium 429.0 Myocarditis, unspecified |
| Thromboembolism (DVT, PE, stroke, limb ischemia) | 410.x Acute myocardial infraction 415.1x Pulmonary embolism and infarction 453.x Other venous embolism and thrombosis 443.x Other peripheral vascular disease 444.x Arterial embolism and thrombosis 445.x Atheroembolism 433.x Occlusion and stenosis of precerebral arteries 434.x Occlusion of cerebral arteries 435.x Transient cerebral ischemia (TIA) 436.x CVA 437.x Other and ill-defined cerebrovascular disease 451.x Phlebitis and thrombophlebitis 452.x Portal vein thrombosis 453.40 Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity 453.41 Acute venous embolism and thrombosis of deep vessels of proximal lower extremity 453.42 Acute venous embolism and thrombosis of deep vessels of distal lower extremity 459.9 Unspecified circulatory system disorder 325.x Phlebitis and thrombophlebitis and intracranial venous sinuses 286.6x Defibrination syndrome 557.0 Acute vascular insufficiency of intestine 557.9 Unspecified vascular insufficiency of intestine [Procedure codes: 36.0x Removal Of Coronary Artery Obstruction And Insertion Of Stent(s) 36.1x Bypass Anastomosis For Heart Revascularization 36.2x heart revascularization by arterial implant 36.3x other heart revascularization] |
| Coronary artery disease | 410.x-414.x Ischemic Heart Disease V45.81 Presence of aortocoronary bypass graft [Procedure codes: 36.0x Removal Of Coronary Artery Obstruction And Insertion Of Stent(s) 36.1x Bypass Anastomosis For Heart Revascularization 36.2x heart revascularization by arterial implant 36.3x other heart revascularization] |
| Myocardial Infarction | 410.x-414.x Ischemic Heart Disease V45.81 Presence of aortocoronary bypass graft [Procedure codes: 36.0x Removal Of Coronary Artery Obstruction And Insertion Of Stent(s) 36.1x Bypass Anastomosis For Heart Revascularization 36.2x heart revascularization by arterial implant 36.3x other heart revascularization] |
| Venous thromboembolism | 415.1x Pulmonary embolism and infarction 453.xx Other venous embolism and thrombosis |
| Arterial thromboembolism | 433.xx Occlusion and stenosis of precerebral arteries 434.xx Occlusion of cerebral arteries 435.x Transient cerebral ischemia 436 Acute but ill-defined cerebrovascular disease 437.0 Cerebral atherosclerosis 437.1 Other generalized ischemic cerebrovascular disease 437.6 Nonpyogenic thrombosis of intracranial venous sinus 437.7 Transient global amnesia 437.8 Other ill-defined cerebrovascular disease 437.9 Unspecified cerebrovascular disease |
| Haemorrhagic disease | 286.5x Hemorrhagic disorder due to intrinsic circulating anticoagulants 286.7 Acquired coagulation factor deficiency 287.xx Purpura and other hemorrhagic conditions 430.x Subarachnoid hemorrhage 431.x Intracerebral hemorrhage 432.x Nontraumatic extradural hemorrhage [Procedure codes: 99.06 Transfusion of coagulation factors] |
| Single Organ Cutaneous Vasculitis | 709.1 Vascular disorders of skin 446.2x Hypersensitivity angiitis 287.0 Allergic purpura |
| Acute liver injury | 570.x Liver acute (subacute) 573.3 (Hepatitis, toxic) |
| Acute kidney injury | 584.x Acute kidney failure 586.xx Renal failure unspecified [Lab parameters: ≥1.5-fold increase in serum creatinine within 7 days or ≥ 26.5 μmol/L absolute increase in serum creatinine within 2 days] |
| Acute pancreatitis | 577.0 Acute pancreatitis |
| Generalized convulsion | 345.xx Epilepsy and recurrent seizures 780.3x Convulsions 779.0 Convulsions in newborn 333.2 Myoclonus 649.4 Epilepsy complicating pregnancy, childbirth, or the puerperium |
| Meningoencephalitis | 322.9x Meningitis, unspecified 323.0x Encephalitis, myelitis and encephalomyelitis in viral diseases classified elsewhere 323.4x Other encephalitis, myelitis and encephalomyelitis due to infections classified elsewhere 323.5x Encephalitis, myelitis and encephalomyelitis following immunization procedures 323.6x Postinfectious encephalitis, myelitis, and encephalomyelitis 323.8x Other causes of encephalitis, myelitis and encephalomyelitis 323.9x Unspecified causes of encephalitis, myelitis, and encephalomyelitis 323.7 Toxic encephalitis 330.8 Acute necrotizing hemorrhagic encephalopathy 377.7 Disorders of visual cortex 046.3 Telencephalic leukoencephalopathy 049.8 Rio Bravo Fever 036.1 Bacterial encephalitis 056.0 Rubella with neurological complications 136.2 Specific infections by free-living amebae 130.xx Toxoplasmosis 054.3 Herpetic meningoencephalitis 049.0 Lymphocytic choriomeningitis 094.1 General paresis 072.2 Mumps encephalitis 013.0 Meningoencephalitis (infectious origin) 062.4 Murray valley encephalitis 049.9 Viral encephalitis 045.0 Polio encephalitis 062.xx Mosquito-borne viral encephalitis |
| Transverse myelitis | 323.0x Encephalitis, myelitis, and encephalomyelitis in viral diseases classified elsewhere 323.4x Other encephalitis, myelitis, and encephalomyelitis due to infection classified elsewhere 323.5x Encephalitis, myelitis, and encephalomyelitis following immunization procedures 323.6x Postinfectious encephalitis, myelitis, and encephalomyelitis 323.8x Other causes of encephalitis, myelitis, and encephalomyelitis 341.2x Acute (transverse) myelitis |
| Bell’s palsy | 351.0 Bell’s palsy 351.8 (other facial nerve disorders) 351.9 (facial nerve disorder, unspecified) |
| Acute respiratory distress syndrome | 518.8x Other pulmonary insufficiency, not elsewhere classified 518.5x Pulmonary insufficiency following trauma and surgery [Procedure codes: 96.7x Continuous mechanical ventilation] |
| Erythema multiforme | 695.1x Erythema multiforme |
| Chilblain – like lesions | 991.5 Chilblains |
| Anosmia, ageusia | 781.1 Disturbances of sensation of smell and taste |
| Anaphylaxis | 995.0 Anaphylactic reaction, unspecified 995.1 Angioneurotic edema 995.3 Allergy, unspecified, not elsewhere classified 995.4 Shock due to anesthesia, not elsewhere classified 999.4x Anaphylactic reaction to serum 708.9 Urticaria 519.1 Other diseases of trachea and bronchus not elsewhere classified 786.1 Stridor 458.9 Hypotension |
| Multisystem inflammatory syndrome in children | 446.1 Mucocutaneous lymph node syndrome (Kawasaki disease) |
| Sudden death | 798.x Sudden death cause unknown 799 Other ill- defined and unknown causes of morbidity and mortality |
| Rhabdomyolysis | 728.8 Other disorders of muscle ligament and fascia 791.3 Myoglobinuria |