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Original article

Waning protection after vaccination and prior infection against COVID-19-related mortality over 18 months

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ABSTRACT

Objectives: Evidence on waning patterns in protection from vaccine-induced, infection-induced, and hybrid immunity against death is scarce. The aim of this study is to assess the temporal trends in protection against mortality.

Methods: Population-based case-control study nested in the total population of Scania Region, Sweden using individual-level registry data of COVID-19-related deaths (<30 days after positive SARS-CoV-2 test) between 27 December 2020 and 3 June 2022. Controls were matched for age, sex, and index date. Conditional logistic regression was used to estimate the preventable fraction (PF) from vaccination (PF_{vac} corresponding to vaccine effectiveness; ≥2 vaccine doses vs. 0 doses), prior infection (PF_{inf}), and hybrid immunity (PF_{hybrid}). PF was calculated as one minus odds ratio. Models were adjusted for comorbidities, long-term care facility residence, prior infection (for PF_{vac}), country of birth, socio-economic conditions, and time since last vaccination (for PF_{inf}).

Results: In total, 14 936 individuals (1440 COVID-19-related deaths and 13 496 controls) were included in the case-control analyses (45% females, median age: 84 years). PF_{vac} was above 90% during the first month after vaccination, regardless of the number of vaccine doses. After 6 months, PF_{vac} of two doses waned to 34% (95% CI: −30% to 66%). PF_{inf} for people surviving a SARS-CoV-2 infection waned from 88% (−16% to 99%) 3 months after infection to 62% (34–79%) after 9 months. No differences in waning patterns in PF_{vac} were seen between virus variants, gender, and age.

Discussion: Given the waning of protection against death, continuous surveillance of population immunity status, particularly among the most vulnerable population groups, could help to further fine-tune vaccination recommendations. **Dominik Dietler, Clin Microbiol Infect 2023;29:1573**

Introduction

Vaccination campaigns, together with other public health measures, have drastically reduced COVID-19-related mortality and morbidity [1,2]. Available vaccines are highly protective particularly against severe forms of COVID-19 [3–6]. However, the emergence of the omicron variant, initially detected in late November 2021, changed the dynamic of the SARS-CoV-2 pandemic [7]. Omicron has a higher transmissibility as vaccine protection against infection decreases more rapidly compared leading to increasing numbers of breakthrough infections [8–14].

Omicron also affected the preventable fraction from vaccination (PF_{vac}; also referred to as vaccine effectiveness) against more severe outcomes of COVID-19. Against hospitalization, PF_{vac} remained above 80% for 10 months after the last dose before omicron emerged [14,15]. Against omicron, PF_{vac} wanes more rapidly from around 90% during the first month to 36% 10 months after the last dose [14]. In general, the peak and the waning patterns in PF_{vac} depend on age, gender, type of vaccine, and pre-existing comorbidities [14,16], although evidence is not conclusive across studies [17].

Evidence on waning patterns in PF_{vac} against COVID-19-related death is more scarce, partly because deaths are often analysed

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together with other severe COVID-19-related outcomes, such as intensive care unit admissions [5,13,18–20]. In a study conducted during the dominance of the delta variant (a predecessor of omicron), only limited waning in PF_{vac} against death was found during 6 months after vaccination [15]. In another study that also includes the period when omicron was widely abundant, PF_{vac} against death decreased rapidly after a 5-month period of high protection at around 90% [14]. Still, how the emergence of omicron affects waning patterns in PF_{vac} against COVID-19-related mortality and how vaccine protection varies among different subgroups is poorly understood [18,21]. Furthermore, the increasing number of infections with the omicron variant among the vaccinated warrants further investigation on how protection from hybrid immunity changes over time [22].

Given the higher transmissibility of the omicron variants and the predominant reliance on vaccines as primary public health protection measures to curb the burden of the pandemic, assessing waning immunity patterns is pertinent to guide vaccination and disease prevention campaigns [11]. Therefore, the aim of this study was to assess the temporal trends in the preventable fraction (PF) from vaccination, infection, and hybrid immunity against COVID-19-related mortality.

Methods

Study design and study population

The study was conducted in the Scania Region (Skåne) in southern Sweden. The source population for this study consisted of the entire population living in the region at baseline, i.e. the start of the vaccination campaign on 27 December 2020 ($N = 1\ 385\ 479$; Fig. 1). From this cohort, COVID-19-related deaths occurring until the end of follow-up (3 June 2022) were included as cases. For each case, ten controls were selected on the respective date of death (index date), thereby accounting for factors related to the calendar period (e.g. dominant virus variant, prioritization of vaccination groups). Cases and controls were further matched with respect to gender and 5-year age group (0–4, 5–9, 10–14, …, 95–99, 100+ years). Controls could be resampled until emigration from the region or death.

Data sources

The Swedish personal identification number was used to link data at baseline and during follow-up from different registry sources with complete population coverage [23]. Information at baseline included data on individual characteristics, residence, country of birth, and vital status from the Swedish Total Population Register. Information on comorbidities, diagnoses, and medical procedures within inpatient and specialized care was obtained from health records of the Scania Region between 2016 and 2020.

For the follow-up period, the Swedish Public Health Agency provided data on positive SARS-CoV-2 tests and vaccinations (vaccination dates, type of vaccine, and number of doses) through SMINet and the National Vaccination Register, respectively. Deaths and changes in residential status during follow-up were reported in the Swedish Total Population Register. Furthermore, data on residence in long-term care facilities (LTCF) for the population above 65 years were retrieved from Senior Alert [24].

Variables

The outcome was COVID-19-related death defined as any death occurring within 30 days after a positive SARS-CoV-2 test. This follows the definition by Swedish Public Health Agency and is in line with previous research finding that around 90% of deaths because of COVID-19 occur in this time window [25]. Vaccination status was defined as the number of vaccine doses received on the index date or earlier. Individuals with one vaccine dose on the index date were excluded since the vaccination regimen is incomplete with only minor beneficial effects on mortality [26]. Unvaccinated individuals were used as reference group. Infections at least 90 days before the index date were considered as prior SARS-CoV-2 infection, whereas individuals who had a positive test between 30 and 90 days were excluded from analyses because their infection might have affected their survival status. Only controls with matching index case were retained in the final dataset. For the assessment of waning patterns, the time since last vaccination was classified based on the number of months since last dose (in 30-day periods) and time since the last infection (in 3-month periods).

Comorbidities were categorized into seven groups [27]: cardiovascular disease, diabetes or obesity, kidney or liver disease, respiratory disease, neurological disease (including dementia), cancer or immunosuppression, and other conditions, including mental health conditions, HIV, or sickle cell anaemia (Table A1). Each comorbidity group was considered a separate variable in the analyses. As additional measure of frailty residence in LTCF at the index date was used as a proxy. Because the actual moving date to the LTCF was not available in the Senior Alert data, the date of the first health risk assessment was used. These assessments are regularly conducted with LTCF residents starting a few days after the moving date [24]. The countries of birth were grouped into six categories (Sweden, Nordic countries except Sweden, Western

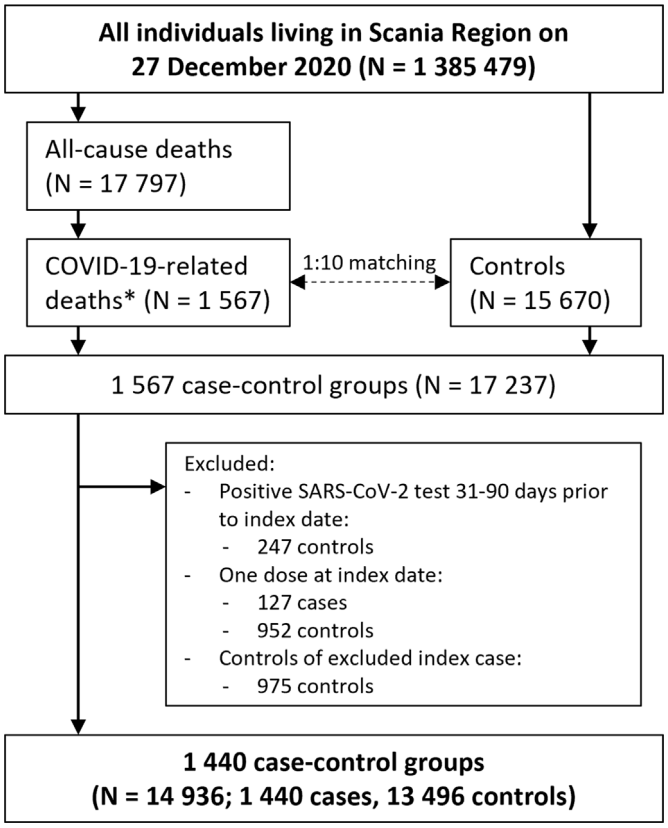

Fig. 1. Selection of cases and controls.
*Cases include all COVID-19-related deaths (occurring within 30 d after a positive SARS-CoV-2 test) during the study period from 27 December 2020 to 3 June 2022. Controls were matched with respect to age, gender, and index date.

Europe, Eastern Europe, Middle East, and other). The neighbourhood socio-economic conditions were determined for the regional statistical areas and categorized into five levels based on the proportion of people with low economic status, tertiary education, and receivers of financial assistance for at least 10 months or unemployed for longer than 6 months.

Statistical analyses

To estimate the protective fraction from vaccination (PF_{vac}), infection (PF_{inf}), and hybrid immunity (PF_{hybrid}) against COVID-19-related mortality, conditional logistic regression accounting for individual-level clustering was used. The obtained ORs were used

Table 1
Descriptive statistics of cases (COVID-19-related deaths in Sweden, between 27 December 2020 and 3 June 2022) and controls (matched with respect to age, gender, and index date) by vaccination status

	COVID-19-related deaths[a]			Controls		
Vaccination status[b]	Unvaccinated	Vaccinated	Total	Unvaccinated	Vaccinated	Total
N	920	520	1440	7331	6165	13 496
Female	405 (44.0%)	245 (47.1%)	650 (45.1%)	3205 (43.7%)	2877 (46.7%)	6082 (45.1%)
Age (y)						
<65	70 (7.6%)	37 (7.1%)	107 (7.4%)	537 (7.3%)	421 (6.8%)	958 (7.1%)
65–79	247 (26.8%)	126 (24.2%)	373 (25.9%)	1920 (26.2%)	1593 (25.8%)	3513 (26.0%)
≥80+	603 (65.5%)	357 (68.7%)	960 (66.7%)	4874 (66.5%)	4151 (67.3%)	9025 (66.9%)
Dominant virus variant[c]						
Pre-omicron	795 (86.4%)	74 (14.2%)	869 (60.3%)	7012 (95.6%)	902 (14.6%)	7914 (58.6%)
Transition pre-omicron–omicron	4 (0.4%)	13 (2.5%)	17 (1.2%)	8 (0.1%)	159 (2.6%)	167 (1.2%)
Omicron	121 (13.2%)	433 (83.3%)	554 (38.5%)	311 (4.2%)	5104 (82.8%)	5415 (40.1%)
Vaccine doses						
0	920 (100.0%)	NA	920 (63.9%)	7331 (100.0%)	NA	7331 (54.3%)
2	NA	181 (34.8%)	181 (12.6%)	NA	1374 (22.3%)	1374 (10.2%)
3	NA	310 (59.6%)	310 (21.5%)	NA	4279 (69.4%)	4279 (31.7%)
4	NA	29 (5.6%)	29 (2.0%)	NA	512 (8.3%)	512 (3.8%)
Months since last dose						
<1	NA	39 (7.5%)	39 (2.7%)	NA	1015 (16.5%)	1015 (7.5%)
1	NA	43 (8.3%)	43 (3.0%)	NA	926 (15.0%)	926 (6.9%)
2	NA	81 (15.6%)	81 (5.6%)	NA	1350 (21.9%)	1350 (10.0%)
3	NA	122 (23.5%)	122 (8.5%)	NA	1568 (25.4%)	1568 (11.6%)
4–5	NA	114 (21.9%)	114 (7.9%)	NA	847 (13.7%)	847 (6.3%)
6–8	NA	72 (13.8%)	72 (5.0%)	NA	314 (5.1%)	314 (2.3%)
≥9	NA	49 (9.4%)	49 (3.4%)	NA	145 (2.4%)	145 (1.1%)
Vaccine type						
Comirnaty (Pfizer)	NA	441 (84.8%)	441 (30.6%)	NA	4668 (75.7%)	4668 (34.6%)
Spikevax (Moderna)	NA	15 (2.9%)	15 (1.0%)	NA	151 (2.4%)	151 (1.1%)
Vaxzevria (Astra Zeneca)	NA	14 (2.7%)	14 (1.0%)	NA	110 (1.8%)	110 (0.8%)
Mixed	NA	50 (9.6%)	50 (3.5%)	NA	1236 (20.0%)	1236 (9.2%)
Current SARS-CoV-2 infection[d]	920 (100.0%)	520 (100%)	1440 (100%)	96 (1.3%)	113 (1.8%)	209 (1.5%)
Prior SARS-CoV-2 infection[e]	4 (0.4%)	20 (3.8%)	24 (1.7%)	78 (1.1%)	311 (5.0%)	389 (2.9%)
Months since prior infection						
3–5	0 (0.0%)	3 (0.6%)	3 (0.2%)	30 (0.4%)	28 (0.5%)	58 (0.4%)
≥6	4 (0.4%)	17 (3.3%)	21 (1.5%)	48 (0.7%)	283 (4.6%)	331 (2.5%)
Comorbidities						
Cardiovascular diseases	494 (53.7%)	292 (56.2%)	786 (54.6%)	2662 (36.3%)	2287 (37.1%)	4949 (36.7%)
Diabetes or obesity	253 (27.5%)	131 (25.2%)	384 (26.7%)	1097 (15.0%)	987 (16.0%)	2084 (15.4%)
Kidney or liver diseases	93 (10.1%)	47 (9.0%)	140 (9.7%)	230 (3.1%)	186 (3.0%)	416 (3.1%)
Respiratory diseases	166 (18.0%)	90 (17.3%)	256 (17.8%)	538 (7.3%)	462 (7.5%)	1000 (7.4%)
Neurological diseases	294 (32.0%)	192 (36.9%)	486 (33.8%)	1094 (14.9%)	952 (15.4%)	2046 (15.2%)
Cancer or immunosuppressed state	217 (23.6%)	155 (29.8%)	372 (25.8%)	1592 (21.7%)	1398 (22.7%)	2990 (22.2%)
Other conditions	81 (8.8%)	45 (8.7%)	126 (8.8%)	227 (3.1%)	206 (3.3%)	433 (3.2%)
LTCF resident	189 (20.5%)	145 (27.9%)	334 (23.2%)	307 (4.2%)	445 (7.2%)	752 (5.6%)
Country/region of birth						
Sweden	718 (78.0%)	437 (84.0%)	1155 (80.2%)	6204 (84.6%)	5393 (87.5%)	11 597 (85.9%)
Nordic countries except Sweden	34 (3.7%)	20 (3.8%)	54 (3.8%)	244 (3.3%)	190 (3.1%)	434 (3.2%)
Western Europe	19 (2.1%)	6 (1.2%)	25 (1.7%)	161 (2.2%)	137 (2.2%)	298 (2.2%)
Eastern Europe	81 (8.8%)	34 (6.5%)	115 (8.0%)	393 (5.4%)	242 (3.9%)	635 (4.7%)
Middle East	26 (2.8%)	9 (1.7%)	35 (2.4%)	104 (1.4%)	60 (1.0%)	164 (1.2%)
Other	42 (4.6%)	14 (2.7%)	56 (3.9%)	225 (3.1%)	143 (2.3%)	368 (2.7%)
Neighbourhood socio-economic conditions						
Major socio-economic challenges	100 (10.9%)	23 (4.4%)	123 (8.6%)	358 (4.9%)	227 (3.7%)	585 (4.3%)
Socio-economic challenges	135 (14.7%)	83 (16.0%)	218 (15.2%)	835 (11.4%)	683 (11.1%)	1518 (11.3%)
Socio-economically mixed	254 (27.7%)	150 (28.9%)	404 (28.1%)	1942 (26.5%)	1637 (26.6%)	3579 (26.6%)
Good socio-economic conditions	380 (41.4%)	229 (44.1%)	609 (42.4%)	3528 (48.2%)	3059 (49.7%)	6587 (48.9%)
Very good socio-economic conditions	48 (5.2%)	34 (6.6%)	82 (5.7%)	658 (9.0%)	553 (9.0%)	1211 (9.0%)

LTCF, long-term care facility.
[a] Deaths within 30 d after positive SARS-CoV-2.
[b] Unvaccinated: 0 doses; vaccinated: ≥2 doses.
[c] Pre-omicron: 27 December 2020–28 November 2021, transition pre-omicron–omicron: 29 November 2021–26 December 2021, omicron: 27 December 2021–3 June 2022.
[d] Within 30 d before death/selection date.
[e] More than 90 d before death/selection date.

for calculating PF as follows: PF = (1 − OR) × 100%. Estimates were adjusted for comorbidities, prior SARS-CoV-2 infection, LTCF residence, country of birth, and neighbourhood socio-economic conditions.

To assess waning patterns of PF_{vac} among the whole study population, the number of vaccine doses was used. In stratified models, individuals with at least two doses were grouped together. Stratification was done for age (<80 vs. ≥80 years), gender, and dominant SARS-CoV-2 variant (before [i.e. until 28 November 2021] vs. after [i.e. from 27 December 2021] the emergence of omicron in Sweden [11]). Stratification for dominant variant was also done for PF_{inf}. The models for estimating the PF_{inf} were additionally adjusted for the time since last vaccine dose. For assessing PF_{hybrid}, an interaction term between time since last dose and last infection was used.

Stata SE 14.2 (Stata Corp, College Station, Texas, United States) was used for estimating PF, whereas visualizations were produced using R v4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

The Swedish Ethical Review Authority granted ethical approval for this study (2021–00059).

Results

Between the start of the vaccination campaign on 27 December 2020 and the end of follow-up on 3 June 2022, 17 797 all-cause deaths occurred among the entire population living in the Scania Region of Sweden (N = 1 385 479; annual mortality rate: 9.0 per 1000 population). Of these, 1567 deaths occurred within 30 days after a SARS-CoV-2 infection (Fig. 1). Among the 15 670 controls, 247 had a positive SARS-CoV-2 test between 31 and 90 days before the index date and were excluded from analyses. In total, 1079 individuals (127 cases and 952 controls) had one dose at index date. After the exclusion of partially vaccinated individuals, 975 controls without matching index cases were excluded. The final dataset used for analyses comprised of 14 936 individuals (1440 cases and 13 496 controls). Median age was 84 years (interquartile range: 76–90).

Overall, compared with controls, individuals that died after a SARS-CoV-2 infection were more often unvaccinated (63.9% vs. 54.3%), received their last dose longer before the index date and prior SARS-CoV-2 infection was less frequent (Table 1). Furthermore, comorbidities were more frequent among the deceased individuals and these more often lived in LTCF.

Descriptive statistics among the controls stratified by dominant virus variant revealed factors associated with vaccination coverage in the population (Table A2). People born in Sweden, living in LTCF, and those with comorbidities were more often vaccinated. Furthermore, people in more affluent areas had a higher vaccination coverage, although no differences were seen among the areas with very high socio-economic conditions.

Protection from vaccination

Regardless the number of vaccine doses, PF_{vac} against COVID-19-related mortality remained high during the first 6 months after the last dose (Fig. 2 and Table A3). More specifically, PF_{vac} peaked during the first month at 92% (81–97%), 92% (81–96%), and 92% (79–97%) for two, three, and four doses, respectively. Overall, only minor differences in waning patterns in PF_{vac} were seen between individuals receiving two, three, and four doses. After 4–5 months, PF_{vac} declined to 83% (59–93%) for two doses and 66% (29–84%) for three doses. After 6–8 and ≥9 months, PF_{vac} of two doses declined to 34% (−30% to 66%) and 36% (−36% to 70%), respectively.

Similar waning patterns were seen before and after the omicron variants emerged (Fig. 3 and A1). Again, waning was predominantly affected by the time since the last dose rather than the number of doses. Furthermore, the dip in PF_{vac} after 6 months since the last vaccine dose was seen among all age groups (Fig. 3). Although CIs were largely overlapping, PF_{vac} was consistently lower among females compared with males.

Protection from prior infection

Overall, people surviving a prior SARS-CoV-2 infection had 62% (36–78%) protection from dying of a subsequent infection (Fig. 4 and Table A4). Similar to the PF_{vac}, the protection of prior infection on COVID-19-related mortality waned over time. PF_{inf} declined from 88% (−16% to 99%) 3 months after infection to 62% (34–79%) after ≥9 months. PF_{inf} was higher during the pre-omicron phase, although differences were not statistically significant (pre-omicron: 64% [−21% to 89%], omicron: 57% [−21% to 77%]).

Hybrid immunity

Protection from prior infection differed depending on the vaccination status (Fig. 5). Among the unvaccinated, surviving a SARS-CoV-2 infection protected against death in a subsequent infection (88% [62–96%]). Among the vaccinated, prior infections only had marginal additional protective effects. For example, protection of two doses was 70% (52–82%) without and 78% (44–91%) with previous infection.

Recent vaccination (i.e. less than 6 months ago) in combination with a prior SARS-CoV-2 infection showed very high protection of around 90% and higher against death (Table 2 and A5). Again, the additional protective effect of prior infection was limited among the vaccinated even when accounting for the time since the last dose or infection. Regardless of prior infection, the protection from the vaccine waned off after 6 months.

Discussion

In this population-based study of all COVID-19-related deaths over 18 months follow-up in southern Sweden, PF_{vac} against mortality peaked at more than 90% and remained high during 6 months after vaccination but declined thereafter. Furthermore, waning in PF_{vac} was predominantly related to the increasing time since the last inoculation rather than the total number of doses received. No differences in waning of PF_{vac} between age groups and sex as well

Table 2
Protection against COVID-19-related mortality in % (95% CIs) from the interaction between time since last vaccination dose and time since last SARS-CoV-2 infection (PF_{hybrid})

	Time since last vaccine dose			
Time since last infection	Unvaccinated	<3 month	3–5 month	≥6 month
No infection	Ref.	90 (82 to 94)	80 (64 to 89)	39 (−10 to 66)
3–5 mo	100 (100 to 100)	89 (31 to 98)	100 (100 to 100)	43 (−783 to 96)
≥6 mo	81 (40 to 94)	97 (89 to 99)	92 (76 to 97)	44 (−59 to 80)

Cases and controls are matched for age, gender, and index date. The conditional logistic regression model was adjusted for comorbidities, long-term care facility residence, country of birth, and neighbourhood socio-economic conditions.
PF, preventable fraction.

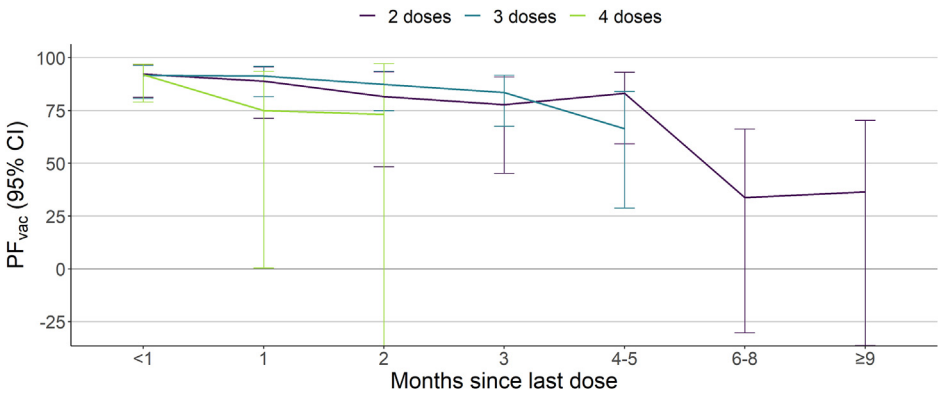

Fig. 2. Preventable fraction of COVID-19-related deaths from vaccination (PF_{vac}, corresponding to vaccine effectiveness) by time since last vaccine dose and number of doses.
Cases (deaths within 30 d after positive SARS-CoV-2 test) and controls are matched for age, gender, and index date. Models were adjusted for prior infections, comorbidities, long-term care facility residence, country of birth, and neighbourhood socio-economic conditions.

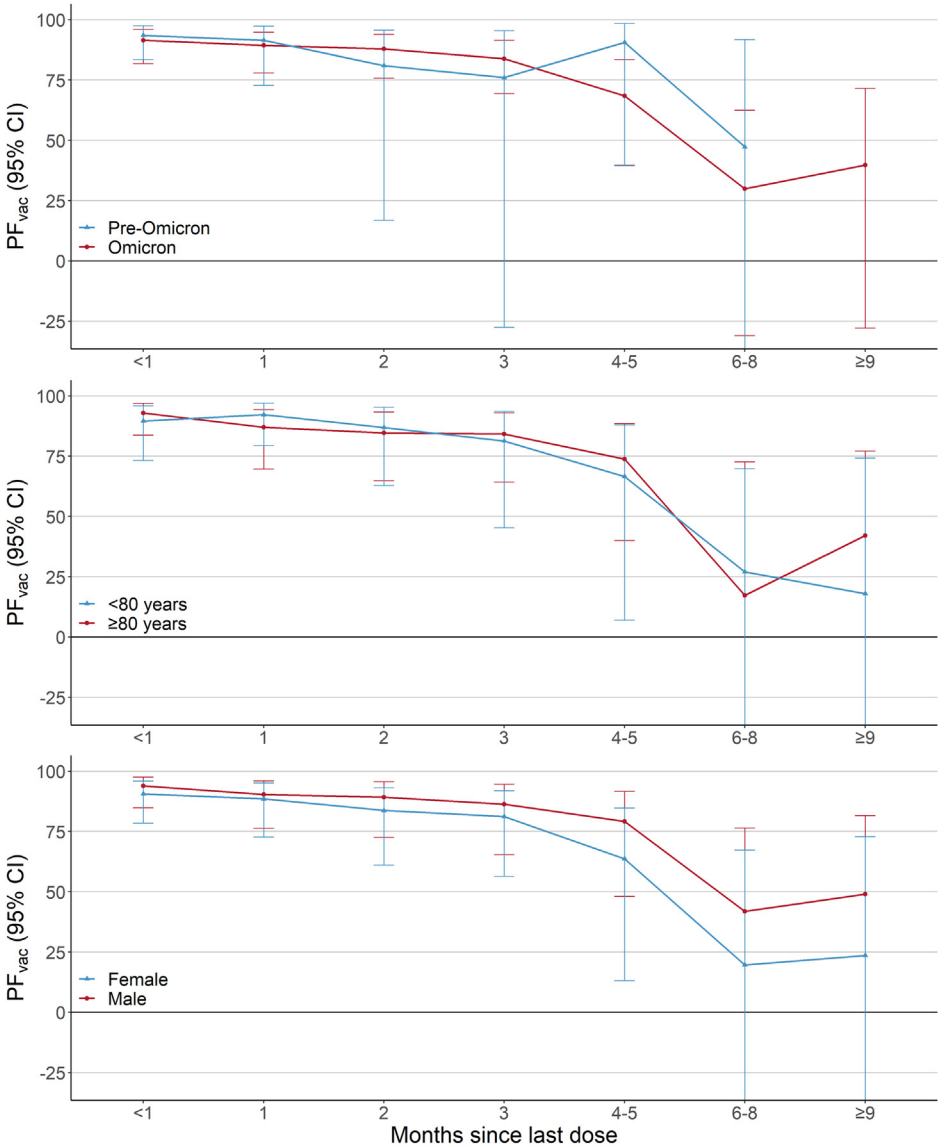

Fig. 3. Preventable fraction of COVID-19-related deaths from vaccination (PF_{vac}, corresponding to vaccine effectiveness) by time since last vaccine dose stratified by dominant virus variant, age, and gender.
The stratification includes a comparison when omicron (27 December 2021–3 June 2022) and earlier variants (pre-omicron, 27 December 2020–28 November 2021) were dominant. Cases (deaths within 30 d after positive SARS-CoV-2 test) and controls are matched for age, gender, and index date. Models were adjusted for prior infections, comorbidities, long-term care facility residence, country of birth, and neighbourhood socio-economic conditions.

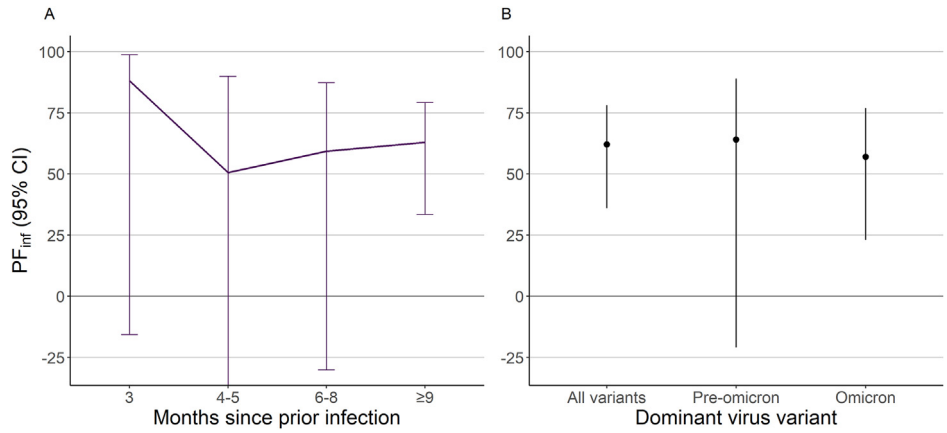

Fig. 4. Preventable fraction of COVID-19-related deaths from prior SARS-CoV-2 infection (PF_{inf}).
A: Waning of protection by time since prior infection. B: Protection from prior infection against death from a subsequent infection before (27 December 2020–28 November 2021) and after (27 December 2021–3 June 2022) the emergence of omicron. Cases and controls are matched for age, gender, and index date. Models were adjusted for comorbidities, long-term care facility residence, country of birth, neighbourhood socio-economic conditions, and time since last vaccination dose.

as before and after the emergence of omicron were observed. Protection from prior infection was larger among the unvaccinated, whereas among the vaccinated, the additional protection was marginal.

The waning of protection found in this study is in line with results from other studies on severe COVID-19-related outcomes of the omicron variant [14,19,28]. Interestingly, booster doses did not affect the longevity of protection against death as opposed to a study conducted in the USA [29]. These contrasting findings might be due to the longer follow-up or more comprehensive adjustment for comorbidities in this study. Nevertheless, the waning trends in PF_{vac} also among people receiving booster doses call for continuous surveillance of the immunity of the most vulnerable population groups [30].

In contrast to findings on severe COVID-19 that also include hospitalization or intensive care unit admittance, there was no evidence for increased waning of the protective effect against death after the emergence of the omicron variants [13,14,31]. At the end of the study period, omicron subvariant BA.2 was dominant. Further research is needed to evaluate whether the additional mutations of the omicron variant affect vaccine effectiveness against death. This should also include analyses of the protection of the bivalent vaccine boosters that are adapted to the omicron variants which have not been introduced by the end of the study period yet.

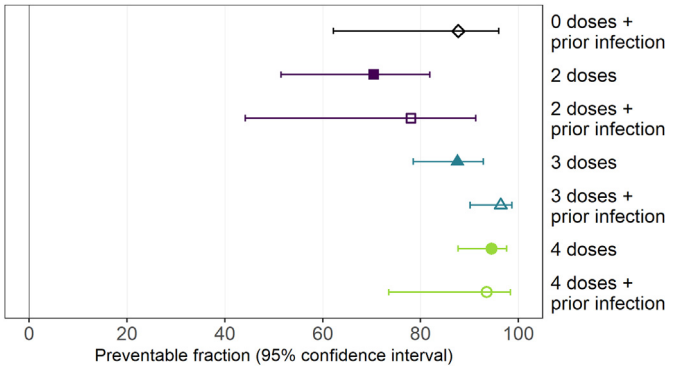

Fig. 5. Preventable fraction of COVID-19-related deaths from COVID-19 vaccination and prior infection (PF_{hybrid}).
Cases (deaths within 30 d after positive SARS-CoV-2-test) and controls are matched for age, gender, and index date. Models were adjusted for comorbidities, long-term care facility residence, country of birth, and neighbourhood socio-economic conditions.

Prior infections did not substantially reduce the risk of dying among vaccinated individuals contrasting other studies on SARS-CoV-2 infections [12,32,33]. There could be two possible reasons for this finding. First, the additional effect of prior infections may be limited because vaccinated individuals already exhibit high protection against death. Second, survival selection is likely to be stronger among the unvaccinated since they have a higher risk of dying from the first infection, particularly the frailest individuals. Overall, given that PF_{inf} and PF_{hybrid} wane over time and with the COVID-19 pandemic transitioning into the endemic phase, further research on how different vulnerable groups are protected through hybrid immunity over time is needed. This would allow us to further refine booster recommendations based on individual infection and vaccination histories.

The strengths of this study are the availability of individual-level data on the entire population of the Scania Region and the long follow-up period. At the same time, there are some limitations. First, the case definition was based on positive SARS-CoV-2 tests before death. This approach is widely used and captures the majority of deaths due to COVID-19 [25]. However, towards the end of the study period, the number of deaths using this definition increasingly differed from the COVID-19 deaths registered in the cause of death certificates, mainly due to more widespread disease transmission and prolonged survival upon infection [34]. Second, there is a potential for residual confounding due to the observational design of this study. Still, the availability of individual-level health registry data with complete population coverage allowed for adjustment for major confounders. Third, PF_{vac} estimates are based on the comparison to the unvaccinated population. Although the adjustment set includes a broad variety of confounders, it cannot be ruled out that particularly towards the end of the study period, other unmeasured factors are inherent to the unvaccinated population that may affect their survival. The unvaccinated population may not only be subject to survival selection but may also have less often prior infections registered due to the testing propensity [35]. Taken together, this would potentially lead to an underestimation of PF_{vac} when adjusting for prior infection.

In conclusion, although vaccination and prior infection are protective against COVID-19 mortality, protection wanes considerably after 6 months. With SARS-CoV-2 increasingly moving towards endemicity, the continuous threat of new virus mutations, and the

public health response predominantly relying on vaccines, waning of infection-induced, vaccine-induced and hybrid immunity should be monitored. This may allow identifying vulnerable population groups with insufficient immunity and provide the evidence base to further fine-tune vaccination recommendations.

Author contributions

Conceptualization: DD, FK, MI, and JB. Methodology: DD, FK, MI, and JB. Formal analysis: DD. Writing—original draft: DD. Writing—review and editing: FK, MI, and JB. Visualization: DD. Funding acquisition: FK, MI, and JB.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.08.007.

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