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High vaccine effectiveness against severe COVID-19 in the elderly in Finland before and after the emergence of Omicron

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Abstract

Background: The elderly are highly vulnerable to severe COVID-19. Waning immunity and emergence of Omicron have caused concerns about reduced effectiveness of COVID-19 vaccines. The objective was to estimate vaccine effectiveness (VE) against severe COVID-19 among the elderly.

Methods: This nationwide, register-based cohort analysis included all residents aged 70 years and over in Finland. The follow-up started on December 27, 2020, and ended on March 31, 2022. The outcomes of interest were COVID-19-related hospitalization and intensive care unit (ICU) admission timely associated with SARS-CoV-2 infection. VE was estimated as one minus the hazard ratio comparing the vaccinated and unvaccinated and taking into account time since vaccination. Omicron-specific VE was evaluated as the effectiveness observed since January 1, 2022.

Results: The cohort included 896,220 individuals. Comirnaty (BioNTech/Pfizer) VE against COVID-19-related hospitalization was 93% (95% CI 89–95%) and 85% (95% CI 82–87%) 14–90 and 91–180 days after the second dose; VE increased to 95% (95% CI 94–96%) 14–60 days after the third dose. VE of other homologous and heterologous three dose series was similar. Protection against severe COVID-19 requiring ICU treatment was even better. Since January 1, 2022, Comirnaty VE was 98% (95% CI 92–99%) and 92% (95% CI 87–95%) 14–90 and 91–180 days after the second and 98% (95% CI 95–99%) 14–60 days after the third dose.

Conclusions: VE against severe COVID-19 is high among the elderly. It waned slightly after two doses, but a third restored the protection. VE against severe COVID-19 remained high even after the emergence of Omicron.

Keywords: COVID-19 hospitalization, COVID-19 vaccines, Elderly cohort, SARS-CoV-2 omicron variant, Waning vaccine effectiveness

Background

The elderly are highly vulnerable to severe coronavirus disease 2019 (COVID-19) [1] and, therefore, protecting them is essential to reduce the disease burden caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 vaccinations prevent SARS-CoV-2 infections and decrease the number of COVID-19 hospitalizations in a population [2–7].

As many other European countries, Finland has mainly used two mRNA COVID-19 vaccines, Comirnaty and Spikevax, and one adenovirus vector COVID-19 vaccine, Vaxzevria (Table 1). In September 2021, Finland started its booster vaccination campaign to improve the protection especially for the elderly [8]. The initial recommendation was to adhere to homologous vaccine series, but

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lately with increasing evidence of good effectiveness [9, 10], heterologous series have also been encouraged.

Vaccine effectiveness (VE) generally describes the protective direct effect of vaccination. In the elderly, VE against severe COVID-19 is high after the second dose, but it decreases during the following six months [4, 11–14]. A third dose increased the VE against infection among adults in multiple observational studies [11, 15–18]. However, only a few studies have investigated how well the third dose boosts the VE against severe disease among the elderly [17, 19, 20]. Furthermore, VE may decrease because of the recently emerged Omicron variant, which is more capable of evading both natural and vaccine-induced immunity than previous variants [15, 16, 21–23]. Knowledge of VE against severe COVID-19 caused by Omicron is still limited [16, 21, 23–25] and discussion of the need for further booster doses in the elderly has commenced.

The objective of this study was to estimate the effectiveness of COVID-19 vaccines against severe COVID-19 requiring hospitalization or intensive care unit (ICU) treatment in the elderly in Finland after two and three doses. The effects of time since vaccination, different vaccine series, age and presence of comorbidities on VE were of particular interest. In addition, this study aimed to evaluate the impact of the recently emerged Omicron variant on VE.

Methods

To estimate the effectiveness of COVID-19 vaccines in the elderly population in Finland, we conducted a nationwide, register-based cohort analysis starting on December 27, 2020, and ending on March 31, 2022. The study population was defined as all individuals aged 70 years and over at the beginning of the study and registered in the Population Information System as resident in Finland since January 1, 2020. The unique personal identity code assigned to all permanent residents in Finland allowed linking individual-level data from different sources.

The primary outcome was COVID-19-related hospital admission timely associated with a laboratory-confirmed (by polymerase chain reaction or antigen detection assay) SARS-CoV-2 infection. Using the Care Register for Health Care, which records data on all patients discharged from inpatient care in Finland, we defined COVID-19-related hospitalization as any inpatient encounter with a primary diagnosis of COVID-19 (International Classification of Diseases, 10th revision: U07.1, U07.2), acute respiratory tract infection (J00–J22, J46) or severe complication of lower respiratory tract infections (J80–84, J85.1, J86). A hospitalization was considered timely associated with an infection recorded in the National Infectious Diseases Register if the positive specimen was collected up to 14 days before or seven days after the hospital admission.

The secondary outcome was COVID-19-related ICU admission. ICU admissions were identified from the Finnish Intensive Care Consortium's Quality Register for Intensive Care, which records data on all patients treated in an ICU in Finland. We considered any admission as COVID-19 related if it was marked by the treating physician as due to COVID-19 and if the patient was laboratory-confirmed SARS-CoV-2 positive during the stay.

The exposure was COVID-19 vaccination recorded in the National Vaccination Register, which covers the whole population irrespective of whether they are served by public or private primary health care providers. We distinguished between the three vaccine brands Comirnaty, Spikevax and Vaxzevria and the number of administered doses. The time since vaccination was taken into account by categorizing the time since the last dose using the following cut points: days 21 and 84 after the first dose, days 14, 91 and 181 after the second dose, and days 14 and 61 after the third dose. Thus, a vaccinee's exposure state changed over time. Being unvaccinated was the reference state.

We considered age, sex, region of residence, residence in a long-term care facility, influenza vaccination in 2019–2020, number of nights hospitalized between 2015 and 2019 and presence of predisposing comorbidities or medical therapies as confounders. The first three confounders were taken from the Population Information System. Information on whether a subject was in long-term care at the beginning of the study or vaccinated against influenza in the last pre-pandemic season were collected from the Care Register for Social Care and the National Vaccination Register, respectively. We used the data in the Care Register for Health

Table 1 COVID-19 vaccines under study

Trade name	International nonproprietary name	Trial name	Manufacturer	Vaccine type	Available in Finland
Comirnaty	Tozinameran	BNT162b2	BioNTech/Pfizer	mRNA vaccine	Since December 27, 2020
Spikevax	Elasomeran	mRNA-1273	Moderna	mRNA vaccine	Since January 20, 2021
Vaxzevria	ChAdOx1-S [recombinant]	AZD1222	Oxford/AstraZeneca	Adenovirus vector vaccine	From February 10 to November 30, 2021

Care from 2015 onwards to count the number of nights hospitalized between 2015 and 2019 and to assess the presence of comorbidities or medical therapies that predispose to severe COVID-19 according to a recent study of predictors of COVID-19 hospitalization [26]. We completed the collection of data on predisposing comorbidities and medical therapies with primary health care records and prescription data as outlined in Additional file 1: Tables S1, S2.

Each study subject was considered at risk of the primary and secondary outcomes from the beginning of the study until the first occurrence of any of the following events: outcome of interest, death, day 14 after any laboratory-confirmed SARS-CoV-2 infection, vaccination with an unidentified vaccine, a heterologous second vaccination, vaccination with the third dose prior to the start of the booster campaign (approximated by September 17, 2021), a fourth vaccination, or end of study. All those events other than the outcome of interest led to censoring before or at the end of the study.

Using Cox regression with time in the study as the underlying time scale, we compared the hazard of the two outcomes in vaccinated study subjects with the corresponding hazard in the unvaccinated. The effect measure of interest was VE, quantified as one minus the hazard ratio adjusted for the seven confounders categorized as outlined in Table 2. For each VE estimate, we computed either the 95% Wald confidence interval (CI) or, if there were no cases in one of the two groups, the p-value of the likelihood-ratio test. We stratified the analysis by age group and presence of comorbidities or medical therapies. Because of the emergence of Omicron (Additional file 1: Fig. S1), we also estimated VE by calendar time, conducting a separate regression analysis for each quarter.

To rule out residual confounding, we quantified the association between COVID-19 vaccination and a potential negative control outcome: inpatient encounters due to injury, poisoning and certain other consequences of external causes (International Classification of Diseases, 10th revision: S00–T98) recorded in the Care Register for Health Care. Each study subject was considered at risk of this outcome from the beginning of the study until the first occurrence of any of the following events: injury, death, vaccination with an unidentified vaccine or a heterologous two-dose series, vaccination with the third dose prior to September 17, 2021, or with a fourth dose, or end of study. We compared the hazard of the control outcome in vaccinated study subjects with the corresponding hazard in the unvaccinated using Cox regression and expected to find no difference between the groups.

The significance level was set to 5%. The validity of the proportional hazards assumption was examined visually by plotting the cumulative hazards over time. All analyses were performed in R 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). To reduce the risk for a breach of confidentiality, all non-zero counts which are less than five are suppressed. Results concerning the first dose, less common (less than 2000 person-years) vaccine series and the first two weeks after vaccination are presented in the supplementary data only.

Results

The study cohort included 896,220 individuals aged 70 years and over, and thus 99.8% of the elderly population in Finland (Additional file 1: Tables S3, S4). At the end of the study, only 5% of those still considered at risk of COVID-19 hospitalization were unvaccinated; the majority (6% and 65%) were double- or triple-vaccinated with Comirnaty (Additional file 1: Table S5, Additional file 1: Fig. S2). The median length of the dosing interval between the first and second dose and the second and third dose was 84 (interquartile range, 84–84) and 188 (interquartile range, 181–199) days, respectively. At the end of the study, the triple vaccinated who were still considered at risk of COVID-19 hospitalization had received their third dose, on average, 106 (interquartile range, 93–120) days ago. Table 2 shows the distribution of person-years by vaccination status. The younger and community-dwelling elderly contributed proportionally less vaccinated person-time than older individuals or those in long-term care. The younger and community-dwelling elderly had, however, received their first dose later than older individuals and those in long-term care (Additional file 1: Table S5).

We observed 2234 COVID-19 hospitalizations and 296 ICU admissions, of which 793 and 159 were among the unvaccinated (Table 3, Additional file 1: Fig. S3, Additional file 1: Tables S6, S7). In the first 14–90 days since the second dose of Comirnaty, the VE against hospitalization was 93% (95% CI 89–95%). In the following 90 days, VE decreased to 85% (95% CI 82–87%) and subsequently rose to 95% (95% CI 94–96%) in the first 14–60 days since the third dose (Fig. 1, Additional file 1: Table S8). The point estimates of VE against ICU admission were even higher (Fig. 1, Additional file 1: Table S9). The only vaccine series with a statistically significantly lower VE than the corresponding homologous Comirnaty series was the two-dose homologous Vaxzevria series whose effectiveness against hospitalization was 74% (95% CI 60–83%) in the first 91–180 days.

Increasing age and comorbidities decreased the VE against hospitalization, yet the observed trend of waning remained unchanged (Additional file 1: Tables S10,

Table 2 Distribution of person-years in the study of vaccine effectiveness against COVID-19 hospitalization

	Not vaccinated, person-years (%)	Vaccinated, person-years (%)
Age in years		
70–79	173 830 (24)	535 938 (76)
80–89	57 939 (19)	246 105 (81)
90–115	13 068 (22)	47 634 (78)
Sex		
Male	105 628 (23)	350 917 (77)
Female	139 209 (23)	478 761 (77)
Region of residence		
Helsinki-Uusimaa	56 435 (22)	202 126 (78)
Åland	1145 (19)	4786 (81)
Northern and Eastern Finland	61 478 (23)	205 852 (77)
Southern Finland	59 279 (23)	197 393 (77)
Western Finland	66 501 (23)	219 521 (77)
In long-term care		
No	233 993 (23)	779 369 (77)
Yes	10 844 (18)	50 309 (82)
Influenza vaccination in 2019–2020		
No	133 875 (29)	335 681 (71)
Yes	110 963 (18)	493 997 (82)
Nights hospitalized between 2015 and 2019		
0	132 975 (24)	429 964 (76)
1–5	50 008 (22)	181 812 (78)
6–20	35 615 (22)	126 826 (78)
21+	26 240 (22)	91 077 (78)
Presence of comorbidities or medical therapies[a]		
No predisposing comorbidities	84 412 (24)	261 428 (76)
Only moderately predisposing comorbidities or medical therapies	65 980 (22)	232 391 (78)
At least one highly predisposing comorbidity or medical therapy	94 445 (22)	335 859 (78)
Presence of particular comorbidities or medical therapies[a]		
Severe heart disease	93 843 (22)	337 889 (78)
Type 2 diabetes mellitus	52 035 (22)	182 964 (78)
Immunosuppressive medication	35 443 (22)	127 002 (78)
Actively treated cancer	31 410 (22)	114 354 (78)
Severe chronic respiratory disease	26 198 (22)	93 213 (78)
Neurological condition affecting breathing	22 431 (22)	79 939 (78)
Autoimmune disease	17 062 (22)	60 089 (78)
Type 1 diabetes mellitus or adrenal insufficiency	13 627 (23)	46 922 (77)
Sleep apnea	11 867 (21)	43 736 (79)
Severe kidney disease	5548 (22)	19 162 (78)
Psychotic disease	3833 (29)	9282 (71)
Severe chronic liver disease	1165 (25)	3568 (75)
Organ or stem cell transplantation	560 (22)	1962 (78)
Severe disorder of the immune system	398 (23)	1369 (77)
Down syndrome	3 (19)	13 (81)

[a] See study of predictors of COVID-19 hospitalization [26] and Additional file 1: Tables S1, S2

This tabulation uses a binary vaccination status without distinguishing between vaccine brands, number of doses and time since vaccination

Table 3 Cases, person-years and cumulative risk (per 100,000) by vaccine, dose and days since last vaccination

	COVID-19-related hospital admission			COVID-19-related ICU admission		
	Cases	Person-years	Risk[a]	Cases	Person-years	Risk[a]
Not vaccinated	793	244 838	1313	159	244 856	238
Comirnaty + Comirnaty 14–90	33	144 412	108	< 5	144 413	8
Comirnaty + Comirnaty 91–180	210	158 116	277	26	158 121	29
Comirnaty + Comirnaty 181 +	200	31 354	457	22	31 360	55
Comirnaty + Comirnaty + Comirnaty 14–60	107	69 468	84	9	69 472	3
Comirnaty + Comirnaty + Comirnaty 61 +	359	74 262	125	26	74 271	55
Comirnaty + Comirnaty + Spikevax 14–60	28	9222	118	5	9222	13
Comirnaty + Comirnaty + Spikevax 61 +	39	5601	325	< 5	5602	4
Spikevax + Spikevax 14–90	5	16 589	201	0	16 589	0
Spikevax + Spikevax 91–180	34	17 796	277	< 5	17 797	45
Spikevax + Spikevax 181 +	23	3315	433	< 5	3316	30
Spikevax + Spikevax + Comirnaty 14–60	6	2167	137	0	2167	0
Spikevax + Spikevax + Comirnaty 61 +	10	2092	70	0	2092	0
Spikevax + Spikevax + Spikevax 14–60	8	6630	27	0	6630	0
Spikevax + Spikevax + Spikevax 61 +	41	5948	109	0	5949	0
Vaxzevria + Vaxzevria 14–90	< 5	8248	16	< 5	8248	10
Vaxzevria + Vaxzevria 91–180	23	9067	205	5	9067	13
Vaxzevria + Vaxzevria + Comirnaty 14–60	< 5	3044	24	0	3044	0
Vaxzevria + Vaxzevria + Comirnaty 61 +	12	2434	363	< 5	2434	307

[a] Estimated based on the Kaplan–Meier estimator

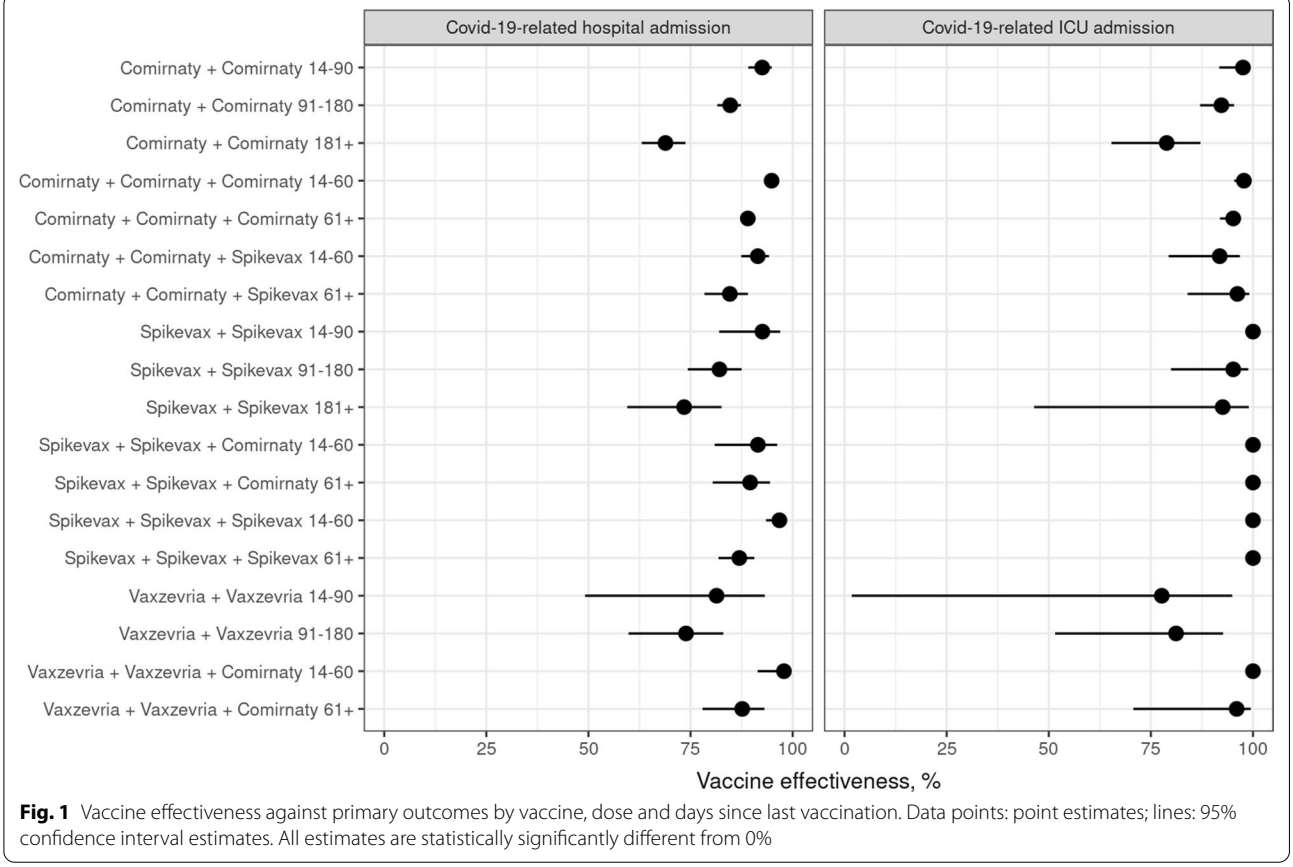

Fig. 1 Vaccine effectiveness against primary outcomes by vaccine, dose and days since last vaccination. Data points: point estimates; lines: 95% confidence interval estimates. All estimates are statistically significantly different from 0%

S11). In the 14–90 and 91–180 days after the second dose, the effectiveness of Comirnaty was 95% and 87% in 70–79-year-olds and 87% and 81% in 80–89-year-olds. In the 91–180 days after the second dose, the presence of either moderately or highly predisposing comorbidities reduced the VE from 92% to 83% or 82%. In the 14–60 days after the third dose of Comirnaty, the presence of comorbidities lowered the VE from 98% to 95% or 93%.

The effectiveness of Comirnaty was nearly constant over calendar time (Fig. 2, Additional file 1: Fig. S4). In the fourth quarter of 2021 (Q4), the VE against hospitalization was 90% (95% CI 78–96%) in the first 14–90 days since the second vaccination and 96% (95% CI 93–97%) in the first 14–60 days since the third vaccination (Fig. 2, Additional file 1: Table S12). The corresponding estimates for the first quarter of 2022 (Q1), which was dominated by Omicron, were 91% (95% CI 83–95%) and 94% (95% CI 92–95%), respectively (Fig. 2, Additional file 1: Table S13). However, while in Q4 there was almost no difference in point estimates in the 14–90 and 91–180 days after the second dose, in Q1 VE seemed to drop to 75% (95% CI 62–83%) in the 91–180 days after the second dose (Fig. 2). In both quarters, the median times since the second dose among those vaccinated 14–90 days ago (Q4: 63 days; Q1: 59 days) and 91–180 days ago (Q4: 146 days; Q1: 130 days) were similar.

The control outcome, i.e., injuries, occurred 36,747 times in the study cohort. Without differentiating between vaccines, number of doses and time since vaccination, we estimated the hazard ratio at 0.96 (95% CI 0.93–1.00) and, thus, detected no statistically significant difference between the vaccinated and the unvaccinated. However, the hazard of injury in those vaccinated with Spikevax was higher than in the unvaccinated (Additional file 1: Table S14). The cumulative hazards in vaccinated and unvaccinated individuals were proportional over time (Additional file 1: Fig. S5).

Discussion

In this study of a nationwide elderly cohort, the COVID-19 vaccines used in Finland were highly effective against severe COVID-19. After the second and third dose, the VE against COVID-19-related hospitalization and ICU admission was over 90% for both Comirnaty and Spikevax. However, already during the first 6 months after the second dose, we observed signs of waning VE. Although the confidence intervals overlapped, VE against

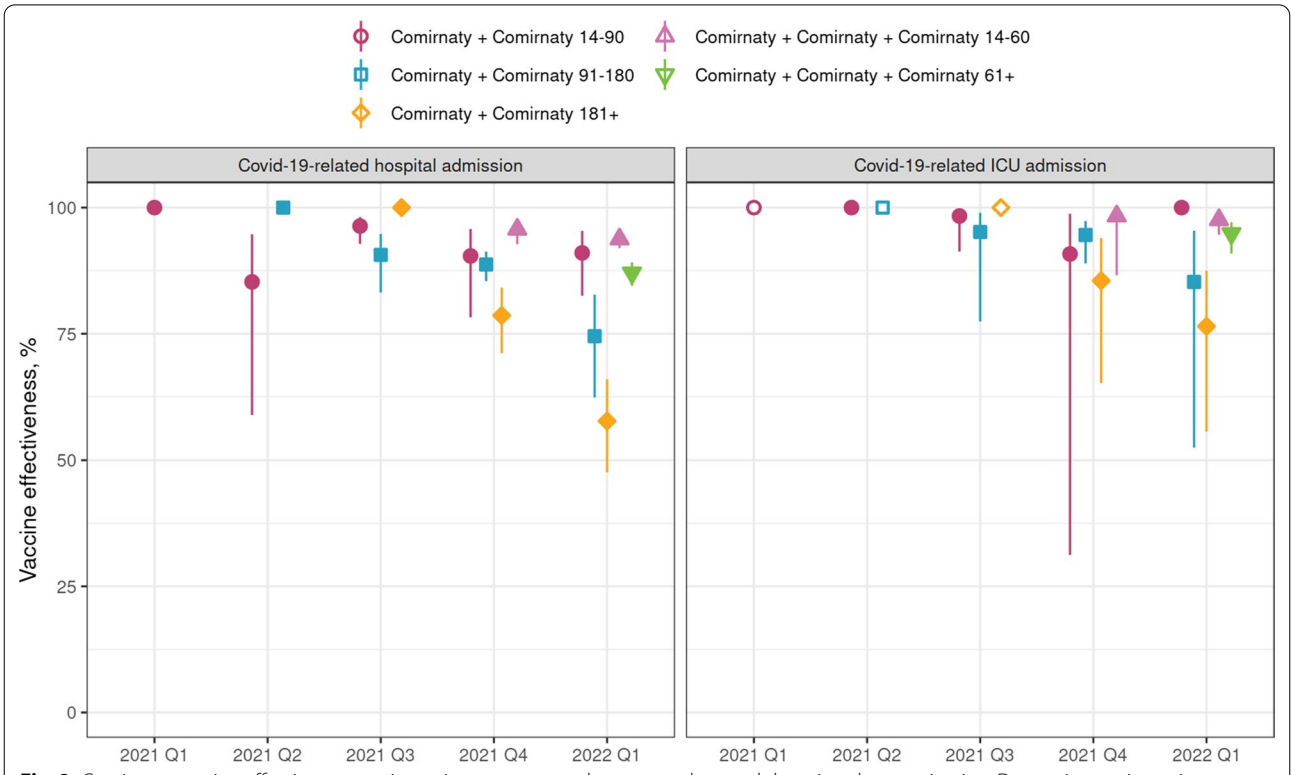

Fig. 2 Comirnaty vaccine effectiveness against primary outcomes by quarter, dose and days since last vaccination. Data points: point estimates; lines: 95% confidence interval estimates. A filled symbol indicates that the estimate is statistically significantly different from 0%, while an empty symbol indicates that the estimate is not statistically significantly different from 0%

hospitalization appeared to decrease faster than VE against ICU admission. A third dose restored the level of protection to over 90%. Interestingly, the VE was nearly constant during the study period despite the sporadic emergence of new variants. However, the gradual drop in point estimates of VE against hospitalization was more evident in the first quarter of 2022, which might be an indicator of intensified waning after the second dose due to Omicron.

We found no meaningful difference in the effectiveness of the two mRNA vaccines. The effectiveness of Vaxzevria was, however, slightly lower, although it was still better than the average protection observed among the elderly after seasonal influenza vaccination [27, 28]. Nevertheless, individuals who were first vaccinated with two doses of Vaxzevria and later boosted with mRNA vaccine were as well protected as those who received three doses of mRNA vaccine.

The present study is concordant with other studies that were conducted prior to the emergence of Omicron and found limited waning of VE against COVID-19-related hospitalization during the first 6 months after the second dose in the elderly [4, 7, 13, 14, 29]. In England, the VE against hospitalization decreased from initially excellent 98 to 91% within 5 months from the second vaccination with Comirnaty [4]. As in the present study, Vaxzevria did not offer as high protection as Comirnaty and the VE was generally lower among individuals with chronic illnesses [4]. In line with our findings, VE has also been reported to be reduced in the elderly aged 80 years and over compared to the younger elderly [14]. Due to enhanced immunosenescence and illness- or treatment-induced immunosuppression, the protection offered by COVID-19 vaccines may, thus, be weaker among the very fragile elderly, such as residents of long-term facilities.

Recent studies of adult populations have estimated the VE against severe COVID-19 caused by Omicron at 50–90% after the second dose [16, 21, 24, 25, 30] and at approximately 90% after the third dose [16, 21, 25, 30]. Surprisingly, our results from the Omicron-dominated first quarter of 2022 match the upper limits of these estimates, although our study was restricted to elderly adults, in which VE is expected to be lower than that in younger adults [4, 13, 31]. High VE against severe COVID-19 caused by Omicron may partially explain the relatively low hospital burden during the Omicron wave in many European countries despite skyrocketing infection rates [32]. It is difficult to foresee how long the high level of protection will last. However, this study and another analysis [30] showed that the VE against severe COVID-19 remained at approximately 90% for at least 2–3 months after the third vaccination. The decision-making regarding the recommendation of a fourth dose for risk groups, such as the elderly, needs further evidence on the duration of natural and vaccine-induced immunity as well as VE against severe COVID-19 in various epidemiological settings.

Finland is one of the few countries that used an extended dosing interval of 12 weeks between the first and second dose due to shortage of COVID-19 vaccines in the early stage of the vaccination campaign [33]. This interval is considered more immunogenic and might enhance VE against severe disease compared to the standard dosing interval of 3–4 weeks [7, 34, 35]. Therefore, our results of higher VE might be explained by the longer dosing interval.

The present study has three major strengths. First, the nationwide cohort was highly representative as it covered essentially the whole elderly population in Finland. Second, the Finnish setting minimizes the risk of detection bias. Hospital care in Finland is equally accessible to all permanent residents due to the national health insurance resulting in low or no out-of-pocket costs. Hospitalized patients with COVID-19 symptoms have been tested at low threshold irrespective of their vaccination status and the testing capacities in hospitals were at no point exhausted. Therefore, we assume that practically all elderly COVID-19 cases with severe symptoms requiring hospital care were identified as part of routine clinical practice and were thus eligible for inclusion in this study. Furthermore, we were able to exclude cases with concomitant asymptomatic or mild SARS-CoV-2 infection primarily hospitalized for other reasons than COVID-19. Third, we performed a negative control outcome analysis, which demonstrated that residual confounding after covariate adjustment would be negligible. Only those vaccinated with Spikevax had a statistically significantly higher risk of injuries than the unvaccinated indicating the presence of residual confounding due to differential behavior or frailty.

Although the national registers are known to be comprehensive and have been well maintained before and during the COVID-19 pandemic, the accuracy of the data has not been validated and information bias cannot be ruled out. Moreover, we assumed that the study population was randomly mixing so that vaccinated and unvaccinated subjects were equally exposed to the virus. Unfortunately, we have no data to support this assumption and differential vaccine uptake in particularly sheltered subpopulations such as residents of long-term care facilities may have thus led to bias. Although our findings may also apply to other populations of similar age, they do not necessarily apply to other outcomes. VE against mild disease or asymptomatic infection is likely lower than VE against severe disease. Another limitation is that the data do not allow estimation of variant-specific VE. As a surrogate

we stratified the analysis by calendar time and used sequencing data to show which variant dominated each quarter.

Conclusions

Since their introduction at the end of 2020, COVID-19 vaccines have been highly effective in preventing severe outcomes, such as COVID-19-related hospitalization and ICU admission, in the elderly, who carry the heaviest disease burden in a population. In our study, we observed signs of waning VE during the first six months after completion of a two-dose series, but a third dose restored the high level of protection for at least 2–3 months. Our analysis of data from the first quarter of 2022 suggests that the third dose still confers high protection against severe COVID-19 even after emergence of Omicron.

Abbreviations

VE: Vaccine effectiveness; ICU: Intensive care unit; CI: Confidence interval; Q4: Fourth calendar quarter; Q1: First calendar quarter.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-022-07814-4.

Additional file 1: Table S1. Highly predisposing comorbidities or medical therapies. **Table S2.** Moderately predisposing comorbidities or medical therapies. **Table S3.** Enrollment of the study cohort. **Table S4.** Distribution of baseline characteristics. **Table S5.** Number of days until first dose. **Table S6.** Number of COVID-19-related hospital admissions by vaccine, dose and days since last vaccination. **Table S7.** Number of COVID-19-related ICU admissions by vaccine, dose and days since last vaccination. **Table S8.** VE against COVID-19-related hospital admission. **Table S9.** VE against COVID-19-related ICU admission. **Table S10.** VE against COVID-19-related hospital admission by age group. **Table S11.** VE against COVID-19-related hospital admission by presence of comorbidities. **Table S12.** VE against COVID-19-related hospital admission in 2021 Q4, i.e., between October 1 and December 31. **Table S13.** VE against COVID-19-related hospital admission in 2022 Q1, i.e., between January 1 and March 31. **Table S14.** Negative control outcome analysis. **Figure S1.** Distribution of SARS-CoV-2 variants by calendar month. **Figure S2.** Distribution of exposure states by calendar month. **Figure S3.** Number of cases by calendar month. **Figure S4.** Cumulative hazard of COVID-19-related hospital admission between December 27, 2020, to March 31, 2022 by calendar time in days and by vaccine, dose and days since last vaccination. **Figure S5.** Cumulative hazard of negative control outcome.

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Author contributions

UB, EP, TL, TK, HN and AAP participated in the conceptualization of the study. UB conducted the statistical analysis and EP reviewed the literature. UB and EP drafted the manuscript. UB, EP, TL, TK, HN and AAP gave comments and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available to protect personal data. De-identified data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Finnish Institute for Health and Welfare (THL) is the national expert institution to carry out surveillance on the impact of vaccinations in Finland (Communicable Diseases Act, https://www.finlex.fi/en/laki/kaannokset/2016/en20161227.pdf). Neither specific ethical approval of this study nor informed consent from the participants was needed (Communicable Diseases Act).

Consent for publication

Not applicable.

Competing interests

The Finnish Institute for Health and Welfare (THL) conducts Public–Private Partnership with vaccine manufacturers and has received research funding from Sanofi Inc., Pfizer Inc., and GlaxoSmithKline Biologicals SA for non-COVID-19-related studies. AAP has been an investigator in these studies but has received no personal remuneration. The authors declare that they have no other competing interests.

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References

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;324(8):782.
2. El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med. 2021;385(19):1774–85.
3. Baum U, Poukka E, Palmu AA, Salo H, Lehtonen TO, Leino T. Effectiveness of vaccination against SARS-CoV-2 infection and COVID-19 hospitalisation among Finnish elderly and chronically ill—an interim analysis of a nationwide cohort study. PLoS ONE. 2021;16(11): e0258704.
4. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Duration of protection against mild and severe disease by COVID-19 vaccines. N Engl J Med. 2022;386(4):340–50.
5. WHO. WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines. https://www.who.int/publications-detail-redirect/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines. Accessed 2 Mar 2022.
6. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine through 6 months. N Engl J Med. 2021;385(19):1761–73.
7. Skowronski DM, Febriani Y, Ouakki M, Setayeshgar S, El Adam S, Zou M, et al. Two-dose severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada. Clin Infect Dis. 2022;ciac290.

8. THL recommends offering a third coronavirus vaccine dose to those over 60 and for medical high-risk groups—Press release—THL. Finnish Institute for Health and Welfare (THL), Finland. https://thl.fi/en/web/thlfi-en/-/thl-recommends-offering-a-third-coronavirus-vaccine-dose-to-those-over-60-and-for-medical-high-risk-groups. Accessed 16 Dec 2021.
9. Poukka E, Baum U, Palmu AA, Lehtonen TO, Salo H, Nohynek H, et al. Cohort study of COVID-19 vaccine effectiveness among healthcare workers in Finland, December 2020–October 2021. Vaccine. 2022;40(5):701–5.
10. Nordström P, Ballin M, Nordström A. Effectiveness of heterologous ChAdOx1 nCoV-19 and mRNA prime-boost vaccination against symptomatic COVID-19 infection in Sweden: a nationwide cohort study. Lancet Reg Health Europe. 2021;11: 100249.
11. Berec L, Šmíd M, Přibylová L, Májek O, Pavlík T, Jarkovský J, et al. Protection provided by vaccination, booster doses and previous infection against covid-19 infection, hospitalisation or death over time in Czechia. PLoS ONE. 2022;17(7): e0270801.
12. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med. 2021;385(24): e85.
13. Lin DY, Gu Y, Wheeler B, Young H, Holloway S, Sunny SK, et al. Effectiveness of COVID-19 vaccines over a 9-month period in North Carolina. N Engl J Med. 2022;386(10):933–41.
14. Machado A, Kislaya I, Rodrigues AP, Sequeira D, Lima J, Cruz C, et al. COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infections, COVID-19 related hospitalizations and deaths, among individuals aged ≥65 years in Portugal: a cohort study based on data-linkage of national registries February–September 2021. PLoS ONE. 2022;17(9): e0274008.
15. Hansen CH, Schelde AB, Moustsen-Helm IR, Emborg HD, Krause TG, Mølbak K, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: a Danish cohort study. Infect Dis (except HIV/AIDS). 2021. https://doi.org/10.1101/2021.12.20.21267966.
16. Buchan SA, Chung H, Brown KA, Austin PC, Fell DB, Gubbay JB, et al. Effectiveness of COVID-19 vaccines against Omicron or Delta symptomatic infection and severe outcomes. Infect Dis (except HIV/AIDS). 2022. https://doi.org/10.1101/2021.12.30.21268565.
17. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against COVID-19 by BNT162b2 booster across age groups. N Engl J Med. 2021;385(26):2421–30.
18. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. COVID-19 vaccine effectiveness against the Omicron (B.1.1.529) Variant. N Engl J Med. 2022;386(16):1532–46.
19. Barda N, Dagan N, Cohen C, Hernán MA, Lipsitch M, Kohane IS, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet. 2021;398(10316):2093–100.
20. Drawz PE, DeSilva M, Bodurtha P, Benitez GV, Murray A, Chamberlain AM, et al. Effectiveness of BNT162b2 and mRNA-1273 second doses and boosters for SARS-CoV-2 infection and SARS-CoV-2 related hospitalizations: a statewide report from the Minnesota Electronic Health Record Consortium. Clin Infect Dis. 2022 Feb 7;ciac110.
21. Thompson MG, Natarajan K, Irving SA, Rowley EA, Griggs EP, Gaglani M, et al. Effectiveness of a third dose of mRNA vaccines against COVID-19–associated emergency department and urgent care encounters and hospitalizations among adults during periods of Delta and Omicron variant predominance—VISION Network, 10 States, August 2021–January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(4):139–45.
22. Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med. 2022;28(5):1063–71.
23. Kahn F, Bonander C, Moghaddassi M, Rasmussen M, Malmqvist U, Inghammar M, et al. Risk of severe COVID-19 from the Delta and Omicron variants in relation to vaccination status, sex, age and comorbidities—surveillance results from southern Sweden, July 2021 to January 2022. Eurosurveillance. 2022. https://doi.org/10.2807/1560-7917.ES.2022.27.9.2200121.
24. Collie S, Champion J, Moultrie H, Bekker LG, Gray G. Effectiveness of BNT162b2 vaccine against Omicron variant in South Africa. N Engl J Med. 2022;386(5):494–6.
25. Public Health England. COVID-19 vaccine surveillance report—week 8. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1057599/Vaccine_surveillance_report_-_week-8.pdf. Accessed 2 Mar 2022.
26. Salo H, Lehtonen T, Auranen K, Baum U, Leino T. Predictors of hospitalisation and death due to SARS-CoV-2 infection in Finland: a population-based register study with implications to vaccinations. Vaccine. 2022;40(24):3345–55.
27. Baum U, Kulathinal S, Auranen K. Spotlight influenza: estimation of influenza vaccine effectiveness in elderly people with assessment of residual confounding by negative control outcomes, Finland, 2012/13 to 2019/20. Eurosurveillance. 2021. https://doi.org/10.2807/1560-7917.ES.2021.26.36.2100054.
28. Rose A, Kissling E, Emborg HD, Larrauri A, McMenamin J, Pozo F, et al. Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020. Eurosurveillance. 2020. https://doi.org/10.2807/1560-7917.ES.2020.25.10.2000153.
29. Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. The Lancet. 2021;398(10309):1407–16.
30. Chemaitelly H, Ayoub HH, AlMukdad S, Coyle P, Tang P, Yassine HM, et al. Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar. Nat Commun. 2022;13(1):3082.
31. Lytras T, Kontopidou F, Lambrou A, Tsiodras S. Comparative effectiveness and durability of COVID-19 vaccination against death and severe disease in an ongoing nationwide mass vaccination campaign. J Med Virol. 2022;jmv.27934.
32. Mathieu E. How do key COVID-19 metrics compare to previous waves?. Our World in Data. https://ourworldindata.org/covid-metrics-previous-waves. Accessed 2 Mar 2022.
33. THL. Expert group on vaccines recommends longer gap between coronavirus vaccinations and giving AstraZeneca vaccine to those under 70—Press release—THL. Finnish Institute for Health and Welfare (THL), Finland. https://thl.fi/en/web/thlfi-en/-/expert-group-on-vaccines-recommends-longer-gap-between-coronavirus-vaccinations-and-giving-astrazeneca-vaccine-to-those-under-70. Accessed 2 Mar 2022.
34. Payne RP, Longet S, Austin JA, Skelly DT, Dejnirattisai W, Adele S, et al. Immunogenicity of standard and extended dosing intervals of BNT162b2 mRNA vaccine. Cell. 2021;184(23):5699-5714.e11.
35. Amirthalingam G, Bernal JL, Andrews NJ, Whitaker H, Gower C, Stowe J, et al. Serological responses and vaccine effectiveness for extended COVID-19 vaccine schedules in England. Nat Commun. 2021;12(1):7217.

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