Safety of an inactivated, whole-virion COVID-19 vaccine (CoronaVac) in people aged 60 years or older in Hong Kong: a modified self-controlled case series

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Summary

Background Because evidence on the safety of COVID-19 vaccines in older adults is scarce, we aimed to evaluate the incidence and risk of adverse events after CoronaVac (Sinovac Biotech) vaccination in adults aged 60 years or older.

Methods In this modified self-controlled case series, we enrolled adults aged 60 years or older who had received at least one dose of CoronaVac in Hong Kong between Feb 23, 2021, and Jan 31, 2022. We extracted population-based, electronic health record data from the clinical management system of the Hospital Authority on adverse events of special interest (from Jan 1, 2005, to Feb 23, 2022) and patients' demographic information (from Jan 1, 2018, to Jan 31, 2022), previous diagnoses (from Jan 1, 2018, to Jan 31, 2022), medication history (from Jan 1, 2018, to Jan 31, 2022), and laboratory tests, including those for SARS-CoV-2 infection (from Jan 1, 2018, to Jan 31, 2022). Details of vaccination status were provided by the Department of Health of the Hong Kong Government and were linked to data from the Hospital Authority with identity card numbers or passport numbers. Our outcomes were the overall incidence of any adverse event of special interest and the incidence rates of 30 adverse events of special interest, as suggested by the WHO Global Advisory Committee on Vaccine Safety, in the inpatient setting within 21 days (2 days for anaphylaxis) of either the first, second, or third CoronaVac dose compared with a baseline period. Individuals who had a history of a particular event between Jan 1, 2005, and Feb 23, 2021, were excluded from the corresponding analysis. We evaluated the risk of an adverse event of special interest using conditional Poisson regression, adjusting for seasonal effects.

Findings Of 1 253 497 individuals who received at least one dose of CoronaVac during the study period, 622 317 (49·6%) were aged at least 60 years and were included in the analysis. Our analysis sample received 1 229 423 doses of CoronaVac and had a mean age of 70·40 years (SD 8·10). 293 086 (47·1%) of 622 317 participants were men and 329 231 (52·9%) were women. The incidence of individual adverse events of interest ranged from 0·00 per 100 000 people to 57·49 per 100 000 people (thromboembolism). The first and third doses of CoronaVac were not associated with a significant excess risk of an adverse event of special interest within 21 days (or 2 days for anaphylaxis) of vaccination. After the second dose, the only significantly increased risk was for anaphylaxis (adjusted incidence rate ratio 2·61, 95% CI 1·08–6·31; risk difference per 100 000 people 0·61, 95% CI 0·03–1·81).

Interpretation Because older age is associated with poor outcomes after SARS-CoV-2 infection, the benefits of CoronaVac vaccination in older adults outweigh the risks in regions where COVID-19 is prevalent. Ongoing monitoring of vaccine safety is warranted.

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Introduction

Older age is a well recognised risk factor for complications after SARS-CoV-2 infection—individuals aged 60 years or older have a five-times increased risk of mortality after symptomatic SARS-CoV-2 infection compared with adults aged 30–59 years.[1] In view of this increased risk, older adults have been prioritised for COVID-19 vaccination in many countries and territories, including, but not limited to, the USA, the UK, and Hong Kong.[2] CoronaVac from Sinovac Biotech (Hong Kong; equivalent

to Sinovac Life Sciences) has been available for emergency use in Hong Kong during the COVID-19 pandemic.

Two inactivated COVID-19 vaccines, namely CoronaVac and BBIBP-CorV (Sinopharm), have contributed to almost half of the COVID-19 vaccine doses administered around the globe.[3] Although accounting for around 75% of the COVID-19 vaccines administered in Brazil,[4] there have been few post-marketing clinical studies evaluating the safety of CoronaVac, especially in the older population. There have been infrequent reports of

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Research in context

Evidence before this study

We searched PubMed and Embase for articles published in
English between database inception and March 23, 2022, using
the search terms "adverse event", "older adults", "vaccines", and
"CoronaVac". Most studies were case reports describing adverse
events, such as ischaemic stroke and thrombotic events, after
CoronaVac (Sinovac Biotech) vaccination. Evidence other than
case reports is still sparse. Although randomised controlled
trials of CoronaVac have not shown major adverse events after
vaccination, our search did not identify any analytical studies
on the risk of adverse events following CoronaVac vaccination
in older adults.

Added value of this study

To our knowledge, this population-based study is the first to
investigate the safety of CoronaVac in people aged 60 years or
older. This self-controlled case series evaluates the risk of
adverse events of special interest after the first, second, and

third doses of CoronaVac vaccine. The self-controlled case series
method was developed to investigate vaccine safety, and the
advantage is that it minimises measured and unmeasured
time-invariant confounding through within-individual
comparisons. This study found that participants did not have a
significantly higher risk of adverse events of special interest
after CoronaVac vaccination compared with a baseline period,
except for anaphylaxis after the second dose. However, the
absolute risk increment for anaphylaxis was small.

Implications of all the available evidence

Given the extensive use of inactivated COVID-19 vaccines
worldwide and the association of older age with poorer
outcomes after SARS-CoV-2 infection, the potential risks of
CoronaVac vaccination are outweighed by its benefits in places
where COVID-19 is prevalent. More pharmacovigilance studies
are warranted to confirm the safety of COVID-19 vaccines in
older adults.

myocarditis in people aged 70 years after Ad.26.COV2.S
(Janssen) and mRNA-1273 (Moderna) vaccination.[5,6]
Some case reports also describe ischaemic stroke and
thrombotic events after CoronaVac vaccination.[7,8]
Nonetheless, evidence of post-vaccination adverse events
in older adults beyond case reports is still scarce.
Although randomised controlled trials of CoronaVac
have not shown major adverse events after vaccination,[9,10]
they only included a small proportion of older participants
and were not able to evaluate rare events due to small
numbers of events. People aged 60 years or older were
excluded from the phase 3 trial of CoronaVac in Turkey[9]
and represented the minority (37 [9%] of 434) of
participants enrolled in the phase 3 trial of CoronaVac in
Chile.[10] Despite the large number of CoronaVac doses
being administered worldwide, vaccine-related adverse
events might be under-reported in resource-limited
areas,[11] rendering pharmacovigilance studies necessary.

Unlike myocarditis, which has been more frequently
observed in young males who have received BNT162b2
(Pfizer–BioNTech) than in unvaccinated controls,[12] no
significantly increased risk of adverse events has been
found in the older vaccinated population versus the older
unvaccinated population so far. One study[13] found that
older adults (≥65 years) were more likely to be hospitalised
after COVID-19 vaccination than were younger adults
(18–64 years), but relatedness to vaccination is unknown
because older adults generally have a higher risk of
hospitalisation than do younger adults. Other studies
have described a lower prevalence of local and systemic
side-effects after BNT162b2 or ChAdOx1 nCov-19
(AstraZeneca) vaccination in participants older than
55 years (*vs* those aged ≤55 years)[14] or in participants aged
50 years or older (*vs* those aged 20–29 years).[15]
Discrepancies and inconsistencies among previous
studies reveal a need to evaluate vaccine safety in the

older population. Whether the multiple comorbidities
that are commonly seen in older people put them at
higher risk of developing adverse reactions to COVID-19
vaccines is unknown. Older adults (aged ≥65 years) have
reported reduced reactogenicity (local and systemic
reactions) following mRNA-based COVID-19 vaccines
compared with younger adults (aged <65 years),[16] hence
raising the question of whether post-vaccination event
rates might be different in older, compared with younger,
adults. We aimed to examine the incidence and risk of
adverse events of special interest after vaccination with
CoronaVac in older adults.

Methods

Study design and participants

In this modified self-controlled case series, adults aged
60 years or older at the time of vaccination who had
received CoronaVac (one dose or more) in Hong Kong
between Feb 23, 2021, and Jan 31, 2022, were included.
Adverse events of special interest were based on primary
diagnoses upon hospitalisation. The self-controlled case
series design relies on within-individual comparisons
and is now an established study design for the evaluation
of vaccine safety. This design has been applied in several
studies of vaccine safety, including studies of COVID-19
vaccines.[17–21] The benefit of a self-controlled case series is
that it treats individuals as their own control, thereby
minimising measured or unmeasured time-invariant
confounding.

Ethical approval for this study was granted by the
Institutional Review Board of the University of
Hong Kong and Hospital Authority Hong Kong
West Cluster (UW21–149 and UW21–138) and the
Department of Health Ethics Committee (LM21/2021).
As anonymous data were extracted from an electronic
health database, under Hong Kong regulations and

approval from the Hospital Authority and the Department of Health, consent from participants was not required. The study protocol is available online on the website of the COVID-19 Vaccines Adverse Events Response and Evaluation Programme.

Data source

We extracted data from the clinical management system of the Hospital Authority, which stores electronic health records in Hong Kong, on adverse events of special interest (from Jan 1, 2005, to Feb 23, 2022) and patients' demographic information (from Jan 1, 2018, to Jan 31, 2022), previous diagnoses (from Jan 1, 2018, to Jan 31, 2022), medication history (from Jan 1, 2018, to Jan 31, 2022), and laboratory tests, including those for SARS-CoV-2 infection (from Jan 1, 2018, to Jan 31, 2022). Being a statutory administrative body in the Hong Kong Special Administrative Region, China, the Hospital Authority manages 43 public hospitals, 49 specialist outpatient clinics, and 73 primary care clinics in Hong Kong. Electronic health record data from all these Hospital Authority facilities, including emergency room visits, are captured by the clinical management system. The information recorded in the clinical management system of the Hospital Authority has been applied to several COVID-19 vaccine pharmacovigilance studies.[12,13,20,21]

Mortality data were extracted between Feb 23, 2021, and Jan 31, 2022, from the Deaths Registry under the Immigration Department of the Government of the Hong Kong Special Administrative Region, China, entries to which are mandatory for all residents in Hong Kong and are used by all Government departments in Hong Kong. The mass vaccination programme in Hong Kong was launched on Feb 23, 2021. Information regarding vaccination status and vaccine type from Feb 23, 2021, to Jan 31, 2022, was provided by the Department of Health of the Hong Kong Government.[22] Details of vaccination status were linked to pre-existing data in the clinical management system with a deidentified, unique Hong Kong identity card number or passport number for each participant.

Outcomes

Our outcomes were the overall incidence rate of any adverse event of special interest and the incidence rates of 30 adverse events of special interest, which were obtained from the list of events suggested by the WHO Global Advisory Committee on Vaccine Safety,[23] in the inpatient setting within 21 days (2 days for anaphylaxis) of either the first, second, or third CoronaVac vaccine dose compared with a baseline period. The adverse events of special interest were: autoimmune diseases (Guillain–Barré Syndrome, acute disseminated encephalomyelitis, narcolepsy, acute aseptic arthritis, type 1 diabetes, [idiopathic] thrombocytopenia, and subacute thyroiditis); cardiovascular diseases (microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia,

and myocarditis); diseases of the circulatory system (thromboembolism, haemorrhagic disease, and single organ cutaneous vasculitis); diseases of the hepatorenal system (acute liver injury, acute kidney injury, and acute pancreatitis); diseases of peripheral nerves and the CNS (generalised convulsion, meningoencephalitis, transverse myelitis, and Bell's palsy); disease of the respiratory system (acute respiratory distress syndrome); diseases of the skin, mucous membranes, and joints (erythema multiforme and chilblain-like lesions); and other system diseases (anaphylaxis, anosmia, ageusia, Kawasaki disease, and rhabdomyolysis). These adverse events of special interest were based on a single principal inpatient diagnosis with procedure codes and codes in the International Classification of Diseases, Ninth Revision, Clinical Modification. The detailed definition of each adverse event of special interest is displayed in appendix 2 (p 4).

Statistical analysis

To achieve 80% power to detect an incidence rate ratio in the exposure period between 1·5 to 3·0 at the 0·05 significance level, the required sample size for our self-controlled case series analysis ranged from 32 to 278. More details on sample size calculation are provided in appendix 2 (pp 2–3).

Theoretically, three assumptions must be fulfilled when adopting the self-controlled case series model. To satisfy these assumptions, we used a modified self-controlled case series model and only considered the first incidence of a specific adverse event of special interest during the observation period, excluding subsequent episodes in the same participant. More detail on these assumptions can be found in appendix 2 (p 1).

When measuring the separate incidences of adverse events of special interest, individuals who had a history of a particular event between Jan 1, 2005, and Feb 23, 2021, were excluded from the corresponding analysis. For all adverse events of special interest except anaphylaxis, only the first incidence of an event in an individual within 21 days (inclusive of the day of vaccination) of the first, second, or third dose of CoronaVac (ie, 0–20 days post-vaccination) would be regarded as an incident adverse event of special interest. The duration of 21 days was chosen such that medium-term adverse events could be identified, while the risk of short-term outcomes would not be underestimated because of dilution caused by further extending the observation period.[24] Previous population-based pharmacovigilance studies that evaluated COVID-19 vaccine safety also adopted 21 days as the duration of the risk period.[24,25] Because classifying allergic reactions with a symptom onset of 2 days or more after vaccination would have been difficult, the risk period for anaphylaxis was defined as 2 days (ie, 0–1 day post-vaccination). This approach has also been applied by the Centers for Disease Control and Prevention in the USA when monitoring anaphylaxis events after BNT162b2
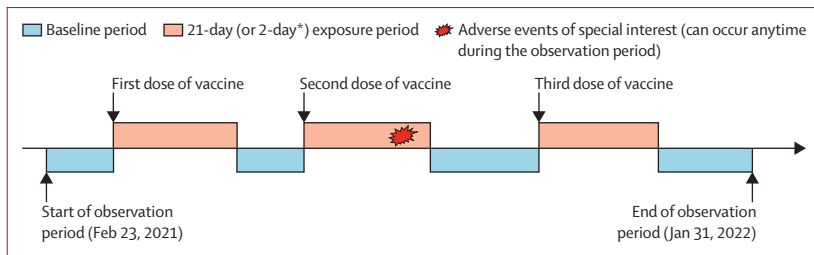
Figure 1: Observation timeline of a hypothetical patient in the self-controlled case series
*The exposure period was 2 days for anaphylaxis.

vaccination.[26] The incidences of adverse events of special interest are presented in three ways: incidence per 100 000 doses, incidence per 100 000 people, and incidence rate (cases per 100 000 person-days). 95% CIs for these measurements were calculated as the exact binomial CIs.[27] Futhermore, as the modified self-controlled case series design is not applicable for evaluating the risk of mortality after vaccination, we report all-cause mortality as a descriptive statistic.

Three exposure periods were considered in the self-controlled case series analysis: 0–20 days (0–1 day for anaphylaxis) after the first dose, 0–20 days (0–1 day for anaphylaxis) after the second dose, and 0–20 days (0–1 day for anaphylaxis) after the third dose of vaccine (figure 1). Other risk periods during the study period apart from the exposure periods were considered a baseline period (figure 1). The self-controlled case series analysis was done for a particular adverse event of special interest only when the overall number of events recorded for that event was at least five. To examine event-dependent exposure, the modified self-controlled case series model was applied by use of the R function *eventdepenexp* in the R package, SCCS. By comparing the incidence rates of adverse events of special interest in different risk periods with those in the baseline period, we calculated incidence rate ratios and corresponding 95% CIs using conditional Poisson regression, adjusting for seasonal effects in monthly categories. The model was not adjusted for any additional confounders because the self-controlled case series design does not require adjustment for any time-invariant confounders given that individuals serve as their own control. We checked the overdispersion assumption. Additionally, we calculated risk differences per 100 000 people using the difference in incidences between risk periods and the baseline period. Incidence in the risk periods was calculated by use of the observational data collected in this study, whereas incidence in the baseline period was calculated by dividing the incidence in the risk period by the adjusted incidence rate ratio.

Moreover, we did prespecified subgroup analyses of adjusted incidence rate ratios and risk differences, stratifying by age (<80 years *vs* ≥80 years) and Charlson Comorbidity Index (<3 *vs* ≥3), to confirm whether results

were consistent among different age and comorbidity groups. Three prespecified sensitivity analyses were done to ensure robustness. In the first sensitivity analysis, individuals who were infected with SARS-CoV-2 before or during the study period were excluded, owing to the possible increased risk of post-vaccination adverse events of special interest after SARS-CoV-2 infection. In the second and final sensitivity analyses, the duration of exposure periods for all adverse events of special interest, except for anaphylaxis, was changed from 21 days to 14 days or 28 days, respectively, to investigate whether similar results could be reproduced.

All statistical tests were two-sided. R (version 4.0.3) was used to conduct all statistical analyses. At least two investigators (YW, WX, or VKCY) independently conducted each analysis for quality assurance.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Of 1 253 497 individuals who received CoronaVac in Hong Kong between Feb 23, 2021, and Jan 31, 2022, 622 317 (49·6%) were aged at least 60 years and were included in the analysis. Overall, 1 229 423 doses of CoronaVac were administered to these 622 317 people within the study period, among whom 126 736 (20·4%) had one dose, 384 056 (61·7%) had two doses, and 111 525 (17·9%) had three doses of the vaccine. The mean age of CoronaVac recipients was 70·40 years (SD 8·10), of whom 47·1% were men and 52·9% were women (table 1). Pre-existing comorbidities and medication use within the past 90 days among included individuals are shown in appendix 2 (p 5).

By and large, the incidences of adverse events of special interest and all-cause mortality within 21 days (or 2 days for anaphylaxis) of vaccination with CoronaVac were small (table 2). The incidence of individual adverse events of special interest ranged from 0·00 per 100 000 doses to 31·81 per 100 000 doses (thromboembolism), from 0·00 per 100 000 people to 57·49 per 100 000 people (thromboembolism), and from 0·00 per 100 000 person-days to 1·43 per 100 000 person-days (thromboembolism; table 2). Adverse events of special interest that were not observed within 21 days of vaccination were: type 1 diabetes; subacute thyroiditis; microangiopathy; stress cardiomyopathy; single organ cutaneous vasculitis; chilblain-like lesions; and Kawasaki disease. Only three adverse events of special interest—coronary artery disease, arrhythmia, and thromboembolism—had an incidence of more than 20 cases per 100 000 people (table 2).

The first and third doses of CoronaVac were not associated with a significant excess risk of an adverse event of special interest within 21 days (or 2 days for

	Overall (n=622 317)	CoronaVac recipients with 1 dose (n=126 736)	CoronaVac recipients with 2 doses (n=384 056)	CoronaVac recipients with 3 doses (n=111 525)
Demographics and comorbidities				
Age, years	70·40 (8·10)	73·81 (9·08)	69·69 (7·79)	68·95 (6·80)
Sex				
Female	329 231 (52·9%)	74 769 (59·0%)	205 705 (53·6%)	48 757 (43·7%)
Male	293 086 (47·1%)	51 967 (41·0%)	178 351 (46·4%)	62 768 (56·3%)
Charlson Comorbidity Index	3·00 (1·16)	3·43 (1·32)	2·92 (1·11)	2·76 (0·96)
History of adverse events of special interest				
Guillain–Barré Syndrome	921 (0·1%)	216 (0·2%)	568 (0·1%)	137 (0·1%)
Acute disseminated encephalomyelitis	18 (<0·1%)	6 (<0·1%)	11 (<0·1%)	1 (<0·1%)
Narcolepsy	16 067 (2·6%)	3134 (2·5%)	9362 (2·4%)	3571 (3·2%)
Acute aseptic arthritis	5145 (0·8%)	1517 (1·2%)	2953 (0·8%)	675 (0·6%)
Type 1 diabetes	179 (<0·1%)	59 (<0·1%)	102 (<0·1%)	18 (<0·1%)
Thrombocytopenia (idiopathic)	2099 (0·3%)	581 (0·5%)	1259 (0·3%)	259 (0·2%)
Subacute thyroiditis	71 (<0·1%)	17 (<0·1%)	41 (<0·1%)	13 (<0·1%)
Microangiopathy	16 (<0·1%)	4 (<0·1%)	11 (<0·1%)	1 (<0·1%)
Heart failure	10 391 (1·7%)	3810 (3·0%)	5635 (1·5%)	946 (0·8%)
Stress cardiomyopathy	0	0	0	0
Coronary artery disease	47 628 (7·7%)	12 971 (10·2%)	27 463 (7·2%)	7194 (6·5%)
Arrhythmia	30 377 (4·9%)	9397 (7·4%)	17 173 (4·5%)	3807 (3·4%)
Myocarditis	2128 (0·3%)	590 (0·5%)	1206 (0·3%)	332 (0·3%)
Thromboembolism	64 505 (10·4%)	18 835 (14·9%)	37 602 (9·8%)	8068 (7·2%)
Haemorrhagic disease	28 190 (4·5%)	8543 (6·7%)	16 532 (4·3%)	3115 (2·8%)
Single organ cutaneous vasculitis	1680 (0·3%)	453 (0·4%)	993 (0·3%)	234 (0·2%)
Acute liver injury	17 672 (2·8%)	3536 (2·8%)	11 183 (2·9%)	2953 (2·6%)
Acute kidney injury	16 256 (2·6%)	5099 (4·0%)	9203 (2·4%)	1954 (1·8%)
Acute pancreatitis	2646 (0·4%)	710 (0·6%)	1562 (0·4%)	374 (0·3%)
Generalised convulsion	3676 (0·6%)	1063 (0·8%)	2231 (0·6%)	382 (0·3%)
Meningoencephalitis	666 (0·1%)	169 (0·1%)	399 (0·1%)	98 (0·1%)
Transverse myelitis	24 (<0·1%)	8 (<0·1%)	15 (<0·1%)	1 (<0·1%)
Bell's palsy	4637 (0·7%)	1129 (0·9%)	2811 (0·7%)	697 (0·6%)
Acute respiratory distress syndrome	8243 (1·3%)	2391 (1·9%)	4792 (1·2%)	1060 (1·0%)
Erythema multiforme	139 (<0·1%)	30 (<0·1%)	80 (<0·1%)	29 (<0·1%)
Chilblain-like lesions	85 (<0·1%)	21 (<0·1%)	51 (<0·1%)	13 (<0·1%)
Anosmia or ageusia	688 (0·1%)	131 (0·1%)	418 (0·1%)	139 (0·1%)
Anaphylaxis	14 379 (2·3%)	3785 (3·0%)	8645 (2·3%)	1949 (1·7%)
Kawasaki disease	558 (0·1%)	127 (0·1%)	353 (0·1%)	78 (0·1%)
Rhabdomyolysis	902 (0·1%)	269 (0·2%)	539 (0·1%)	94 (0·1%)

Data are mean (SD) or n (%).

Table 1: **Baseline characteristics of CoronaVac recipients**

anaphylaxis) of vaccination (figure 2). However, we found a significantly increased risk of anaphylaxis (adjusted incidence rate ratio 2·61, 95% CI 1·08–6·31; risk difference per 100 000 people 0·61, 95% CI 0·03–1·81) within 2 days of the second vaccine dose compared with the baseline period (figure 2). No other significant increased risk of an adverse event of special interest was noted after the second dose (figure 2). There was no overdispersion for all adverse events of special interest as none of the outcome variables had larger variance values than mean values (appendix 2 p 7).

For our subgroup analyses, post-hoc, we grouped adverse events of special interest into disease categories (ie, autoimmune diseases, cardiovascular diseases, diseases of the circulatory system, diseases of the hepatorenal system, disease of the peripheral nerves and CNS, and disease of the respiratory system) due to rare incidences of individual events. Significant excess risk of any adverse event of special interest category was not observed after vaccination in those younger than 80 years or in those aged 80 years or older (appendix 2 p 8) or in those with a Charlson Comorbidity Index of less than 3

	n	Incidence per 100 000 doses (95% CI)	Incidence per 100 000 people (95% CI)	Incidence rate* (95% CI)
Any adverse event of special interest	668	79·97 (74·02–86·27)	145·45 (134·64–156·91)	3·59 (3·32–3·87)
Autoimmune disease	108	10·05 (8·25–12·14)	18·07 (14·82–21·81)	0·45 (0·37–0·55)
Guillain–Barré syndrome	1	0·09 (0·00–0·50)	0·16 (0·00–0·90)	0·00 (0·00–0·02)
Acute disseminated encephalomyelitis	1	0·09 (0·00–0·50)	0·16 (0·00–0·90)	0·00 (0·00–0·02)
Narcolepsy	80	7·35 (5·83–9·15)	13·20 (10·47–16·43)	0·33 (0·26–0·41)
Acute aseptic arthritis	26	2·35 (1·53–3·44)	4·21 (2·75–6·17)	0·11 (0·07–0·16)
Type 1 diabetes	0	0·00 (0·00–0·33)	0·00 (0·00–0·59)	0·00 (0·00–0·01)
Thrombocytopenia (idiopathic)	1	0·09 (0·00–0·50)	0·16 (0·00–0·90)	0·00 (0·00–0·02)
Subacute thyroiditis	0	0·00 (0·00–0·33)	0·00 (0·00–0·59)	0·00 (0·00–0·01)
Cardiovascular diseases	336	34·06 (30·52–37·91)	61·60 (55·19–68·55)	1·54 (1·38–1·71)
Microangiopathy	0	0·00 (0·00–0·33)	0·00 (0·00–0·59)	0·00 (0·00–0·01)
Heart failure	67	6·09 (4·72–7·73)	10·96 (8·49–13·91)	0·28 (0·21–0·35)
Stress cardiomyopathy	0	0·00 (0·00–0·33)	0·00 (0·00–0·59)	0·00 (0·00–0·01)
Coronary artery disease	161	15·56 (13·25–18·16)	28·05 (23·89–32·73)	0·70 (0·60–0·82)
Arrhythmia	166	15·58 (13·30–18·14)	28·08 (23·97–32·69)	0·70 (0·60–0·82)
Myocarditis	7	0·63 (0·25–1·29)	1·13 (0·45–2·33)	0·03 (0·01–0·06)
Circulatory system	352	35·31 (31·72–39·20)	63·85 (57·36–70·88)	1·59 (1·43–1·77)
Thromboembolism	320	31·81 (28·42–35·50)	57·49 (51·37–64·15)	1·43 (1·28–1·60)
Haemorrhagic disease	39	3·65 (2·59–4·98)	6·57 (4·67–8·98)	0·16 (0·12–0·22)
Single organ cutaneous vasculitis	0	0·00 (0·00–0·33)	0·00 (0·00–0·59)	0·00 (0·00–0·01)
Hepatorenal system	40	3·79 (2·71–5·16)	6·82 (4·87–9·29)	0·17 (0·12–0·23)
Acute liver injury	5	0·46 (0·15–1·07)	0·83 (0·27–1·93)	0·02 (0·01–0·05)
Acute kidney injury	19	1·74 (1·05–2·72)	3·14 (1·89–4·90)	0·08 (0·05–0·12)
Acute pancreatitis	18	1·62 (0·96–2·56)	2·91 (1·72–4·59)	0·07 (0·04–0·12)
Peripheral nerves and CNS	65	5·90 (4·55–7·52)	10·60 (8·18–13·51)	0·27 (0·21–0·34)
Generalised convulsion	17	1·53 (0·89–2·45)	2·75 (1·60–4·40)	0·07 (0·04–0·11)
Meningoencephalitis	2	0·18 (0·02–0·65)	0·32 (0·04–1·16)	0·01 (0·00–0·03)
Transverse myelitis	1	0·09 (0·00–0·50)	0·16 (0·00–0·90)	0·00 (0·00–0·02)
Bell's palsy	46	4·15 (3·04–5·53)	7·45 (5·45–9·94)	0·19 (0·14–0·25)
Respiratory system (acute respiratory distress syndrome)	56	5·08 (3·83–6·59)	9·12 (6·89–11·85)	0·23 (0·17–0·30)
Skin, mucous membranes, and joints	1	0·09 (0·00–0·50)	0·16 (0·00–0·90)	0·00 (0·00–0·02)
Erythema multiforme	1	0·09 (0·00–0·50)	0·16 (0·00–0·90)	0·00 (0·00–0·02)
Chilblain-like lesions	0	0·00 (0·00–0·33)	0·00 (0·00–0·59)	0·00 (0·00–0·01)
Others	8	0·72 (0·31–1·42)	1·29 (0·56–2·54)	0·03 (0·01–0·06)
Anosmia or ageusia	1	0·09 (0·00–0·50)	0·16 (0·00–0·90)	0·00 (0·00–0·02)
Kawasaki disease	0	0·00 (0·00–0·33)	0·00 (0·00–0·59)	0·00 (0·00–0·01)
Rhabdomyolysis	7	0·63 (0·25–1·29)	1·13 (0·45–2·32)	0·03 (0·01–0·06)
Anaphylaxis†	6	0·55 (0·20–1·20)	0·99 (0·36–2·15)	0·25 (0·09–0·54)
All-cause mortality	175	15·65 (13·42–18·15)	28·12 (24·11–32·61)	0·71 (0·61–0·82)

*Cases per 100 000 person-days. †The follow-up period for the incidence of anaphylaxis was 2 days (ie, 0–1 day post-vaccination) and anaphylaxis was not included in the calculation of the overall incidence of adverse events of special interest.

Table 2: Incidence of adverse events of special interest and all-cause mortality among patients receiving CoronaVac vaccines

or a Charlson Comorbidity Index of 3 or more (appendix 2 p 9). The results of our three sensitivity analyses were similar to our main findings (appendix 2 pp 10–12).

Discussion

Until now, safety data for CoronaVac have been insufficient. In this large-scale, self-controlled case series, adults aged 60 years or older did not have a significantly higher risk of adverse events of special interest after CoronaVac vaccination compared with a baseline period, except for anaphylaxis within 2 days of the second dose. The absolute risk increment for anaphylaxis after the second vaccine dose was only six cases per 1 million people. In comparison with the excess risk of mortality and complications from COVID-19 in people aged 60 years or older observed in previous studies,[1] the benefits of vaccination still exceed

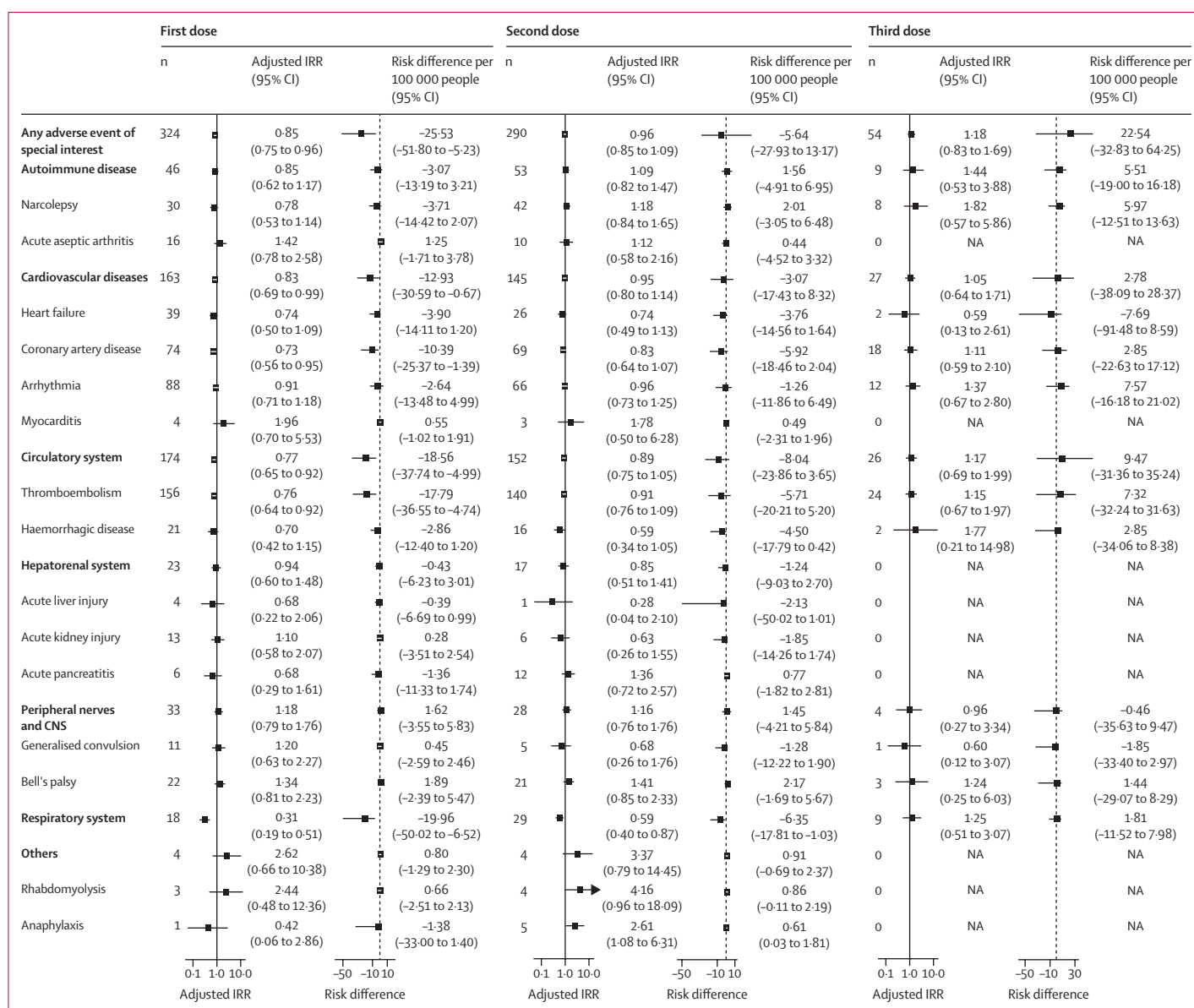|	First dose			Second dose			Third dose		
	n	Adjusted IRR (95% CI)	Risk difference per 100 000 people (95% CI)	n	Adjusted IRR (95% CI)	Risk difference per 100 000 people (95% CI)	n	Adjusted IRR (95% CI)	Risk difference per 100 000 people (95% CI)
Any adverse event of special interest	324	0.85 (0.75 to 0.96)	−25.53 (−51.80 to −5.23)	290	0.96 (0.85 to 1.09)	−5.64 (−27.93 to 13.17)	54	1.18 (0.83 to 1.69)	22.54 (−32.83 to 64.25)
Autoimmune disease	46	0.85 (0.62 to 1.17)	−3.07 (−13.19 to 3.21)	53	1.09 (0.82 to 1.47)	1.56 (−4.91 to 6.95)	9	1.44 (0.53 to 3.88)	5.51 (−19.00 to 16.18)
Narcolepsy	30	0.78 (0.53 to 1.14)	−3.71 (−14.42 to 2.07)	42	1.18 (0.84 to 1.65)	2.01 (−3.05 to 6.48)	8	1.82 (0.57 to 5.86)	5.97 (−12.51 to 13.63)
Acute aseptic arthritis	16	1.42 (0.78 to 2.58)	1.25 (−1.71 to 3.78)	10	1.12 (0.58 to 2.16)	0.44 (−4.52 to 3.32)	0	NA	NA
Cardiovascular diseases	163	0.83 (0.69 to 0.99)	−12.93 (−30.59 to −0.67)	145	0.95 (0.80 to 1.14)	−3.07 (−17.43 to 8.32)	27	1.05 (0.64 to 1.71)	2.78 (−38.09 to 28.37)
Heart failure	39	0.74 (0.50 to 1.09)	−3.90 (−14.11 to 1.20)	26	0.74 (0.49 to 1.13)	−3.76 (−14.56 to 1.64)	2	0.59 (0.13 to 2.61)	−7.69 (−91.48 to 8.59)
Coronary artery disease	74	0.73 (0.56 to 0.95)	−10.39 (−25.37 to −1.39)	69	0.83 (0.64 to 1.07)	−5.92 (−18.46 to 2.04)	18	1.11 (0.59 to 2.10)	2.85 (−22.63 to 17.12)
Arrhythmia	88	0.91 (0.71 to 1.18)	−2.64 (−13.48 to 4.99)	66	0.96 (0.73 to 1.25)	−1.26 (−11.86 to 6.49)	12	1.37 (0.67 to 2.80)	7.57 (−16.18 to 21.02)
Myocarditis	4	1.96 (0.70 to 5.53)	0.55 (−1.02 to 1.91)	3	1.78 (0.50 to 6.28)	0.49 (−2.31 to 1.96)	0	NA	NA
Circulatory system	174	0.77 (0.65 to 0.92)	−18.56 (−37.74 to −4.99)	152	0.89 (0.75 to 1.05)	−8.04 (−23.86 to 3.65)	26	1.17 (0.69 to 1.99)	9.47 (−31.36 to 35.24)
Thromboembolism	156	0.76 (0.64 to 0.92)	−17.79 (−36.55 to −4.74)	140	0.91 (0.76 to 1.09)	−5.71 (−20.21 to 5.20)	24	1.15 (0.67 to 1.97)	7.32 (−32.24 to 31.63)
Haemorrhagic disease	21	0.70 (0.42 to 1.15)	−2.86 (−12.40 to 1.20)	16	0.59 (0.34 to 1.05)	−4.50 (−17.79 to 0.42)	2	1.77 (0.21 to 14.98)	2.85 (−34.06 to 8.38)
Hepatorenal system	23	0.94 (0.60 to 1.48)	−0.43 (−6.23 to 3.01)	17	0.85 (0.51 to 1.41)	−1.24 (−9.03 to 2.70)	0	NA	NA
Acute liver injury	4	0.68 (0.22 to 2.06)	−0.39 (−6.69 to 0.99)	1	0.28 (0.04 to 2.10)	−2.13 (−50.02 to 1.01)	0	NA	NA
Acute kidney injury	13	1.10 (0.58 to 2.07)	0.28 (−3.51 to 2.54)	6	0.63 (0.26 to 1.55)	−1.85 (−14.26 to 1.74)	0	NA	NA
Acute pancreatitis	6	0.68 (0.29 to 1.61)	−1.36 (−11.33 to 1.74)	12	1.36 (0.72 to 2.57)	0.77 (−1.82 to 2.81)	0	NA	NA
Peripheral nerves and CNS	33	1.18 (0.79 to 1.76)	1.62 (−3.55 to 5.83)	28	1.16 (0.76 to 1.76)	1.45 (−4.21 to 5.84)	4	0.96 (0.27 to 3.34)	−0.46 (−35.63 to 9.47)
Generalised convulsion	11	1.20 (0.63 to 2.27)	0.45 (−2.59 to 2.46)	5	0.68 (0.26 to 1.76)	−1.28 (−12.22 to 1.90)	1	0.60 (0.12 to 3.07)	−1.85 (−33.40 to 2.97)
Bell's palsy	22	1.34 (0.81 to 2.23)	1.89 (−2.39 to 5.47)	21	1.41 (0.85 to 2.33)	2.17 (−1.69 to 5.67)	3	1.24 (0.25 to 6.03)	1.44 (−29.07 to 8.29)
Respiratory system	18	0.31 (0.19 to 0.51)	−19.96 (−50.02 to −6.52)	29	0.59 (0.40 to 0.87)	−6.35 (−17.81 to −1.03)	9	1.25 (0.51 to 3.07)	1.81 (−11.52 to 7.98)
Others	4	2.62 (0.66 to 10.38)	0.80 (−1.29 to 2.30)	4	3.37 (0.79 to 14.45)	0.91 (−0.69 to 2.37)	0	NA	NA
Rhabdomyolysis	3	2.44 (0.48 to 12.36)	0.66 (−2.51 to 2.13)	4	4.16 (0.96 to 18.09)	0.86 (−0.11 to 2.19)	0	NA	NA
Anaphylaxis	1	0.42 (0.06 to 2.86)	−1.38 (−33.00 to 1.40)	5	2.61 (1.08 to 6.31)	0.61 (0.03 to 1.81)	0	NA	NA

Figure 2: Adjusted IRRs and risk differences of adverse events of special interest within 21 days of CoronaVac vaccination

Adjusted IRRs were obtained from conditional Poisson regression adjusted for seasonal effects in our self-controlled case series analysis. The dashed line represents a risk difference of 0. IRR=incidence rate ratio. NA=not applicable.

its risks in places where COVID-19 is prevalent. Our results are consistent with the findings of previous studies of COVID-19 inactivated vaccines among a group of immunocompromised patients[4] and people with chronic hepatitis B virus infection.[28] Previous studies have revealed that multimorbidity does not translate to an additional risk of adverse events after COVID-19 vaccination[29] and that the composition of the gut microbiota might contribute to differences in post-vaccination adverse event rates.[30]

Anaphylaxis is an inherent risk associated with all vaccines and medicinal products. According to a previous study,[31] the estimated rate of anaphylaxis was 2·2 cases per 1 million doses of CoronaVac, which is slightly lower than our estimation (5·5 cases per 1 million doses [95% CI 2·0–12·0]). Allergic reactions can be directed towards the inactive excipients that stabilise the vaccine, such as polyethylene glycol and polysorbate, and, rarely, to the active component of the vaccine.[32] CoronaVac does not contain the aforementioned excipients,[33] yet theoretically carries a risk of anaphylaxis. Although it remains possible that we did not have sufficient statistical power to detect an increased risk of anaphylaxis after the first dose, the higher risk of anaphylaxis after the second

dose compared with the baseline period can potentially be attributed to a genuine anaphylactic reaction to the vaccine components, which only happens on re-exposure to the same allergen when it cross- links IgE on sensitised mast cells and triggers their degranulation.[34] Allergic reactions developing after the second dose, but not the first dose, of BNT162b2 have also been reported in the literature.[35] Because only 111 525 people in our study received a third dose of CoronaVac, it is very probable that our study did not have sufficient power to detect anaphylaxis after the third dose because the event rate was low. Despite anaphylaxis being potentially life-threatening, no deaths from allergic reactions after COVID-19 vaccination have been reported so far.[36]

The main result of our study—that there were no major adverse events after vaccination—is in accordance with findings from randomised controlled trials of CoronaVac done in populations mainly consisting of younger people (8·5% of participants were aged ≥60 years).[9,10] Some post-marketing observational studies[12,24,37–41] have raised specific concerns regarding the safety of CoronaVac and other COVID-19 vaccines using different platforms, such as mRNA and viral vectors. They have found associations with myocarditis following mRNA-based COVID-19 vaccines,[12,24,37,38] vascular events and thromboembolism following mRNA-based and viral vector-based COVID-19 vaccines,[39,40] and Bell's palsy following the CoronaVac COVID-19 vaccine.[41]

After vaccination with BNT162b2 or Ad.26.COV2.S vaccines, myocarditis in boys and men aged 12–24 years has been an issue of concern.[42,43] We did not find such an association in adults aged 60 years or older who received CoronaVac. As it is probably an immune-mediated reaction, post-vaccination myocarditis might be attributed to heightened immune responses in some clinically susceptible adolescents,[44] although the exact mechanism is not well understood. Our findings are in line with previous studies reporting a low incidence of myocarditis in older people after receiving mRNA vaccines.[45,46]

Although an increased risk of thromboembolism has been reported with BNT162b2 and the adenoviral vector vaccine ChAdOx1 nCoV-19,[39,40] we did not find an increased risk of thromboembolism with CoronaVac in our study; it is possible that we did not have sufficient statistical power to detect such rare events. With regards to the proposed mechanism of vaccine-associated thromboembolism, free DNA in the vaccine might trigger the production of antibodies against platelet factor 4, which in turn could activate platelets and promote immune thrombotic thrombocytopenia, resulting in bleeding or thrombosis.[47] As a whole-virion vaccine,[9] whether CoronaVac is associated with a lower risk of thromboembolism than other COVID-19 vaccines has been inadequately explored. A Thai study[48] revealed that CoronaVac recipients had a low prevalence of antibodies against platelet factor 4, but the relevance of this finding to vaccine-induced thrombotic thrombocytopenia is unknown. Presently, thromboembolic

events are most common with ChAdOx1 nCoV-19,[39] with an estimated incidence of vaccine-induced immune thrombocytopenia and thrombosis of at least one case per 100 000 people aged 50 years or older.[49] As the approximate incidence of acute cerebrovascular disease in people with COVID-19 is 1·4% (95% CI 1·0–1·9),[50] the potential risk associated with vaccination is still substantially lower.

By contrast to a study[41] in Hong Kong that suggested that the risk of Bell's palsy in adults (aged ≥18 years) was increased after CoronaVac vaccination, we did not find an association between Bell's palsy and CoronaVac in recipients aged 60 years or older. This discrepancy could be ascribed to these events being rare in this older age group, resulting in inadequate power to detect such risk; previous studies report that the background incidence of Bell's palsy typically peaks at around 40–50 years of age.[51,52] More importantly, the risk of Bell's palsy is actually higher in those who are infected with SARS-CoV-2 than in COVID-19 vaccine recipients.[53] Indeed, current evidence regarding post-vaccination Bell's palsy remains largely inconsistent and limited in scope. Further studies with large sample sizes are needed to confirm our findings.

Our study has several strengths. First, in an area of sparse data, our study provides reassuring evidence regarding the safety of CoronaVac for adults aged 60 years or older. Second, we extracted data from the vaccine registry provided by the Department of Health of the Hong Kong Government, which covers the entire population of Hong Kong, and so our sample size was large and population-based. Third, the prevalence of COVID-19 in Hong Kong was low during the study period (ie, 14 197 COVID-19 cases confirmed as of Jan 31, 2022, among a population size of around 7·5 million),[54] and, therefore, the likelihood of SARS-CoV-2 infection interfering with post-vaccination reactions was minimal. Finally, our findings were robust to several sensitivity analyses.

Our study also has limitations. First, considering the relatively small number of events recorded, it is possible that this study did not have adequate statistical power to detect infrequent events. Second, we only enrolled patients who had ever attended clinics or hospitals under the Hospital Authority. Theoretically, people who had been vaccinated but had never used any public health-care service would not have been captured by our study. However, this number would have been reasonably small because more than 90% of inpatient care in Hong Kong is provided by the Hospital Authority.[55] Third, events might have been underdiagnosed or misclassified as they were defined by diagnostic codes in the database. Nevertheless, this limitation is probably minimal; the coding accuracy of the electronic health database of the Hospital Authority has been shown in previous studies in Hong Kong, showing that the positive predictive values for the diagnoses were high.[56–58] Fourth, no causal relationship can be established due to the observational nature of our study. Fifth, we cannot rule out the possibility that some

potentially vaccine-related events occurred outside the 21-day exposure period, and the list of adverse events of special interest that we adopted in this study is not exhaustive. Finally, we did not evaluate characteristics or predictors associated with an increased risk of adverse events of special interest after vaccination. Further studies are warranted to evaluate the long-term risks of COVID-19 vaccines and predictors for the risk of post-vaccination adverse events of special interest in the older population.

In summary, no increased risk of adverse events of special interest, except for anaphylaxis after the second dose, was detected in CoronaVac recipients aged 60 years or older. The absolute risk increment for anaphylaxis after the second vaccine dose was small. Because older age is associated with poor outcomes after SARS-CoV-2 infection, the benefits of vaccination in this population far outweigh the risks in places where COVID-19 is prevalent. More pharmacovigilance studies of COVID-19 vaccines among older people are warranted.

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