Observed protection against SARS-CoV-2 reinfection following a primary infection: A Danish cohort study using two years of nationwide PCR-test data

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Research in Context

Evidence before this study

We searched PubMed, bioRxiv and medRxiv preprint servers for publications on protection against SARS-CoV-2 reinfections between January 2020 and January 31, 2022, without applying language restrictions. The search terms we used were: "SARS-CoV-2" OR "COVID-19" OR "coronavirus" AND "reinfection" AND "protection". We included the search term “human” for articles published on the preprint servers bioRxiv and medRxiv. On PubMed we found 194 peer-reviewed articles, and after filtering by human studies we identified 119 publications on this topic. For preprint articles, we identified 1320 articles of which 421 and 899 were published on bioRxiv and medRxiv preprint servers, respectively. Based on two biological, six epidemiological and two large clinical studies on SARS-CoV-2 reinfections, including our previous cohort study, it was reported that protection against reinfection was consistently above 80% for all SARS-CoV-2 variants before the emergence of Omicron. In all of these studies, reinfections occurred in very few cases and was typically below 1%. Duration of this protective effect or prior infection was stable for a minimum of 10 months after initial infection. However, a recent report from the UK, including over 140,000 Delta and 6,000 Omicron cases showed that the protective effect of prior SARS-CoV-2 infection dropped to 19% compared to the Delta variant. The authors estimated that the likelihood of reinfection is 5.5 fold higher for Omicron compared to previous variants of SARS-CoV.2. In support of this report, another epidemiological study from Qatar showed that protection against SARS-CoV-2 variants dropped from 90% to 60% after the emergence of Omicron.

Added value of this study

Analysis of the unvaccinated Danish population since the beginning of the pandemic of SARS-CoV-2 until January 2022 revealed a consistently high protection of 83.5% from reinfection for Wuhan, and Alpha variants. However, protection diminished with time when Delta appeared and with the emergence of the Omicron variant in Denmark, the level of protection offered by previous infection with other variants was estimated at 43% after three months, declining to 22% after six months between the two infections. The protective effect was lower in elderly people but generally higher following a first symptomatic as opposed to asymptomatic infection.

Implications of all the available evidence

We found that protection against SARS-CoV-2 was sustained for more than one year based on the unvaccinated Danish population and was above 80%. However, we saw reduced protection against SARS-CoV2 with the emergence of new viral variants Alpha, Delta and, in particular, Omicron. This indicates that the observed reduction in protection against reinfection is largely driven by viral evolution rather than waning antibody levels. If these results holds true also for the Omicron variant, substantial protection at the population level might result from the many Omicron infections currently seen.

SUMMARY

Background The level of protection after a SARS-CoV-2 infection against reinfection and COVID-19 disease remains important with much of the world still unvaccinated.

Methods Analysing nationwide, individually referable, Danish register data including RT-PCR-test results, we conducted a cohort study using Cox regression to compare SARS-CoV-2 infection rates before and after a primary infection among still unvaccinated individuals, adjusting for sex, age and residency region. The prevalence of infections classified as symptomatic or asymptomatic was compared for primary infections and reinfections. The study also assessed protection against each of the main viral variants after an earlier variant primary infection by restricting follow-up time to distinct, mutually exclusive periods during which each variant dominated.

Findings Until 1 July 2021 the estimated protection against reinfection was 83.5% (95%CI: 82.2%–84.6%); but lower for the 65+ year-olds (72.0%; 95%CI: 56.1%–82.2%). First-time cases who reported no symptoms were more likely to experience a reinfection (OR: 1.48; 95%CI: 1.36–1.62). By autumn 2021, when infections were almost exclusively by the Delta variant, the estimated protection of a recent infection was 91.3% (95%CI: 89.7%–92.7%) compared to 71.3% (95%CI: 66.8%–75.2%) after a first infection over a year earlier. With Omicron, a first infection in the past 3-6 months gave an estimated 43.1% (95%CI: 41.6%-44.4%) protection, whereas a first infection longer than 12 months earlier provided only 14.6% (12.7-16.4%) protection.

Interpretation SARS-CoV-2 infection offered a high level of sustained protection against reinfection, comparable with that offered by vaccines, but decreased with the introduction of new main virus variants; dramatically so when Omicron appeared. Protection was lower among the elderly but appeared more pronounced following symptomatic compared to asymptomatic infections. Decreases in protection against reinfection, seemed primarily to be driven by viral evolution.

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INTRODUCTION

Two years into the pandemic, COVID-19 continues to have a pronounced effect on public health globally. Though mass vaccinations have been rolled out in high-income countries, a sizable proportion of the population may remain unvaccinated. In many low- and middle-income countries, many have not yet been offered vaccination. Immunity afforded by vaccination against infection is short-lived and increasingly so against newer variants such as Delta, and in particular, Omicron, which represents a major immune-evasion of SARS-CoV-2. One study from the UK showed that protection against reinfection fell from approximately 85% with earlier variants to 19% against Omicron infection[1]. This effect is associated with the ability of Omicron to evade neutralizing antibody responses elicited towards prior SARS-CoV-2 infection[2]. Understanding the longevity of the immune response to SARS-CoV-2 after natural infection and the protection conferred against subsequent infection and disease remains important.

Based on test data from Denmark from 2020, we have previously assessed the level of protection after a previous infection against re-infection to be 80% overall, though significantly lower among the elderly[3]. Studies worldwide have shown that reinfections with SARS-CoV-2 remain infrequent, with estimates of protection after a first infection ranging from 80-90% and lasting for at least 8-10 months[3-9]. However, the strength and duration of protection remain incompletely understood partly due to the limited follow-up time available since the beginning of the pandemic. Studies suggest that age and clinical severity are important factors contributing to the likelihood of becoming reinfected with SARS-CoV-2[3,5,10], although reinfections are likely to become increasingly more common as the pandemic progresses[11,12].

Community studies of reinfections are influenced by test intensity, vaccination coverage and viral variants in circulation in the setting under study, factors that are all well monitored in Denmark. The aim of the present study was therefore to make use of the Danish, national, individual level-identifiable test and vaccination records to, within the confines of an observational study, answer questions as to the overall level of protection including within distinct age groups, in particular the elderly, longevity of protection, severity of the reinfections and effect of main viral variants.

METHODS

Study design, data sources, and surveillance system

We used a cohort study design to analyse nationwide routinely collected, individual-level register data comprising the entire Danish population as the source population. Information on age, sex, vital status and area of residence was obtained from the Danish Civil Registration System and linked with person information from other data sources through the unique civil registry number assigned to all Danish residents[13].

Information on SARS-CoV-2 tests was obtained from the Danish Microbiology Database[14] which contains records on all RT-PCR-tests performed for SARS-CoV-2 in Denmark. The SARS-CoV-2 surveillance system and details of the Danish national, widely available, and free for all, testing system have been described previously[3]. We used data on all RT-PCR-tests done in Denmark, both those done within the national health-care system and the "TestCenter Denmark" system[3]. The capacity of this system was increased during 2021; by 1 July 2021 it encompassed approx. 300 test stations placed throughout the country. Throughout 2021, rapid antigen testing also became widely and freely available from public test stations but we did not include these tests because of the sub-optimal test performance offered by the various antigen tests used. Persons with positive antigen tests were encouraged to take a PCR-test for validation.

Person level information on vaccinations given, including dates and type of vaccine was collected from the Danish Vaccination Registry, which includes data on all vaccines administered against SARS-CoV-2 in Denmark[15]. Information on presence or absence of symptoms was obtained from the telephone contact tracing system operated by the Danish Patient Safety Authority. Cases have been contacted with the aim of breaking transmission chains and as part hereof, respondents were asked whether they had experienced any symptoms consistent with COVID-19. Person-level information on hospitalisation was obtained from the national SARS-CoV-2 surveillance system, based on information in the Danish National Patient

Registry[16]. A COVID-19 related hospitalisation was defined as any hospital admission occurring no earlier than two days before, and no later than 14 days after, a positive PCR-test.

For most of the pandemic, almost all RT-PCR positive samples in Denmark have been subjected to a variant-specific RT-PCR and/or whole-genome sequencing (WGS)[17], however person-level virus variant information was not used directly in the present study. Instead the study period was divided into five separate time intervals each dominated by one of the main virus variants as follows: Wuhan period: 1 February 2020 to 31 December 2020; Alpha period: 15 March to 30 June, 2021; Delta period: 15 July to 15 November, 2021; and Omicron period: 28 December, 2021 to 31 January, 2022. The intermediary transition period was left out.

This study was performed under the authority task of the Danish national infectious disease control institute, Statens Serum Institut. It used data from existing Danish national COVID-19 surveillance systems and did not require ethical approval.

Study population

We included all Danish residents above the age of 2 years with at least one PCR-test for SARS-CoV-2 (whether negative or positive) and who had not yet received their first SARS-CoV-2 vaccination at date of study inclusion. The date of study inclusion was 90 after the first PCR-test for SARS-CoV-2.

Statistical analyses

In our first time-to-event analysis, time was calculated from the date of study inclusion until the earliest of June 30, 2021, COVID-19 vaccination, emigration or death and was categorised as either pre-SARS-CoV-2 time (time until first positive PCR-SARS-CoV-2 test) or post-SARS-CoV-2 time (time from 90 days after first positive SARS-CoV-2 test). Outcomes were first positive SARS-CoV-2-test in the respective time categories.

Infection rates in the pre- and post-SARS-CoV-2 categories were analysed using Cox proportional hazards regression models and contrasts calculated as hazard ratios (HR). The model was adjusted for sex,

10-year age groups, and residency region (categorical variable with five levels), and using calendar time as the underlying time scale to control for temporal effects, e.g. on infection and testing rates, during the epidemic. Estimates of natural protection were calculated as 1–HR, analogous to the method of estimating vaccine effectiveness.

We further expanded the analysis to include interaction terms with age group (restricted to four age groups [2–<18, 18–<30, 30–<65, ≥65 years] to avoid strata with few events). This expansion allowed us to calculate a protective effect estimate separately for each age group, and to test for evidence of effect modification using a likelihood ratio test. However, to mitigate the influence of protracted primary infections that continue to result in positive PCR-tests beyond 90 days, and are relatively more common among those aged above 65 years, the age-stratified analyses were repeated with reinfection defined as a new positive PCR-test at least 180 days after the primary infection.

In a further analysis, we investigated the longevity of protection conferred by a past infection against subsequent main viral variants. We first examined protection conferred by infection with the original (Wuhan) SARS-CoV-2 strain, against a new infection with the Alpha variant. For this analysis, we restricted the study population described above to those with a first PCR-test for SARS-CoV-2 in the Wuhan period (*i.e*. in 2020). The date of study inclusion was 90 days after the date of the first PCR-test or 15 March, 2021, whichever was later.

Time was separated into five categories: (1) pre-SARS-CoV-2, *i.e.* time until the first positive SARS-CoV-2 test; and four post-SARS-CoV-2 time periods: (2) time from 90-179 days, (3) time from 180-269 days, (4) time from 270-359 days, and (5) time from 360 days onwards after the first positive test. The rate of infection in each of categories 2 to 5 were compared with that in category 1 during the Alpha period. Follow-up ended at the end of the Alpha period (on June 30, 2021) with earlier censoring as in the first analysis. To illustrate, a case who tested positive on 27 November, 2020 would contribute time in category 2 between 15 March and 25 May, 2021, and assuming no censoring or event, in category 3 between 26

May and 30 June, 2021. Time after an infection occurring in the Alpha period was not included in the analysis.

The analysis was then repeated to investigate protection against infection with Delta after a primary infection with the Alpha variant or the Wuhan strain. For this analysis, the dates of follow-up were changed to that of the 'Delta period' (see above) with participants required to have had a first PCR-test in the Wuhan or Alpha period (*i.e*. before 30 June 2020). Lastly the analysis was repeated to investigate protection against infection with Omicron after primary infection with the Wuhan, Alpha, or Delta strain, using the Omicron period for follow-up with participants required to have had a first PCR-test in the Wuhan, Alpha or Delta periods (*i.e*. before 15 November 2020).

Role of funding source

There was no funding source for this study.

RESULTS

The COVID-19 epidemic in Denmark, has been characterised by winter peaks, and four main viral variants (figure 1). For the estimation of overall protection against reinfection, including analysis by age group and presence of symptoms, we included all tests done between 1 February 2020 and 30 June 2021 (35 million) when the Alpha period was ending and overall vaccination coverage (at least one vaccination) was 57.2% (figure 1).

During this period, there were 134,006 incident cases in those without a previous infection compared with 722 cases among previously infected individuals. After adjusting for sex, age group and region of residence, the estimated protection against infection was 83.5% (95%CI: 82.2%–84.6%) among those who had previously tested positive (table 1). The result was practically unaffected when changing the definition of a reinfection to require at least 180 days between positive tests.

When stratifying the analysis by age group and using a definition of reinfection that requires at least 180 days between repeat positive tests, the estimated protection from a prior infection was similarly high across the younger age groups but lower (72.0%; 95%CI: 56.1%–82.2%) among those aged over 65 years (p= 0.112 for the interaction). When decreasing the minimal gap required between repeat positive tests from 180 to 90 days, the estimated protection from a prior infection among those aged above 65 years was considerably reduced whereas the estimates among the other age groups were only minimally affected (table 1). As the subsequent analyses include only very few elderly, non-vaccinated persons, we maintained the 90-days definition in these.

Among first-time cases, 56.9% (56.7%-57.1%) reported that they had experienced symptoms because of their infection whereas 41.9% (39.7%-44.0%) reported symptoms as a result of a second infection (table 2). First-time cases who reported no symptoms were nearly 50% more likely (OR: 1.48; 1.36–1.62) to experience a reinfection compared with symptomatic primary cases (table 2).

Next, we compared the levels of estimated protection for the time periods in which the main circulating variants, Alpha, Delta and Omicron contributed virtually all infections in Denmark. Details on the number and characteristics, including censoring, of participants contributing to each of the parts are shown in table 3. Protection against infection during the Alpha period was estimated at 86.6% (84.8%-88.2%) and 83.1% (79.9%-85.8%) respectively in months 4-6 and 7-9 after the primary infection (figure 2; table s1). Thereafter protection appeared initially to wane somewhat and then rebound, although the estimates after nine months were less reliably estimated due to smaller participant numbers and a reliance on reinfections among cases identified during the first months of the epidemic before PCR-testing became widely accessible.

During the four-month period in 2021 when the Delta variant accounted for virtually all SARS-CoV-2 infections in Denmark, those who had tested positive during 2020 or the first part of 2021 were less likely to become infected than were previously uninfected individuals. The protection was strongest among those with a recent primary infection and ranged from 93.3% (89.7%–92.7%) among cases with a first infection 3-6 months earlier to 71.3% (66.8%–75.2%) among cases with a first infection over a year earlier (figure 2; table s2). Prior infection was also seen to be highly protective against hospitalisation with the Delta variant (estimated protection: 91.3%; 95%CI: 83.8%–95.4%) with no noticeable evidence among the relatively few hospitalisations of waning over time (p=0.415).

Contrary to reinfections with the Wuhan, Alpha or Delta variants, a previous infection was not nearly as protective against a new infection with the Omicron variant (figure 2; table s3). Those with a primary infection in the past 3-6 months before the introduction of the Omicron variant were 43.1% (41.6%–44.4%) less likely to become infected with Omicron than those previously uninfected. Furthermore, the protective effect appeared to decline rapidly with time since the primary infection, to 22.2% (19.6–24.8%) or less after six months. In the Omicron period, prior infection was also less protective against hospitalisation (47.1%; 95%CI: 33.1%–58.2%) than in the Delta variant period.

DISCUSSION

We used person-level data from the Danish integrated COVID-19 surveillance system, including data on tests, vaccines, demographics, and self-reported symptoms to estimate protection against infection following a primary infection with SARS-CoV-2. In an unvaccinated population, we find the overall protection against a secondary infection to be around 83.5%, albeit lower among those above 65 years of age. Protection was higher in those undergoing a symptomatic primary infection compared to an asymptomatic infection, and symptoms less often presented during the course of the second infection. Diminishing protection with time was seen over the period in which the Delta variant was circulating, while when Omicron took over, previous infection offered only little protection against infection.

We found that protection was sustained for more than one year. This is in line with our previous study and other large observational cohort studies looking at the risk of reinfections among various populations, which have showed level of protection after natural infection above 80%, lasting for a minimum of 8-10 months [4,6,8,18,19]. However, we saw reduced protection during the period in which the Alpha variant was almost exclusively present, in the spring of 2021, and further reduced protection and clear signs of waning over time, during the period where the Delta variant predominated, from July to November 2021. After the introduction of Omicron into Denmark, protection against SARS-CoV-2 dropped sharply. This indicates that introduction of each new main variant, albeit only marginally for Alpha, resulted in lower overall protection against reinfection in the previously infected population. Ferguson and colleagues have calculated that the risk of reinfection for Omicron is 5.4 times greater than for Delta, highlighting the fact that viral variants of SARS-CoV-2 are able to escape at least some natural or vaccine-induced immune responses and that reinfections are becoming increasingly more common overall[1]. It should be noted, that we were not able to estimate the protection of Omicron against a previous Omicron infection, as not enough time has passed yet. Protective antibody levels against the Delta variant have been found to wane within 4-9 months or even less time after vaccination with two doses of the most predominant vaccines in use depending on the population[20] while a meta-analysis have showed that levels

of protection after either vaccination or natural infection are comparable[21]. Our study suggests that protection from natural infection is at least comparable to and possibly sustained for longer than vaccine-induced protection, but the inference is challenged by the real-life evolution of virus, which makes it hard to disentangle the different factors of waning immunity.

We found evidence that those with a symptomatic first infection compared with an asymptomatic first infection, were less likely to encounter a second infection. Additionally, the second infection generally led to a milder course of disease. This might be explained by serum anti-S antibodies levels, since mild or asymptomatic COVID-19 infection have been found to result in a rapid decline of antibodies within four months after infection[10]. Several other studies have showed that asymptomatic infections may lead to a lower immune response compared to symptomatic infections, and that people with severe disease mounted a higher antibody titer than for mild disease[7,22-24]. Furthermore a large retrospective cohort study revealed that prior infection protects against reinfection and symptomatic disease due to humoral and cellular immune responses[4].

Among people above the age of 65, we estimated the protection to be around 72% compared with 85% among the younger age groups. Based on data from 2020 only, we previously estimated protection among people above the age of 65 of just 47%[3]. With a larger dataset, we believe this to have been an underestimate caused by sustained illness among a subset of older individuals rather than actual reinfection. Elderly patients with serious underlying disease may host replicating virus and stay PCR-positive for a prolonged time post-infection, for some more than 3 months, due to the inability to clear virus. We found evidence of this in the data, in so far as increasing the time window definition, separating the first from the second infection from 3 months up to 6 months influenced the estimates for the above 65+ age groups but not the other age groups. Older age, immunosuppression and having a haematological disease is known to decrease the likelihood of seroconversion for SARS-CoV-2 and prolonged viral shedding[12,25,26]. Furthermore, increased age leads to a substantial reduction in peripheral naive immune cells, in particular naive T cells, and increased inflammation, which are both hallmarks of immunosenescence[27,28].

This study has limitations. Importantly, we analyse reinfections only among those not yet vaccinated. With time, this increasingly limits representativity of the study population relative to the source population. In the second half of 2021 and onwards, the unvaccinated population contained adults that for unknown reasons choose to opt out of the vaccination program and also contained many younger people, including children, who were either not eligible for vaccination or had been offered it late and therefore had lower coverage. Therefore, the behaviour of this unvaccinated group is potentially different from those vaccinated and this may alter the risk of immunity and reinfection. For the analyses including follow-up time after July 2021, focusing on the Delta and in particular the Omicron variants, bias may therefore have affected the analyses. To address this, we performed sub-analyses excluding persons under the age of 18 years, and saw even lower protection levels for Omicron. We find it likely that a bias will have affected the Omicron analysis, however believe the overall trends to be correct, i.e. that there was markedly lower protection provided against Omicron infections by an infection with previously circulating variants. A different potential limitation involves including repeat PCR positive cases not constituting true reinfections. To examine this, we performed additional analyses changing the interval between the suspected first and second infection episode from 90 to 180 days, obtaining similar results to our main analysis. Comparison of periods characterised by different circulating variants also limits the risk of repeat PCR-positive cases not being true reinfections. As a further limitation, data on whether symptoms were present were self-reported and not complete, and some respondents would have been contacted soon after testing positive via PCR and thus possibly before symptom onset.

Among the strengths of this study are the unusual size and quality of the data material. The analyses are based on data involving almost 60 million tests performed with a unified national set-up. Testing has been offered by the Danish state, has been free for all, widely available and test information recorded centrally. The Danish vaccination program has also been done by invitation to national test centres and similar to test data, vaccination data have been recorded in a person-identifiable format. This has allowed for a national cohort design, excluding those having received vaccination, by which we have been able to also study protection by age and its duration and to bring in national hospitalisation data. We further have

been able to use data sources on presences of symptoms collected from direct phone interviews, and of the proportion of different viral variants in circulation, stemming from the Danish large-scale national WGS programme[29].

In conclusion, our results imply that the level of protection after natural infection appears to be comparable with that offered by vaccines, both in terms of protection against infection and severe disease, but possibly lasting for longer. Protection was lower among the elderly and more pronounced following symptomatic compared to asymptomatic infections. Reduced protection was increasingly seen with the introduction of new main virus variants, and protection dramatically reduced for Omicron infections. This indicate that reduction of immunity is largely driven by microbial evolution rather than waning of the initial immunological response to infection. This is important knowledge for health authorities planning the epidemic response to future emerging new variants of concern.

CONTRIBUTIONS

SE, CHH and DM conceived the idea for the study and provided methodological input. PVB, PB, NO, CHM, FTM, RL, BD, KM, DM and CHH provided further input into the methodology and study design. CHH did the statistical analyses and SMG verified the underlying data. DM, CHH, and SE wrote the first draft of the manuscript. SMG and her team at SSI developed and maintained the data management systems for surveillance. All authors had full access to the data and contributed to interpreting the data and writing of the manuscript. CHH and SMG accessed and verified the underlying data for the study. All authors approved the final version and had final responsibility for the decision to submit for publication.

DECLARATION OF INTERESTS

All authors declare no competing interests.

DATA SHARING

Health data are considered person-sensitive, and normally cannot be shared due to data protection regulations. Part of the data can however, be made available for access to members of the scientific and medical community for non-commercial use only, in a de-identified format by contacting the authors.

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Age at start of follow-up	Population	Person-years of follow-up	Positive SARS-CoV-2 test during follow-up	Infection rate$ during follow-up	Adjusted‡ hazard ratio (95%CI)	Estimated natural protection from prior infection
Reinfection defined as a new positive PCR-test 90+ days after primary infection						
Any age, ≥2 years						
No prior infection	4,060,409	1,776,714	134,006	75.42	-	-
Previously infected	199,964	57,812	722	12.49	0.165 (0.154–0.178)	83.5% (82.2–84.6%)
2-17 years						p < 0.001 *
No prior infection	788,531	359,921	24,114	67.00	1	-
Previously infected	41,339	12,106	120	9.91	0.148 (0.124; 0.178)	85.2% (82.2; 87.6%)
18-29 years						
No prior infection	747,532	364,391	38,896	106.74	1	-
Previously infected	48,680	15,069	219	14.53	0.143 (0.125; 0.163)	85.7% (83.7; 87.5%)
30-64 years						
No prior infection	1,944,867	859,499	62,686	72.93	1	-
Previously infected	94,996	27,453	302	11.00	0.159 (0.142; 0.178)	84.1% (82.2; 85.8%)
65+ years						
No prior infection	579,479	192,902	8,310	43.08	1	-
Previously infected	14,949	3,184	81	25.44	0.642 (0.516; 0.799)	35.8% (20.1; 48.4%)
Reinfection defined as a new positive PCR-test 180+ days after primary infection						
Any age, ≥2 years						
No prior infection	3,156,094	882,282	67,345	76.33	-	-
Previously infected	119,077	17,506	258	14.74	0.171 (0.151–0.193)	82.9% (80.7–84.9%)
2-17 years						p=0.112 *
No prior infection	671,683	181,718	11,075	60.95	1	-
Previously infected	28,559	3,392	38	11.20	0.170 (0.124; 0.234)	83.0% (76.6; 87.6%)
18-29 years						
No prior infection	635,515	192,776	20,583	106.77	1	-
Previously infected	33,616	4,658	94	20.18	0.179 (0.147; 0.220)	82.1% (78.0; 85.3%)
30-64 years						
No prior infection	1,499,081	430,527	31,923	74.15	1	-
Previously infected	52,529	8,447	107	12.67	0.154 (0.127; 0.186)	84.6% (81.4; 87.3%)
65+ years						
No prior infection	350,621	77,494	3,785	48.84	1	-
Previously infected	4,388	1,012	19	18.77	0.280 (0.178; 0.439)	72.0% (56.1; 82.2%)

Notes: Participants remained in follow-up until the date of their first vaccination, death, out-migration, a positive SARS-CoV-2 PCR-test or the end of the follow-up period (30 June 2021). Some participants contributed initially with unexposed follow-up time and, subsequently after infection, with exposed follow-up time. $ rate of infection per 1,000 person-years of follow-up. ‡from a Cox regression model controlling for sex, age group and country region. *multivariate Wald test for effect heterogeneity across age strata.

Table 1: Comparison of SARS-CoV-2 infection rates before and after a first infection until 30 June 2021.

	Total	% symptomatic on first infection (95%CI)	Total experiencing reinfection	Adjusted odds ratio* (95%CI)	Total with symptomatic reinfection	% symptomatic on reinfection (95%CI)
All	247,087		1,989 (0.80%)		833	41.9% (39.7-44.0%)
Asymptomatic first infection	106,593		1,056 (0.99%)	1.48 (1.36; 1.62)	392	37.1% (34.2-40.0%)
Symptomatic first infection	140,494	56.9% (56.7-57.1%)	933 (0.66%)	-	441	47.3% (44.1-50.5%)

Notes: Data collected between 1 February, 2020 and 15 November, 2021

* Comparing odds of reinfection among those with asymptomatic versus symptomatic primary infection: odds ratio adjusted for sex, age group and country region.

Table 2: Self-reports of COVID-19 symptoms elicited during contact tracing telephone conversations with recent SARS-CoV-2 PCR-confirmed cases.

	Alpha period		Delta period		Omicron period	
	No prior infection	**Previously infected**	**No prior infection**	**Previously infected**	**No prior infection**	**Previously infected**
Total	3,201,224 (100)	142,877 (100)	1,324,932 (100)	115,022 (100)	499,614 (100)	82,022 (100)
Age (years)						
median (IQR)	36 (20 to 54)	32 (19 to 50)	17 (9 to 31)	23 (12 to 34)	12 (5 to 31)	20 (9 to 32)
min – max	2-100+	2-100+	2-100+	2-100+	2-100+	2-100+
Female	1,613,091 (50)	69,275 (48)	664,471 (50)	56,752 (49)	243,553 (49)	40,510 (49)
Censored due to						
death	2,189 (0)	78 (0)	1,042 (0)	48 (0)	170 (0)	5 (0)
emigration	3,735 (0)	249 (0)	3,517 (0)	278 (0)	295 (0)	33 (0)
vaccination	1,746,349 (55)	69,703 (49)	541,553 (41)	43,133 (38)	27,842 (6)	4,538 (6)
study end	1,399,092 (44)	72,446 (51)	726,192 (55)	70,411 (61)	349,614 (70)	60,723 (74)
infection	49,859 (2)	401 (0)	52,628 (4)	1,152 (1)	121,693 (24)	16,723 (20)

Notes: Data shown are number (percentage) unless otherwise specified.

Table 3: Number and characteristics of participants contributing to the analysis of protection against infection with the Alpha, Delta, and Omicron SARS-CoV-2 variants following a prior infection with an earlier variant.

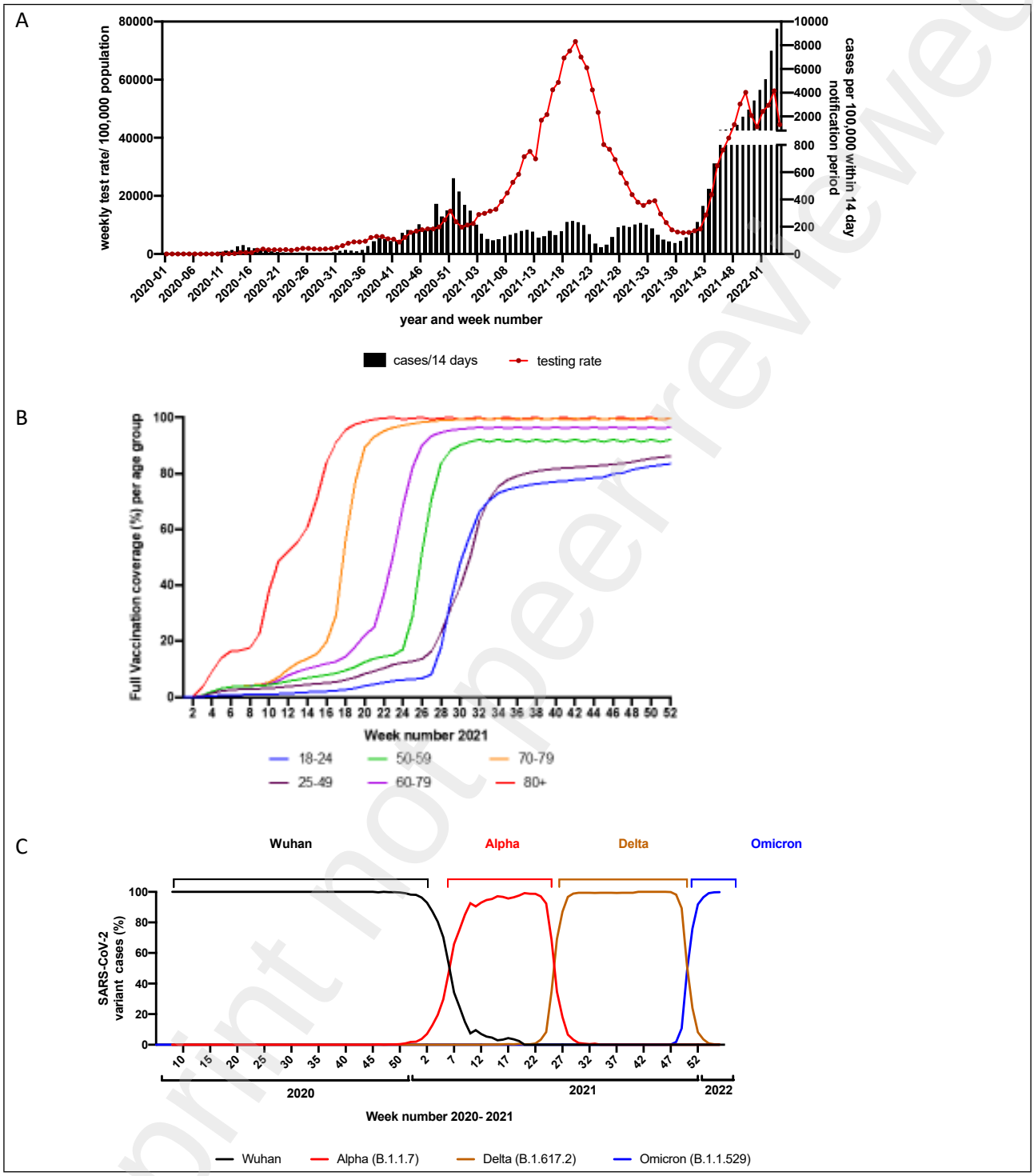

Figure 1: **Fortnightly incidence of SARS-CoV-2 infections and weekly test rate (A) over the course of the epidemic in Denmark (A), vaccination coverage by age group in 2021 (B) and the percentage of the main variants, Wuhan, Alpha, Delta and Omicron circulating in Denmark over the course of the epidemic (C).**

For the analysis, four main variant periods were defined: Wuhan: 1 February - 31 December 2020; Alpha: 15 March - 30 June 2021, Delta: 15 July - 15 November 2021, and Omicron: 28 December, 2021 - 31 January, 2022.

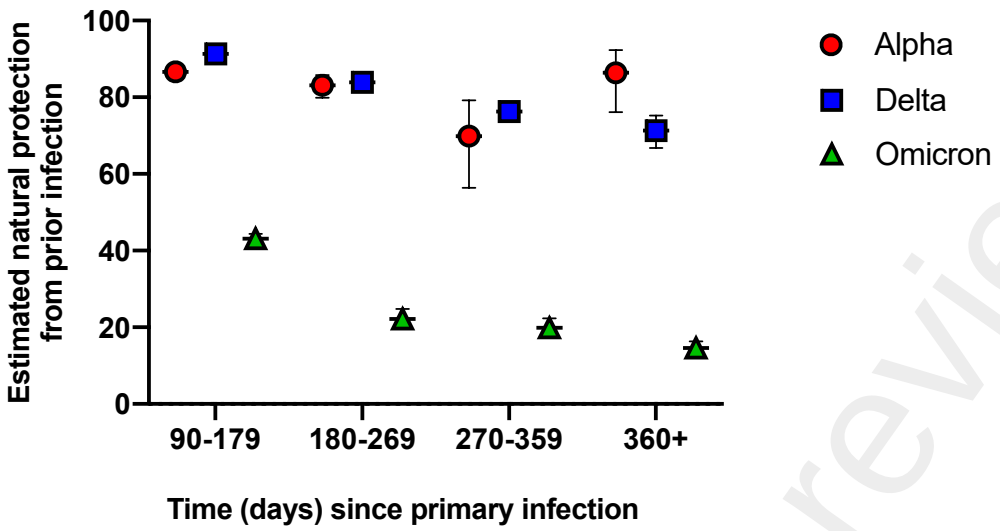

Figure 2: **Natural protection among unvaccinated individuals against infection with Alpha (red dots), Delta (blue dots) or Omicron (green dots) variants after primary infection with an earlier SARS-CoV-2 variant.**