



Risk of infection, hospitalisation, and death up to 9 months after a second dose of COVID-19 vaccine: a retrospective, total population cohort study in Sweden

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Summary

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Background Vaccine effectiveness against COVID-19 beyond 6 months remains incompletely understood. We aimed to investigate the effectiveness of COVID-19 vaccination against the risk of infection, hospitalisation, and death during the first 9 months after vaccination for the total population of Sweden.

Methods This retrospective, total population cohort study was done using data from Swedish nationwide registers. The cohort comprised all individuals vaccinated with two doses of ChAdOx1 nCoV-19, mRNA-1273, or BNT162b2, and matched unvaccinated individuals, with data on vaccinations and infections updated until Oct 4, 2021. Two outcomes were evaluated. The first was SARS-CoV-2 infection of any severity from Jan 12 to Oct 4, 2021. The second was severe COVID-19, defined as hospitalisation for COVID-19 or all-cause 30-day mortality after confirmed infection, from March 15 to Sept 28, 2021.

Findings Between Dec 28, 2020, and Oct 4, 2021, 842974 individuals were fully vaccinated (two doses), and were matched (1:1) to an equal number of unvaccinated individuals (total study cohort n=1685948). For the outcome SARS-CoV-2 infection of any severity, the vaccine effectiveness of BNT162b2 waned progressively over time, from 92% (95% CI 92 to 93; p<0.001) at 15–30 days, to 47% (39 to 55; p<0.001) at 121–180 days, and to 23% (–2 to 41; p=0.07) from day 211 onwards. Waning was slightly slower for mRNA-1273, with a vaccine effectiveness of 96% (94 to 97; p<0.001) at 15–30 days and 59% (18 to 79; p=0.012) from day 181 onwards. Waning was also slightly slower for heterologous ChAdOx1 nCoV-19 plus an mRNA vaccine, for which vaccine effectiveness was 89% (79 to 94; p<0.001) at 15–30 days and 66% (41 to 80; p<0.001) from day 121 onwards. By contrast, vaccine effectiveness for homologous ChAdOx1 nCoV-19 vaccine was 68% (52 to 79; p<0.001) at 15–30 days, with no detectable effectiveness from day 121 onwards (–19% [–98 to 28]; p=0.49). For the outcome of severe COVID-19, vaccine effectiveness waned from 89% (82 to 93; p<0.001) at 15–30 days to 64% (44 to 77; p<0.001) from day 121 onwards. Overall, there was some evidence for lower vaccine effectiveness in men than in women and in older individuals than in younger individuals.

Interpretation We found progressively waning vaccine effectiveness against SARS-CoV-2 infection of any severity across all subgroups, but the rate of waning differed according to vaccine type. With respect to severe COVID-19, vaccine effectiveness seemed to be better maintained, although some waning became evident after 4 months. The results strengthen the evidence-based rationale for administration of a third vaccine dose as a booster.

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Introduction

Randomised clinical trials have shown a high efficacy of the BNT162b2 (Pfizer-BioNTech),¹ mRNA-1273 (Moderna),² and ChAdOx1 nCoV-19 (Oxford-AstraZeneca) COVID-19 vaccines,^{3,4} and observational studies have estimated a high real-world effectiveness.^{5–8} However, reports on breakthrough infections⁹ and waning immunity^{10–14} have raised concerns regarding the duration of protection.

With respect to severe COVID-19 outcomes such as hospitalisation or death, follow-ups of clinical trials showed that after 4 months the efficacy of BNT162b2 was about 84%¹⁵ and the efficacy of mRNA-1273 was about 92%,¹⁶ with similar results reported by the US Centers for Disease Control and Prevention.¹⁷ Observational studies from the USA and Qatar also

showed that the effectiveness of BNT162b2 against hospitalisation and death persisted up to 6 months,^{18,19} whereas preliminary data from the UK indicate a slight waning, especially in older adults and of ChAdOx1 nCoV-19 compared with BNT162b2.²⁰ In terms of ChAdOx1 nCoV-19, another observational study reported waning effectiveness against hospitalisation and death within 3 months in Brazil and Scotland.²¹ Altogether, although evidence suggests that vaccine effectiveness against severe COVID-19 is relatively well maintained, the data are inconsistent. Similarly, the duration of protection against SARS-CoV-2 infection of any severity is unclear. After 4–5 months of follow-up, the effectiveness of BNT162b2 has been estimated as greater than 80% in one study,¹⁵ around 50% in two

Research in context

Evidence before this study

We did not conduct a formal literature search; however, we searched standard databases such as PubMed for published studies and used Google to identify relevant preprint articles. Randomised clinical trials have shown high efficacy of COVID-19 vaccines against infection and severe illness. However, reports on breakthrough infections and waning immunity have raised concerns regarding the duration of vaccine protection, and whether additional doses are warranted. There is some evidence to suggest waning vaccine effectiveness against infection up to 6 months after vaccination, whereas protection against severe illness seems to be better maintained. However, the evidence is limited and inconsistent, in part due to evaluations of vaccines that might have different long-lasting effects, different age of study participants, and varying follow-up times.

Added value of this study

The findings from this study show there was a progressive waning vaccine effectiveness of BNT162b2 against SARS-CoV-2 infection of any severity, with no vaccine

effectiveness detected from 7 months onwards. The vaccine effectiveness of mRNA-1273 and heterologous ChAdOx1 nCoV-19 plus an mRNA vaccination waned slightly more slowly, whereas vaccine effectiveness of homologous ChAdOx1 nCoV-19 vaccination waned faster. For the outcome of COVID-19 hospitalisation or death, vaccine effectiveness was better maintained, although waned from 4 months onwards. Generally, there was some evidence for lower vaccine effectiveness in men than in women and in older individuals than in younger individuals.

Implications of all the available evidence

Our results suggest that vaccine protection against SARS-CoV-2 infections of any severity wanes progressively over time across all subgroups, but the rate of waning seems to be influenced by the type of vaccine. The protection against COVID-19 hospitalisation or death seems to be better maintained, although with some waning more than 4 months after vaccination. The results strengthen the evidence-based rationale for administration of a third vaccine dose as a booster to specific high-risk populations.

other studies,^{19,20} and as low as around 20% in a study from Qatar.¹⁸ For ChAdOx1 nCoV-19, preliminary data from the UK suggest about 50% remaining effectiveness after 5 months of follow-up,²⁰ whereas a published study showed that the effectiveness was down to about 50% in Scotland and 60% in Brazil after about 4 months.²¹

The different results in recent studies might relate to several factors, such as the evaluations of vaccines that might have different long-lasting effects,^{16,18–20} different age of the participants,¹⁸ varying and relatively short follow-up times,^{15,16,22} different patterns of risk compensation in the populations, different severities and definitions of infections included as outcomes, and variations in infection pressure and variant exposure during follow-up. Collectively, vaccine effectiveness beyond 6 months remains incompletely understood. In this study, we investigated the effectiveness of COVID-19 vaccination against the risk of infection, hospitalisation, and death during the first 9 months after vaccination for the total population of Sweden.

Methods

Study design and participants

This retrospective, total population cohort study was done in Sweden. We included all individuals (n=3 640 421) vaccinated with at least one dose of any COVID-19 vaccine (ChAdOx1 nCoV-19, BNT162b2, or mRNA-1273) in Sweden until May 26, 2021, and all individuals with a documented SARS-CoV-2 infection until May 24, 2021 (n=1 331 989). Each individual was then matched (1:1) by Statistics Sweden, the national

agency for statistics, to one randomly sampled individual from the total population of Sweden on birth year, sex, and municipality. In total, the cohort (vaccinated, those with documented infection, and matches) consisted of 5 833 003 individuals. This cohort was updated with respect to data on vaccinations and documented infections until Oct 4, 2021. From this cohort, each individual who was vaccinated with two doses, with no documented SARS-CoV-2 infection and alive within 14 days of vaccination, was matched (1:1) to one randomly sampled individual from the rest of the cohort on birth year and sex. Baseline for both individuals in each matched pair was set to the date of the second dose of vaccine in the vaccinated individual. Matched individuals were excluded if they received a first dose of vaccine, had a documented previous SARS-CoV-2 infection, or died within 14 days of baseline, whereby a new individual was searched from the remaining total cohort. This procedure was repeated five times. Data on individuals vaccinated against COVID-19 and data on documented SARS-CoV-2 infections were collected from the Swedish Vaccination Register and the SmiNet register, respectively, both of which are managed by the Public Health Agency of Sweden.^{23,24} All health-care providers in Sweden are obliged to report to these registers according to Swedish law, with 100% coverage of the total population.

In the main cohort, cases of SARS-CoV-2 infections of any severity were recorded from Jan 12 to Oct 4, 2021, and cases of severe COVID-19 were recorded from March 15 to Sept 28, 2021. From the main cohort, we also formed four subcohorts according to specific vaccine types

For Statistics Sweden see <https://www.scb.se>

(BNT162b2, mRNA-1273, ChAdOx1 nCoV-19) and schedule (heterologous ChAdOx1 nCoV-19 plus an mRNA vaccine).

We also formed a second cohort to be used in a sensitivity analysis. This second cohort was formed using less strict matching criteria to increase the size of the cohort. In this dataset, each vaccinated individual was matched to the rest of the cohort on age only, with an allowance of a 5-year difference in age within each pair. This procedure was repeated ten times and one matched unvaccinated individual could be paired with several vaccinated individuals.

This study was approved by the Swedish Ethical Review Authority (number 495/2021), who waived the requirement of obtaining informed consent given the retrospective study design.

Exposures and outcomes

The exposure variable was vaccination status (vaccinated with two doses *vs* unvaccinated). Vaccination status was defined according to each specific vaccine schedule, as well as a composite variable (any vaccine). There were two outcomes of the study. The first was SARS-CoV-2 infection of any severity until Oct 4, 2021. In 94.4% of cases, infections were confirmed using PCR and in 4.8% by sequencing, according to the SmiNet register. The second outcome was a composite endpoint of severe COVID-19, defined as inpatient hospitalisation with COVID-19 as the main diagnosis, and all-cause mortality within 30 days after confirmed SARS-CoV-2 infection. This outcome was collected until Sept 28, 2021. Data on patients admitted to hospital were collected from the Swedish National Inpatient Register using the International Classification of Diseases version 10 (ICD-10), code U071, and Statistics Sweden provided data on mortality. All outcomes were collected from more than 14 days after baseline.

Covariates

From Statistics Sweden, we obtained information on whether individuals were born in Sweden or not, birth year, birth month, and sex for all individuals. From Statistics Sweden, we also obtained individual-level data on highest education during 2019. Individual-level data regarding diagnoses, prescription medications, and homemaker services were obtained from national registers managed by the Swedish National Board of Health and Welfare. Homemaker services include domestic services provided to individuals (primarily older individuals) who live at home but need help with shopping, cleaning, meal preparation, and similar tasks. From the Swedish National Inpatient Register and National Outpatient Register for specialist care, diagnoses from 1998 and 2001 and later were obtained using ICD-10 codes. Prescription medications from 2018 and later were obtained from the Prescribed Drug Register using Anatomic Therapeutic Chemical

classification system codes. These three registers are complete for all specialist care and medications prescribed in Sweden for the years selected. The diagnoses and medications selected as covariates for this study were selected a priori based on the results from a previous nationwide study.²⁵ Definitions of comorbidities are shown in the appendix (p 2).

Statistical analysis

Hazards over time for the outcome SARS-CoV-2 infection of any severity, based on exposure status (vaccinated *vs* unvaccinated), are shown using proportional hazards models with 95% CIs and restricted cubic splines. To compare the risk of the outcomes based on exposure status (vaccinated *vs* unvaccinated), Cox regression was used to calculate hazard ratios (HRs). To adjust for the matched samples, 95% CIs were estimated using robust SEs by the variance-covariance matrix of the estimators procedure and robust option in Stata. To formally test whether the associations were time dependent, Schoenfeld's residuals were evaluated using estat phtest command (Stata software). Given that the test indicated that the proportional hazard assumption was violated ($\chi^2=3184.25$; $p<0.001$) in the main analyses, the associations were evaluated in time intervals. The first model was adjusted for age and baseline date (date of second dose of vaccine) to adjust for variations in infection pressure during follow-up. The second model included the additional covariates sex, homemaker service (yes or no), education (six categories), whether the individual was born in Sweden or not, and eight diagnoses at baseline (yes or no). The HR was used to calculate vaccine effectiveness using the following formula: vaccine effectiveness = $(1 - HR) \times 100\%$. To investigate whether vaccine effectiveness was influenced by the prespecified covariates, interaction analyses were done, using product terms created by multiplying the variable coding for vaccination status at baseline (vaccinated *vs* unvaccinated) by each respective covariate, which were added to the fully adjusted Cox model. Given that the interaction terms were highly significant ($p<0.001$) for age, sex, homemaker service, and all diagnoses at baseline except asthma, vaccine effectiveness was also estimated in subgroups according to these covariates. Follow-up time in days was counted until date of confirmed outcome, date of first vaccination after baseline among unvaccinated individuals, death, or end of possible follow-up time (described earlier), whichever occurred first. All analyses were done in SPSS (version 27.0 for Mac), and Stata (version 16.1 for Mac). A two-sided *p* value less than 0.05 or HR with 95% CIs not crossing one were considered significant.

Role of the funding source

There was no funding source for this study.

See Online for appendix

For the Swedish National Board of Health and Welfare see <https://www.socialstyrelsen.se>

Results

Between Dec 28, 2020, and Oct 4, 2021, 842 974 individuals were fully vaccinated (two doses), and were matched (1:1) to an equal number of unvaccinated individuals. Thus, the total study cohort comprised 842 974 pairs ($n=1\,685\,948$; figure 1). The mean date for the second dose of vaccine in the vaccinated group according to each vaccine schedule is shown in table 1, together with baseline characteristics. Compared with unvaccinated individuals, vaccinated individuals more often had homemaker service, were more often born in Sweden, had more comorbidities, and had a higher level of education at baseline ($p<0\cdot001$ for all; table 1). Similar differences were evident between vaccinated and unvaccinated individuals in the different vaccine subcohorts. SARS-CoV-2 variants sequenced in Sweden during the study period are shown in the appendix (p 2).

During a median follow-up of 108 days (IQR 69–145), a SARS-CoV-2 infection was confirmed in 27 918 individuals, of whom 6147 were vaccinated (4·9 infections per 100 000 person-days) and 21 771 were unvaccinated (31·6 infections per 100 000 person-days). The vaccine effectiveness associated with two doses of any vaccine peaked at 15–30 days (92% [95% CI 91 to 93]; $p<0\cdot001$) and declined marginally at 31–60 days (89% [88 to 89]; $p<0\cdot001$; table 2, figure 2). From thereon, the waning became more pronounced, and from day 211 onwards there was no remaining detectable vaccine effectiveness (23% [–2 to 41]; $p=0\cdot07$).

The estimated vaccine effectiveness was influenced significantly by vaccine type, age, sex, homemaker service, and all diagnoses at baseline ($p_{\text{interaction}}<0\cdot001$ for all), except asthma ($p_{\text{interaction}}=0\cdot86$). At 61–120 days, vaccine effectiveness declined to 50% (95% CI 30 to 64; $p<0\cdot001$) in individuals aged 80 years or older, and to 61% (47–72; $p<0\cdot001$) in individuals with homemaker service (table 3). With respect to sex, there was no detectable vaccine effectiveness in men (17% [95% CI –13 to 40]; $p=0\cdot23$) from day 181 onwards, whereas it remained in women (34% [22 to 45]; $p<0\cdot001$). With respect to vaccine type, vaccine effectiveness waned progressively for all vaccines during follow-up, but at different speeds (table 2). The vaccine effectiveness of BNT162b2 was 92% (95% CI 92 to 93; $p<0\cdot001$) at 15–30 days, 47% (39 to 55; $p<0\cdot001$) at 121–180 days, and 23% (–2 to 41; $p=0\cdot07$) from day 211 onwards. Waning was slightly slower for mRNA-1273, with a vaccine effectiveness of 96% (94 to 97; $p<0\cdot001$) at 15–30 days and 59% (18 to 79; $p=0\cdot012$) from day 181 onwards. Waning was also slightly slower for heterologous ChAdOx1 nCoV-19 plus mRNA vaccine schedules, with a vaccine effectiveness of 89% (79 to 94; $p<0\cdot001$) at 15–30 days and 66% (41 to 80; $p<0\cdot001$) from day 121 onwards. By contrast, vaccine effectiveness for homologous ChAdOx1 nCoV-19 was 68% (52 to 79; $p<0\cdot001$) at 15–30 days, with no detectable effectiveness from day 121 onwards (–19% [95% CI –98 to 28]; $p=0\cdot49$).

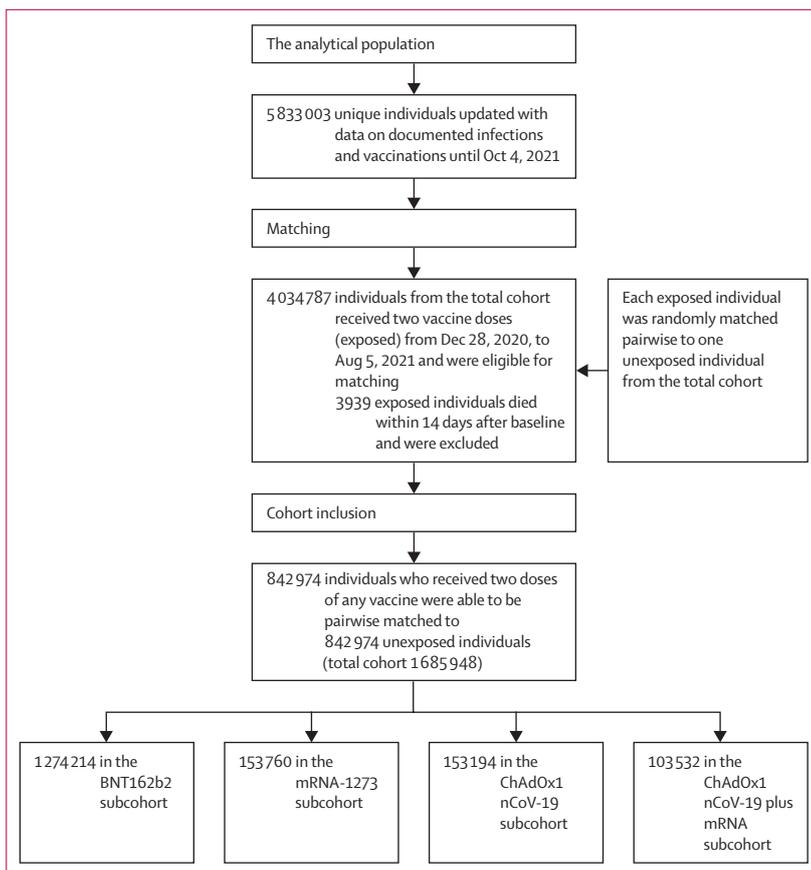


Figure 1: Selection of the cohort

During a median follow-up of 124 days (IQR 98–208), there were 277 cases of COVID-19 hospitalisation or death among vaccinated individuals (0·23 hospitalisations or deaths per 100 000 person-days) and 825 cases among unvaccinated individuals (1·20 hospitalisations or deaths per 100 000 person-days; appendix pp 3, 7). The vaccine effectiveness associated with two doses of any vaccine was 89% (95% CI 83 to 93; $p<0\cdot001$) at 15–30 days, which declined to 64% (44 to 77; $p<0\cdot001$) from day 121 onwards (appendix p 3).

In a sensitivity analysis using less strict matching criteria, a second matched cohort (1983 315 matched pairs; $n=3\,996\,630$) more than twice the size of the original cohort was created. Mean age of vaccinated individuals was 5 years higher in the second cohort than in the main cohort, whereas all other characteristics were similar between the cohorts (appendix p 3). In this larger cohort, the waning vaccine effectiveness was confirmed with respect to a SARS-CoV-2 infection of any severity (appendix p 4), including the different rate of waning for different vaccine schedules (appendix p 5). In addition, it was confirmed that vaccine effectiveness was better maintained against the outcome of severe COVID-19 (appendix p 6), than against SARS-CoV-2 infection of any severity (appendix p 4).

	Total study cohort (any vaccine)		BNT162b2 subcohort		mRNA-1273 subcohort		ChAdOx1 nCoV-19 subcohort		ChAdOx1 nCoV-19 and an mRNA vaccine* subcohort	
	Vaccinated (n=842 974)	Unvaccinated (n=842 974)	Vaccinated (n=637 107)	Unvaccinated (n=637 107)	Vaccinated (n=76 880)	Unvaccinated (n=76 880)	Vaccinated (n=76 597)	Unvaccinated (n=76 597)	Vaccinated (n=51 766)	Unvaccinated (n=51 766)
Mean baseline date	May 5, 2021	May 5, 2021	April 27, 2021	April 27, 2021	May 20, 2021	May 20, 2021	June 5, 2021	June 5, 2021	May 28, 2021	May 28, 2021
Days between doses	42 (28-45)	..	37 (24-42)	..	42 (29-42)	..	70 (65-82)	..	87 (82-97)	..
Age, years	52.7 (37.0-67.5)	52.7 (37.0-67.5)	54.8 (39.2-68.5)	54.8 (39.1-68.5)	41.1 (34.7-61.7)	48.0 (34.7-61.7)	64.6 (36.5-71.0)	64.6 (36.5-71.0)	35.2 (28.3-43.0)	35.2 (28.3-43.0)
Male	342 677 (40.7%)	342 677 (40.7%)	263 866 (41.4%)	263 866 (41.4%)	34 461 (44.8%)	34 461 (44.8%)	30 141 (39.4%)	30 141 (39.4%)	13 926 (26.9%)	13 926 (26.9%)
Female	500 297 (59.3%)	500 297 (59.3%)	373 241 (58.6%)	373 241 (58.6%)	42 419 (55.2%)	42 419 (55.2%)	46 456 (60.6%)	46 456 (60.6%)	37 840 (73.1%)	37 840 (73.1%)
Homemaker service	87 004 (10.3%)	30 680 (3.6%)	81 704 (12.8%)	25 718 (4.0%)	42 97 (5.6%)	19 50 (2.5%)	6 98 (0.9%)	2 82 (3.7%)	262 (0.5%)	174 (0.3%)
Born in Sweden	703 666 (83.5%)	578 647 (68.6%)	533 572 (83.8%)	442 799 (69.5%)	63 288 (82.3%)	50 259 (65.4%)	64 951 (84.8%)	50 178 (65.5%)	41 363 (79.9%)	35 011 (67.6%)
Education										
Elementary school, <9 years	61 022 (7.2%)	79 375 (9.4%)	51 598 (8.1%)	63 360 (9.9%)	4 234 (5.5%)	6 381 (8.3%)	4 420 (5.8%)	7 608 (9.9%)	737 (1.4%)	1 967 (3.8%)
Elementary school, 9 years	81 455 (9.7%)	97 948 (11.6%)	61 814 (9.7%)	73 709 (11.6%)	8 309 (10.8%)	9 458 (12.3%)	6 929 (9.1%)	9 084 (11.9%)	4 344 (8.4%)	5 621 (10.9%)
Secondary school, 2 years	180 672 (21.4%)	182 971 (21.7%)	143 917 (22.6%)	145 325 (22.8%)	14 824 (19.3%)	15 810 (20.6%)	16 391 (21.4%)	16 065 (21.0%)	5 424 (10.5%)	5 641 (10.9%)
Secondary school, >2 years	171 349 (20.3%)	168 922 (20.0%)	125 590 (19.7%)	122 362 (19.2%)	15 848 (20.6%)	16 511 (21.5%)	15 669 (20.5%)	14 927 (19.5%)	14 117 (27.3%)	14 982 (28.9%)
University education	324 660 (38.5%)	275 444 (32.7%)	237 148 (37.2%)	204 663 (32.1%)	30 503 (39.7%)	24 708 (32.1%)	31 973 (41.7%)	24 994 (32.6%)	24 770 (47.9%)	20 893 (40.4%)
Unknown	23 816 (2.8%)	38 314 (4.6%)	17 040 (2.7%)	27 688 (4.4%)	3 162 (4.1%)	4 012 (5.2%)	12 15 (1.6%)	3 919 (5.1%)	2 374 (4.6%)	2 662 (5.1%)
Comorbidities										
Myocardial infarction	21 885 (2.6%)	18 530 (2.2%)	18 167 (2.9%)	15 190 (2.4%)	16 37 (2.1%)	13 35 (1.7%)	19 74 (2.6%)	19 10 (2.5%)	99 (0.2%)	86 (0.2%)
Stroke	29 493 (3.5%)	16 808 (2.0%)	26 037 (4.1%)	13 727 (2.2%)	17 51 (2.3%)	11 85 (1.5%)	15 43 (2.0%)	17 85 (2.3%)	143 (0.3%)	101 (0.2%)
Diabetes	91 203 (10.8%)	62 198 (7.4%)	74 361 (11.7%)	49 614 (7.8%)	8 136 (10.6%)	4 880 (6.4%)	6 944 (9.1%)	6 744 (8.8%)	16 98 (3.3%)	9 22 (1.8%)
Hypertension	262 659 (31.2%)	207 862 (24.7%)	212 647 (33.4%)	170 772 (26.8%)	21 358 (27.8%)	15 295 (19.9%)	24 624 (32.2%)	19 387 (25.3%)	3 857 (7.5%)	2 281 (4.4%)
Kidney failure	20 027 (2.4%)	10 317 (1.2%)	16 711 (2.6%)	8 481 (1.3%)	2 251 (2.9%)	706 (0.9%)	815 (1.1%)	990 (1.3%)	242 (0.5%)	134 (0.3%)
COPD	17 257 (2.1%)	13 353 (1.6%)	14 709 (2.3%)	10 768 (1.7%)	12 48 (1.6%)	9 28 (1.2%)	11 89 (1.6%)	15 663 (20.0%)	102 (0.2%)	83 (0.2%)
Asthma	50 341 (6.0%)	36 671 (4.4%)	38 234 (6.0%)	27 717 (4.4%)	5 118 (6.7%)	3 267 (4.3%)	3 710 (4.8%)	3 254 (4.3%)	3 242 (6.3%)	2 400 (4.6%)
Cancer	48 512 (5.8%)	37 092 (4.4%)	39 720 (6.2%)	30 696 (4.8%)	3 908 (5.1%)	2 613 (3.4%)	4 225 (5.5%)	3 323 (4.3%)	635 (1.2%)	438 (0.9%)
SARS-CoV-2 infection	0	0	0	0	0	0	0	0	0	0

Data are median (IQR) or n(%), unless otherwise specified. COPD=chronic obstructive pulmonary disease. *Either BNT162b2 or mRNA-1273.

Table 1: Baseline characteristics of the cohort at second dose of vaccine, according to vaccine schedule and in total

	Number of individuals	Vaccinated		Unvaccinated		Vaccine effectiveness (95% CI)	
		Number of events	Incidence per 100 000 person-days	Number of events	Incidence per 100 000 person-days	Adjusted for age and baseline date	Fully adjusted*
Total study cohort (any vaccine)	1 685 948	6147	4.9	21 771	31.6	84% (83 to 84)	84% (83 to 84)
15–30 days	1 685 948	397	1.6	4 719	19.5	92% (91 to 93)	92% (91 to 93)
31–60 days	1 544 326	1 254	2.5	8 908	22.5	89% (88 to 90)	89% (88 to 89)
61–120 days	1 363 616	2 436	2.6	7 522	14.4	83% (82 to 83)	82% (81 to 83)
121–180 days	635 402	820	1.0	399	1.8	52% (46 to 58)	48% (41 to 54)
181–210 days	327 257	718	1.2	161	2.1	42% (31 to 51)	32% (19 to 43)
>210 days	239 822	522	1.0	62	1.2	23% (0 to 41)	23% (-2 to 41)
BNT162b2 subcohort	1 274 214	5 062	5.1	19 121	36.4	84% (84 to 85)	85% (84 to 85)
15–30 days	1 274 214	333	1.7	4 039	22.1	92% (91 to 93)	92% (92 to 93)
31–60 days	1 166 247	1 095	2.9	7 982	26.7	89% (88 to 90)	89% (88 to 90)
61–120 days	1 032 971	1 796	2.6	6 601	16.6	85% (84 to 85)	84% (84 to 85)
121–180 days	480 153	631	1.0	292	1.7	52% (45 to 58)	47% (39 to 55)
181–210 days	304 298	688	1.2	145	2.1	39% (26 to 49)	29% (15 to 41)
>210 days	231 006	519	1.1	62	1.3	23% (1 to 41)	23% (-2 to 41)
mRNA-1273 subcohort	153 760	300	2.9	1 722	28.2	89% (88 to 91)	89% (88 to 90)
15–30 days	153 760	20	0.9	493	22.5	96% (94 to 98)	96% (94 to 97)
31–60 days	139 532	67	1.5	743	21.1	93% (91 to 95)	93% (90 to 94)
61–120 days	123 610	116	1.4	418	9.0	86% (82 to 88)	85% (82 to 88)
121–180 days	52 254	65	1.0	53	2.6	72% (59 to 80)	71% (56 to 80)
>180 days	22 755	32	0.8	15	2.4	69% (44 to 83)	59% (18 to 79)
ChAdOx1 nCoV-19 subcohort	153 194	465	5.0	469	7.2	49% (42 to 55)	44% (36 to 52)
15–30 days	153 194	33	1.4	93	4.2	66% (50 to 77)	68% (52 to 79)
31–60 days	144 772	53	1.2	88	2.3	55% (36 to 68)	49% (28 to 64)
61–120 days	129 103	293	3.5	262	4.9	48% (39 to 56)	41% (29 to 51)
>120 days	53 060	86	1.6	26	1.4	0% (-55 to 36)	-19% (-98 to 28)
ChAdOx1 nCoV-19 and an mRNA vaccine† subcohort	103 532	316	4.8	442	11.8	68% (63 to 72)	65% (58 to 70)
15–30 days	103 532	11	0.7	92	6.2	89% (79 to 94)	89% (79 to 94)
31–60 days	92 623	37	1.2	88	4.0	74% (62 to 82)	72% (59 to 82)
61–120 days	76 924	230	3.8	234	8.8	63% (55 to 69)	55% (45 to 64)
>120 days	49 664	38	0.8	28	1.8	61% (36 to 76)	66% (41 to 80)

*Adjusted for age, baseline date, sex, homemaker service, place of birth, education, and comorbidities at baseline. †The mRNA vaccine was either BNT162b2 or mRNA-1273.

Table 2: Vaccine effectiveness against SARS-CoV-2 infection of any severity up to 9 months after full vaccination (>14 days after the second dose) by number of days after the second dose

Discussion

This study showed a progressive waning vaccine effectiveness against SARS-CoV-2 infection of any severity during up to 9 months of follow-up. In the main cohort, the estimated vaccine effectiveness was more than 90% in the first month, with a progressive waning starting soon thereafter, ultimately resulting in a non-detectable vaccine effectiveness after 7 months. Vaccine effectiveness waned across all subgroups, although differently according to vaccine schedule and type. Vaccine effectiveness with respect to the risk of COVID-19

hospitalisation or death seemed to be better maintained than effectiveness against infection, although some waning became evident after 4 months. Overall, there was also some evidence suggesting lower vaccine effectiveness in men than in women and in older individuals than in younger individuals.

Waning vaccine effectiveness against SARS-CoV-2 infection has previously been reported in preliminary observational studies from the UK and in published observational studies from the USA and Qatar,^{18–20} whereas follow-up studies of clinical trials show high remaining

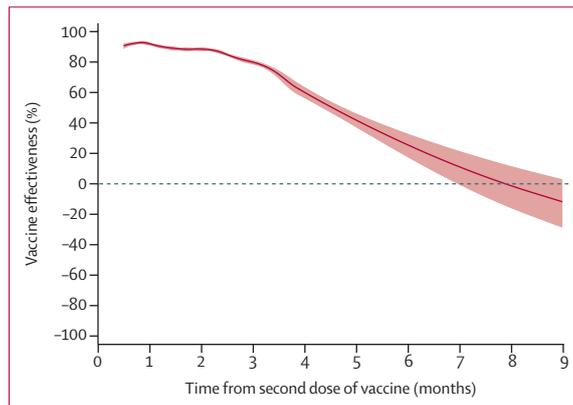


Figure 2: Vaccine effectiveness (any vaccine) against SARS-CoV-2 infection of any severity in 842 974 vaccinated individuals matched to an equal number of unvaccinated individuals for up to 9 months of follow-up
The association is shown using proportional hazards models with 95% CIs (shaded areas) and restricted cubic splines. The model was adjusted for age, baseline date, sex, homemaker service, place of birth, education, and comorbidities at baseline.

efficacy of both BNT162b2 after 4 months,¹⁵ and mRNA-1273 after more than 4 months.¹⁶ Our data add to these previous studies with a follow-up time of up to 9 months, about 28 000 confirmed SARS-CoV-2 infections in the main cohort, and the evaluation of four different vaccine schedules in a real-world setting. Overall, our results showed notable waning vaccine effectiveness against SARS-CoV-2 infection of any severity across all subgroups, although with higher remaining vaccine effectiveness for mRNA-1273 and for heterologous vaccine schedules. The latter finding is of particular interest, and is supported by clinical trials showing superior vaccine-elicited immunogenicity from heterologous vaccine schedules.^{26,27} Our finding is in addition to previous observational studies estimating high vaccine effectiveness of heterologous schedules in the short-term.^{28,29} By contrast, we were not able to detect any remaining vaccine effectiveness against SARS-CoV-2 infection of any severity from homologous ChAdOx1 nCoV-19 vaccination after more than 4 months. This finding contradicts preliminary evidence from the UK,²⁰ but is in line with a recent study reporting waning vaccine effectiveness for this vaccine against both SARS-CoV-2 infection and severe COVID-19 in Brazil and Scotland within 3 months of the second dose.²¹ The different estimates of vaccine effectiveness in all of these studies could be influenced by several factors—eg, different patterns of risk compensation, undiagnosed previous infections in individuals used as controls, varying follow-up times, the prevalence of risk factors that reduce the immune response to vaccination, the severity and definition of infections included as outcomes, variations in infection pressure and SARS-CoV-2 variants during follow-up, and different age of the studied populations.

In the present study, vaccine effectiveness against severe COVID-19 was better maintained than against

SARS-CoV-2 infections of any severity, although some waning was evident after more than 4 months. These results were confirmed in a sensitivity analysis done in a second, even larger cohort, and have some support from preliminary data originating from the UK.²⁰ In the same report, waning seemed greater in individuals belonging to a clinically vulnerable group and in older adults,²⁰ as indicated also from the sensitivity analysis in the present study. A reasonable explanation of waning effectiveness predominantly in older adults, would be that the adaptive immune response mediated by B cells that produce antibodies, as well as T cells is impaired with older age.³⁰ In support, one of the risk factors associated with lower vaccine effectiveness in the present study was older age. Among other risk factors for lower vaccine effectiveness were male sex. Although there has been no previous study reporting waning vaccine effectiveness according to sex, these findings are supported by studies showing a lower vaccine-elicited immunogenicity along with a more rapid decline in neutralising antibody titres in men compared with in women.^{13,31}

The results of our study have important clinical implications, as they strengthen the evidence-based rationale for administration of a third vaccine dose as a booster, especially to specific high-risk populations. Recent preliminary phase 3 data from Pfizer-BioNTech show that a third dose of BNT162b2, administered a median of 11 months after the second dose, had 95.6% efficacy (95% CI 89.3–98.6) against symptomatic COVID-19 compared with those who had only received two primary doses, with consistent results irrespective of age, sex, and comorbidities.³² In addition, data from an Israeli observational study showed that individuals who received a third dose of BNT162b2 had a reduced rate of infections and hospitalisations compared with individuals given two doses.³³ Currently, many countries are recommending a third vaccine dose as a booster to select populations at increased risk of severe COVID-19. The implication of the results from the present study and previous studies is that older individuals and individuals with known suboptimal or waning vaccine-elicited immunogenicity should be prioritised for booster doses, because these individuals also are at highest risk for severe COVID-19 manifestations if infected.

Other than the observational design, the present study has some limitations to consider. Although we adjusted our analyses for several potential confounders, the possibility of residual and unmeasured confounding remains, including a higher risk of selection bias in unvaccinated individuals with longer follow-up time. Moreover, although we excluded all individuals with a documented previous infection, some individuals with a previous asymptomatic infection are likely to have been included in the analyses. Furthermore, the SARS-CoV-2 infections registered in the SmiNet register included infections of any severity, and the definition of severe COVID-19 included death from any cause within 30 days

	Number of individuals	Vaccinated		Unvaccinated		Vaccine effectiveness (95% CI)	
		Number of events	Incidence per 100 000 person-days	Number of events	Incidence per 100 000 person-days	Adjusted for age and baseline date	Fully adjusted*
15–30 days	1 685 948
Men	685 354	133	1.3	1687	17.1	93% (91 to 94)	93% (91 to 94)
Women	1 000 594	264	1.8	3032	21.1	92% (91 to 93)	92% (91 to 93)
Age <50 years	769 391	191	1.7	3494	31.6	95% (95 to 96)	95% (94 to 95)
Age 50–64 years	431 159	106	1.6	876	13.9	88% (86 to 90)	88% (86 to 90)
Age 65–79 years	327 850	47	1.0	213	4.5	80% (72 to 85)	82% (75 to 88)
Age ≥80 years	157 548	53	2.3	136	6.3	67% (55 to 76)	74% (63 to 82)
Any comorbidity	619 248	184	1.8	897	11.7	85% (83 to 87)	86% (84 to 88)
Homemaker service	117 684	72	2.8	68	7.9	76% (65 to 84)	76% (65 to 84)
31–60 days	1 544 326
Men	629 873	361	1.8	2900	17.9	90% (89 to 91)	90% (89 to 91)
Women	914 453	893	3.0	6008	25.8	88% (87 to 89)	88% (87 to 89)
Age <50 years	704 877	706	3.1	6683	37.2	91% (91 to 92)	91% (90 to 92)
Age 50–64 years	410 305	303	2.3	1776	15.7	85% (83 to 87)	85% (83 to 87)
Age 65–79 years	298 770	145	1.5	315	4.2	69% (62 to 74)	71% (64 to 76)
Age ≥80 years	130 374	100	2.1	134	5.0	69% (60 to 76)	73% (65 to 79)
Any comorbidity	563 605	439	2.1	1571	13.2	84% (83 to 86)	85% (83 to 86)
Homemaker service	108 919	149	2.9	64	5.1	71% (59 to 79)	70% (59 to 79)
61–120 days	1 363 616
Men	558 636	721	2.0	2360	10.9	84% (82 to 85)	83% (82 to 85)
Women	804 980	1715	3.1	5162	16.8	82% (81 to 83)	82% (81 to 83)
Age <50 years	618 008	1531	3.7	5697	24.3	84% (83 to 84)	83% (82 to 84)
Age 50–64 years	380 804	492	2.1	1510	9.5	81% (79 to 83)	81% (79 to 83)
Age 65–79 years	260 405	227	1.2	255	2.6	66% (59 to 72)	65% (56 to 72)
Age ≥80 years	104 399	186	2.0	60	2.0	48% (30 to 61)	50% (30 to 64)
Any comorbidity	497 270	852	2.2	1252	8.3	79% (77 to 81)	79% (77 to 80)
Homemaker service	101 580	247	2.5	64	3.5	64% (51 to 73)	61% (47 to 72)
121–180 days	635 402
Men	220 596	273	1.0	97	1.2	33% (15 to 47)	29% (9 to 45)
Women	414 806	547	1.1	302	2.1	58% (52 to 64)	54% (46 to 61)
Age <50 years	269 241	503	1.6	293	2.7	55% (48 to 61)	51% (43 to 58)
Age 50–64 years	115 938	161	1.0	36	1.1	40% (14 to 58)	29% (–5 to 52)
Age 65–79 years	156 187	92	0.5	27	0.5	40% (3 to 63)	30% (–16 to 58)
Age ≥80 years	94 036	64	0.5	43	1.3	53% (31 to 68)	46% (15 to 66)
Any comorbidity	269 919	273	0.7	97	1.4	58% (47 to 67)	55% (42 to 65)
Home maker service	90 347	81	0.6	24	1.5	35% (–14 to 63)	29% (–24 to 59)
>180 days	327 257
Men	104 220	351	1.7	51	2.1	25% (0 to 45)	17% (–13 to 40)
Women	223 037	889	2.0	172	3.1	41% (30 to 50)	34% (22 to 45)
Age <80 years	260 172	1005	1.9	204	3.3	40% (30 to 48)	33% (21 to 43)
Age ≥80 years	67 085	235	1.8	19	1.0	4% (–50 to 39)	5% (–53 to 41)
Any comorbidity	160 790	536	1.6	41	1.6	22% (–8 to 43)	15% (–17 to 38)

*Adjusted for age, baseline date, sex, homemaker service, place of birth, education, and comorbidities at baseline.

Table 3: Vaccine effectiveness against SARS-CoV-2 infection of any severity up to 9 months after full vaccination with any vaccine (>14 days after the second dose) by number of days after the second dose, according to sex, age, homemaker service, and any comorbidity at baseline

after a confirmed infection. More strict definitions might have increased the estimates of vaccine effectiveness for both outcomes. However, it should be noted that vaccine effectiveness was greater than 90% early after

vaccination. Finally, the follow-up in the present study was completed before the emergence of the recent omicron (B.1.1.529) variant of SARS-CoV-2. This study also has several important strengths. First, the results

were confirmed in sensitivity analyses based on a second cohort where less strict matching criteria were used. Second, vaccinated individuals had received different types and combinations of vaccines, allowing us to investigate how this differentially affected vaccine effectiveness and duration of vaccine protection in a real-world setting. Third, all the registers used to obtain data on COVID-19 cases, vaccinations, hospitalisations, and deaths have a nationwide coverage and zero loss to follow-up. This reduces the risk of misclassification of unvaccinated individuals included in the analyses. Using these registers, we were also able to obtain covariates that have previously been identified as risk factors for COVID-19 in the Swedish population.²⁵ Finally, the study cohort was based on the total population of Sweden, increasing the external validity of the findings to other countries with similar population structure.

In summary, our results suggest a substantial waning of vaccine protection against SARS-CoV-2 infection of any severity across all subgroups, but with variations related to vaccine types and schedules. By contrast, protection against severe COVID-19 was better maintained for up to 9 months of follow-up, although some waning became evident after more than 4 months. These findings might have implications for vaccination strategies and public health by strengthening the evidence-based rationale for administration of a third vaccine dose as a booster, where the priority should be specific populations who are at higher risk of severe consequences of COVID-19 due to weaker and more rapidly waning vaccine-elicited immunogenicity.

Contributors

All authors conceived and designed the study. PN acquired the data. PN did the statistical analyses. PN and MB accessed and verified the underlying data. All authors interpreted the data. PN and MB drafted the manuscript. All authors critically revised the manuscript for intellectual content. PN and AN supervised the work. All authors gave final approval of the version to be published. All authors had full access to all the data and had final responsibility for the decision to submit for publication

Declaration of interests

We declare no competing interests.

Data sharing

The data files used for the present study are publicly unavailable according to regulations under Swedish law. However, all data used for the present study can be applied for from the National Board of Health and Welfare, Statistics Sweden, and the Public Health Agency of Sweden.

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