Manuscript Click here to view linked References

Effectiveness of Covid-19 vaccination against risk of symptomatic infection, hospitalization, and death up to 9 months: a Swedish total-population cohort study

Peter Nordström, MD, PhD, Marcel Ballin, MSc., Anna Nordström, MD, PhD

Department of Community Medicine and Rehabilitation, Unit of Geriatric Medicine, Umeå University, Umeå, Sweden (Peter Nordström and Marcel Ballin)

Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, Umeå, Sweden (Marcel Ballin and Anna Nordström)

School of Sport Sciences, UiT the Arctic University of Norway, Tromsø, Norway (Anna Nordström)

Abstract word count: 299

Main text word count: 3467

Corresponding author:

Peter Nordström, Professor

Unit of Geriatric Medicine

Department of Community Medicine and Rehabilitation

Umeå University

90187 Umeå

Sweden

Phone: +4670 899 65 99

E-mail: peter.nordstrom@umu.se

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Abstract

Background: Whether vaccine effectiveness against Coronavirus disease 2019 (Covid-19) lasts longer than 6 months is unclear.

Methods: A retrospective cohort study was conducted using Swedish nationwide registries. The cohort comprised 842,974 pairs (N=1,684,958), including individuals vaccinated with 2 doses of ChAdOx1 nCoV-19, mRNA-1273, or BNT162b2, and matched unvaccinated individuals. Cases of symptomatic infection and severe Covid-19 (hospitalization or 30-day mortality after confirmed infection) were collected from 12 January to 4 October 2021.

Findings: Vaccine effectiveness of BNT162b2 against infection waned progressively from 92% (95% CI, 92-93, P<0·001) at day 15-30 to 47% (95% CI, 39-55, P<0·001) at day 121-180, and from day 211 and onwards no effectiveness could be detected (23%; 95% CI, -2-41, P=0·07). The effectiveness waned slightly slower for mRNA-1273, being estimated to 59% (95% CI, 18-79) from day 181 and onwards. In contrast, effectiveness of ChAdOx1 nCoV-19 was generally lower and waned faster, with no effectiveness detected from day 121 and onwards (-19%, 95% CI, -97-28), whereas effectiveness from heterologous ChAdOx1 nCoV-19 / mRNA was maintained from 121 days and onwards (66%; 95% CI, 41-80). Overall, vaccine effectiveness was lower and waned faster among men and older individuals. For the outcome severe Covid-19, effectiveness waned from 89% (95% CI, 82-93, P<0·001) at day 15-30 to 42% (95% CI, -35-75, P=0·21) from day 181 and onwards, with sensitivity analyses showing notable waning among men, older frail individuals, and individuals with comorbidities.

Interpretation: Vaccine effectiveness against symptomatic Covid-19 infection wanes progressively over time across all subgroups, but at different rate according to type of vaccine, and faster for men and older frail individuals. The effectiveness against severe illness seems to remain high through 9 months, although not for men, older frail individuals, and

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

individuals with comorbidities. This strengthens the evidence-based rationale for administration of a third booster dose.

Research in context

Evidence before this study

Clinical trials have demonstrated high efficacy of Coronavirus disease 2019 (Covid-19) vaccines against the risk of 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. Currently, there is some evidence to suggest waning vaccine effectiveness against infection up to 6 months after vaccination, with protection against severe illness appearing to be better maintained. Yet, the evidence is limited and consistent, in part due to evaluations of vaccines that may have different long-lasting effects, a low proportion of old participants, and varying and relatively short follow-up times. Specifically, whether vaccine effectiveness persist beyond 6 months is unknown.

Added value of this study

In this study, vaccine effectiveness of BNT162b2 against symptomatic infection waned progressively from 92% during the first month, to 47% by month 4-6 and from 7 months and onwards no effectiveness was detected. Effectiveness waned slightly slower for mRNA-1273, whereas effectiveness of ChAdOx1 nCoV-19 was generally lower. Overall, effectiveness was lower and waned faster among men and older individuals. For the outcome of hospitalization or death, effectiveness (any vaccine) waned from 89% during the first month to 42% from month 6 and onwards in the total population. There was notable waning among especially men, older frail individuals, and individuals with comorbidities.

Implications of all the available evidence

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Vaccine effectiveness against symptomatic Covid-19 infection wanes progressively over time across all subgroups, but at different rate according to type of vaccine, and faster for older frail individuals. The effectiveness against hospitalization or death seems to remain high through 9 months, but not for men, older frail individuals, and individuals with comorbidities. This strengthens the evidence-based rationale for administration of a third booster dose.

Introduction

Initial clinical trials showed a high efficacy of the BNT162b2 (Pfizer-BioNTech)[1], mRNA-1273 (Moderna)[2], and ChAdOx1 nCoV-19 (Oxford/AstraZeneca) Coronavirus disease 2019 (Covid-19) vaccines[3 4], and observational studies have estimated a high real-world effectiveness[5-8]. However, reports on breakthrough infections[9] and waning immunity[10-14] have raised concerns regarding the duration of protection.

With respect to severe Covid-19 such as hospitalization or death, follow-ups of clinical trials showed about 84% and 92% efficacy of BNT162b2 and mRNA-1273 after 4 months[15 16], with similar results reported by the CDC, although slightly lower maintained protection of BNT162b2[17]. Also, studies from US and Qatar showed that the effectiveness of BNT162b2 against hospitalization and death persisted through 6 months[18 19], whereas preliminary data from UK indicate a slight waning, most notably for older adults and for ChAdOx1 nCoV-19 compared to BNT162b2[20]. Altogether, although current evidence suggests that vaccine effectiveness against severe Covid-19 is relatively well maintained, the data are inconsistent. Similarly, also the duration of protection against less severe infection is unclear. After 4-5 months of follow-up, the effectiveness of BNT162b2 has been estimated to above 80%[15], 50%[19,20], down to about 20%[18] in a study from Qatar. For the ChAdOx1 nCoV-19,

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

preliminary data from UK suggest about 50% remaining effectiveness after 5 months of follow-up[20].

The different results in recent studies may relate to several factors, such as the evaluations of vaccines that may have different long-lasting effects[16 18-20], a low proportion of old participants[18], varying and relatively short follow-up times[15 16 21]. Collectively, there is insufficient evidence to determine vaccine effectiveness beyond 6 months. In this study, we investigate the effectiveness of Covid-19 vaccination, against the risk of symptomatic infection, hospitalization, and death through the first 9 months for the total population of Sweden.

Methods

Study design and cohort

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. The individuals considered for inclusion were 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 26 May 2021, and all individuals with a confirmed infection until 24 May 2021 (N=1,331,989). To these individuals, Statistics Sweden (the national agency for statistics, www.scb.se) randomly sampled one individual from the total population of Sweden, matched on birth year, sex and municipality. These matched individuals had neither been vaccinated nor infected with Covid-19 on the date of first vaccination dose or infection in the vaccinated individual. The total population consisted of 5,833,003 unique individuals that was considered for inclusion in this study. This population was updated with respect to vaccination status and Covid-19 infections until 4 October, 2021 (Figure 1). From this cohort,

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

the main study cohort was formed. Specifically, from the total cohort, each fully vaccinated (2 doses) individual was matched 1:1 to one randomly sampled unvaccinated individual on birth year, and sex, with baseline set to the date of the second dose of vaccine, in both vaccinated and matched unvaccinated individuals. Matched unvaccinated individuals were excluded if they received a first dose of vaccine or died within 14 days of baseline, and a new individual was searched from the remaining total cohort. This procedure was repeated 5 times. The final study cohort comprised 842,974 matched pairs of vaccinated/unvaccinated individuals (N=1,684,958). Data on individuals vaccinated or diagnosed with Covid-19 were collected from the Swedish Vaccination Register and SmiNet register, respectively, both of which are managed by the Public Health Agency of Sweden[22 23]. All health care providers in Sweden are obliged to report to these registers according to Swedish law, with a 100% coverage of the total population.

We also formed a second cohort to be used in a forthcoming sensitivity analysis. This cohort was formed using less strict matching criteria to increase the size of the cohort. In this data set, 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 process was repeated 10 times and one unvaccinated individual could be paired with several vaccinated individuals. This resulted in a cohort of 1,983,315 pairs (N=3,966,630).

Exposure, outcome, and baseline date for the analyses

In the analyses, the exposure variables were vaccination status (vaccinated with 2 doses/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 symptomatic infection until 4 October, 2021 latest. In 94·4% of cases,

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

symptomatic infection was confirmed using polymerase chain reaction and in 4·8% by sequencing, according to the SmiNet registry[23]. The term "symptomatic" was defined on the basis that in Sweden, health authorities have urged citizens to take a test if they experience any symptoms of Covid-19. The second outcome was a composite endpoint of severe disease until 28 September 2021 latest, defined as inpatient hospitalization with Covid-19 as main diagnosis, or all-cause mortality within 30 days after confirmed infection. Hospitalized cases were collected from the Swedish National Inpatient Register using the International Classification of Disease (ICD, version 10) code U071 and Statistics Sweden provided data on mortality. All outcomes were collected from >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[24]. From Statistics Sweden, we also obtained individual-level data on highest education during year 2019. Individual-level data regarding diagnoses, prescription medications, country of birth, and homemaker service were obtained from national registries managed by the Swedish National Board of Health and Welfare (www.socialstyrelsen.se). Homemaker services includes domestic services provided to individuals (primarily older individuals) who live at home but need help with shopping, cleaning, meal preparation, and similar tasks. Local governments are responsible for determining eligibility for these services. From the Swedish National Inpatient Register and National Outpatient Register for specialist care, diagnoses from 1998 and 2001 and later, respectively, were obtained, based on 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

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

selected as covariates for this study were based on the results from a previous nationwide study[25]. See Supplemental Table 1 for definitions.

Statistical analysis

Time-to-event for the outcomes (symptomatic infection/severe disease) based on vaccination status (vaccinated/unvaccinated) was illustrated using proportional hazards models with 95% confidence intervals (CI), and restricted cubic splines with four knots in default positions. To compare the risk of the outcomes based on the level of exposure (vaccinated/unvaccinated), Cox regression was used to calculate hazard ratios (HR). To adjust for the matched samples, 95% CIs were estimated using robust standard errors by the VCE 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 (χ^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/no), education (six categories), whether the individual was born in Sweden or not, and eight diagnoses at baseline (yes/no). The adjusted HR was used to calculate vaccine effectiveness using the following formula: vaccine effectiveness = (1-adjusted HR) x 100%. To investigate whether effectiveness was influenced by the covariates as listed in Table 1, interaction analyses were performed, using product terms created by multiplying the variable coding for vaccination status at baseline (vaccinated/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, effectiveness was also estimated for subgroups

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

according to these covariates. Follow-up time in days was counted until date of confirmed outcome (symptomatic infection or severe Covid-19), 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 performed in SPSS v27·0 for Mac (IBM Corp, Armonk, NY, USA), and Stata v16·1 for Mac (Statcorp, College Station, Texas, USA). A two-sided P-value <0·05 or HR with 95% CIs not crossing one were considered significant.

Role of the funding source

The present study was not funded.

Results

Study cohort

Between 28 December 2020 and 4 October 2021, 842,974 individuals were fully vaccinated (2 doses), and were matched 1:1 to an equal number of unvaccinated individuals. Thus, the total study cohort comprised 842,974 pairs (N=1,684,958). The mean date for the second dose of vaccine in the vaccinated group according to each vaccine schedule are shown in Table 1. Outcomes were collected between 12 January to 4 October, 2021. Baseline characteristics for the study cohort are presented in Table 1. Compared to unvaccinated individuals, vaccinated individuals more often had homemaker service, were more often born in Sweden, had more medical diagnoses, and had a higher level of education at baseline (P<0·001 for all, Table 1). Similar differences were evident when comparing different vaccines schedules.

Vaccine effectiveness against symptomatic infection

During a mean (range) follow-up of 116 (15-280) days, a symptomatic infection was confirmed in a total of 27,918 individuals, of which 6,147 were vaccinated individuals

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

(incidence rate [IR], 4·9/100,000 person-days) and 21,771 were unvaccinated individuals (IR, 31·6/100,000 person-days). As shown in Figure 2 and Table 2, there was a progressive waning in vaccine effectiveness (2 doses of any vaccine) against symptomatic infection over time. Effectiveness peaked at day 15-30 (92%; 95% CI, 91-93, P<0·001) and declined marginally at day 31-60 (89%; 95% CI, 88-89, P<0·001). From thereon, the waning became more pronounced, and from day 211 days onwards, there was no remaining detectable effectiveness (23%; 95% CI, -2-41, P=0·07).

Vaccine effectiveness was influenced significantly by type of vaccine, age, sex, home maker service and all diagnoses at baseline ($P_{interaction}$ <0·001 for all), but asthma ($P_{interaction}$ =0·86). At day 61-120, effectiveness declined to 50% (95% CI, 30-64, P<0·001) among individuals aged ≥80 years, and to 70% (95% CI, 59-79, P<0·001) among individuals with home maker service (Table 3). With respect to sex, there was no detectable effectiveness in men (17%; 95% CI, -13-40, P=0·23) from day 181 and onwards, whereas it remained in women (34%; 95% CI, 22-45, P<0·001). With respect to vaccine type, there was a waning in effectiveness for all vaccines during follow-up (Table 2). Effectiveness of BNT162b2 waned to 47% (95% CI, 39-55, P<0·001) at day 121-180, and no effectiveness was detected from day 211 and onwards (23%; 95% CI, -2-41, P=0·07). Waning was slightly slower for mRNA-1273, with a remaining effectiveness of 59% (95% CI, 18-79, P<0·001) after more than 180 days of follow up, and for heterologous ChAdOx1 nCoV-19 / mRNA schedules (66%; 95% CI, 41-80, P<0.001 from day 121 and onwards). In contrast, there was no detectable effectiveness for homologous ChAdOx1 nCoV-19 from day 121 and onwards (-19%; 95% CI, -97-28, P=0·49).

Vaccine effectiveness against hospitalization and death

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

During a mean follow-up of 113 (15-274) days, there were 277 cases of Covid-19 hospitalization or death among vaccinated individuals (IR, 0·23/100,000 person-days) and 825 cases among unvaccinated individuals (IR, 1·21/100,000 person-days) (Supplemental Figure 1 and Supplemental Table 2). Vaccine effectiveness (any vaccine) was 89% at day 15-30 (95% CI, 83-93, P<0·001), which declined to 74% (95% CI, 47-87, P<0·001) by day 121-180, and from day 181 and onwards, there was no detectable associated effectiveness (42%; 95% CI, -35-75, P=0·21). In a sensitivity analysis, individuals ≥80 years old were excluded. In the remaining cohort, the effectiveness was 80% (95% CI, 41-93, P=0·003), from day 181 and onwards. If individuals with homemaker service were excluded, the effectiveness was 69% (95% CI, 2-91, P=0·04) from day 181 and onwards.

In a sensitivity analysis, using less strict matching criteria, a second matched cohort (N=3,996,630) of more than twice the size of the original cohort was created. Mean age of vaccinated individuals was 5 years higher in this cohort with similar other characteristics as in the main cohort (Supplemental Table 3). In this cohort, the waning effectiveness was confirmed, both with respect to symptomatic infection (Supplemental Table 4) and severe disease (Supplemental Table 5). In addition, it was confirmed that effectiveness declined especially with respect to severe Covid-19 for older, frail individuals, in men and individuals with any comorbidity (Supplemental Table 5).

Discussion

This study showed a progressive waning in vaccine effectiveness against symptomatic Covid-19 through 9 months of follow-up. Following the peak during the first month after vaccination, effectiveness of BNT162b2 and mRNA-1273 declined to about 30% and 60% respectively, after 6 months. From 7 months and onwards, no effectiveness of BNT162b2

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

could be detected. The effectiveness waned across all subgroups although it was lower and waned more rapidly among men and older frail individuals, and for ChAdOx1 nCoV-19. Effectiveness against hospitalization and death was maintained through 9 months, although not in men, older frail individuals, and individuals with any comorbidity. Together, these findings strengthen the evidence-based rationale for administration of a booster dose, where the parts of the population who are at high risk of severe illness and death should be prioritized.

A main result from the present study is the waning vaccine effectiveness against symptomatic infection. We found that following the peak in the first month, the effectiveness after 4 months declined to 47% and 71% for BNT162b2 and mRNA-1273 respectively. From 7 months and onwards, an effectiveness of BNT162b2 could no longer be detected. These findings for the mRNA vaccines are similar to preliminary observational data from UK and to published observational data from US and Qatar[18-20]. In contrast, follow-up studies of clinical trials showed 84% efficacy of BNT162b2 after 4 months[15], and >90% efficacy of mRNA-1273 after >4 months[16]. In the present study, there was no remaining effectiveness for ChAdOx1 nCoV-19 after 4 months, which is in contrast to the preliminary findings from UK[20]. The different estimates in these studies could be influenced by differences related to the populations included, varying follow-up time, 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 during follow-up, and the fact that Delta variant has been more dominating in the real-world observational studies compared to in the clinical trials.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Another interesting finding from the present study was that vaccine effectiveness from heterologous ChAdOx1 nCoV-19 / mRNA schedules seemed to be better maintained than that from homologous ChAdOx1 nCoV-19 vaccination. While there is no other long-term follow-up of the effectiveness from heterologous vaccine schedules to support these findings, we recently found that heterologous ChAdOx1 nCoV-19 / mRNA schedules was associated with greater effectiveness against symptomatic infection compared with homologous ChAdOx1 nCoV-19 during 2.5 months of follow-up[26]. In addition, earlier studies support superior vaccine-elicited immunogenicity from heterologous schedules[27 28].

In the present study, vaccine effectiveness against severe disease was better maintained, as illustrated by the 74% effectiveness against Covid-19 hospitalization or death at 4-6 months after vaccination in the total population. These findings are consistent with the results from the Qatar study showing an 89% effectiveness from 6 months and onwards in a relatively young population[18], as well as preliminary data from UK[20]. Yet, it is of similar importance that our results, which were confirmed through sensitivity analyses, suggested a notable waning vaccine effectiveness against severe disease among older frail individuals and individuals with any comorbidity from 6 months through 9 months after vaccination. Although no previous study has had a follow-up time up as long as 9 months to support these results, these findings extend those from the UK, showing waning effectiveness against hospitalization among older adults in a clinically extremely vulnerable group after 5 months[20]. A reasonable explanation to waning effectiveness in older adults is that the vaccine induces a lower induction of memory T- and B-cells in older adults, and that production of plasma cells that could produce lower levels of antibody for decades is impaired[29]. In support, in the present study the overall most important risk factor for lower vaccine effectiveness was higher age, both for symptomatic infection and severe disease. Other risk factors included

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

individuals with homemaker service and underlying common medical conditions, such as diabetes and hypertension, as well as male sex, where similar waning effectiveness against severe disease was noted. For example, from 6 months through 9 months after vaccination, the effectiveness against severe disease was a borderline significant 52% in men compared to a robust 73% in women. 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 immune response along with a more rapid decline in neutralizing antibody titers in men compared to in women[14 30].

The results have important clinical implications, as they strengthen the evidence-based rationale for administration of a third booster dose, and especially to certain high-risk populations. Recent preliminary phase III data from Pfizer-BioNTech show that administration of a third booster dose of BNT162b2 administered a median of 11 months after the second dose, had 95·6% efficacy against symptomatic Covid-19 compared to those who had only received two primary doses, with consistent results irrespective of age, sex, and comorbidities[31]. 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 hospitalizations compared with individuals given two doses[32]. Currently, many countries such as UK, US, Canada, Israel, and Sweden are giving recommendations on a third booster dose to select populations at increased risk of severe Covid-19. The results of the present study, including waning effectiveness against symptomatic infection across all subgroups, support the administration of a third dose, although individuals manifesting with suboptimal or waning vaccine-elicited immunogenicity, including men, older frail individuals, and individuals with certain medical conditions, should be prioritized given that they also experience waning vaccine protection against severe Covid-19.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

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. Moreover, although we excluded all individuals with a previous confirmed infection, it is likely that some individuals with a previous asymptomatic infection were still included. If these individuals belonged to the unvaccinated cohort, this could potentially mean that their natural immunity due to a previous infection attenuated the estimated vaccine effectiveness. In addition, the infection pressure during the major part of follow-up was rather low, which could also have attenuated the estimated vaccine effectiveness, as well as influenced the statistical power especially for the outcome of severe Covid-19. Yet, it should be noted that the vaccine effectiveness was time-dependent during follow-up, and the estimates for most of the different time periods was significantly different from each other based on the CIs. This study also has several important strengths. First, all results could be confirmed through sensitivity analyses in a second much larger cohort where less strict matching criteria were used. Second, the study cohort was based on the total population of Sweden, increasing the external validity of the findings. Third, the vaccinated individuals had received different types and combinations of vaccines, allowing us to investigate how this differentially affected the effectiveness and duration of vaccine protection. Fourth, the registries used to obtain data on Covid-19 cases, vaccinations, hospitalizations, and deaths, have a nationwide coverage, with zero loss to follow-up, reducing the risk of misclassification of unvaccinated individuals included in the analyzes. Using these registries, we were also able to obtain covariates which have previously been identified as risk factors for Covid-19 in the Swedish population[25]. Finally, a timely component of the study is that the results apply primarily to the Delta variant of the virus, according to sequencing analyses presented by the Public Health Agency of Sweden.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

In summary, the results suggest a significant waning in vaccine protection against symptomatic Covid-19 infection across all subgroups, and a notable waning vaccine protection against severe illness in men, older frail individuals, and individuals with certain medical conditions. These findings may have implications for vaccination strategies and public health by strengthening the evidence-based rationale for administration of a third booster dose, where the priority should be certain high-risk populations who are at higher risk of severe consequences of Covid-19 due to weaker and more rapidly waning vaccine-elicited immunogenicity.

Contributors

Concept and design: PN, MB.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: PN, MB.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: PN.

Data availability: All authors-

Supervision: PN, AN-

Declaration of interests

None.

Data availability statement

The data files used for the present study is publicly unavailable according to regulations under Swedish law. However, all data used for the present study can be applied for from the

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

National Board of Health and Welfare, Statistics Sweden, and the Public Health Agency of Sweden.

References

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020;383(27):2603-15. doi: 10.1056/NEJMoa2034577 [published Online First: 2020/12/11]
2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021;384(5):403-16. doi: 10.1056/NEJMoa2035389 [published Online First: 2020/12/31]
3. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397(10269):99-111. doi: 10.1016/S0140-6736(20)32661-1 [published Online First: 2020/12/12]
4. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* 2021;397(10277):881-91. doi: 10.1016/S0140-6736(21)00432-3 [published Online First: 2021/02/23]
5. Chemaitelly H, Yassine HM, Benslimane FM, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. *Nature Medicine* 2021 doi: 10.1038/s41591-021-01446-y
6. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *N Engl J Med* 2021 doi: 10.1056/NEJMoa2108891 [published Online First: 2021/07/22]
7. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *The Lancet* 2021;397(10287):1819-29. doi: 10.1016/S0140-6736(21)00947-8
8. Chung H, He S, Nasreen S, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study. *BMJ* 2021;374:n1943. doi: 10.1136/bmj.n1943 [published Online First: 2021/08/22]
9. Keehner J, Horton LE, Binkin NJ, et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. *N Engl J Med* 2021 doi: 10.1056/NEJMc2112981 [published Online First: 2021/09/02]
10. Shrotri M, Navaratnam AMD, Nguyen V, et al. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. *Lancet* 2021;398(10298):385-87. doi: 10.1016/S0140-6736(21)01642-1 [published Online First: 2021/07/19]
11. Naaber P, Tserel L, Kangro K, et al. Dynamics of antibody response to BNT162b2 vaccine after six months: a longitudinal prospective study. *The Lancet Regional Health – Europe* doi: 10.1016/j.lanepe.2021.100208

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

12. Iacobucci G. Covid-19: Protection from two doses of vaccine wanes within six months, data suggest. *BMJ* 2021;374:n2113. doi: 10.1136/bmj.n2113
13. Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. *medRxiv* 2021:2021.08.24.21262423. doi: 10.1101/2021.08.24.21262423
14. Levin EG, Lustig Y, Cohen C, et al. Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. *New England Journal of Medicine* 2021 doi: 10.1056/NEJMoa2114583
15. Thomas SJ, Moreira ED, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. *New England Journal of Medicine* 2021 doi: 10.1056/NEJMoa2110345
16. El Sahly HM, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. *New England Journal of Medicine* 2021 doi: 10.1056/NEJMoa2113017
17. Self WH, Tenforde MW, Rhoads JP, et al. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021. MMWR Morb Mortal Wkly Rep. ePub: 17 September 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7038e1.
18. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. *New England Journal of Medicine* 2021 doi: 10.1056/NEJMoa2114114
19. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *The Lancet* doi: 10.1016/S0140-6736(21)02183-8
20. Andrews A, Tessier E, Stowe J, et al. Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID to 19 in the UK. 2021. Available from: https://khub.net/documents/135939561/338928724/Vaccine+effectiveness+and+duration+of+protection+of+covid+vaccines+against+mild+and+severe+COVID-19+in+the+UK.pdf/10dcd99c-0441-0403-dfd8-11ba2c6f5801. Accessed 15 Sep 2021.
21. Falsey AR, Sobieszczyk ME, Hirsch I, et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. *New England Journal of Medicine* 2021 doi: 10.1056/NEJMoa2105290
22. Public Health Agency of Sweden. The National Vaccination Register. Available from: https://www.folkhalsomyndigheten.se/smittskydd-beredskap/vaccinationer/nationella-vaccinationsregistret/. Accessed 16 June, 2021.
23. Public Health Agency of Sweden. SmiNet. Available from: https://www.folkhalsomyndigheten.se/smittskydd-beredskap/overvakning-och-rapportering/sminet/. Accessed 17 June, 2021.
24. The Statistics Sweden Database. The official agency for goverment statistics. Sweden. Available at: https://www.scb.se/en/.
25. Bergman J, Ballin M, Nordstrom A, et al. Risk factors for COVID-19 diagnosis, hospitalization, and subsequent all-cause mortality in Sweden: a nationwide study. *Eur J Epidemiol* 2021;36(3):287-98. doi: 10.1007/s10654-021-00732-w [published Online First: 2021/03/12]

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

26. Nordström P, Ballin M, Nordström A. Effectiveness of heterologous ChAdOx1 nCoV-19 and mRNA prime-boost vaccination against symptomatic Covid-19 infection in Sweden: A nationwide cohort study. *The Lancet Regional Health – Europe* 2021 doi: 10.1016/j.lanepe.2021.100249
27. Normark J, Vikström L, Gwon Y-D, et al. Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination. *New England Journal of Medicine* 2021 doi: 10.1056/NEJMc2110716
28. Liu X, Shaw RH, Stuart ASV, et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. *The Lancet* 2021;398(10303):856-69. doi: 10.1016/S0140-6736(21)01694-9
29. Pollard AJ, Bijker EM. A guide to vaccinology: from basic principles to new developments. *Nature Reviews Immunology* 2021;21(2):83-100. doi: 10.1038/s41577-020-00479-7
30. Lustig Y, Sapir E, Regev-Yochay G, et al. BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: a prospective, single-centre, longitudinal cohort study in health-care workers. *The Lancet Respiratory medicine* 2021;9(9):999-1009. doi: 10.1016/S2213-2600(21)00220-4 [published Online First: 2021/07/06]
31. Pfizer and BioNTech Announce Phase 3 Trial Data Showing High Efficacy of a Booster Dose of Their COVID-19 Vaccine, October 21, 2021. https://investors.biontech.de/news-releases/news-release-details/pfizer-and-biontech-announce-phase-3-trial-data-showing-high.
32. Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. *New England Journal of Medicine* 2021 doi: 10.1056/NEJMoa2114255

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

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

	Total study cohort		BNT162b2 / BNT162b2		mRNA-1273 / mRNA-1273		ChAdOx1 nCoV-19 / ChAdOx1 nCoV-19		BNT162b2 /mRNA vaccine*	
	Vaccinated	**Unvaccinated**	**Vaccinated**	**Unvaccinated**	**Vaccinated**	**Unvaccinated**	**Vaccinated**	**Unvaccinated**	**Vaccinated**	**Unvaccinated**
	N=842,974	N=842,974	N=637,107	N=637,107	N=76,880	N=76,880	N=76,597	N=76,597	N=51,766	N=51,766
Baseline date, mean	04/05/2021	04/05/2021	27/4/2021	27/4/2021	20/5/2021	20/5/2021	5/6/2021	5/6/2021	28/5/2021	28/5/2021
Age, mean ± SD	53·0±19·0	53·0±19·0	54·5±19·0	54·5±19·0	49·3±18·0	49·3±18·1	54·6±18·9	54·6±18·9	36·5±10·9	36·5±10·9
Female sex, N (%)	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, N (%)	87,004 (10·3)	30,680 (3·6)	81,704 (12·8)	25,718 (4·0)	4,297 (5·6)	1,950 (2·5)	698 (0·9)	2,823 (3·7)	262 (0·5)	174 (0·3)
Born in Sweden, N (%)	703,666 (83·5)	578,647 (68·6)	533,572 (83·7)	442,799 (69·5)	63,288 (82·3)	50,259 (71·2)	64,951 (84·8)	50,178 (65·5)	41,363 (79·9)	35,011 (67·6)
Education, N (%)										
Elementary school < 9yrs	61,022 (7·2)	79,375 (9·4)	51,598 (8·1)	63,360 (10·4)	4,236 (5·5)	6,390 (8·3)	4,420 (5·8)	7,608 (9·9)	737 (1·4)	1,967 (3·8)
Elementary school 9yrs	81,455 (9·7)	97,948 (11·6)	61,818 (9·7)	73,709 (12·1)	8,311 (10·8)	9,469 (12·3)	6,939 (9·1)	9,084 (11·9)	4,344 (8·4)	5,621 (10·9)
Secondary school, 2 yrs	180,672 (21·4)	182,971 (21·7)	143,917 (22·6)	145,325 (22·8)	14,844 (19·3)	15,824 (20·6)	16,391 (21·4)	16,065 (21·0)	5,424 (10·5)	5,642 (10·9)
Secondary school, >2 yrs	171,349 (20·3)	168,922 (20·0)	125,590 (19·7)	122,362 (19·2)	15,862 (20·6)	16,522 (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 (32·8)	237,148 (37·2)	204,663 (31·2)	30,503 (39·6)	24,708 (32·0)	31,973 (41·7)	24,994 (32·6)	24,770 (47·9)	20,893 (40·4)
Unknown	23,816 (2·8)	38,314 (4·5)	17,040 (2·7)	27,688 (4·3)	3,163 (4·1)	4,014 (5·2)	1,215 (1·6)	3,919 (5·1)	2,374 (4·6)	2,662 (5·1)
Comorbidities, N (%)										
Myocardial infarction	21,885 (2·6)	18,530 (2·2)	18,167 (2·9)	15,190 (2·4)	1,637 (2·1)	1,335 (1·7)	1,974 (2·6)	1,910 (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)	1,751 (2·3)	1,185 (1·5)	1,543 (2·0)	1,785 (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)	1,698 (3·3)	922 (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)
Chronic obstructive pulmonary disease	17,257 (2·0)	13,353 (1·6)	14,709 (2·3)	10,768 (1·7)	1,248 (1·6)	928 (1·2)	1,189 (1·6)	1,563 (2·0)	102 (0·2)	83 (0·2)

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

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)
Covid-19 infection	0	0	0	0	0	0	0	0	0	0

* Either the BNT162b2 or mRNA-1273

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Table 2. Vaccine effectiveness against symptomatic infection up to 9 months after full vaccination (>14 days after the second dose)

	Vaccinated (N=842,974)		Unvaccinated (N=842,974)		Vaccine effectiveness, % (95% CI)	
	No. of events	IR/100000 person-days	No. of events	IR/100000 person-days	Adjusted for age and baseline date	Fully adjusted*
Total (2 doses of any vaccine) (N=1,684,958)	6,147	4·9	21,771	31·6	84 (83-84)	84 (83-84)
15-30 days (N=1,684,958)	397	1·6	4,719	19·5	92 (91-93)	92 (91-93)
31-60 days (N=1,548,326)	1,254	2·5	8,908	22·5	89 (88-90)	89 (88-89)
61-120 days (N=1,363,616)	2,436	2·6	7,522	14·4	83 (82-83)	82 (81-83)
121-180 days (N=635,402)	820	1·0	399	1·8	52 (46-58)	48 (41-54)
181-210 days (N=327,257)	718	1·2	161	2·1	42 (31-51)	32 (19-44)
>210 days (N=239,822)	522	1·0	62	1·2	23 (0-41)	23 (-2-41)
BNT162b2 / BNT162b2 (N=1,274,214)	5,062	5·1	19,121	36·4	84 (84-85)	85 (84-85)
15-30 days (N=1,274,214)	333	1·7	4,039	22·1	92 (91-93)	92 (92-93)
31-60 days (N=1,166,247)	1,095	2·9	7,982	26·7	89 (88-90)	89 (88-90)
61-120 days (N=1,032,971)	1,796	2·6	6,601	16·6	85 (84-85)	85 (84-85)
121-180 days (N=480,153)	631	1·0	292	1·7	52 (45-58)	47 (39-55)
181-210 days (N=304,298)	688	1·2	145	2·1	39 (26-49)	29 (15-42)
>210 days (N=231,006)	519	1·1	62	1·3	23 (1-41)	23 (-2-41)
mRNA-1273 / mRNA-1273 (N=153,760)	300	2·9	1,722	28·2	89 (88-91)	89 (88-90)
15-30 days (N=153,760)	20	0·9	493	22·5	96 (94-98)	96 (94-97)
31-60 days (N=139,532)	67	1·5	743	21·1	93 (91-95)	93 (90-94)
61-120 days (N=123,610)	116	1·4	418	9·0	86 (82-88)	85 (82-88)
121-180 days (N=52,254)	65	1·0	53	2·6	72 (59-80)	71 (56-81)
>180 days (N=22,755)	32	0·8	15	2·4	69 (44-83)	59 (18-79)
ChAdOx1 nCoV-19 / ChAdOx1 (N=153,194)	465	5·0	469	7·2	49 (42-55)	44 (36-52)
15-30 days (N=153,194)	33	1·4	93	4·2	66 (50-77)	68 (52-79)
31-60 days (N=144,772)	53	1·2	88	2·3	55 (36-68)	49 (28-64)
61-120 days (N=129,103)	293	3·5	262	4·9	48 (39-56)	41 (29-51)
>120 days (N=53,060)	86	1·6	26	1·4	0 (-55-36)	-19 (-97-28)
ChAdOx1 nCoV-19 / mRNA vaccine (N=103,532)†	316	4·8	442	11·8	68 (63-72)	65 (59-70)
15-30 days (N=103,532)	11	0·7	92	6·2	89 (79-94)	89 (79-94)
31-60 days (N=92,623)	37	1·2	88	4·0	74 (62-82)	72 (59-82)
61-120 days (N=76,924)	230	3·8	234	8·8	63 (55-69)	55 (45-64)
>120 days (N=49,664)	38	0·7	28	1·8	61 (36-76)	66 (41-80)

*Adjusted for age, baseline date, sex, home maker service, place of birth, education, and comorbidities according to Table 1.

† Either the BNT162b2 or mRNA-1273

CI denotes confidence interval. IR denotes incidence rate.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Table 3. Vaccine effectiveness against symptomatic infection up to 9 months after full vaccination (>14 days after the second dose) according to sex, age and for individuals with homemaker service and with any comorbidity at baseline

	Vaccinated		Unvaccinated		Vaccine effectiveness, % (95% CI)	
Total (2 doses of any vaccine)	**No. of events**	**IR/100000 person-days**	**No. of events**	**IR/100000 person-days**	**Adjusted for age and baseline date**	**Fully adjusted[a]**
15-30 days (N=1,684,958)						
Men (N=685,354)	133	1·3	1,687	17·1	93 (91-94)	93 (91-94)
Women (N=1,000,594)	264	1·8	3,032	21·1	92 (91-93)	92 (91-93)
<50 years (N=769,391)	191	1·7	3,494	31·6	95 (94-96)	95 (94-95)
50-64 years (N=431,159)	106	1·6	876	13·9	88 (86-90)	88 (86-91)
65-79 years (N=327,850)	47	1·0	213	4·5	80 (72-85)	82 (75-88)
≥80 years (N=157,548)	53	2·2	136	6·3	67 (55-76)	74 (63-82)
Any diagnosis at baseline (N=619,248)	184	1·8	897	11·7	85 (83-87)	86 (84-89)
Homemaker service (N=117,684)	72	2·8	68	7·9	76 (66-84)	76 (65-84)
31-60 days (N=1,548,326)						
Men (N=629,873)	361	1·8	2,900	17·9	90 (89-91)	90 (89-91)
Women (N=914,453)	893	3·0	6,008	25·8	88 (87-89)	88 (87-89)
<50 years (N=704,877)	706	3·1	6,683	37·2	91 (91-92)	91 (90-92)
50-64 years (N=410,305)	303	2·3	1,776	15·7	85 (83-87)	85 (83-87)
65-79 years (N=298,770)	145	1·5	315	4·2	69 (62-74)	71 (64-76)
≥80 years (N=130,374)	100	2·2	134	5·0	69 (60-76)	73 (65-79)
Any diagnosis at baseline (N=563,605)	439	2·1	1,571	13·2	84 (83-86)	85 (83-86)
Homemaker service (N=108,919)	149	2·9	64	5·2	72 (60-80)	71 (50-79)
61-120 days (N=1,363,616)						
Men (N=558,636)	721	2·0	2,360	10·9	84 (83-85)	83 (82-85)
Women (N=804,980)	1,715	3·1	5,162	16·8	82 (81-83)	82 (81-83)
<50 years (N=618,008)	1,531	3·8	5,697	24·6	84 (83-85)	84 (83-84)
50-64 years (N=380,804)	492	2·2	1,510	9·5	82 (80-84)	81 (79-83)
65-79 years (N=260,405)	227	1·2	255	2·6	66 (58-72)	65 (56-72)
≥80 years (N=104,399)	186	2·0	60	2·0	48 (30-61)	50 (30-64)
Any diagnosis at baseline (N=497,270)	852	2·2	1,252	8·4	79 (77-81)	79 (77-80)
Homemaker service (N=101,580)	247	2·9	64	5·1	71 (59-79)	70 (59-79)
121-180 days (N=635,402)						
Men (N=220,596)	273	1·0	97	1·2	33 (15-47)	29 (9-45)
Women (N=414,806)	547	1·0	302	2·1	58 (52-64)	54 (46-61)
<50 years (N=269,241)	503	1·6	293	2·7	55 (48-61)	51 (43-58)
50-64 years (N=115,938)	161	1·0	36	1·1	40 (14-59)	27 (-8-50)

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

65-79 years (N=156,187)	92	0·5	27	0·5	40 (3-63)	30 (-16-58)
≥80years (N=94,036)	64	0·5	43	1·3	53 (31-68)	44 (15-66)
Any diagnosis at baseline (N=269,919)	273	0·7	97	1·3	61 (47-67)	55 (42-65)
Home maker service (N=90,347)	81	0·6	24	1·5	35 (-14-63)	29 (-24-59)
>180 days (N=327,257)						
Men (N=104,220)	351	1·7	51	2·1	26 (0-45)	17 (-13-40)
Women (N=223,037)	889	2·0	172	3·1	41 (30-50)	34 (22-45)
<50 years (N=109,334)	544	2·6	164	4·3	46 (36-55)	37 (24-48)
50-64 years (N=73,212)	261	1·7	28	2·0	20 (-18-46)	8 (-36-38)
65-79 years (N=77,626)	200	1·3	12	1·2	16 (-50-53)	11 (-32-40)
≥80 years (N=67,085)	235	1·8	19	1·0	4 (-50-39)	5 (-53-41)
Any diagnosis at baseline (N=160,790)	536	1·6	41	1·6	22 (-8-43)	15 (-17-38)
Homemaker service (N=78,080)	319	1·9	14	1·7	31 (-18-60)	28 (-24-58)

*Adjusted for age, baseline date, sex, home maker service, place of birth, education, and comorbidities according to Table 1.

CI denotes confidence interval. IR denotes incidence rate.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Supplemental Table 1. Definitions of comorbidities included. Diabetes and hypertension was defined based on prescribed medications or a diagnosis as specified below

Variable	Definition	Code Type	Codes
Comorbidities			
Myocardial infarction		ICD-10-SE	I21
Stroke		ICD-10-SE	I60-I64
Hypertension	Hypertension	ICD-10-SE	I10
	Angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker	ATC	C09
	Calcium-receptor blocker	ATC	C08
	Diuretic	ATC	C03
Diabetes	Diabetes	ICD-10-SE	E10, E11
	Antidiabetics	ATC	A10
Chronic obstructive pulmonary disease		ICD-10-SE	J40-J44
Asthma		ICD-10-SE	J45, J46
Cancer	Malignant neoplasm	ICD-10-SE	C
Renal failure/chronic kidney disease		ICD-10-SE	N17-N19
Covid-19		ICD-10-SE	U071

Abbreviations: ATC, Anatomical Therapeutic Chemical; ICD-10-SE, International Classification of Diseases, 10th Revision

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Supplemental Table 2. Vaccine effectiveness against Covid-19 hospitalization or death up to 9 months after full vaccination (>14 days after the second dose)

	Vaccinated		Unvaccinated		Vaccine effectiveness, % (95% CI)	
	No. of events	IR/100000 person-days	No. of events	IR/100000 person-days	Adjusted for age and baseline date	Fully adjusted*
15-30 days (N=1,685,948)	22	0·09	136	0·56	86 (78-91)	89 (82-93)
31-60 days (N=1,549,267)	65	0·13	354	0·89	88 (85-91)	91 (88-93)
61-120 days (N=1,341,155)	102	0·09	308	0·46	87 (84-90)	90 (87-92)
121-180 days (N=575,432)	27	0·03	21	0·08	79 (61-89)	74 (47-87)
>180 days (N=327,981)	61	0·10	6	0·07	20 (-80-75)	42 (-35-75)

*Adjusted for age, baseline date, sex, home maker service, place of birth, education, and comorbidities according to Table 1.

CI denotes confidence interval. IR denotes incidence rate.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Supplemental Table 3. Baseline characteristics of the second matched cohort (N=3,966,630) at second dose of vaccine

	Vaccinated N=1,983,315	**Unvaccinated** N=1,983,315
Baseline date, mean	19/05/2021	19/05/2021
Age, mean ± SD	59·4±17·2	56·8±20·2
Female sex, N (%)	1,119,761 (56·5)	1,022,813 (51·6)
Homemaker service, N (%)	167,481 (8·4)	97,297 (4·9)
Born in Sweden, N (%)	1,682,511 (84·8)	1,320,344 (66·6)
Education, N (%)		
Elementary school < 9yrs	171,954 (8·7)	228,702 (11·5)
Elementary school 9yrs	184,453 (9·3)	249,703 (12·6)
Secondary school, 2 yrs	507,517 (25·6)	490,785 (24·7)
Secondary school, >2 yrs	341,513 (17·2)	311,037 (15·7)
University education	743,795 (37·5)	517,708 (26·1)
Unknown	34,083 (1·7)	186,010 (9·4)
Diagnoses at baseline, N (%)		
Myocardial infarction	65,950 (3·3)	57,839 (2·9)
Stroke	68,991 (3·5)	52,203 (2·6)
Diabetes	231,561 (11·7)	184,588 (9·3)
Hypertension	770,155 (38·8)	592,423 (29·9)
Kidney failure	44,177 (2·2)	30,497 (1·5)
Chronic obstructive pulmonary disease	44,187 (2·2)	41,708 (2·1)
Asthma	101,710 (5·1)	89,472 (4·5)
Cancer	137,929 (7·0)	101,158 (5·1)
Covid-19 infection	0	0

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Supplemental Table 4. Vaccine effectiveness against symptomatic infection up to 9 months after full vaccination (>14 days after the second dose) in the second matched cohort (N=3,966,630) according to age and for individuals with homemaker service and with any comorbidity at baseline

	Vaccinated		Unvaccinated		Vaccine effectiveness, % (95% CI)	
	No. of events	IR/100000 person-days	No. of events	IR/100000 person-days	Adjusted for age and baseline date	Fully adjusted*
Total (2 doses of any vaccine) 15-30 days (N=3,966,630)						
Men (N=1,824,056)	235	0·9	3,502	12·6	89 (88-91)	90 (89-91)
Women N=2,142,574)	420	1·3	3,411	11·6	90 (88-91)	90 (89-91)
<50 years (N=1,129,195)	255	1·5	4,600	28·2	94 (93-95)	94 (93-95)
50-64 years (N=1,306,783)	186	1·0	1,370	7·1	87 (85-89)	87 (85-89)
65-79 years (N=1,072,599)	83	0·5	499	3·3	84 (79-87)	85 (81-88)
≥80 years (N=458,053)	131	1·9	444	7·2	77 (72-81)	79 (74-82)
Any diagnosis at baseline (N=1,700,258)	326	1·1	1,692	7·9	85 (83-86)	86 (84-87)
Homemaker service (N=264,778)	136	2·7	207	7·5	78 (72-83)	77 (71-82)
31-60 days (N=3,667,937)						
Men (N=1,683,085)	681	1·3	6,400	13·6	85 (84-87)	86 (85-88)
Women (N=1,984,852)	1,383	2·1	6,589	13·3	85 (84-86)	86 (85-86)
<50 years (N=1,044,921)	913	2·7	8,780	31·9	91 (90-91)	90 (90-91)
50-64 years (N=1,237,496)	646	1·7	3,165	9·2	83 (81-84)	82 (80-84)
65-79 years (N=997,293)	254	0·8	663	2·5	71 (66-75)	73 (68-77)
≥80 years (N=388,227)	251	1·8	381	4·5	72 (68-76)	75 (71-79)
Any diagnosis at baseline (N=1,561,378)	835	1·5	2,813	8·1	81 (80-83)	80 (80-83)
Homemaker service (N=244,561)	284	2·9	208	4·7	74 (67-79)	72 (65-78)
61-120 days (N=3,353,855)						
Men (N=1,533,402)	1,417	1·5	6,259	9·0	79 (78-80)	79 (78-80)
Women (N=1,820,453)	2,672	2·2	6,639	9·1	79 (78-80)	79 (78-80)
<50 years (N=936,779)	1,939	3·4	8,100	21·8	83 (82-84)	83 (82-83)
50-64 years (N=1,163,704)	1,226	1·8	3,606	6·9	78 (76-79)	76 (74-78)
65-79 years (N=919,304)	541	0·9	1,011	2·4	69 (65-72)	63 (59-67)
≥80 years (N=334,068)	383	1·4	181	1·5	55 (47-62)	55 (45-63)
Any diagnosis at baseline (N=1,429,158)	1,685	1·6	2,911	5·7	76 (74-77)	74 (72-75)
Homemaker service (N=228,320)	437	2·3	194	2·7	57 (48-64)	52 (41-61)
121-180 days (1,428,433)						
Men (N=582,945)	420	0·7	363	1·2	45 (36-53)	49 (40-56)
Women (N=855,488)	771	0·8	461	1·3	52 (46-58)	48 (40-54)
<50 years (N=320,382)	536	1·6	367	2·5	50 (43-57)	49 (41-56)

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

50-64 years (N=280,596)	243	0·8	91	0·8	45 (38-57)	33 (11-50)
65-79 years (N=533,415)	212	0·4	145	0·6	52 (39-62)	43 (27-56)
≥80 years (N=304,040)	200	0·5	221	1·6	65 (57-71)	60 (50-68)
Any diagnosis at baseline (N=755,262)	524	0·6	345	1·2	60 (54-66)	56 (48-62)
Home maker service (N=194,230)	145	0·5	125	1·9	69 (58-77)	64 (51-73)
181-210 days (N=504,501)						
Men (N=170,689)	259	0·9	107	1·7	33 (15-47)	29 (9-55)
Women (N=333,812)	618	1·0	148	1·8	46 (35-56)	40 (37-51)
<50 years (N=118,953)	386	2·0	163	3·3	47 (35-57)	41 (27-51)
50-64 years (N=91,762)	195	1·1	22	1·4	21 (-23-49)	18 (-49-43)
65-79 years (N=108,479)	127	0·6	10	0·6	9 (-74-52)	-5 (-213-48)
≥80 years (N=185,307)	169	0·5	60	1·0	59 (47-69)	55 (39-66)
Any diagnosis at baseline (N=292,863)	380	0·7	79	1·2	54 (41-64)	41 (24-55)
Homemaker service (N=146,546)	208	0·8	31	1·3	61 (43-74)	55 (34-70)
>210 days (N=317,272)						
Men (N=97,393)	183	1·0	38	1·1	14 (-22-40)	15 (-24-41)
Women (N=219,879)	486	1·0	41	1·0	-2 (-40-26)	-11 (-55-20)
<50 years (N=95,801)	181	1·0	55	1·3	36 (13-53)	34 (8-52)
50-64 years (N=72,440)	123	0·8	7	0·5	-52 (-325-31)	-77 (-390-19)
65-79 years (N=52,586)	97	0·8	4	0·6	-37 (-373-49)	-32 (-376-54)
≥80 years (N=96,445)	268	1·3	13	0·7	-44 (-251-17)	-66 (-296-7)
Any diagnosis at baseline (N=164,108)	379	1·1	26	1·1	11 (-33-40)	1 (-147-33)
Homemaker service (N=96,138)	277	1·3	5	0·6	-68 (-405-31)	-77 (-427-27)

*Adjusted for age, baseline date, sex, home maker service, place of birth, education, and comorbidities according to Table 1.

CI denotes confidence interval. IR denotes incidence rate.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Supplemental Table 5. Vaccine effectiveness in the second matched cohort (N=3,966,630) against Covid-19 hospitalization or death up to 9 months after full vaccination (>14 days after the second dose)

	Vaccinated		Unvaccinated		Vaccine effectiveness (95% CI)	
	No. of events	IR/100000 person-days	No. of events	IR/100000 person-days	Adjusted for age and baseline date	Fully adjusted*
15-30 days (N=3,966,630)	42	0·07	398	0·70	91 (88-94)	92 (89-94)
Men (N=1,824,056)	25	0·10	199	0·70	88 (81-92)	90 (84-93)
Women (N=2,142,574)	17	0·05	199	0·70	94 (89-96)	94 (90-97)
<80 years (N=3,508,577)	22	0·04	213	0·42	91 (85-94)	92 (87-95)
≥80 years (N=458,053)	20	0·28	185	3·00	92 (87-95)	92 (88-95)
Any diagnosis (1,700,258)	41	0·14	281	1·31	89 (85-92)	86 (84-87)
Homemaker service (N=264,778)	23	0·46	101	3·64	92 (88-95)	92 (87-95)
31-60 days (N=3,675,040)	128	0·11	750	0·77	90 (88-91)	90 (88-91)
Men (N=1,686,584)	66	0·13	368	0·78	86 (82-90)	88 (84-91)
Women (N=1,988,456)	62	0·09	282	0·77	91 (89-93)	91 (88-93)
<80 years (N=3,286,444)	53	0·05	487	0·55	92 (89-94)	92 (89-94)
≥80 years (N=388,596)	75	0·54	263	3·13	88 (84-91)	88 (84-91)
Any diagnosis (N=1,563,063)	123	0·22	478	1·37	88 (85-90)	87 (85-90)
Homemaker service (N=244,779)	76	0·76	120	2·69	89 (85-92)	89 (84-92)
61-120 days (N=3,282,190)	168	0·08	674	0·49	89 (87-91)	89 (87-90)
Men (N=1,499,366)	98	0·11	357	0·53	87 (83-89)	88 (85-90)
Women (N=1,782,824)	70	0·06	317	0·45	91 (89-93)	90 (86-92)
<80years (N=2,947,640)	73	0·04	562	0·45	93 (91-959	92 (92-94)
≥80 years (N=334,550)	95	0·35	112	0·98	83 (78-87)	84 (79-89)
Any diagnosis (N=1,421,723)	157	0·15	424	0·85	88 (86-90)	86 (83-89)
Homemaker service (N=228,454)	112	0·58	82	1·15	82 (75-88)	81 (73-87)
121-180 days (N=1,194,976)	54	0·04	96	0·18	85 (80-89)	83 (75-88)
Men (N=468,292)	28	0·06	33	0·14	77 (62-86)	75 (55-86)
Women (N=726,684)	26	0·03	63	0·22	89 (83-93)	87 (79-92)
<80 years (N=893,317)	21	0·02	29	0·07	87 (77-93)	87 (75-93)
≥80 years (N=301,659	33	0·09	67	0·50	83 (75-79)	78 (65-86)
Any diagnosis (N=642,329)	44	0·06	77	0·33	88 (82-92)	85 (77-90)
Homemaker service (N=189,080)	32	0·12	41	0·71	80 (74-89)	72 (51-84)
>180 days (N=495,577)	87	0·10	22	0·14	66 (47-79)	75 (43-78)
Men (N=167,494)	44	0·15	9	0·13	50 (1-75)	52 (0-77)
Women (N=328,083)	43	0·07	13	0·15	75 (54-86)	73 (49-85)

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

<80 years (N=321,154)	25	0·04	10	0·10	82 (74-91)	83 (72-93)
≥80 years (N=174,423)	62	0·20	12	0·22	56 (20-75)	51 (2-74)
Any diagnosis (N=280,974)	79	0·15	14	0·23	62 (34-78)	58 (26-77)
Homemaker service (N=143,534)	67	0·23	6	0·28	60 (10-82)	57 (7-80)

*Adjusted for age, baseline date, sex, home maker service, place of birth, education, and comorbidities according to Table 1.

CI denotes confidence interval. IR denotes incidence rate.

Legends to Figures

Figure 1. Description of selection of the cohort.

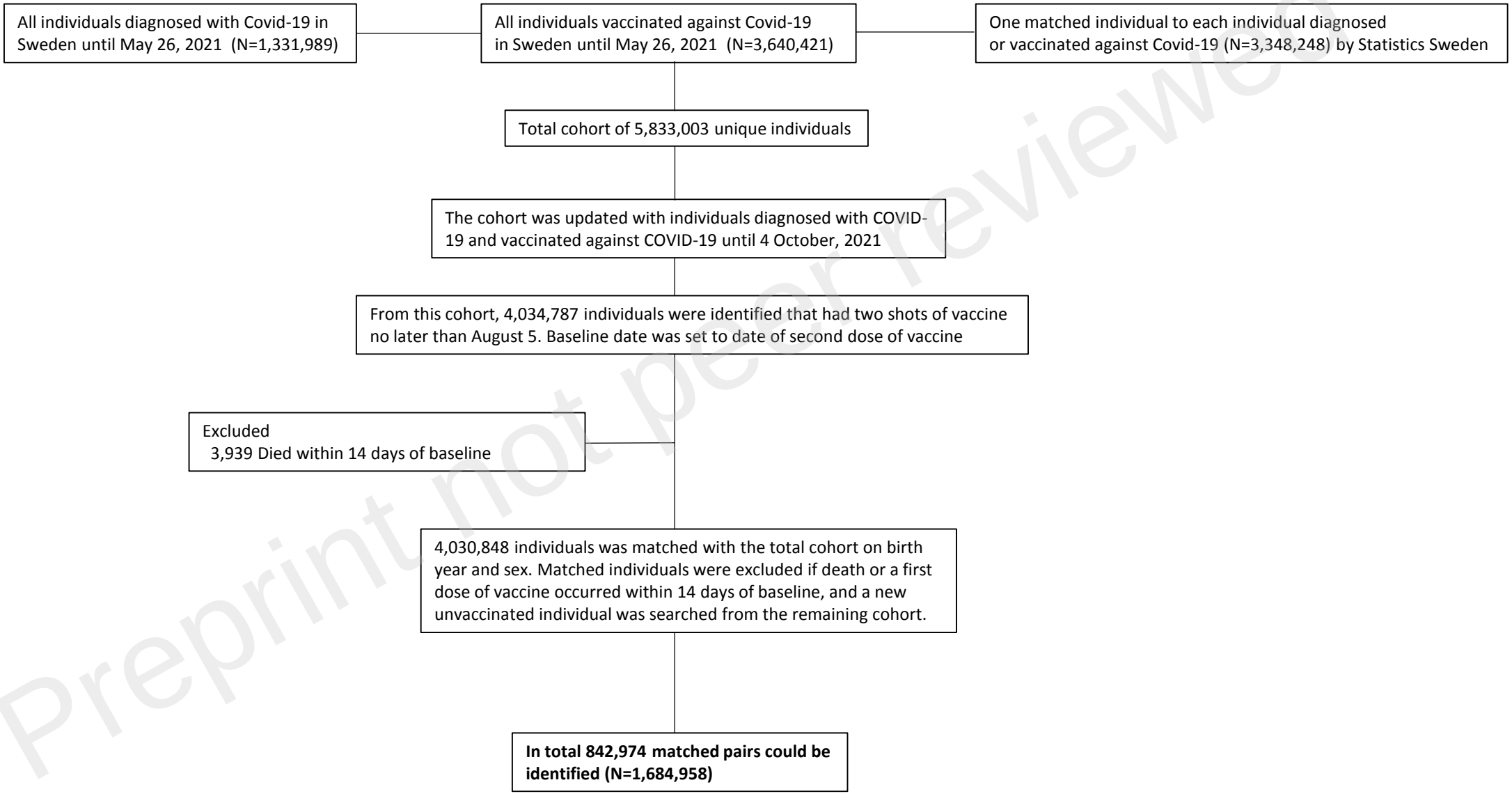
Figure 2. Adjusted vaccine effectiveness (any vaccine) against symptomatic Covid-19 infection among 842,974 vaccinated individuals matched to equally number of unvaccinated individuals through 9 months of follow-up. To model the association between vaccine effectiveness during follow-up, restricted cubic splines were used with 5 degrees of freedom.

Supplemental Figure 1. Adjusted vaccine effectiveness (any vaccine) against Covid-19 hospitalization or death among 842,974 vaccinated individuals matched to equally number of unvaccinated individuals through 9 months of follow-up. To model the association between vaccine effectiveness during follow-up, restricted cubic splines were used with 5 degrees of freedom.

Preprint not peer reviewed

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Figure 1



Preprint not peer reviewed

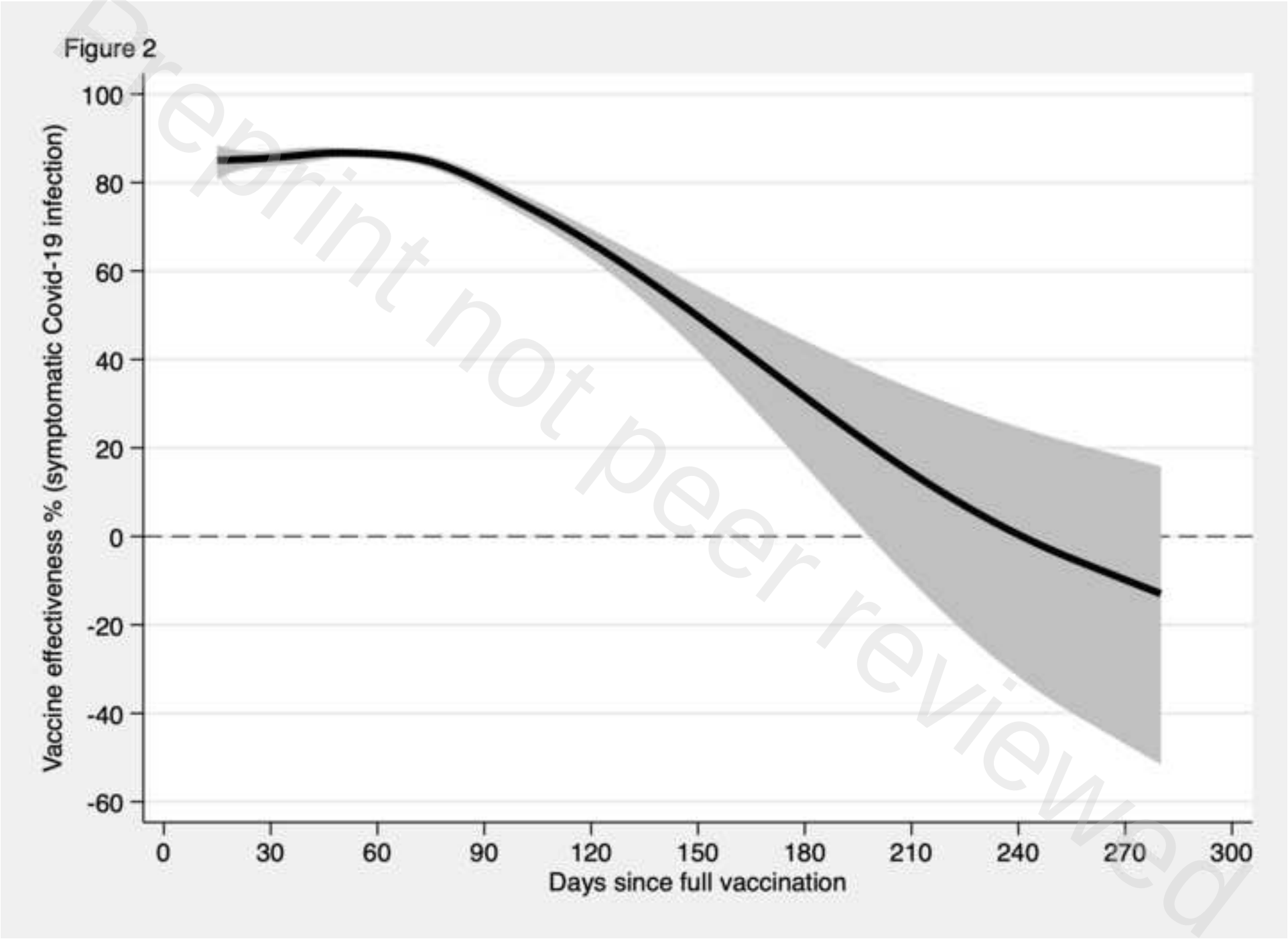
This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Figure 2

Click here to access/download;Figure;Figure 2 - Final.tif

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Preprint not peer reviewed



Click here to access/download;Figure;Figure S1 - Final.tif

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3949410

Preprint not peer reviewed