Bivalent booster effectiveness against severe COVID-19 outcomes in Finland, September 2022 – January 2023

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Abstract

Bivalent COVID-19 vaccines were introduced in 2022 but knowledge of how their effectiveness against severe COVID-19 outcomes is sustained over time is currently limited. In Finnish register-based cohort analyses, we compared the risk of severe COVID-19 outcomes among those who received bivalent vaccination (exposed) between 1 September 2022 and 31 January 2023 to those who did not (unexposed). Among elderly aged 65–120 years, bivalent vaccination reduced the risk of hospitalisation and death due to COVID-19. Among the elderly the hazard ratios comparing exposed and unexposed ranged from 0.36 to 0.43 during the first 14–30 days since bivalent vaccination but signs of waning were observed as soon as two months after vaccination. Among the chronically ill aged 18–64 years bivalent vaccination did not reduce the risk of severe COVID-19 outcomes. These results are crucial for further developing COVID-19 vaccination programme worldwide.

Main text

Due to the emergence of new SARS-CoV-2 variants with immune evasive capabilities[1], new, bivalent COVID-19 vaccines, containing mRNA that encodes the spike proteins of the original virus strain and the Omicron variant, were developed in 2022. The European Medicines Agency authorized the first (BA.1 and BA.4-5) bivalent vaccines in September 2022[2,3], which were promptly recommended in Finland as a booster for all people aged 65 years or more and those aged 18–64 years with underlying medical conditions predisposing to severe COVID-19.

In previous studies, bivalent vaccines have increased the protection against severe outcomes[4–9]. However, the duration of this protection is currently unclear. Thus, studies estimating the effectiveness of bivalent vaccines over time are needed as policy makers are considering recommendation of a second bivalent booster. Presently, policies vary between countries: some countries decided to recommend a second bivalent booster[10], while others do not yet recommend further boosters for spring 2023.

The aim of this study was to estimate the effectiveness of BA.1 and BA.4-5 bivalent COVID-19 vaccines against severe COVID-19 outcomes one, two and three months after vaccination in Finland based on national register data. Since bivalent boosters were primarily offered to individuals who had received at least two monovalent doses, our study was restricted to these vaccinees. To control for confounding, all analyses were adjusted for a set of potential confounders; a negative control outcome was used to assess the presence of residual confounding.

Results

The study cohorts included 1,197,700 elderly aged 65–120 years and 444,683 chronically-ill individuals aged 18–64 years (Supplementary Table S3). Only a small proportion of each cohort had been laboratory-confirmed SARS-CoV-2-positive prior to the study (Supplementary Table S4). The 2022–2023 influenza vaccination coverage reached 58% in the elderly cohort and 37% in the chronically ill cohort.

During the study 627,378 (52%) elderly and 66,871 (15%) chronically ill were vaccinated with a bivalent booster; approximately a third of them received Comirnaty BA.1 while the other two thirds received Comirnaty BA.4-5. Spikevax bivalent vaccines were used only in small quantities. The median time since bivalent vaccination by the end of follow-up was 75 days (interquartile range 61–85 days) and 73 days (interquartile range 54–88 days) among the elderly and chronically ill, respectively.

Among the elderly, we observed 1,721 hospitalisations due to COVID-19, 1,002 deaths due to COVID-19 and 809 deaths in which COVID-19 was a contributing factor. During the first 14–30 and 31–60 days since vaccination, a bivalent booster lowered the risk of hospitalisation due to COVID-19 (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.33–0.57; HR 0.43, 95% CI 0.33–0.57), death due to COVID-19 (0.39, 0.26–0.57; 0.57, 0.42–0.77) and death in which COVID-19 was a contributing factor (0.36, 0.24–0.54; 0.41, 0.29–0.57) (Fig. 1, Supplementary Table S5). Thereafter, the HRs increased: during the third month, i.e. 61–90 days since vaccination, the HR estimates for the aforementioned outcomes were 0.74 (95% CI 0.50–1.09), 0.74 (0.49–1.13) and 0.42 (0.25–0.69). When stratified by age, the HRs for 65-79-year-olds and 80-120-

year-olds were similar (Fig. 2, Supplementary Table S6). Both BA.1 and BA.4–5 bivalent vaccines reduced the risk of severe COVID-19 outcomes and the HRs were similar (Supplementary Table S7).

Among the chronically ill we observed 240 hospitalisations due to COVID-19, 16 deaths due to COVID-19 and 18 deaths in which COVID-19 was a contributing factor. HR of hospitalisation due to COVID-19 was estimated at 0.82 (95% CI 0.32–2.07) for days 14–30 since bivalent vaccination and 1.57 (0.78–2.07) for the subsequent 30 days. The HR for the other two outcomes could not be estimated (Supplementary Table S8).

In our negative control outcome analysis, we observed 9,447 emergency room visits due to injury among the elderly and 2,173 such visits among the chronically ill. We found no difference in the risk of injury among elderly who received a bivalent booster and those who did not (Supplementary Table S5). However, among the chronically ill the risk of injury appeared slightly elevated (Supplementary Table S8).

Figure 1. Hazard ratios among the elderly. Covariate-adjusted hazard ratios (with 95% confidence intervals) comparing the hazards of severe COVID-19 outcomes in 65-to-120-year-olds who received a bivalent COVID-19 vaccine with the corresponding hazards in those who did not receive a bivalent COVID-19 vaccine, Finland, September 2022–January 2023.

Figure 2. Age-stratified hazard ratios among the elderly. Covariate-adjusted hazard ratios (with 95% confidence intervals) comparing the hazards of severe COVID-19 outcomes in 65-to-120-year-olds who received a bivalent COVID-19 vaccine with the corresponding hazards in those who did not receive a bivalent COVID-19 vaccine stratified by age group, Finland, September 2022–January 2023.

Discussion

In our Finnish study, bivalent boosters reduced the risk of severe COVID-19 outcomes among the elderly. By contrast, among the chronically-ill 18–64-year-olds the risk was similar among those who received bivalent vaccine and those who did not. Among the elderly a bivalent booster provided highest protection during the first two months after vaccination, but thereafter signs of waning were observed. The effectiveness among individuals aged 65–79 years and those aged 80 years or more was similar.

Previously, the effectiveness of bivalent vaccines against severe COVID-19 outcomes has been studied in the USA, Israel, the United Kingdom, Italy and in the Nordic countries[4–9,11,12]. Compared to our analyses, a similar Israeli study[8] conducted among people aged 65 years or more reported slightly higher BA.4-5 bivalent booster effectiveness against severe COVID-19 outcomes. In an English analysis including individuals aged 50 years or more, the BA.1 bivalent booster effectiveness against hospitalisation due to COVID-19 was similar to our results, but no waning was observed after ten weeks since bivalent vaccination[7]. This English study is currently the only study, apart from ours, estimating the bivalent booster effectiveness against severe COVID-19 outcomes over time. Therefore, further studies assessing the existence and rate of waning will be needed to decide 1) whether annual boosters should be recommended for vulnerable groups and 2) whether the development of new COVID-19 vaccines inducing longer-lasting immune responses should be pursued.

Among the chronically ill we did not observe bivalent vaccination to reduce the risk of severe COVID-19 outcomes, although previous studies have found a benefit among working-age adults[6,12]. This may be due to several reasons. Firstly, only a small proportion of the cohort received a bivalent booster, and the negative control outcome analysis indicated the presence of residual confounding. Secondly, individuals who did not receive the booster might have had higher likelihood of unregistered SARS-CoV-2 infection and thus hybrid immunity prior to the study, which could have led to underestimation of the effectiveness. Thirdly, the number of cases among the chronically ill was small, which together with the low bivalent vaccine uptake led to unprecise estimates for that group. Fourthly, a good baseline protection due to

105 monovalent vaccinations and hybrid immunity among the chronically ill might have limited the additional
106 benefit of a bivalent booster.

107 As another limitation, we observed a decreased risk of severe COVID-19 outcomes during the first 0–13
108 days since bivalent vaccination. This was probably caused by selection (i.e. healthy vaccinee) bias as
109 individuals with acute respiratory symptoms, a predeterminant of severe COVID-19 outcomes, were not
110 advised to seek vaccination. However, it should be noted that the effect of this bias diminishes over time
111 and is likely negligible after 13 or latest 30 days since vaccination.

112 Our study has also several strengths. The study was timely and representative. We used the monovalent
113 vaccinated as the reference group, whose characteristics are probably more like the characteristics of the
114 bivalent vaccinated compared to those of the unvaccinated. Furthermore, we did not observe meaningful
115 residual confounding in the negative control outcome analysis among the elderly. The recording of
116 vaccinations and COVID-19 outcomes is mandatory, and the utilised registers have been well maintained as
117 they have been used for routine surveillance of the COVID-19 vaccination programme and the COVID-19
118 pandemic in Finland.

119 In conclusion, bivalent boosters reduced the risk of hospitalisation and death due to COVID-19 among the
120 elderly but not among chronically-ill, working-age adults. Because we found signs of waning already after
121 60 days since bivalent vaccination additional boosters for the elderly could be an option at some time point
122 in the future. However, the need for further boosting should also be considered in the light of the epidemic
123 situation and economic analyses.

124

125 **Authors' contributions.** EP, UB, HN and TL conceptualised the study. UB conducted the statistical analysis
126 and SG provided the death certificate data. EP and HN reviewed the literature. EP and UB drafted the
127 manuscript. EP, UB, SG HN and TL gave comments and revised the manuscript.

Conflict of interests. HN is a member of Finnish National Immunization Technical Advisory Groups and chairman of Strategic Advisory Group of Experts on Immunization for World Health Organization.

Funding. EP received a grant from The Finnish Medical Foundation. No other sources of external funding.

Research ethics. By Finnish law, 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.

Data availability. By Finnish law, the authors are not permitted to share individual-level register data. The computing code is available upon request.

Acknowledgements. We thank Erika Lindh and Aapo Juutinen for providing Supplementary Figure 1 as well as Heini Salo and Toni Lehtonen for the register-based identification of individuals with medical conditions predisposing to severe COVID-19. Additional thanks go to all the colleagues at the Finnish Institute for Health and Welfare (THL) who curate the register data. Lastly, we are grateful for our fruitful collaboration with Statistics Finland.

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Online Methods

We conducted population-based cohort analyses linking national register data from Finland using a unique person identifier. The study period was from 1 September 2022 to 31 January 2023, when Omicron BA.5 and its sublineages were the dominant SARS-CoV-2 strains (Supplementary Figure S1). In analogy to our previous study[13], we formed two cohorts of individuals aged 65–120 years (the elderly) and individuals aged 18–64 years with comorbidities or medical therapies predisposing to severe COVID-19 (the chronically ill, Supplementary Tables S1-2). We included only individuals that had received at least two monovalent COVID-19 vaccine doses (Comirnaty/ tozinameran/ BNT162b2, Spikevax/ elasomeran/ mRNA-1273, or Vaxzevria/ ChAdOx1-SARS-COV-2/ AZD1222). In addition, we excluded individuals that were hospitalised due to COVID-19 at the beginning of the study or had received a COVID-19 vaccination with too short dosing interval or a bivalent vaccination prior to the study (Supplementary Table S3).

The exposure was defined as vaccination with a BA.1 or BA.4-5 bivalent vaccine recorded in the Finnish Vaccination Register and was time-dependently categorized into seven groups: not vaccinated with a bivalent booster (the reference), and 0–13, 14–30, 31–60, 61–90, 91–120 and 121 or more days since vaccination with a bivalent booster. The bivalent vaccines included in this study were either based on Comirnaty or Spikevax as other bivalent vaccines were not available in Finland during the study period.

The severe COVID-19 outcomes were hospitalisation due to COVID-19, death due to COVID-19 and death in which COVID-19 was a contributing factor. Hospitalisations, recorded in the Care Register for Health Care, had to fulfil the following two criteria to be considered as hospitalisations due to COVID-19:

1) The primary diagnosis was 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).
2) A positive PCR- or antigen SARS-CoV-2 sample was taken from the hospitalized patient in the period extending from 14 days before to 7 days after hospital admission and registered in the National Infectious Diseases Register.

206 To define the two COVID-19 death outcomes, we used data collected from death certificates. In Finland,
207 physicians record the cause of death of their patients as well as other significant conditions contributing to
208 death in death certificates that are thereafter reviewed by medico-legal specialists at the Finnish Institute
209 for Health and Welfare prior to forming statistics. In our study, death due to COVID-19 included all deaths
210 in which COVID-19 was recorded as the cause of death in the death certificate. The cases in which COVID-
211 19 was a contributing factor to death were equally retrieved from the death certificates. For the study, the
212 data from reviewed death certificates were computerized into a database by medico-legal specialists
213 accepting the ICD10 codes U07.1, U07.2, U09, and U10 as COVID-19 diagnosis.

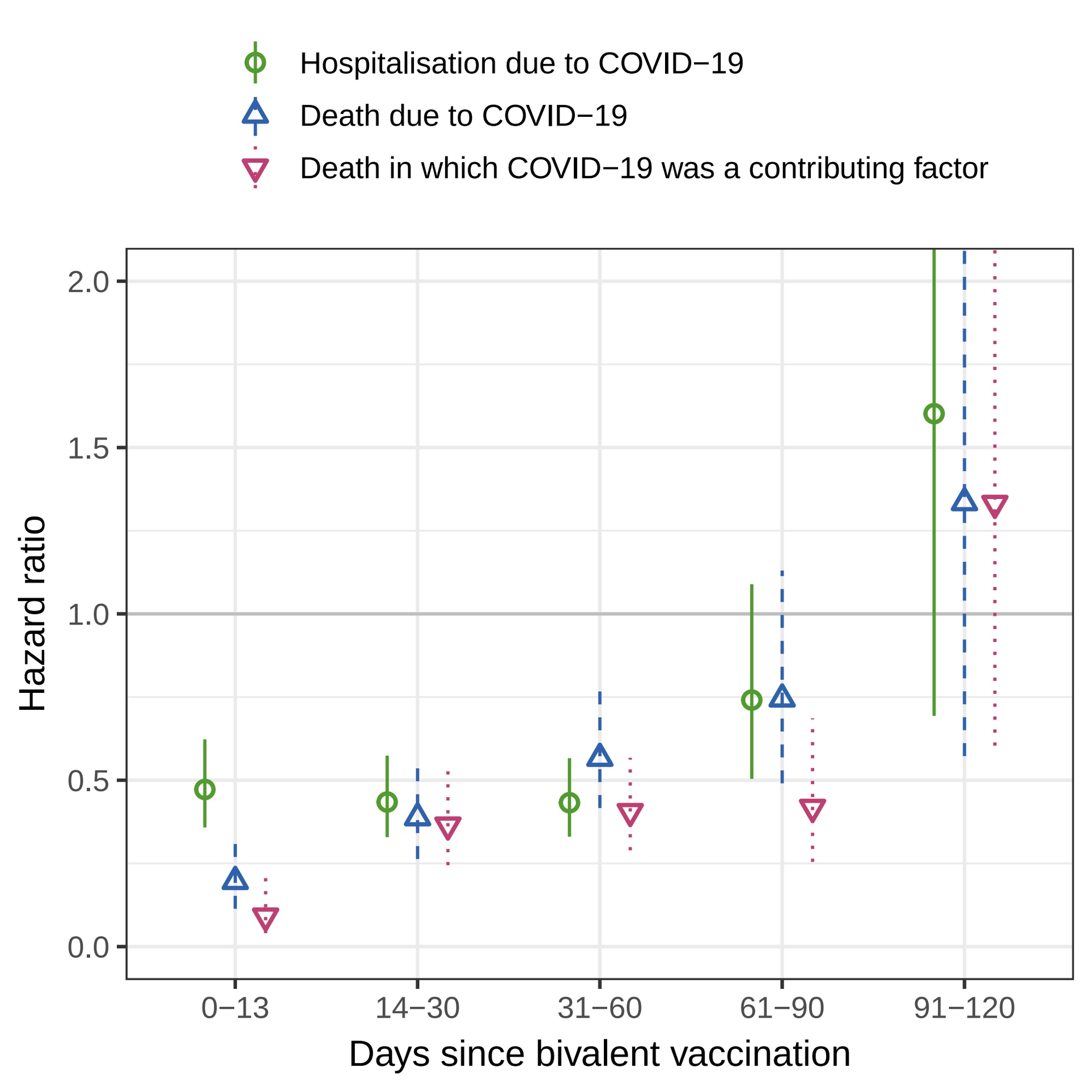
214 In addition, we defined a fourth endpoint, which we assumed to be unaffected by the exposure. This
215 negative control outcome was any emergency room visit due to injury (International Classification of
216 Diseases, 10th revision: S00–T14) recorded in the Care Register for Health Care.

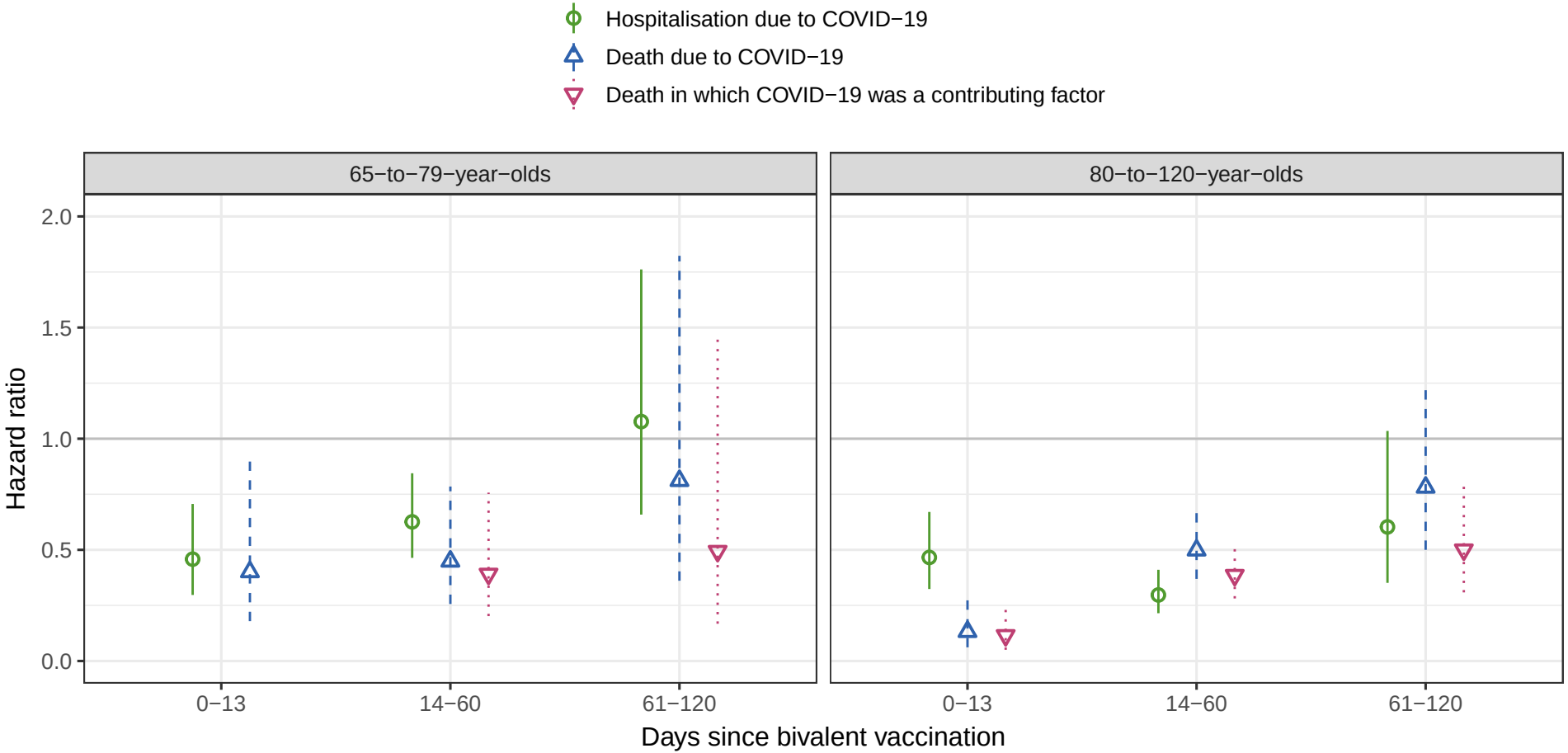
217 We considered nine covariates as confounders in our study: age group, region of residency, sex (Population
218 Information System), hospitalisation between 1 September 2021 and 31 August 2022 (Care Register for
219 Health Care), presence of comorbidities or medical therapies predisposing to severe COVID-19 (Care
220 Register for Health Care, Register of Primary Health Care visits, Special Reimbursement Register for
221 Medicine Expenses and Prescription Centre database, residency in a long-term care facility (Care Register
222 for Social Care), seasonal influenza vaccination in 2022–2023, number of monovalent COVID-19
223 vaccinations (Finnish Vaccination Register) and last laboratory-confirmed SARS-CoV-2 infection prior to the
224 study (National Infectious Diseases Register). SARS-CoV-2 infections were categorised into pre-Omicron
225 infections (before 2022) and Omicron infections (since 2022).

226 The individual follow-up period started earliest on 1 September 2022 and latest 91 days after the last
227 monovalent COVID-19 vaccination or laboratory-confirmed SARS-CoV-2 infection prior to the study. Each
228 individual was followed until death, outcome of interest, day 14 (if the outcome of interest was
229 hospitalisation due to COVID-19) or day 60 after laboratory-confirmed SARS-CoV-2 infection, a second
230 bivalent vaccination, a monovalent vaccination and 31 January 2023, whichever occurred first.

Separately for each cohort, we compared the hazard of the three severe COVID-19 outcomes between unexposed and exposed individuals taking into account time since bivalent vaccination. The hazard ratio (HR) was estimated using Cox regression with time in the study as the underlying time scale and adjusted for the aforementioned covariates. Additionally, we stratified the elderly cohort by age differentiating between individuals aged 65–79 years and those aged 80 years or more and analysed the HR separately for BA.1 and BA.4-5 bivalent vaccines. For these analyses, we combined the second and third and the fourth and fifth time since vaccination interval to account for the expectably small number of cases in these exposure groups.

To evaluate the presence of residual confounding, we estimated the hazard ratio for the negative control outcome and expected to find no difference between the unexposed and exposed. The analysis was conducted as described above considering the negative control outcome as the outcome of interest. However, individuals with residence in Helsinki-Uusimaa had to be excluded due to data collection problems affecting the identification of emergency room visits based on register data in the region. All analyses were performed in R 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).


Hospitalisation due to COVID−19
Death due to COVID−19
Death in which COVID−19 was a contributing factor
Hazard ratio
2.0
1.5
1.0
0.5
0.0
0−13
14−30
31−60
61−90
91−120
Days since bivalent vaccination


Hospitalisation due to COVID−19
Death due to COVID−19
Death in which COVID−19 was a contributing factor
65−to−79−year−olds
80−to−120−year−olds
Hazard ratio
2.0
1.5
1.0
0.5
0.0
0−13
14−60
61−120
Days since bivalent vaccination