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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

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, 842 974 individuals were fully vaccinated (two doses), and were matched (1:1) to an equal number of unvaccinated individuals (total study cohort n=1 685 948). 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% to 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), mRNA-1273 (Moderna), and ChAdOx1 nCoV-19 (Oxford-AstraZeneca) COVID-19 vaccines, and observational studies have estimated a high real-world effectiveness. However, reports on breakthrough infections and waning immunity 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% and the efficacy of mRNA-1273 was about 92%, with similar results reported by the US Centers for Disease Control and Prevention. Observational studies from the USA and Qatar also showed that the effectiveness of BNT162b2 against hospitalisation and death persisted up to 6 months, whereas preliminary data from the UK indicate a slight waning, especially in older adults and of ChAdOx1 nCoV-19 compared with BNT162b2. In terms of ChAdOx1 nCoV-19, another observational study reported waning effectiveness against hospitalisation and death within 3 months in Brazil and Scotland. 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, around 50% in two
Articles

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 homologous 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 and preprints have found that vaccine effectiveness against COVID-19 has waned over time, with the rate of waning varying by age, sex, and type of vaccine.15,16,22–24 Other studies have shown that vaccine effectiveness against COVID-19 may wane more quickly than against other infections.25,26

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.25,26 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...
Drug Register using Anatomic Therapeutic Chemical 2018 and later were obtained from the Prescribed and National Outpatient Register for specialist care, tasks. From the Swedish National Inpatient Register with shopping, cleaning, meal preparation, and similar domestic services provided to individuals (primarily older individuals) who live at home but need help. 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. Definitions of comorbidities are shown in the appendix (p 2).

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 U07.1, 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. 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. Given that the test indicated that the proportional hazard assumption was violated (χ² = 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)×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-tailed 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.

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=1685 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<0·001 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 (3·1 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<0·001) and declined marginally at 31–60 days (89% [88 to 89]; p<0·001; 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=0·07).

The estimated vaccine effectiveness was influenced significantly by vaccine type, age, sex, homemaker service, and all diagnoses at baseline (pinteraction<0·001 for all), except asthma (pinteraction=0·86). At 61–120 days, vaccine effectiveness declined to 50% (95% CI 30 to 64; p<0·001) in individuals aged 80 years or older, and to 61% (47–72; p<0·001) 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=0·23) from day 181 onwards, whereas it remained in women (34% [22 to 45]; p<0·001).

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<0·001) at 15–30 days, 47% (39 to 55; p<0·001) at 121–180 days, and 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 mRNA vaccine schedules, with a vaccine effectiveness of 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 was 68% (52 to 79; p<0·001) at 15–30 days, with no detectable effectiveness from day 121 onwards (–19% [95% CI –98 to 28]; p=0·49).

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<0·001) at 15–30 days, which declined to 64% (44 to 77; p<0·001) 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) | IN162b2 subcohort | mRNA-1273 subcohort | ChAdOx1 nCoV-19 subcohort | ChAdOx1 nCoV-19 and an mRNA vaccine subcohort |
|---------------------------------|--------------------|---------------------|---------------------------|---------------------------------------------|
| **Vaccinated**                  |                    |                     |                           |                                             |
| (n=842 974)                     |                    |                     |                           |                                             |
| 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)                           |
| Male                            | 342.6 (40.7%)      | 342.6 (40.7%)       | 263.866 (41.4%)           | 263.866 (41.4%)                            |
| Female                          | 500.297 (59.3%)    | 500.297 (59.3%)     | 373.241 (58.6%)           | 373.241 (58.6%)                            |
| Homemaker service              | 87.004 (10.3%)     | 36.800 (1.6%)       | 81.704 (12.8%)            | 25.718 (40.0%)                             |
| Born in Sweden                  | 703.666 (83.5%)    | 578.647 (68.6%)     | 533.572 (83.8%)           | 442.799 (69.5%)                            |
| Education                       |                    |                     |                           |                                             |
| Elementary school, <9 years     | 61.022 (7.2%)      | 79.375 (9.4%)       | 51.598 (8.1%)             | 63.360 (9.9%)                              |
| Elementary school, 9 years      | 81.45 (9.7%)       | 97.948 (11.6%)      | 61.814 (9.7%)             | 73.709 (11.6%)                             |
| Secondary school, 2 years       | 180.672 (21.4%)    | 182.971 (21.7%)     | 143.917 (22.6%)           | 145.325 (22.8%)                            |
| Secondary school, >2 years      | 171.349 (20.3%)    | 168.922 (20.0%)     | 122.362 (19.2%)           | 15.848 (20.6%)                             |
| University education            | 324.660 (38.5%)    | 275.444 (32.7%)     | 23.7148 (37.2%)           | 20.466 (32.1%)                             |
| Unknown                         | 238.16 (2.8%)      | 38.314 (4.6%)       | 17.040 (2.7%)             | 27.688 (4.4%)                              |
| **Comorbidities**               |                    |                     |                           |                                             |
| Myocardial infarction           | 21.885 (2.6%)      | 18.530 (2.2%)       | 18.167 (2.9%)             | 15.190 (2.4%)                              |
| Stroke                          | 29.493 (3.5%)      | 16.808 (2.0%)       | 26.037 (4.1%)             | 13.777 (2.2%)                              |
| Diabetes                        | 91.203 (10.8%)     | 62.198 (8.4%)       | 74.361 (11.7%)            | 49.614 (7.8%)                              |
| Hypertension                    | 262.659 (31.2%)    | 207.862 (24.7%)     | 212.647 (33.4%)           | 170.772 (26.8%)                            |
| Kidney failure                  | 20.027 (2.4%)      | 10.137 (1.2%)       | 16.711 (2.6%)             | 8.481 (1.3%)                               |
| COPD                            | 17.257 (2.1%)      | 13.335 (2.6%)       | 14.709 (2.3%)             | 17.086 (1.7%)                              |
| Asthma                          | 50.341 (6.0%)      | 36.671 (4.4%)       | 38.234 (6.0%)             | 7.777 (4.4%)                               |
| Cancer                          | 48.512 (5.8%)      | 37.922 (4.4%)       | 39.720 (6.2%)             | 30.696 (4.8%)                              |
| SARS-CoV-2 infection            | 0.000 (0.0%)       | 0.000 (0.0%)        | 0.000 (0.0%)              | 0.000 (0.0%)                               |

Data are median (IQR) or n(%), unless otherwise specified. COPD=chronic obstructive pulmonary disease. *Either IN162b2 or mRNA-1273.

**Table 1:** Baseline characteristics of the cohort at second dose of vaccine, according to vaccine schedule and in total.
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, whereas follow-up studies of clinical trials show high remaining
efficacy of both BNT162b2 after 4 months, and mRNA-1273 after more than 4 months. Our data add to these previous studies with a follow-up time of 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.

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.

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. 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. 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.
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

| 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            |             |               |                              |                          |                                |               |
| Men                   | 1685948     | 133           | 1.3                          | 1687                     | 17.1                          | 93% (91 to 94) | 93% (91 to 94) |
| Women                 | 1000594     | 264           | 1.8                          | 3032                     | 21.1                          | 92% (91 to 93) | 92% (91 to 93) |
| Age <50 years         | 769391      | 191           | 1.7                          | 3494                     | 31.6                          | 95% (95 to 96) | 95% (94 to 95) |
| Age 50–64 years       | 431159      | 106           | 1.6                          | 876                      | 13.9                          | 88% (86 to 90) | 88% (86 to 90) |
| Age 65–79 years       | 327850      | 47            | 1.0                          | 213                      | 4.5                           | 80% (72 to 85) | 82% (75 to 88) |
| Age ≥80 years         | 157548      | 53            | 2.3                          | 136                      | 6.3                           | 67% (55 to 76) | 74% (63 to 82) |
| Any comorbidity       | 619248      | 184           | 1.8                          | 897                      | 11.7                          | 85% (83 to 87) | 86% (84 to 88) |
| Homemaker service     | 117684      | 72            | 2.8                          | 68                      | 7.9                           | 76% (65 to 84) | 76% (65 to 84) |
| 31–60 days            | 1544246     |               |                               |                          |                                |               |
| Men                   | 629873      | 361           | 1.8                          | 2900                     | 17.9                          | 90% (89 to 91) | 90% (89 to 91) |
| Women                 | 914453      | 893           | 3.0                          | 6008                     | 25.8                          | 88% (87 to 89) | 88% (87 to 89) |
| Age <50 years         | 704877      | 706           | 3.1                          | 6683                     | 37.2                          | 91% (91 to 92) | 91% (91 to 92) |
| Age 50–64 years       | 410305      | 303           | 2.3                          | 1776                     | 15.7                          | 85% (83 to 87) | 85% (83 to 87) |
| Age 65–79 years       | 298770      | 145           | 1.5                          | 315                      | 4.2                           | 69% (62 to 74) | 71% (64 to 76) |
| Age ≥80 years         | 130374      | 100           | 2.1                          | 134                      | 5.0                           | 69% (60 to 76) | 73% (65 to 79) |
| Any comorbidity       | 563605      | 439           | 2.1                          | 1571                     | 13.2                          | 84% (83 to 86) | 85% (83 to 86) |
| Homemaker service     | 108919      | 149           | 2.9                          | 64                      | 5.1                           | 74% (59 to 79) | 70% (59 to 79) |
| 61–120 days           | 1361616     |               |                               |                          |                                |               |
| Men                   | 555636      | 721           | 2.0                          | 2360                     | 10.9                          | 84% (82 to 85) | 83% (82 to 85) |
| Women                 | 804980      | 1755          | 3.1                          | 5162                     | 16.8                          | 82% (81 to 83) | 82% (81 to 83) |
| Age <50 years         | 618008      | 1531          | 3.7                          | 5697                     | 24.3                          | 84% (83 to 84) | 83% (82 to 84) |
| Age 50–64 years       | 380804      | 492           | 2.1                          | 1510                     | 9.5                           | 81% (79 to 83) | 81% (79 to 83) |
| Age 65–79 years       | 266405      | 227           | 1.2                          | 255                      | 2.6                           | 66% (59 to 72) | 65% (56 to 72) |
| Age ≥80 years         | 104399      | 186           | 2.0                          | 60                      | 2.0                           | 48% (30 to 61) | 50% (30 to 64) |
| Any comorbidity       | 4927270     | 852           | 2.2                          | 1252                     | 8.3                           | 79% (77 to 81) | 79% (77 to 80) |
| Homemaker service     | 101580      | 247           | 2.5                          | 64                      | 3.5                           | 64% (51 to 73) | 61% (47 to 72) |
| 121–180 days          | 635402      |               |                               |                          |                                |               |
| Men                   | 220596      | 273           | 1.0                          | 97                      | 1.2                           | 33% (15 to 47) | 29% (9 to 45)  |
| Women                 | 414806      | 547           | 1.1                          | 302                      | 2.1                           | 58% (52 to 64) | 54% (46 to 61) |
| Age <50 years         | 269241      | 503           | 1.6                          | 293                      | 2.7                           | 55% (48 to 61) | 51% (43 to 58) |
| Age 50–64 years       | 115938      | 161           | 1.0                          | 36                      | 1.1                           | 40% (14 to 58) | 29% (5 to 52)  |
| Age 65–79 years       | 156187      | 92            | 0.5                          | 27                      | 0.5                           | 40% (3 to 63)  | 30% (16 to 58) |
| Age ≥80 years         | 94036       | 64            | 0.5                          | 43                      | 1.3                           | 53% (33 to 68) | 46% (35 to 66) |
| Any comorbidity       | 269919      | 273           | 0.7                          | 97                      | 1.4                           | 58% (47 to 67) | 55% (42 to 65) |
| Home maker service    | 90347       | 81            | 0.6                          | 24                      | 1.5                           | 35% (14 to 63) | 29% (9 to 59)  |
| >180 days             | 327257      |               |                               |                          |                                |               |
| Men                   | 104220      | 351           | 1.7                          | 51                      | 2.1                           | 25% (0 to 45)  | 17% (–13 to 40) |
| Women                 | 223037      | 889           | 2.0                          | 172                      | 3.1                           | 41% (30 to 50) | 34% (22 to 45) |
| Age <50 years         | 260172      | 1005          | 1.9                          | 204                      | 3.3                           | 40% (30 to 48) | 33% (21 to 43) |
| Age ≥80 years         | 62085       | 235           | 1.8                          | 19                      | 1.0                           | 4% (–50 to 39) | 5% (–53 to 41) |
| Any comorbidity       | 160790      | 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.
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. 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 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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