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Using nationwide data to examine the relative effectiveness of Covid-19 vaccination against omicron amongst a population with low prior rates of SARS-CoV-2 infection: A cohort study

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ABSTRACT

Background: We used nationwide data to examine relative vaccine effectiveness (rVE) of the Comirnaty mRNA vaccine (Pfizer–BioNTech (original), hereafter Comirnaty, against the Omicron variants (BA.1 and BA.2) during 2022 in Aotearoa New Zealand (NZ).
Method: We analysed a national cohort of 3.15 million adults (18+ years) who had received at least two doses of Comirnaty by March 2022. Data sources included national administrative records of vaccination, hospitalisation, ICU admission and death. Cox regression was used to estimate hazard ratios in recipients of three vaccine doses compared to recipients of two doses.
Results: Amongst adults, three vaccine doses provided significantly greater protection against hospitalisation attributable to Covid-19 than two doses, relative vaccine effectiveness (rVE) was 50 %, 95 % Confidence Interval (CI) 45–55 %) at peak virus circulation. The vaccine was effective for Māori, Pacific Peoples and those aged over 50 years however, the protection given by vaccination waned throughout the study period. The booster was also significantly more effective at preventing ICU admission or death with an rVE (3 vs 2 doses) of 53 %, 95 % CI 49–55 %. It was consistent for Māori, 49 %, 95 %CI 41–56 % and Pacific Peoples 52 %, 95 % CI 41–62 %, and those aged over 50 years, 54 %, 95 % CI 51–57 %.
Conclusion: The study provides important insights into relative vaccine effectiveness of the Comirnaty booster doses against Omicron variants in NZ in 2022 in an infection naive population. The findings highlight the importance of booster doses in combatting hospitalisation, ICU admission and death during the 2022 Omicron wave.

1. Introduction

The Covid-19 pandemic is estimated to have caused 7 million deaths worldwide [1]. The SARS-CoV-2 Omicron variant of concern (VOC) was first detected in November 2021 in South Africa and rapidly spread worldwide [2]. Mutations on the spike protein contributed to the Omicron variant's ability to escape both infection- and vaccine-induced immunity [3–5]. Multiple studies of Comirnaty vaccine effectiveness have been done globally and while some have been done during Omicron dominance, fewer to the authors knowledge have been carried out in the context of the wide exposure of an infection naïve population such as in NZ [6].

NZ's world-leading response to the pandemic resulted in low relative burden of disease and low levels of population disease disparities relative to most other countries internationally [7,8]. At the beginning of 2022, NZ, unlike most other jurisdictions, still had full border controls in

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place which continued until the end of February and the majority of the population vaccinated with Comirnaty [9]. The border controls limited movement and required quarantine on entry until the NZ border reopened to vaccinated New Zealanders and other current eligible travellers from Australia at 11.59 pm on 27th February 2022 and to the same groups from the rest of the world two weeks later on 13th March 2022 [9]. This essentially afforded approximately two months during which to increase uptake of vaccine doses, especially third doses, prior to widespread community transmission of SARS-CoV-2 from the beginning of March 2022. Consequently, NZ first experienced widespread community transmission of SARS-CoV-2 in the context of an infection naïve population with high coverage of at least two mRNA vaccine doses and substantial recent receipt of a third mRNA dose in people aged 50 years and over. Evidence on Covid-19 vaccine effectiveness was initially derived during 2020 from high-income countries which had experienced substantial community transmission of SARS-CoV-2 during Covid-19 vaccine rollout in 2021, which rapidly accelerated after the emergence of the Omicron variant from December 2021 [10–12]. While evidence on vaccine effectiveness has been established less have been carried out in a largely uninfected population [11].

As most evidence on Covid-19 vaccine effectiveness has been derived from settings where substantial community transmission of SARS-CoV-2 had already taken place [13] it is important to understand the effectiveness of Covid-19 vaccines in the unique context of an infection naive population and an evolved new strain (different to the vaccine antigen type) of SARS-CoV-2. Infection itself has been shown to induce significant protective immunity against subsequent disease [14] it is therefore possible that relative vaccine effectiveness seen in these settings may not be replicated in populations with low infection rates. We estimated the relative vaccine effectiveness of three compared to two Covid-19 vaccine doses in relation to severe disease (i.e. hospitalisation or death) from the Omicron VOC in an infection naive population using high quality administrative data and Cox Proportional Hazards regression.

2. Methods

2.1. Study design, data sources and study population

We assembled a retrospective cohort using linked administrative health data. Inclusion criteria were adults aged 18 years and over, who on 01 Mar 2022 had received two or more doses of Comirnaty vaccine. Exclusions were those who had no recorded vaccine doses, or for whom the vaccine type was not Comirnaty or missing or had a recorded notification of a positive test for SARS-CoV-2 or hospitalisation with a specific ICD10 C-19 code before this date.

The Covid Immunisation Register (CIR) was the source of all data on exposure to vaccine doses. This register was established for the specific purpose of recording Covid-19 vaccinations in NZ and is expected to be a comprehensive record of receipt of Covid-19 vaccines in NZ. Hospitalisations and ICU admission were captured using public hospital discharge data (National Minimum Data Set). This national dataset was established in its current form in 1999. Events are expected to be uploaded from the hospital within a month from discharge date. Deaths were captured using the National Health Index (NHI) demographic data and mortality data. These data are the most comprehensive population data available in NZ.

Disease (Covid-19) notification data was collected by ESR. Prior to the 24th February 2022, testing and notification of Covid-19 cases was via health worker administered nasal swabs and laboratory PCR testing. Following the change to Phase 3 of the Covid response most testing done was via rapid antigen tests. Aside from hospital testing of admission all other testing and notification was done using self-administered rapid antigen tests with individuals responsible for reporting their own test results. The lack of consistency likely to occur with self-reported notification and testing by the population is the reason this study focuses on hospitalisation and all-cause mortality as outcomes.

2.2. Study period

The study period of 1st March 2022 to 1st October 2022 was defined to include the period when circulation of BA.1, BA.2 and BA.5 variants were dominant. A truncated study period from 1st March 2022 to 1st June 2022 was used as a sensitivity analysis, to gauge the effect of vaccine waning and different levels of circulating infection numbers on vaccine effectiveness estimates.

2.3. Exposure

The main exposure of interest was Covid-19 Cominarty vaccine doses recorded on the CIR. Adults who on January 1st, 2022, were recorded on the CIR as having received one or more doses of Comirnaty vaccine and who have not been notified with a prior positive test for SARS-CoV-2 or had a hospitalisation with a specific Covid-19 ICD10 code (Table 2) were eligible.

2.4. Outcome

1. Hospitalisation with Covid-19 and linked to a specific Covid-19 ICD-10 code (U07.1, B34.2 or B97.2) hospitalisation code or a Covid-19 notification between 2 days prior to hospital admission date and up to 14 days after hospital admission date.
2. An ICU admission while in hospital with Covid-19 or death (all causes) These ICU admissions will be a subset of the hospitalisations described in 1. This indicates the most severe outcomes.

We also included a sensitivity analysis where the outcome was restricted to hospitalisations that had Australian Refined Diagnosis Related Group Code (DRG) codes [15–17], indicating that the hospitalisation was largely attributable to Covid-19 (Table 1). These codes were based on work investigating severity and characterisation of Covid-19 [15].

2.5. Other exposures of interest

Age group is reported in 10-year age bands with age calculated at the 1st January 2022. We report vaccine effectiveness separately for the population over 50 years of age in addition to the total population. Sex is reported as male or female. Area-level deprivation is summarised as NZ Deprivation Index quintiles, with Quintile Five being the most disadvantaged quintile of the population. Ethnicity is derived from the NHI demographic information table. For the total population analysis there is

Table 1
Diagnostic Related Group codes used to identify hospitalisations more likely to be attributable to Covid-19.

DRG	DRG Description
E41A	Respiratory System Disorders W Non-Invasive Ventilation, Major Complexity
E41B	Respiratory System Disorders W Non-Invasive Ventilation, Minor Complexity
E62A	Respiratory Infections and Inflammations, Major Complexity
E62B	Respiratory Infections and Inflammations, Minor Complexity
E65A	Chronic Obstructive Airways Disease, Major Complexity
E67A	Respiratory Signs and Symptoms, Major Complexity
E67B	Respiratory Signs and Symptoms, Minor Complexity
E69A	Bronchitis and Asthma, Major Complexity
E75A	Other Respiratory System Disorders, Major Complexity
E75B	Other Respiratory System Disorders, Minor Complexity
F76A	Arrhythmia, Cardiac Arrest and Conduction Disorders, Major Complexity
T62A	Fever of Unknown Origin, Major Complexity
T63A	Viral Illnesses, Major Complexity
Z61A	Signs and Symptoms, Major Complexity

two ethic categories, non-Māori/non-Pacific versus Māori or Pacific. Separate models were run for total response Māori only and total response Pacific Peoples only.

2.6. Statistical analysis

Descriptive analyses included presenting group baseline demographic and clinical characteristics were presented with categorical data presented as counts and percentages where appropriate. The study population was described using the following demographic variables and exposures of interest:

- Vaccination status (1, 2, 3 or 4+ doses Covid-19 Cominarty vaccine)
- Total response ethnicity
- Deprivation
- Age groups (18–34, 35–49, 50–54, 55–64, 65–69, 70–74, 75–79 and 80+ years)
- DHB of residence

Covid-19 incidence rates: we reported on incidence of the two more severe outcomes (hospitalisation and ICU or death) by age group within the study period. Person time was calculated as time within the study period, censored if an event occurred and those individuals who were given a dose during the study period could contribute person time to more than one dose category as appropriate.

Vaccine effectiveness: estimated by Cox-regression with separate analyses for each outcome. Analysis time commenced on 01 March 2022 and ended at either the outcome of interest, death from other causes, or 1st October 2022, whichever came first. Vaccination status varied and individuals could contribute person time to both 2 and 3 doses when vaccinations occurred within the study period. Sensitivity analyses were conducted to estimate vaccine effectiveness in a truncated study period when infection rates were highest, 01 March 2022–01 June 2022, and when a more stringent criteria was applied to hospitalisations so that only hospitalisations attributable to Covid-19 were counted. Vaccine doses was time varying i.e. a person who has a vaccination during the study period will contribute follow up time to their initial dose status and when they receive another dose, they will contribute follow up time to the new dose status. VE was calculated as (1 – HR) * 100 %.

3. Results

3.1. Descriptive statistics

There were 3,698,446 individuals in the data provided by Te Whatu Ora (NZ Ministry of Health). After excluding those who had a recorded Covid-19 notification before 01 March 2022, a vaccine other than Comirnaty or recorded as given prior to the start of the NZ immunisation programme, no recorded vaccine dose, excess doses (6 or more) or who died prior to 1 March 2022 3,451,321 individuals were included in the analyses (Fig. 1). For context, Fig. 2 shows the frequency of vaccinations against Covid-19 in NZ by dose number and the number of Covid-19 cases over time.

The cohort was 12 % Māori (total response), 6 % Pacific Peoples (total response) and 82 % (non-Māori/non-Pacific). About 0.7 % of the population was hospitalised (Supplementary Table 1). With higher proportions of Māori (0.9 %) and Pacific Peoples (1 %) hospitalised; the consequence of health system and societal structures that are unable to adequately protect the well-being of Māori and Pacific Peoples. Hospitalisation rates increased with increasing age.

3.2. Incidence of severe outcomes of Covid-19 by vaccination status

The incidence of Covid-19 hospitalisations during the study period differed by both age group and dose number (Table 2). The incidence of Covid-19 hospitalisation increased with increasing age however those who had received 3 doses versus 2 had consistently lower incidence of hospitalisation. For instance, in adults aged 70–79 years the incidence of hospitalisation (/1000-person years) was 39 (95 % CI 26–43) for two doses and decreased to 20 (95 % CI 20–21) for three doses. In adults aged 80+ years, incidence (/1000-person years) was 91 (95 %CI 84–100) for two doses down to 49 (95 % CI 47–50) or three doses. Incidence of ICU admission or death was much lower but consistent with patterns for hospitalisation. Incidence of ICU or death increased markedly from the 60–69 years age group and incidence in those who received 3 doses was consistently lower for all age groups (Table 3).

3.3. Relative vaccine effectiveness

For all ages, after adjustment, relative to those with two doses, those with three doses had a lower risk of hospitalisation, rVE 32 %, 95 % CI 27–37 % (Table 4). Restricted to adults older than 50 years, relative to those who had two doses, those with three doses had greater reduction in risk rVE 45 %, 95 % CI 40–49 %. For Māori of all ages, the comparable estimates for three doses were noted, rVE 32 %, 20–43 %, and for Pacific adults of all ages, those who received three doses were similarly at lower risk, rVE 48 %, 38–57 %, with three doses. Importantly, the estimated protective effects were similar or higher for Māori and Pacific Peoples.

Restricting the study period from March to June resulted in higher relative vaccine effectiveness estimates against hospitalisation (Table 4).

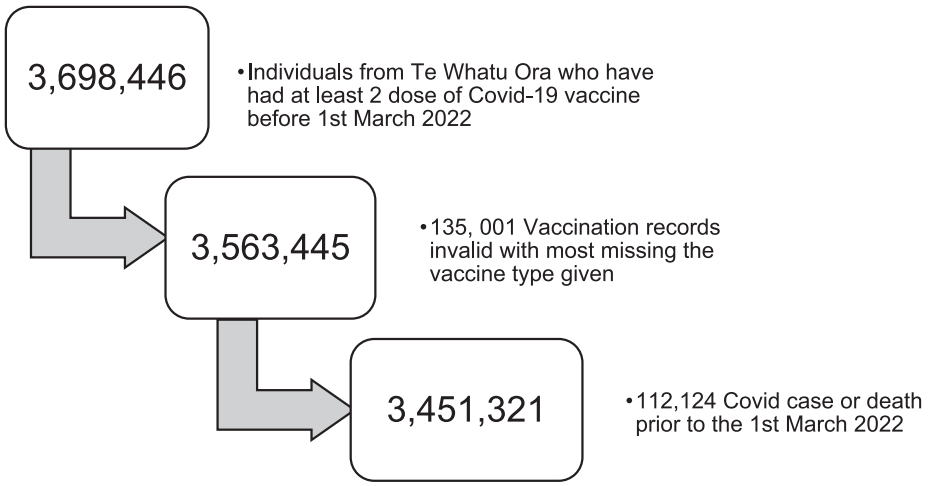

Fig. 1. Flow chart of participant inclusion and exclusions.

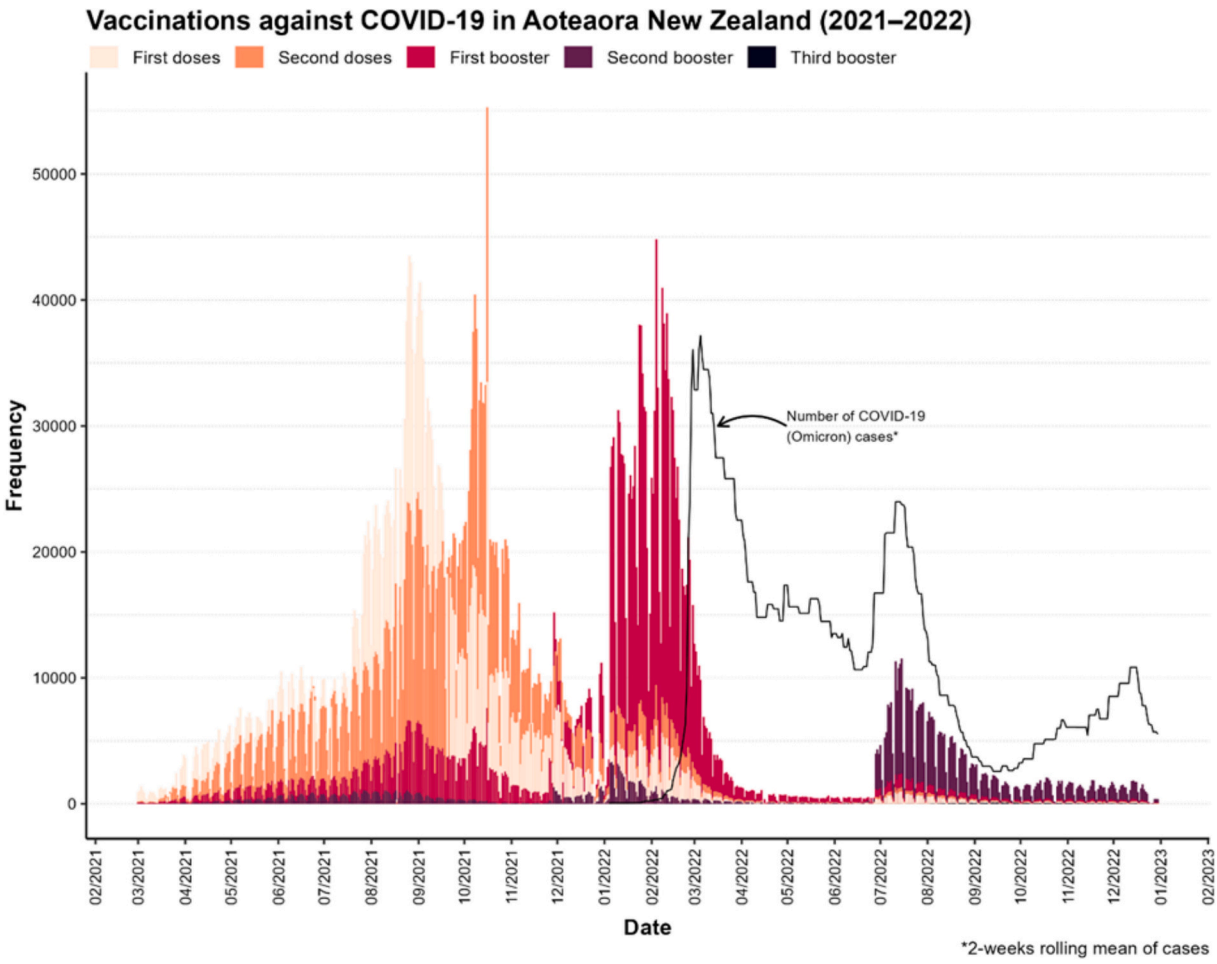

Fig. 2. Demonstrating the frequency of vaccinations against Covid-19 in NZ by dose number and the number of Covid-19 cases from 2021 to 2022.

Table 2
Incidence of hospitalisation with Covid-19 by age group and dose from 01 March 2022–01 October 2022.

Age Group (years)	Doses	Hospitalisation events	Person Years	Rate/1000 person years (95 % CI)
18–29	*2*	1711	183,480	9.33 (8.89–9.78)
	3	1392	209,917	6.63 (6.29–6.99)
30–39	*2*	1335	135,117	9.88 (9.36–10.42)
	3	1708	223,983	7.63 (7.27–8.00)
40–49	*2*	806	86,506	9.32 (8.69–9.98)
	3	1499	229,904	6.52 (6.19–6.86)
50–59	*2*	718	63,534	11.30 (10.49–12.16)
	3	1867	255,642	7.30 (6.98–7.64)
60–69	*2*	613	33,188	18.47 (17.04–19.99)
	3	2391	227,155	10.53 (10.11–10.96)
70–79	*2*	514	13,064	39.35 (36.02–42.9)
	3	3094	153,053	20.22 (19.51–20.94)
80+	*2*	548	5983	91.59 (84.09–99.60)
	3	3994	81,613	48.94 (47.43–50.48)

Table 3
Incidence of ICU admission or all-cause mortality by age group and dose from 01 March 2022–01 October 2022.

Age Group (years)	Doses	ICU or Death events	Person Years	Rate/1000 person years (95 % CI)
18–29	*2*	124	183,423	0.68 (0.56–0.81)
	3	103	209,945	0.49 (0.40–0.60)
30–39	*2*	120	135,049	0.89 (0.74–1.06)
	3	121	224,029	0.54 (0.45–0.65)
40–49	*2*	196	86,431	2.27 (1.96–2.61)
	3	312	229,870	1.36 (1.21–1.52)
50–59	*2*	328	63,383	5.17 (4.63–5.77)
	3	828	255,489	3.24 (3.02–3.47)
60–69	*2*	490	32,971	14.86 (13.57–16.24)
	3	1870	226,665	8.25 (7.88–8.63)
70–79	*2*	578	12,787	45.2 (41.59–49.04)
	3	3697	151,961	24.33 (23.55–25.13)
80+	*2*	1015	5469	185.61 (174.36–197.39)
	3	9082	78,879	115.14 (112.78–117.53)

Table 4
Cox's proportional hazards model estimates for 3 versus 2 doses, vaccination status as time varying, and hospitalisation as the outcome.

Modelled population	*P*-value	HR (95 % CI)	rVE (95 % CI)
Hospitalisation within full study period 1 March 2022–1 October 2022			
All ages baseline	<0.0001	0.62 (0.58–0.66)	38.3 (33.8–42.5)
All ages adjusted	<0.0001	0.68 (0.64–0.73)	31.8 (26.7–36.5)
Over > 50 years baseline	<0.0001	0.51 (0.47–0.55)	49.0 (44.6–53.1)
Over 50 years full adjustment	<0.0001	0.55 (0.51–0.60)	44.6 (39.8–49.1)
Māori Only	<0.0001	0.68 (0.58–0.80)	32.1 (20.0–42.5)
Pacific Peoples only	<0.0001	0.52 (0.43–0.62)	48.2 (37.6–57.0)
Hospitalisations within truncated study period 1 March 2022–1 June 2022			
All ages baseline	<0.0001	0.49 (0.47–0.51)	51.2 (49.1–53.2)
All ages adjusted	<0.0001	0.55 (0.53–0.58)	44.7 (42.3–47.0)
Over > 50 years baseline	<0.0001	0.39 (0.37–0.42)	60.9 (58.4–63.2)
Over 50 years full adjustment	<0.0001	0.44 (0.41–0.47)	56.3 (53.5–58.9)
Māori Only	<0.0001	0.60 (0.55–0.66)	40.1 (34.3–45.4)
Pacific Peoples only	<0.0001	0.47 (0.42–0.52)	53.4 (47.9–58.4)
Hospitalisations within truncated study period 1 March 2022–1 June 2022 and specific DRG codes			
All ages baseline	<0.0001	0.43 (0.39–0.47)	57.1 (53.0–60.9)
All ages adjusted	<0.0001	0.50 (0.46–0.55)	50.0 (45.1–54.5)
Over > 50 years baseline	<0.0001	0.32 (0.28–0.35)	68.5 (64.8–71.8)
Over 50 years full adjustment	<0.0001	0.36 (0.33–0.41)	63.7 (59.4–67.4)
Māori Only	<0.0001	0.55 (0.45–0.68)	44.7 (32.0–55.1)
Pacific Peoples only	<0.0001	0.38 (0.30–0.47)	62.4 (53.2–69.8)

Main outcome is hospitalisation with Covid-19 for the full study period, 1 March 2022–1 October 2022. Second outcome is hospitalisation with Covid-19 for a truncated study period, 1 March 2022–1 June 2022. Third outcome is hospitalisation more likely to be attributable to Covid-19, for the truncated period.

For example, the estimate for protection against hospitalisation for all ages and ethnicities was 51 %, 95 %CI 49–53 % (truncated period) versus 38, 95 % CI 34–43 % (full study period). Restricting hospitalisations to those with diagnostic group codes indicating hospitalisations attributable to Covid-19 also resulted further increases in the estimates for relative vaccine effectiveness. With rVE increasing to 57 %, 95 % CI 53–61 % for all ages, 64 %, 95 % CI 59–67 % for those over years, 45 %, 95 % CI 32–55 % for Māori only and 62 %, 95 % CI 53–70 % for Pacific Peoples only.

Three doses significantly decreased risk of ICU admission or death compared to two doses for all population groups modelled (Table 5).

Table 5
Cox's proportional hazards model estimates for 3 versus 2 doses, vaccination status as time varying, and ICU admission (with a positive Covid-19 test) or death (all-cause mortality) as the outcome.

Modelled population	P-value	HR (95 % CI)	rVE(95 % CI)
ICU or death within full study period 1 March 2022–1 October 2022			
All ages baseline	<0.0001	0.60 (0.58–0.63)	39.6 (37.0–42.0)
All ages adjusted	<0.0001	0.64 (0.61–0.67)	35.9 (33.2–38.6)
Over > 50 years baseline	<0.0001	0.60 (0.58–0.63)	39.9 (37.3–42.5)
Over 50 years full adjustment	<0.0001	0.63 (0.60–0.66)	36.9 (34.0–39.6)
Māori Only	<0.0001	0.60 (0.54–0.66)	40.4 (34.1–46.1)
Pacific only	<0.0001	0.64 (0.55–0.75)	35.6 (24.8–44.8)
ICU or death within the truncated period 1 March 2022–1 June 2022			
All ages baseline	<0.0001	0.45 (0.42–0.47)	55.3 (52.7–57.8)
All ages adjusted	<0.0001	0.48 (0.45–0.51)	52.3 (49.4–55.0)
Over > 50 years baseline	<0.0001	0.43 (0.41–0.46)	56.6 (53.9–59.1)
Over 50 years full adjustment	<0.0001	0.46 (0.43–0.49)	54.0 (51.1–56.7)
Māori Only	<0.0001	0.51 (0.44–0.59)	49.0 (40.7–56.1)
Pacific only	<0.0001	0.48 (0.39–0.59)	52.3 (40.9–61.5)

Main outcome is hospitalisation with Covid-19 for the full study period, 1 March 2022–1 October 2022. Second outcome is hospitalisation with Covid-19 for a truncated study period, 1 March 2022–1 June 2022.

Relative vaccine effectiveness for all ages, adjusted for sex, ethnicity, age group and deprivation was 36 %, 95 % CI 33–39 %. The estimate was slightly higher for those aged over 50 years (37 %, 95 % CI 34–40 %). Three doses were also effective in reducing risk of ICU admission or death amongst Māori only, rVE 40 %, 95 %CI 34–46 % and amongst Pacific Peoples only, rVE 36 %, 95 % CI 25–45 %. Examining a truncated period increased vaccine effectiveness estimates from around 30–40 % up to 49–50 %, which is a result of both vaccine waning and variation in the level of circulating virus across the longer study period.

4. Discussion

This study used a retrospective cohort design to investigate the real-world relative vaccine effectiveness of the Comirnaty booster dose in NZ in preventing severe disease and death in a nationwide sample of infection naïve adults. Our study generated three key findings. First, a third dose of Comirnaty vaccine provided improved protection against severe disease particularly for older adults relative to two doses. Secondly, and importantly, we saw at least equivalent relative vaccine effectiveness for Māori and Pacific populations. This reinforces the important role for vaccines in reducing inequity due to infectious disease. As the pandemic evolves, our study provides an important evaluation of performance of the Covid-19 vaccine in NZ in reducing disease severity and preventing death especially for older adults, Māori and Pacific populations. Third, the differences in estimates for the truncated versus the full study period indicate that vaccine effectiveness waned steadily. This is consistent with other studies which measured VE within one or two months of receiving a booster dose and estimated effectiveness around 70–90 % [3,18–21].

We focussed on relative vaccine effectiveness because a high proportion of the NZ population was vaccinated with at least two doses at that time Omicron VOC was circulating in community transmission and the very small proportion of the population were infected prior to 2022 in NZ. NZ controlled the spread of earlier strains of SARS-CoV-2 virus more effectively than many other countries worldwide by implementing stringent border controls, widespread testing, restricted social interactions, working from home and contact tracing, which contributed to a relatively low prevalence of Covid-19 cases compared to global [7–9]. Vaccines received emergency use authorisation in NZ and these vaccines demonstrated excellent efficacy in preventing hospitalisation and death in clinical trials conducted internationally [22,23]. While these findings were promising, it is crucial to determine how the real-world context of NZ, with its unique demographic, cultural, social and geographic factors, influences relative vaccine effectiveness and largely infection naïve population. This evaluation of any vaccine performance helps inform and evaluate public health strategies and decision-making.

Previous studies examining COVID-19 vaccine effectiveness for preventing severe disease and death have yielded valuable insights into the performance of different vaccines [24,18]. Several studies have demonstrated high vaccine effectiveness in preventing disease and death [18] with vaccines such as Cominarty and Moderna mRNA consistently exhibiting excellent protection. However, variations in study populations, vaccination coverage, and the emergence of new variants have introduced complexities in comparing these findings [13,18]. While some studies have shown lower vaccine effectiveness against specific SARS-CoV-2 variants, notably Delta and Omicron, others have underscored the enduring benefits of vaccination, including reduced hospitalisation and mortality rates [18]. These differences highlight the dynamic nature of the pandemic and the need for ongoing surveillance and research to assess the long-term effectiveness of Covid-19 vaccines in diverse populations and under evolving viral conditions. It is reassuring that in this evaluation the receipt of the vaccine was related to reduced hospitalisation and death.

In this study, relative to two doses, a third dose of Comirnaty vaccine improved protection against severe disease particularly for older adults, those aged 50 years or more. Other studies show vaccine booster doses

increased protection against Covid-19 hospitalisation compared with a primary series especially for older adults [19,24]. Recent evidence including a prospective test negative case–control study from the United Kingdom in 2022 has shown that both fourth monovalent and fifth BA.1/ancestral mRNA bivalent Covid-19 vaccine doses demonstrated benefit as a booster in older adults [19,25–28]. Some studies show higher estimates for vaccine effectiveness of mRNA vaccine boosters against Omicron. This is consistent with previous studies evaluating the booster dose, such as the study carried out by the US CDC, in which a third dose received during the Omicron wave was 90 % effective in preventing hospitalisation associated with Covid-19 compared to being unvaccinated [26]. The Covid-19 pandemic prompted an unprecedented global effort to develop and distribute effective vaccines to mitigate the impact of the pandemic. Positively, and in contrast to many other countries globally, our study population had relatively high vaccine coverage prior to NZ's Omicron outbreak in March 2022.

Our study strengths include the large population, use of a national vaccine register to ascertain vaccination status and national hospital discharge data and national mortality data which allowed estimation of rates of hospitalisation, ICU admission and death. Three main issues affect our study findings. First, while waning vaccine effectiveness over time can be adjusted for by adding decay function to the Cox's proportional hazards model based on time since vaccination this is an estimated waning and is likely to vary from the real rate. Given our relatively short study period we have not used this method but have provided vaccine effectiveness estimates for the whole study period and a truncated period from March to June 2022 to glean a sense of the rate of waning of relative vaccine effectiveness. Second, the changing incidence of disease throughout the study period combined with differential timing of doses means that we may end up comparing doses across periods of differing incidence. In our case incidence was high when most people were in the 2-dose period, it was mostly older people who had received their 3rd dose at that time and then 4th doses were received when Covid-19 incidence was lower. This can be dealt with by matching individuals who have received different dose numbers within a set time or by adjusting for strongly influential covariates such as age. We have adjusted for these covariates. This will lead to an overestimation of relative vaccine effectiveness for higher doses. Third, people getting infected with Covid-19 and suffering only mild disease, have boosted immunity and wait to have another dose. Throughout the outbreak an increasing number of people will have acquired infection and so not have had another dose but nevertheless be protected for the remainder of the study period, diluting the apparent VE of additional vaccine doses causing an underestimation of relative vaccine effectiveness. Overall, as with any real-world vaccine effectiveness study our findings should be interpreted considering these limitations. Finally, we initially examined comorbidities in our study cohort using the M3 framework developed and validated for NZ however, as comorbidities within our cohort were strongly co-linear with age group therefore, we considered adjustment for age group as sufficient.

5. Conclusion

In summary, this study provides compelling evidence for the pivotal role that Covid-19 vaccines have played in mitigating the impact of the ongoing pandemic in NZ and internationally. Our findings reinforce the effectiveness of the Comirnaty vaccine in mitigating hospitalisation, severe illness and mortality for third booster doses relative to two doses amongst older adults. Notably, our study underscores the crucial role of vaccines in addressing health disparities, especially in safeguarding the at-risk elderly, Māori, and Pacific populations. These insights confirm the importance of vaccines in shaping responsive strategies as the pandemic evolves and as future infectious diseases emerge.

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CRediT authorship contribution statement

J. Paynter: Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **P. McIntyre:** Writing – review & editing, Supervision, Investigation, Conceptualization. **J. Wiki:** Writing – review & editing, Methodology. **N. Nghiem:** Writing – review & editing, Methodology, Investigation, Formal analysis. **B. Liu:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **L. Marek:** Writing – review & editing, Visualization, Methodology, Formal analysis, Conceptualization. **M. Hobbs:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Matthew Hobbs reports financial support was provided by Health New Zealand. Janine Paynter reports a relationship with GSK that includes: funding grants. Janine Paynter reports a relationship with Seqirus Australia Pty Ltd that includes: consulting or advisory and speaking and lecture fees. Janine Paynter reports a relationship with Novavax Inc that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Janine Paynter has conducted research funded by GSK, attended advisory board meetings (Novavax, CSL Seqirus) and presented a seminar on behalf of CSL Seqirus and her employer has received funds for these contributions. The other authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2025.100624.

Data availability

The authors do not have permission to share data.

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