Analysis of adverse events following COVID-19 vaccination and infection: A retrospective, comparative cohort study using a claims database from Discovery Health, a managed care organisation in South Africa

K Bernhardt,[1] BCom Hons (Actuarial Science), FASSA; **S Collie,**[1] BSc Hons (Actuarial Science), FASSA; **D W C Jacobs,**[1] MB BCh, FC Paed(SA); **P Mekgwe,**[1] RN, CDI (AHIMA); **G Gray,**[2] MB BCh, FC Paed(SA); **J Peter,**[3] MB BCh, PhD; **L-G Bekker,**[4] MB BCh, PhD

[1] *Discovery Health, Johannesburg, South Africa*
[2] *South African Medical Research Council, Cape Town, South Africa*
[3] *Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*
[4] *Desmond Tutu HIV Centre, University of Cape Town, South Africa*

Corresponding author: *D W C Jacobs (DaveJ@discovery.co.za)*

Background. Adverse events following COVID-19 vaccination have been studied extensively in recent years. However, there remains a paucity of data directly comparing adverse events among COVID-19 vaccinees and individuals with SARS-CoV-2 infection within the insured population in South Africa (SA). Moreover, the breadth of conditions assessed in this study exceeds that of most existing research, providing a unique perspective on potential immune-mediated outcomes. This study therefore contributes to a more comprehensive understanding of the risk-benefit profile of COVID-19 vaccination across different age groups.
Objective. To evaluate the rate of adverse events occurring in COVID-19 vaccinees compared with individuals who have had SARS-CoV-2 infection.
Methods. We conducted a retrospective cohort study, matching vaccinated individuals and those who have had a SARS-CoV-2 infection with comparable unexposed counterparts. Incident risk rates for 99 possible immune-mediated adverse events were compared between populations over a 42-day observation period to estimate relative risk ratios and confidence intervals. We used data from Discovery Health, a large managed care organisation in SA.
Results. A total of 3 112 918 individuals aged ≥12 years who received a COVID-19 vaccination were included in the study, with an average of 76% successfully matched to a suitable comparator based on their risk profile. Additionally, 443 220 individuals with documented SARS-CoV-2 infection were analysed, with an average of 99.7% matched to an appropriate comparator. For recipients of the BNT162b2 vaccine, aged 12 - 17 years, we found an increased risk of lymphadenopathy and vertigo, compared with an increased risk of appendicitis, arrhythmia, encephalomyelitis, lymphadenopathy, myocarditis, seizure, syncope, type 1 diabetes and vertigo post SARS-CoV-2 infection. For those aged ≥18 years, we found no increased risk for any conditions post BNT162b2 vaccination. Additionally, no conditions post AD26.COV2.S vaccination had an increased risk for any age group. Post documented SARS-CoV-2 infection for persons in age groups 18 - 39, 40 - 59 and ≥60 years, we found an increased risk of acute kidney injury, anaemia, appendicitis, arrhythmia, axonal and neuronal neuropathy, cerebrovascular accident, deep-vein thrombosis, encephalomyelitis, endometriosis, eosinophilic oesophagitis, fibrosing alveolitis, glomerulonephritis, inflammatory bowel disease, intracranial haemorrhage, lymphadenopathy, myocardial infarction, myocarditis, myositis, pericarditis, pulmonary embolism, rheumatic fever, seizure, syncope, thrombocytopenia, type 1 diabetes, urticaria, vertigo, multiple sclerosis, cholangitis and/or pancreatitis. Notably, not all conditions presented with an increased risk in each age group.
Conclusions. Across all age subgroups analysed, the risks associated with SARS-CoV-2 infection exceeded the increased risks following COVID-19 vaccination.

Keywords: COVID-19, COVID-19 adverse events, vaccine safety, SARS-CoV-2 infection

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Since 5 May 2023, the COVID-19 pandemic has no longer been classified as a global health emergency. The development and distribution of COVID-19 vaccines provided an essential tool in reducing risk of severe disease,[1,2] and supported the lifting of pandemic restrictions.[3]

Although COVID-19 is no longer classified as a global health emergency, understanding the safety profile of COVID-19 vaccines remains crucial for informing future vaccination strategies and guiding responses to potential pandemics, particularly in the context of the continued rise of vaccine misinformation and denialism. It therefore remains important to evaluate the prevalence and severity of adverse events associated with both COVID-19 vaccination and SARS-CoV-2 infection to better inform the risk-benefit profile of COVID-19 vaccination across different age groups.

Several studies have demonstrated that the vaccines are generally safe and well tolerated, with most adverse events being mild and transient.[4] However, there are reports of several rare severe adverse events, such as anaphylaxis, myocarditis post BNT162b2 vaccination, and thrombosis with thrombocytopenia syndrome (TTS) post vaccination with viral vaccine platforms such as AD26.COV2 and Chadox vaccination.[1,5-7] SARS-CoV-2 infection has been linked to a wide range of serious complications, including respiratory failure,

thromboembolic events, multisystem inflammatory syndrome, long-term sequelae often referred to as 'long-COVID'[8,9] and death.[10,11] In addition, case reports and case series connecting both COVID-19 vaccination and SARS-CoV-2 infection to emergent autoimmune diseases have been published.[12-15]

Objective

To contribute to the understanding of the comparative risks associated with COVID-19 vaccination and SARS-CoV-2 infection by analysing a broad range of immune-mediated conditions using administrative data from Discovery Health, a large South African (SA) managed care service provider.

Methods

Real-world safety studies among large populations are more likely to provide sufficient volumes to power risk-ratio estimates of rare adverse events among the vaccinated population than clinical trials, which typically have lower volumes. A comparison with unvaccinated controls provides greater certainty that identified adverse events are vaccine-induced, as it provides a risk relative to the population's baseline risk over a consistent timeframe. Registries of voluntary vaccine safety adverse events, such as the Vaccine Adverse Events Reporting System by the Centers for Disease Control and Prevention and the US Food and Drug Administration, and the reporting system managed by the SA Health Products Regulatory Agency, lack a relevant temporal comparison of underlying adverse events in the unvaccinated general population.

This study conducts two independent analyses, comparing adverse events in vaccinated individuals and SARS-CoV-2 infected individuals (the study population) with those in their respective unvaccinated or uninfected 'clinical twins' (the comparators). The outcomes of these two analyses are subsequently compared to assess the relative impact of adverse events following COVID-19 vaccination v. infection, which constitutes the primary objective of the study.

Database

The study was conducted using data from Discovery Health, a large SA managed care service organisation. This database is limited to the insured population, who are therefore likely to differ from the general SA population in terms of socioeconomic status, access to healthcare and health-seeking behaviour. Consequently, the results should be interpreted within the context of an insured population. Nevertheless, the database provides a valuable and reliable source for assessing real-world vaccine safety at scale, and has been used in numerous published studies regarding SARS-CoV-2 infection and the effectiveness of vaccinations.[16,17]

The Discovery Health database records extensive details on all submitted claims, including World Health Organization (WHO) ICD-10 diagnosis and National Pharmaceutical Product Index (NAPPI) health product codes. WHO ICD-10 codes were used to identify diagnoses of the conditions analysed, while NAPPI codes were used to track vaccinations. Additionally, vaccination data were supplemented with information from the SA National Department of Health (NDoH). SARS-CoV-2 infections were identified using a combination of claims data (WHO ICD-10 codes) and pathology result data, which included antigen, antibody and polymerase chain reaction (PCR) test results.

Conditions

For the period 17 February 2021 - 30 June 2022, we assessed the risk of 99 conditions post vaccination (Ad26COV2S and BNT162b2) and infection among Discovery Health clients aged ≥12 years who had at least 12 months of medical insurance cover on Discovery Health. The list of conditions analysed includes a compilation of possible immune-related conditions published by the American Autoimmune Related Diseases Association, and conditions of interest identified in other studies of adverse events associated with COVID-19 vaccination.[1,18,19] Conditions were grouped into larger condition cohorts, to ensure sufficient volume while maintaining clinical appropriateness. Conditions were identified in the administrative data according to the WHO ICD-10 code billed. Nonspecific conditions, conditions where an appropriate set of WHO ICD-10 codes could not be mapped, and conditions pertaining to children aged <12 years were not analysed (Appendix Table S1 and Table S2).

Participants and setting

The two study populations were identified as those individuals who had had a COVID-19 vaccination (the 'vaccination analysis') or a SARS-CoV-2 infection (the 'infection analysis') within the study period, and had at least 12 months of medical insurance cover on Discovery Health within SA. The COVID-19 vaccinations considered in the vaccination analysis were Ad26.COV2.S (Janssen vaccine) and BNT162b2 (Pfizer-BioNTech vaccine). Both doses of Ad26.COV2.S were included, as well as the first three doses of BNT162b2. Adverse events were analysed following each dose, with results evaluated separately by vaccine type, thus minimising the need to account for the varying number of doses in each regimen.

For the infection analysis, adverse events were assessed across SA's first four waves of SARS-CoV-2 infection, driven by the D614G, Beta, Delta and Omicron variants. SARS-CoV-2 infections were identified using pathology results and WHO ICD-10 coding (U07.1), which indicates a confirmed positive test. Additionally, registrations and claims under Discovery Health's WHO outbreak benefit were considered in the identification process, as certain benefits under this arrangement were available only to members with confirmed infection.

In the vaccination analysis, individuals with a prior SARS-CoV-2 infection (as defined above) were excluded, while in the infection analysis, individuals were removed from the study population if they had had a vaccination within the last 6 months. This approach was taken to ensure sufficient sample size in both study populations while removing the potential for prior events, such as infections or vaccinations, invalidating the results of the study. In the infection analysis, it was assumed that long-term adverse events from the vaccine were highly unlikely, thus minimising any potential impact on the validity of results in the infection analysis.

It is important to note that many SARS-CoV-2 infections during the pandemic were not diagnosed, primarily because individuals with asymptomatic or mild infection did not seek testing. In addition, some infections may have been missed due to false-negative test results. Consequently, these undetected infections are not reflected in our dataset.

Sample size

A total of 3 112 918 vaccination entries were included in the study across the two vaccine types and the four age categories. The majority of vaccinations (89%) were BNT162b2, with 51% representing the first dose, as shown in Tables 1 and 2. It is important to note that the vaccination types were analysed separately, given the different regimen structure. In the infection analysis, 29 453 individuals aged 12 - 17, 189 857 aged 18 - 39, 163 380 aged 40 - 59, and 60 530 aged ≥60 years were infected with SARS-CoV-2 before the removal of those with a history of the condition.

Table 1. Volume of vaccinations (before matching) by vaccine type and age category

Age group, years	BNT162b2 vaccination volume	Ad26.COV2.S vaccination volume	Total
12 - 17	130 102	-	130 102
18 - 39	831 772	158 713	990 485
40 - 59	962 553	148 754	1 111 307
≥60	856 514	24 510	881 024
Total	2 780 941	331 977	3 112 918

Table 2. Vaccination distribution by dose number (before matching)

	BNT162b2 vaccination volumes, %			Ad26.COV2.S vaccination volumes, %	
Age group, years	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2
12 - 17	71.7	28.2	0.1	-	-
18 - 39	51.8	43.3	4.9	81.5	18.5
40 - 59	47.6	43.2	9.2	76.0	24.0
≥60	41.7	39.2	19.1	68.0	32.0
Total	48.2	41.3	10.5	78.1	21.9

Outcomes

We assessed the rate of new onset of 99 adverse conditions in the study populations over a 42-day period, starting from the date of vaccination and infection (the 'trigger date') for the respective studies. The date of the positive SARS-CoV-2 test, identified using pathology results and WHO ICD-10 coding (U07.1), was used as a proxy for the date of infection. A 'censor date' was also calculated for each matched pair, defined as the date of the earliest occurrence of any of the following events for either the study population or the comparator individual:

- death
- withdrawal from the medical scheme.

For the vaccination analysis:

- SARS-CoV-2 infection for either individual
- COVID-19 vaccination for the comparator.

For the infection analysis:

- COVID-19 vaccination for either individual
- SARS-CoV-2 infection for the comparator.

The 'observation period' is defined as the period between the trigger date and the censor date, and serves as the basis for calculating the rate of each condition.

The primary outcome measure used in the study was the relative risk (RR) ratio between the incidence of the condition in the study population and the respective comparator group. In the formula below, *s* denotes 'study population', *c* denotes 'comparators' and *i* denotes the i^{th} condition:

$$Relative\ risk\ ratio_i = \frac{Diagnoses_{s,i} / Exposure_{s,i}}{Diagnoses_{c,i} / Exposure_{c,i}}$$

A diagnosis was inferred from the administrative data when a participant had a claim linked to one of the respective WHO ICD-10 codes for each condition (Appendix Table S1). Exposure was measured as the number of days between the 'trigger date' and the 'censor date'.

A risk difference per 100 000 lives was also calculated using a similar formula to the one above, with the exception of subtracting the rates from each other rather than dividing. The rate difference was then scaled to reflect a per 100 000 lives measure.

To obtain confidence intervals (CIs) around the outcomes in both the study and comparator population, as well as the relative measures between the populations, we used bootstrapping with replacement, iterating 500 times. This approach enabled the calculation of CIs without assuming any specific statistical distribution. In addition, CIs around the RR ratio between the study and comparator population was calculated.

The 95% CI was obtained for each of the respective measures analysed (i.e. the risk ratio, number of adverse events and risk difference per 100 000 lives), by assessing the 2.5th percentile and 97.5th percentile across bootstraps. The bootstrapping methodology was applied independently between the vaccination and infection analyses.

Study design

In each bootstrap iteration, individuals in our study population were randomly matched to a clinical twin, based on the specified matching criteria below. Once a clinical twin was selected, it was ineligible for further selection within that bootstrap.

Each of the rates were compared with those of matched comparators across the following age subgroups: 12 - 17, 18 - 39, 40 - 59 and ≥60 years. The results were analysed by the various age subgroups to ensure a more appropriate comparison between the vaccination and infection analyses at the end.

The 'clinical twin' approach was used to determine a suitable set of comparators for each of the study populations, ensuring that the comparators had a similar risk composition compared with the study population. Comparators were selected based on the following matching criteria among participants:

- Age: clinical twins were matched within 1 year of age for individuals aged 18 - 64 years; participants aged 12 - 17 years were matched within the same age group, as were those aged ≥65 years.
- Sex: male or female.
- Location: hospital service area in SA.
- Number of chronic conditions: 0, 1, ≥2.
- Number of prior influenza vaccinations in the period 5 years prior to COVID-19 vaccination or SARS-CoV-2 infection: 0, 1, ≥2. People who had an influenza vaccination in the years leading up to and during the COVID-19 pandemic were likely to be more

aware of promoting their general health and wellbeing and to adhere to preventive measures.
- Medical scheme product option: looking at out-of-hospital benefits, we divided 24 plans available through both Discovery Health Medical Scheme and 18 of the Discovery Health administered schemes into 5 groups to account for variation in submission of out-of-hospital claims and associated WHO ICD-10 codes.
- Additionally, comparators were not matched if they had had a prior SARS-CoV-2 infection or if they had had a COVID-19 vaccination in the past 6-month period.

The study aimed to determine the rate of new onset for each condition within the analysis, i.e. individuals with a prior history of a specific condition would be excluded from the analysis for that condition. Consequently, the study population would need to vary for each of the 99 conditions, with bootstrapping applied independently for each condition across the two analyses. However, owing to the large population sizes and the computational resources available, the bootstrapping could not be performed on all the populations.

A two-stage process was therefore introduced. The first stage was set up to identify conditions of interest that might present with an increase in risk post vaccination or infection. In the first stage, for each of the 99 conditions, individuals with a prior history of the condition were removed from the study population after bootstrapping was performed. Adverse events of interest were identified if the incident RR ratio exceeded 0.95 (95% CI), and there were at least 10 total incidents across both the study and comparator populations, on average, across the 500 bootstraps. In the second stage, for each of the conditions of interest identified, individuals with a prior history of the condition were removed from the study population before bootstrapping was performed. Therefore, a new study population was created for each of the conditions, with population inclusion and exclusion criteria applied before bootstrapping.

In the second stage, the conditions associated with an increased risk following vaccination or infection were identified.

Ethical approval

This study used retrospective, anonymised administrative claims data held by Discovery Health. As no identifiable patient information was accessible to the researchers, formal ethics committee approval was not sought.

Results

We analysed 130 102, 990 485, 1 111 307 and 881 024 individuals aged 12 - 17, 18 - 39, 40 - 59 and ≥60 years, respectively, who received a COVID-19 vaccine dose. On average, 99%, 87%, 77% and 59% of participants in these age groups were matched, respectively (Table 3).

Between 1 March 2020 and 30 June 2022, 29 453, 189 857, 163 380 and 60 530 individuals aged 12 - 17, 18 - 39, 40 - 59 and ≥60 years, respectively, who were infected with SARS-CoV-2, were analysed. On average, 99.9%, 99.6%, 99.7% and 99.8% of participants in these age groups met the inclusion criteria and were matched (Table 3).

No increased risk, compared with comparators, was identified in the study for any condition post AD26.COV2 vaccine.

In individuals aged 12 - 17 years, we observed an increased risk difference per 100 000 person years (RD) for lymphadenopathy (148, 95% CI 12 - 288) and for vertigo (114, 95% CI 16 - 212) following BNT162b2 vaccination. The relative risk (RR) of these conditions within 42 days of vaccination was 1.6 (95% CI 1 - 2.4) for lymphadenopathy and 1.9 (95% CI 1.1 - 3.2) for vertigo (Table 4 and Fig. 1). For those aged ≥18 years, we found no increased risk for any conditions relative to matched comparators post BNT162b2 vaccination.

Across all age subgroups, 31 unique adverse event conditions following SARS-CoV-2 infection were identified. For those aged 12 - 17 years, we found an increased RD of appendicitis (1 801, 95% CI 1 286 - 2 395), arrhythmia (365, 95% CI 125 - 623), encephalomyelitis (281, 95% CI 93 - 468), lymphadenopathy (348, 95% CI 69 - 714), myocarditis (332, 95% CI 155 - 526), seizure (1 692, 95% CI 1 101 - 2 253), syncope (772, 95% CI 413 - 1178), type 1 diabetes (306, 95% CI 124 - 528) and vertigo (335, 95% CI 95 - 616) (Table 3 and Fig. 1).

For those aged 18 - 39 years, we found an increased RD of acute kidney injury (497, 95% CI 391 - 605), anaemia (506, 95% CI 330 - 672), appendicitis (564, 95% CI 410 - 715), arrhythmia (378, 95% CI 256 - 495), axonal and neuronal neuropathy (42, 95% CI

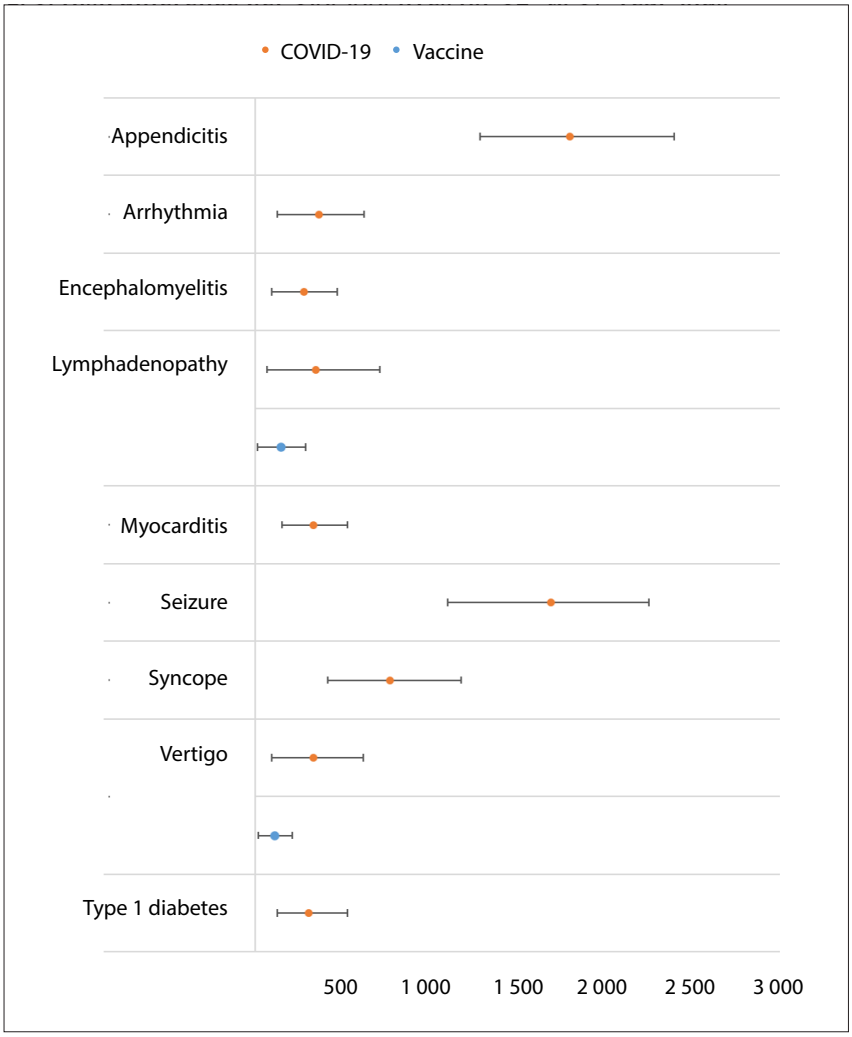

Fig. 1. Risk difference per 100 000 lives for 12 - 17-year-olds.

Table 3. Data characteristics: COVID-19 vaccine and SARS-CoV-2 population (post matching)

	BNT162b2 (*n*=2 036 333)		AD26.COV2 (*n*=329 104)		SARS-CoV-2 (*n*=441 935)	
Characteristic	**Vaccinated**	**Control**	**Vaccinated**	**Control**	**Vaccinated**	**Control**
Age, years, median (IQR)	44 (32 - 59)	43 (32 - 59)	40 (32 - 49)	40 (32 - 48)	40 (30 - 52)	39 (30 - 51)
Age group, years, *n* (%)						
<18	128 546 (0.06)	128 546 (0.06)	0	0	29 415 (0.07)	29 415 (0.07)
18 - 39	704 431 (0.35)	738 259 (0.36)	157 513 (0.48)	162 963 (0.5)	189 166 (0.43)	194 854 (0.44)
40 - 49	390 170 (0.19)	379 779 (0.19)	95 147 (0.29)	93 174 (0.28)	96 577 (0.22)	95 140 (0.22)
50 - 59	316 740 (0.16)	323 211 (0.16)	52 128 (0.16)	50 319 (0.15)	66 358 (0.15)	64 568 (0.15)
60 - 69	269 246 (0.13)	242 133 (0.12)	17 642 (0.05)	14 313 (0.04)	33 430 (0.08)	30 641 (0.07)
70 - 79	165 411 (0.08)	158 969 (0.08)	5 425 (0.02)	5 750 (0.02)	18 454 (0.04)	19 211 (0.04)
≥80	61 789 (0.03)	65 435 (0.03)	1 249 (0)	2 586 (0.01)	8 535 (0.02)	8 107 (0.02)
Sex, *n* (%)						
Female	1 089 593 (0.54)	1 089 593 (0.54)	202 396 (0.61)	202 396 (0.61)	242 558 (0.55)	242 558 (0.55)
Male	946 740 (0.46)	946 740 (0.46)	126 708 (0.39)	126 708 (0.39)	199 377 (0.45)	199 377 (0.45)
Chronic count, *n* (%)						
0	1 257 527 (0.62)	1 257 527 (0.62)	225 391 (0.68)	225 391 (0.68)	265 202 (0.6)	265 202 (0.6)
1	355 196 (0.17)	355 196 (0.17)	60 204 (0.18)	60 204 (0.18)	84 949 (0.19)	84 949 (0.19)
≥2	423 610 (0.21)	423 610 (0.21)	43 509 (0.13)	43 509 (0.13)	91 785 (0.21)	91 785 (0.21)
Flu vaccinated, years *n* (%)						
0	1 776 220 (0.87)	1 776 220 (0.87)	283 092 (0.86)	283 092 (0.86)	386 553 (0.87)	386 553 (0.87)
1	141 019 (0.07)	141 019 (0.07)	30 728 (0.09)	30 728 (0.09)	33 960 (0.08)	33 960 (0.08)
≥2	119 093 (0.06)	119 093 (0.06)	15 284 (0.05)	15 284 (0.05)	21 423 (0.05)	21 423 (0.05)

IQR = interquartile range; flu = influenza.

10 - 81), cerebrovascular accident (151, 95% CI 76 - 229), deep-vein thrombosis (163, 95% CI 82 - 243), encephalomyelitis (99, 95% CI 46 - 153), endometriosis (137, 95% CI 16 - 258), fibrosing alveolitis (57, 95% CI 25 - 96), glomerulonephritis (306, 95% CI 190 - 426), inflammatory bowel disease (66, 95% CI 5 - 131), myocardial infarction (173, 95% CI 106 - 238), myocarditis (450, 95% CI 355 - 540), myositis (126, 95% CI 23 - 220), pericarditis (139, 95% CI 78 - 198), pulmonary embolism (1 313, 95% CI 1 146 - 1 483), rheumatic fever (126, 95% CI 71 - 182), seizure (896, 95% CI 713 - 1 089), syncope (329, 95% CI 201 - 456), thrombocytopenia (144, 95% CI 79 - 208), type 1 diabetes (356, 95% CI 256 - 467), urticaria (157, 95% CI 21 - 279), multiple sclerosis (31, 95% CI 0 - 66) and cholangitis (49, 95% CI 15 - 86) (Table 3 and Fig. 2).

For those aged 40 - 59 years, we found an increased RD of acute kidney injury (4 659, 95% CI 4 335 - 4 986), anaemia (893, 95% CI 651 - 1 125), appendicitis (289, 95% CI 161 - 414), arrhythmia (1 228, 95% CI 1 025 - 1 436), axonal and neuronal neuropathy (173, 95% CI 99 - 248), cerebrovascular accident (743, 95% CI 586 - 901), deep-vein thrombosis (395, 95% CI 256 - 526), encephalomyelitis (180, 95% CI 106 - 259), eosinophilic oesophagitis (77, 95% CI 6 - 146), fibrosing alveolitis (198, 95% CI 130 - 272), glomerulonephritis (449, 95% CI 301 - 606), inflammatory bowel disease (119, 95%

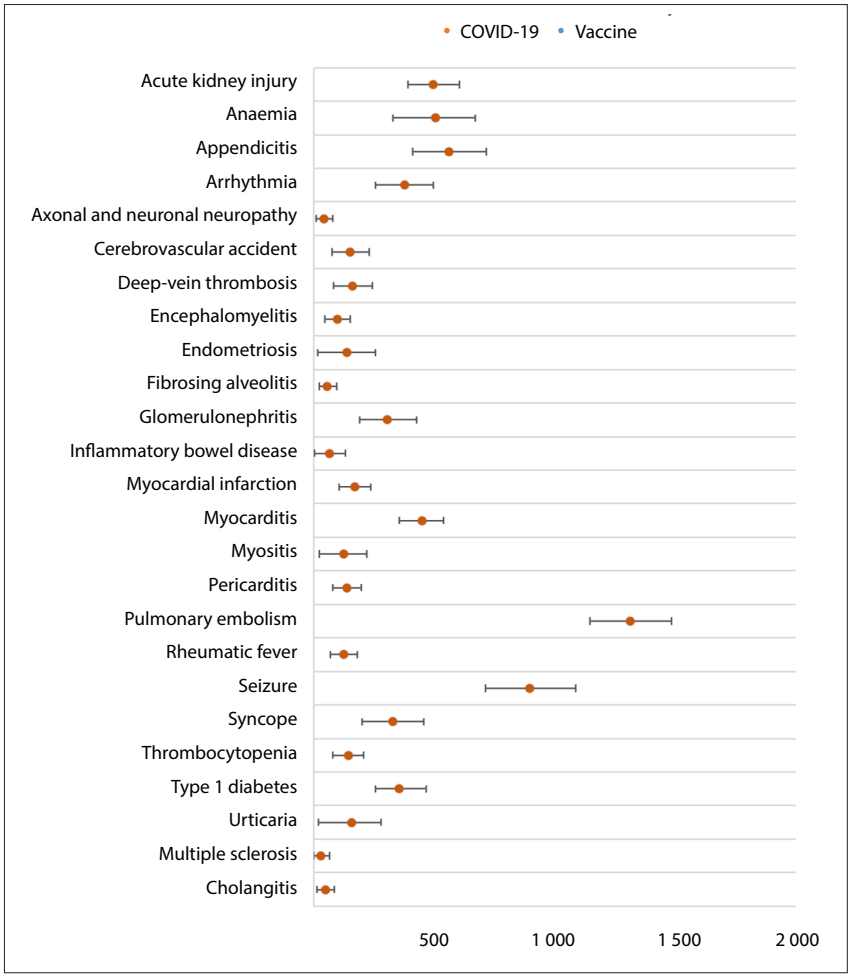

Fig. 2. Risk difference per 100 000 lives for 18 - 39-year-olds.

Table 4. Adverse events within 42 days post vaccination with BNT162b2 dose 1, 2 or 3 in 12 - 17-year-olds (*N*=128 546)

BNT162b2	Average vaccine population exposure, person-half-years	Average clinical twin exposure, person-half-years	Adverse events for study population, per 100 000 person-years (95% CI)	Adverse events for clinical twin population, per 100 000 person-years (95% CI)	Risk ratio (95% CI)
Lymphadenopathy	23 662	23 664	414 (296 - 529)	265 (182 - 355)	1.6 (1 - 2.4)
Vertigo	25 487	25 488	251 (165 - 345)	137 (78 - 200)	1.9 (1.1 - 3.2)

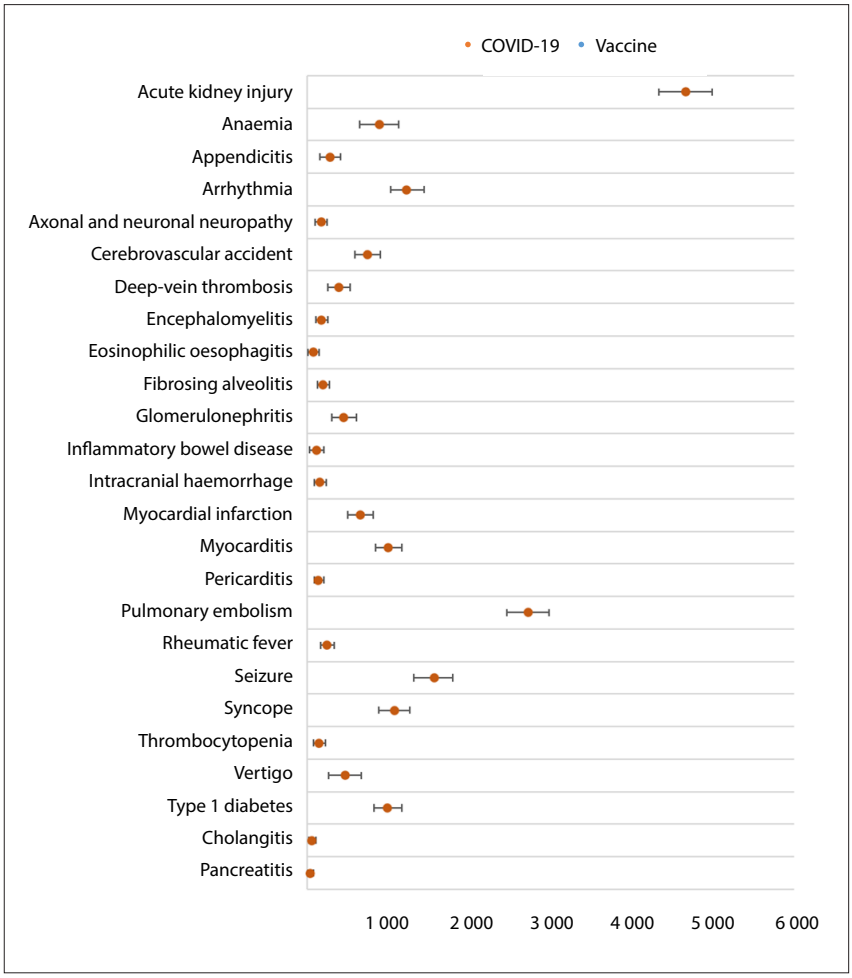

Fig. 3. Risk difference per 100 000 lives for 40 - 59-year-olds.

CI 32 - 209), intracranial hemorrhage (159, 95% CI 84 - 239), myocardial infarction (658, 95% CI 496 - 811), myocarditis (1003, 95% CI 842 - 1 165), pericarditis (140, 95% CI 87 - 205), pulmonary embolism (2 723, 95% CI 2 459 - 2 982), rheumatic fever (242, 95% CI 167 - 338), seizure (1570, 95% CI 1 317 - 1 797), syncope (1077, 95% CI 885 - 1 262), thrombocytopenia (145, 95% CI 75 - 227), type 1 diabetes (986, 95% CI 822 - 1 164), vertigo (469, 95% CI 268 - 666), cholangitis (62, 95% CI 19 - 111) and pancreatitis (40, 95% CI 6 - 80) (Appendix Table S3 and Fig. 3).

For those aged ≥60 years, we found an increased RD of acute kidney injury (17 299, 95% CI 16 185 - 18 595), anaemia (3 258, 95% CI 2 642 - 3 942), appendicitis (251, 95% CI 90 - 414), arrhythmia (5 913, 95% CI 5 005 - 6 759), axonal and neuronal neuropathy (224, 95% CI 89 - 376), cerebrovascular accident (5 273, 95% CI 4 593 - 6 006), deep-vein thrombosis (1 554, 95% CI 1 167 - 1 982), encephalomyelitis (321, 95% CI 144 - 485), eosinophilic oesophagitis (183, 95% CI 37 - 335), fibrosing alveolitis (570, 95% CI 361 - 784), glomerulonephritis (1 304, 95% CI 892 - 1 749), inflammatory bowel disease (168, 95% CI 18 - 343), intracranial haemorrhage (983, 95% CI 677 - 1 297), lymphadenopathy (297, 95% CI 68 - 567), myocardial infarction (3 653, 95% CI 3 029 - 4 273), myocarditis (745, 95% CI 536 - 1 003), pericarditis (132, 95% CI 26 - 252), pulmonary embolism (6 625, 95% CI 5 942 - 7 344), rheumatic fever (977, 95% CI 725 - 1 266), seizure (5 691, 95% CI 5 067 - 6 480), syncope (4 260, 95% CI 3 583 - 4 956), thrombocytopenia (517, 95% CI 308 - 724), type 1 diabetes (1 681, 95% CI 1 235 - 2 089), vertigo (552, 95% CI 88 - 1 058) and cholangitis (148, 95% CI 36 - 286) (Appendix Table S3 and Fig. 4).

After identifying conditions with an increased risk following vaccination or infection, the RDs for these conditions were compared between the vaccination and infection analyses. The RDs for adverse events (identified as having an increased risk) were consistently larger across conditions following SARS-CoV-2 infection (infection analysis) compared with vaccination (vaccination analysis) (Fig. 1).

Discussion

Transient common lymphadenopathy is a relatively common feature following any vaccination.[20-22] Among individuals aged 12 - 17 years, lymphadenopathy was noted as a post-vaccination event following a dose of BNT162b2. Lymphadenopathy was also noted as a post-infection event for individuals aged 12 - 17, as well as ≥60 years. Previous studies have also documented transient lymphadenopathy following COVID-19 vaccination.[1,23,24] For those aged 12 - 17, the RD for lymphadenopathy was greater post infection than post vaccination.

In our analysis, we observed an elevated risk of vertigo in individuals aged 12 - 17 years following BNT162b2 vaccination. Contrary to our findings, a review of the literature did not reveal an increased risk of vertigo following COVID-19 vaccination in this age group. Notably, vertigo has been documented as an adverse event following COVID-19 vaccination in adults, as indicated by case reports and studies.[25,26] Furthermore, transient audiological and vestibular symptoms following SARS-CoV-2 infection and COVID-19 vaccination in children aged 5 - 11 years have been reported.[27]

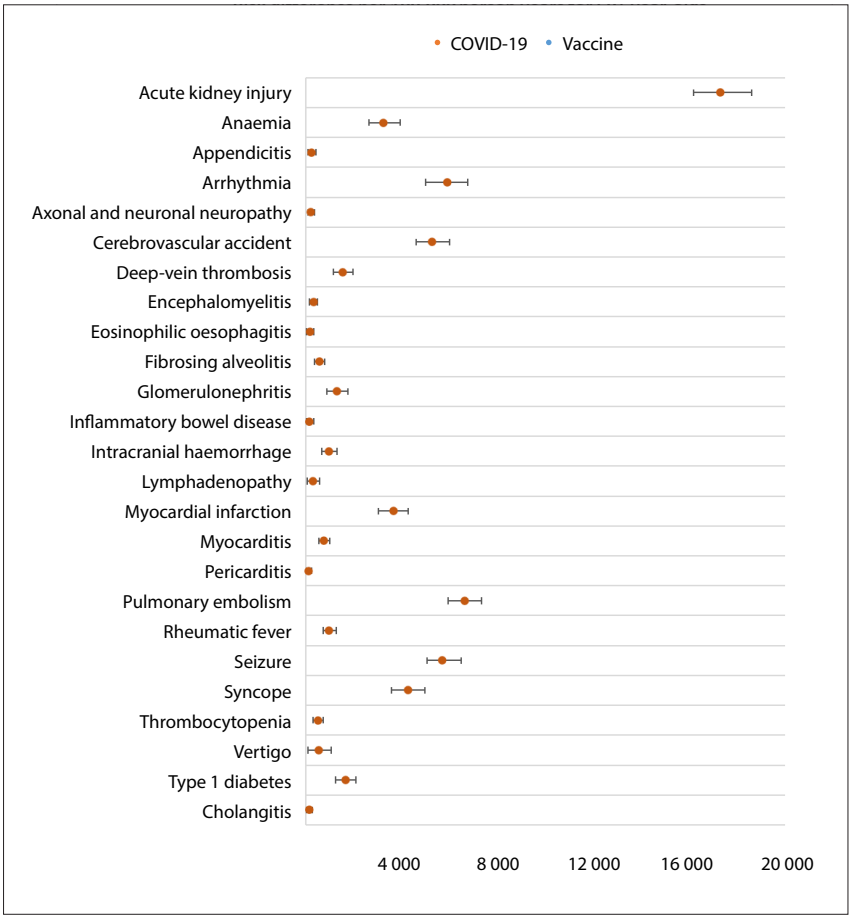

Fig. 4. Risk difference per 100 000 lives for ≥60-year-olds.

In a real-world study of vaccine adverse events using administrative healthcare data, onset risk of 25 medical conditions was assessed following COVID-19 vaccination and documented SARS-CoV-2 infection.[1] We assessed 24 of these conditions in our study. Post vaccination, onset of lymphadenopathy was a consistent finding. Barda *et al.*[1] additionally reported a significant increased risk for myocarditis, herpes zoster and appendicitis, whereas we additionally reported a significant increased risk for vertigo following vaccination.

Furthermore, Straus *et al.*[28] found an increased risk of myocarditis following an mRNA-1273 COVID-19 vaccination for younger males. Additionally, Husby *et al.*[29] found increased risk of myocarditis or myopericarditis following an mRNA-1273 vaccination, driven by a significant increased risk among individuals aged 12 - 39 years. Husby *et al.*[29] also considered the incidence of myocarditis or myopericarditis following the BNT162b2 vaccination, and found an increased risk only among female participants. Although our study did segment the population by age, it was not segmented by sex, which, following a review of the published literature, is probably an important variable to accurately understand the risk of myocarditis following COVID-19 vaccination.

No adverse medical events were identified following Ad26.COV2.S vaccination, which may be due to the lower volumes of vaccination relative to BNT162b2 in SA and in the study population, resulting in insufficient volumes to power estimates of adverse events.

Post-infection adverse events were prominently seen in older age groups: individuals aged ≥60 had an increased risk of 25 unique conditions, while those <18 years had an increased risk for nine conditions. Notably, the following seven conditions were observed as a post-infection event across all age groups: appendicitis, arrhythmia, encephalomyelitis, myocarditis, seizure, syncope and type 1 diabetes. People in older age groups were observed to have a higher RR of adverse events, for a given condition, following documented SARS-CoV-2 infection, with a high risk of onset of acute kidney injury and myocarditis, in particular.

Following SARS-CoV-2 infection, we found results consistent with Barda *et al.*[1] in at least one age group, for 18 of the 24 conditions analysed, following a SARS-CoV-2 infection. Notably, Barda *et al.*[1] reported a significant increased risk for lymphopenia and neutropenia following a documented SARS-CoV-2 infection, findings that we did not observe in our study. Conversely, our study identified a significant increased risk of appendicitis, lymphadenopathy, seizures and vertigo following a SARS-CoV-2 infection, which were not highlighted as significant in Barda *et al.*'s[1] findings. However, these associations are not entirely novel; prior studies have reported increased risks of appendicitis and vertigo following SARS-CoV-2 infection.[30,31] Additionally, several case reports and meta-analyses have linked lymphadenopathy and seizures to SARS-CoV-2 infection.[32,33]

Study limitations

As an analytical retrospective cohort study, this research identifies associations rather than proves causal relationships between vaccination, infection and subsequent adverse events. Even with comprehensive matching to control for confounding, the potential influence of unmeasured factors cannot be entirely excluded. Since exposure to vaccination or infection was not randomised, differences in health status, healthcare-seeking behaviour, or diagnostic practices may have influenced the results.

While this study analysed extensive data and a large variety of conditions using the WHO's ICD-10 codes from administrative records, the data records lack clinical validation.

As detailed in the study, certain cohorts, such as the AD26.COV2 vaccine analysis, were relatively small. This limitation may have resulted in rare conditions not being identified as having an increased risk, because the sample size might not have been sufficient to detect less common adverse events.

Due to the differing regimen sizes, a direct comparison between vaccine types was not feasible. The study's objective was not to assess the effectiveness of any specific vaccine regimen, but rather to evaluate the relative difference in adverse events experienced following vaccination v. SARS-CoV-2 infection.

Vaccine administration dates were known, ensuring that the 42-day observation period was accurate. However, infection dates were inferred from the date of the positive SARS-CoV-2 test, which may occur a few days after actual infection. While this introduces some deviation in the observation periods,

the impact is likely minimal owing to the length of the observation window relative to any potential delay in testing.

Although the study population is diverse in race and socioeconomic status, results may not be generalisable to the full uninsured SA population. Furthermore, the results may not be applicable to populations outside of SA owing to differences in healthcare systems, access to care and underlying population characteristics

Conclusion

In this large study of insured South Africans aged ≥12 years, the RD of adverse events following natural SARS-CoV-2 infection was substantially larger than that following COVID-19 vaccination across all age groups (Figs 1 - 4).

Data availability. Anonymised datasets analysed during the current study are not publicly available. However, they are available upon reasonable request, following ethical approval.

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