



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

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## 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, comorbidity and residency region. Estimates of protection against infection were calculated as 1 minus the hazard ratio. Estimates of protection against symptomatic infections and infections leading to hospitalisation were also calculated. 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 a primary infection with an earlier variant 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 83.4% (95%CI: 82.2–84.6%); but lower for the 65+ year-olds (72.2%; 95%CI: 53.2–81.0%). Moderately higher estimates were found for protection against symptomatic disease, 88.3% overall (95%CI: 85.9–90.3%). First-time cases who reported no symptoms were more likely to experience a reinfection (odds ratio: 1.48; 95%CI: 1.35–1.62). By autumn 2021, when infections were almost exclusively caused by the Delta variant, the estimated protection following a recent first infection was 91.3% (95%CI: 89.7–92.7%) compared to 71.4% (95%CI: 66.9–75.3%) after a first infection over a year earlier. With Omicron, a first infection with an earlier variant in the past 3–6 months gave an estimated 51.0% (95%CI: 50.1–52.0%) protection, whereas a first infection longer than 12 months earlier provided only 19.0% (95%CI: 17.2–20.5%) protection. Protection by an earlier variant-infection against hospitalisation due to a new infection was estimated at: 86.6% (95%CI: 46.3–96.7%) for Alpha, 97.2% (95%CI: 89.0–99.3%) for Delta, and 69.8% (95%CI: 51.5–81.2%) for the Omicron variant.

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**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. The level of estimated protection against serious disease was somewhat higher than that against infection and possibly longer lasting. Decreases in protection against reinfection, seemed primarily to be driven by viral evolution.

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**Keywords:** COVID-19; Cohort studies; Immunity; Reinfection; Herd immunity; SARS-CoV-2 variants; Epidemic

### 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". We included the search term "human" for articles published on the preprint servers bioRxiv and medRxiv. On PubMed we found 966 peer-reviewed articles, and after filtering by human studies we identified 642 publications on this topic. For preprint articles, we identified 1757 articles of which 552 and 1205 were published on bioRxiv and medRxiv, respectively. Epidemiological studies have consistently shown that protection elicited towards SARS-CoV-2 is high, over 80%, after natural infection and protects not only against reinfection but also against symptomatic and severe disease. However, preliminary data suggest that the Omicron variant of SARS-CoV-2 may evade immunity from prior infection and potentially result in a sharp increase in reinfection cases worldwide. Specifically one population-based study from Qatar showed that protection against SARS-CoV-2 variants dropped from 90% to 60% after the emergence of Omicron. However, large cohort studies revealed that reinfections are associated with less severe disease, lower viral loads and decreased infectiousness. Duration of this protective effect after prior infection was stable for over one year after initial infection, with increasingly waning antibody levels over time.

#### *Added value of this study*

Analysis of the unvaccinated Danish population since the beginning of the pandemic until March 2022 revealed a consistently high protection of 83% from reinfection for the Wuhan, and Alpha variants, increasing to 88% when estimated among symptomatic infections. 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

51% after three months, declining to 25% 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%. Better protection against serious disease was seen than against infection. However, we saw reduced protection against SARS-CoV-2 with the emergence of new viral variants Delta and, in particular, Omicron. The results indicate that viral evolution is an important factor for understanding protection against reinfection in the context of cellular and humoral immunity.

### 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 detectable for at least 6–8 months following vaccination but the emergence of new variants of concern for SARS-CoV-2 has resulted in a drop in protection against infection due to major immune-evasion of SARS-CoV-2.<sup>1</sup> Several studies have shown that the emergence of the Omicron variant has resulted in an increased risk of reinfection.<sup>2,3</sup> However studies from Qatar found that natural immunity confers protection against transmission of infection and prevents against symptomatic reinfection.<sup>4,5</sup> In particular the T cell immune response against SARS-CoV-2 was retained and robust against the Omicron variant and likely contributes to less severe COVID-19 infection.<sup>6</sup> Thus,

cellular as well as humoral factors of the immune system are critical for protection against SARS-CoV-2 infection and COVID-19 disease.<sup>6</sup>

Based on test data from Denmark from 2020, we have previously assessed the level of protection after a first infection against reinfection to be 80% overall, though significantly lower among the elderly.<sup>7</sup> Studies worldwide have shown that reinfections with SARS-CoV-2 remain infrequent, with estimates of protection after a first infection ranging from 80% to 90% and lasting for over one year.<sup>8,9</sup> 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,<sup>7,10</sup> although reinfections are likely to become increasingly more common as the pandemic progresses.<sup>2,11,12</sup>

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 and 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.<sup>13</sup>

Information on SARS-CoV-2 tests was obtained from the Danish Microbiology Database<sup>14</sup> 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 testing system have been described previously.<sup>7</sup> 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.<sup>7</sup> The capacity of this system was increased during 2021; by 1 July 2021 it encompassed approximately 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 performance offered by the various antigen tests used. Persons with positive antigen tests were encouraged to take a PCR test for validation. In our data, approximately 87% of people with a positive antigen test (who do not have a positive PCR test in the past month) proceeded to have a confirmatory PCR test within a week.

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.<sup>15</sup> Information on the presence or absence of symptoms was obtained from the telephone contact tracing system operated by the Danish Patient Safety Authority. Cases were 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 and comorbidities was obtained from the national SARS-CoV-2 surveillance system, based on information in the Danish National Patient Registry.<sup>16</sup> A COVID-19 related hospitalisation was defined as a hospital admission associated with ICD-10 primary diagnosis codes B342A or B972A occurring no earlier than two days before, and no later than 14 days after a positive RT-PCR test. Each of the following comorbidities was recorded as either present or absent and a count was calculated for each person indicating the total number of comorbidities: diabetes, adiposity, haematological and other cancers, neurological diseases, kidney diseases cardiovascular diseases, chronic pulmonary diseases, respiratory diseases and immune deficiency conditions.

For most of the pandemic, almost all RT-PCR positive samples in Denmark have been subject to a variant-specific RT-PCR and/or whole-genome sequencing,<sup>17</sup> however person-level virus variant information was not used directly in the present study. Instead the study period was divided into four separate time intervals each dominated by one of the main virus variants as follows: Index (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: 1 January to 10 March, 2022. The intermediary transition periods were left out of the analysis.

This study was performed under the authority task of the Danish national infectious disease control institute, the Statens Serum Institut. It used data from existing Danish national COVID-19 surveillance systems and did not require ethical approval nor individual consent.

### 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 the date of study inclusion.

### Statistical analyses

In our first time-to-event analysis, denoted as Analysis A, time was calculated from the date of study inclusion until the earliest of June 30, 2021, COVID-19 vaccination, emigration, death or outcome and was categorised as either pre-SARS-CoV-2 time (time until first positive RT-PCR SARS-CoV-2 test) or post-SARS-CoV-2 time (time from 90 days after the first positive SARS-CoV-2 test). Outcomes were first positive SARS-CoV-2-test in the respective time categories. We selected 90 days as time window between two SARS-CoV-2 infections based on the case definition of SARS-CoV-2 reinfections, established in the majority of countries in the European Region.<sup>18</sup>

Infection rates in the pre- and post-SARS-CoV-2 categories were analysed using Cox proportional hazards regression models with prior SARS-CoV-2 infection included as a time-updated exposure, and contrasts calculated as hazard ratios (HR). The model was adjusted for sex, 10-year age groups, number of comorbidities (categorical variable with four levels indicating 0, 1, 2 or 3+ comorbidities) 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  $1 - \text{HR}$ , analogous to the method of estimating vaccine effectiveness.<sup>27</sup>

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 multivariate Wald test. However, to mitigate the influence of protracted primary infections that continue to result in positive RT-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 RT-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 refer to this as Analysis B. 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 RT-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 RT-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 to 179 days, (3) time from 180 to 269 days, (4) time from 270 to 359 days, and (5) time from 360 days onwards after the first positive test. The rate of reinfection in each of categories 2 to 5 was compared with the rate of infection 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 Index (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 prior to the beginning of this period (*i.e.* before 30 June 2020). Lastly the analysis was repeated to investigate protection against infection with Omicron after a primary infection with the Index, Alpha, or Delta strain, using the Omicron period for follow-up with participants required to have had a first RT-PCR test before the emergence of Omicron (*i.e.* before 15 November 2020).

### Protection against symptomatic reinfection

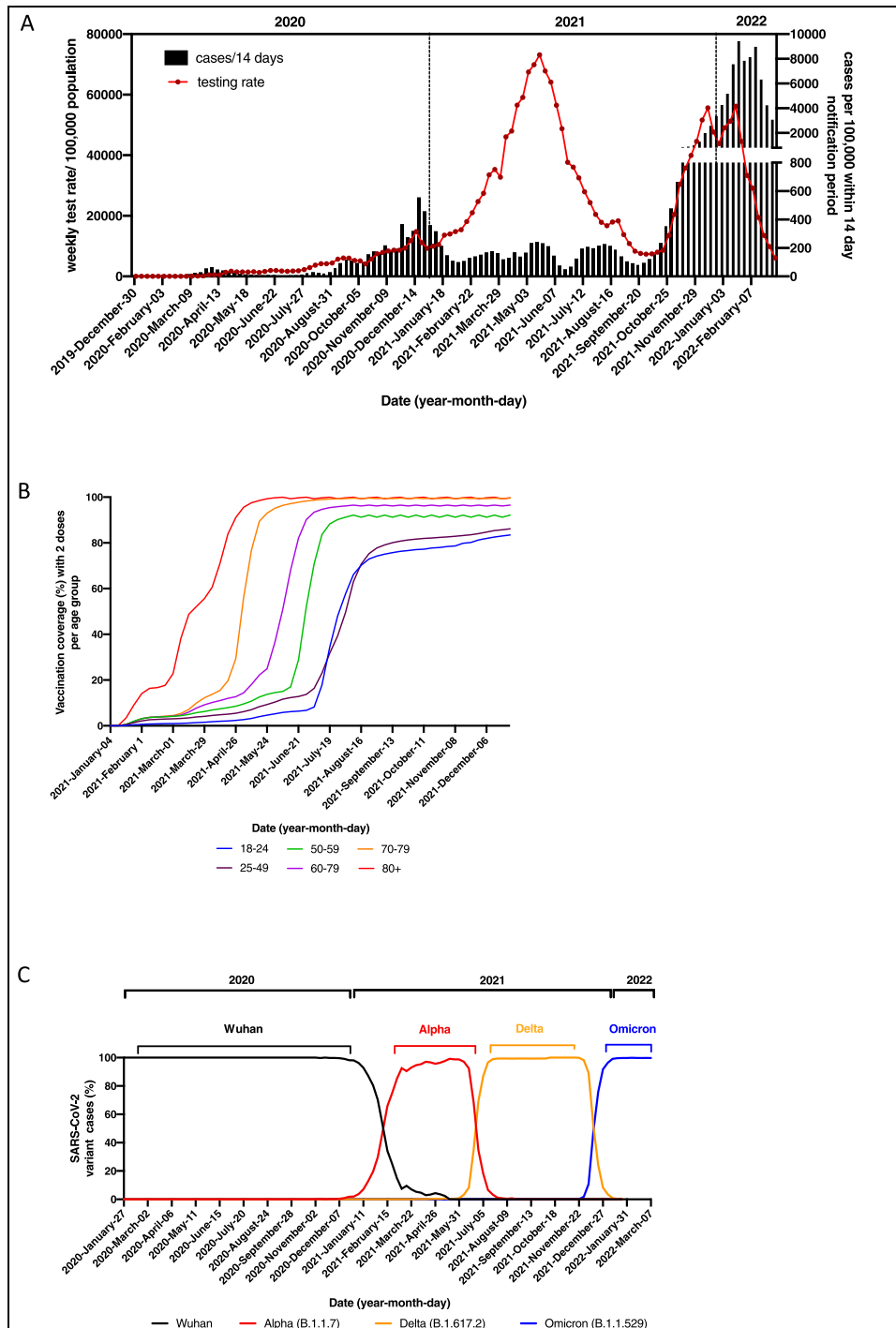
Analysis B was repeated with symptomatic infection as the outcome event of interest rather than any infection. During the period when Alpha and Delta were the predominant variants, 97.8% and 90.0% of cases, respectively, responded to the questions regarding symptoms; however only 18.4% of cases responded during the Omicron period as the Patient Safety Authority was struggling to make contact with the many daily cases infected during this period. To account for the missing symptomatology responses, we used multiple imputation based on a logistic regression prediction model with sex, age group, region, week number, number of comorbidities and previous infection (yes/no) included in the linear predictor. For this we used the MI procedure in SAS with the logistic option of the monotone statement. For each of the three periods ten imputed datasets were created and analysed separately in the Cox regression model. The resultant set of ten log hazard ratios (and their standard errors) were combined using the standard rules as implemented in the MIanalyze procedure in SAS.

### Role of funding source

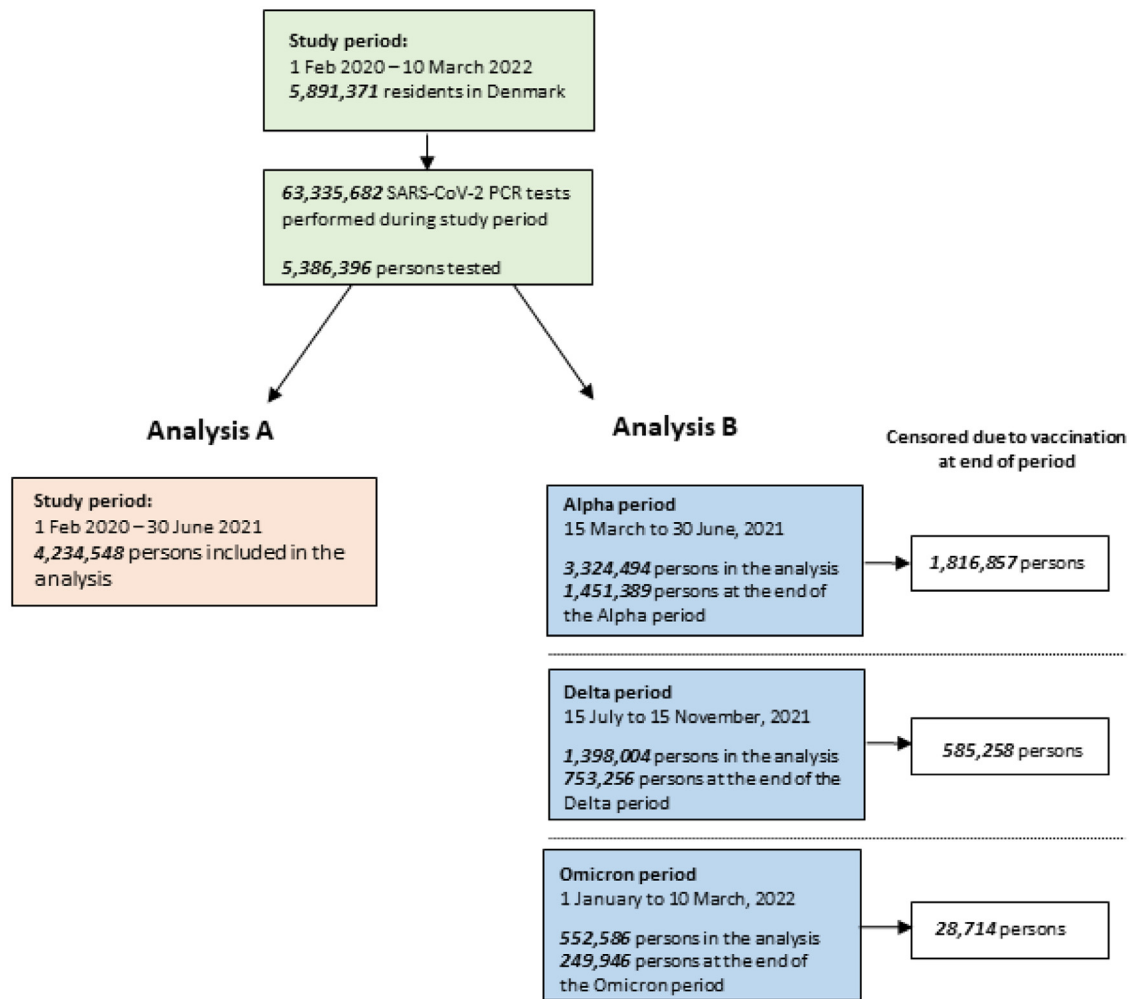
There was no funding source for this study.

### Results

The COVID-19 epidemic in Denmark, has been characterised by winter peaks and four main viral variants (Figure 1).



**Figure 1.** Incidence of SARS-CoV-2 infections and weekly test rate over the course of the epidemic in Denmark (A), vaccination coverage by age group in 2021 (B), and the percentage of the main variants, Index (Wuhan), Alpha, Delta and Omicron, circulating in Denmark over the course of the epidemic (C). Vaccine coverage curves (Panel B) were calculated as per the first dose of vaccination given. For the variant analysis (Panel C), four main variant periods were defined: Index: 1 February – 31 December 2020; Alpha: 15 March – 30 June 2021, Delta: 15 July – 15 November 2021, and Omicron: 1 January – 11 March, 2022.



**Figure 2.** Schematic diagram outlining the two different analyses performed and showing the number of participants in each study cohort.

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 the overall vaccination coverage (at least one vaccination) was 57.2% (Figures 1 and 2).

During this period, there were 133,300 incident cases in those without a previous infection compared with 720 cases among previously infected individuals. After adjusting for sex, age group, region of residence and major comorbidities, the estimated protection against reinfection was 83.4% (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 (70.2%; 95% CI: 53.2–81.0%) among those aged over 65 years ( $p=0.047$  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). Repeating the analysis, censoring out people that reported that they had not had symptoms when testing positive, gave marginally higher estimated protection from prior infection overall. The estimate for persons above the age of 65 years was now less extreme, though the confidence intervals were broad for this group (Table S1). For the analysis on hospitalisations, see below, potentially involving fragile and elderly persons, we used the 180-day definition,

Age at start of follow-up	Population	Person-years of follow-up	Positive SARS-CoV-2 test during follow-up	Infection rate <sup>§</sup> during follow-up	Adjusted hazard ratio (95%CI)	Estimated natural protection from prior infection
<i>Reinfection defined as a new positive PCR test 90+ days after primary infection</i>						
Any age, ≥2 years						
No prior infection	4,035,731	1,766,345	133,300	75.47	-	-
Previously infected	198,817	57,514	720	12.52	0.166 (0.154–0.178)	83.4% (82.2–84.6%)
						<i>p</i> < 0.001*
2–17 years						
No prior infection	806,780	367,840	27,390	74.46	1	-
Previously infected	43,785	12,806	136	10.62	0.143 (0.121; 0.169)	85.7% (83.1; 87.9%)
18–29 years						
No prior infection	747,397	364,661	37,444	102.68	1	-
Previously infected	47,913	14,856	213	14.34	0.147 (0.128; 0.168)	85.3% (83.2; 87.2%)
30–64 years						
No prior infection	1,928,809	849,098	60,813	71.62	1	-
Previously infected	93,195	26,863	294	10.94	0.160 (0.143; 0.180)	84.0% (82.0; 85.7%)
65+ years						
No prior infection	552,745	184,746	7,653	41.42	1	-
Previously infected	13,924	2989	77	25.76	0.667 (0.533; 0.835)	33.3% (16.5; 46.7%)
<i>Reinfection defined as a new positive PCR test 180+ days after primary infection</i>						
Any age, ≥2 years						
No prior infection	3,137,660	877,494	66,973	76.32	-	-
Previously infected	118,440	17,437	258	14.80	0.172 (0.152–0.194)	82.8% (80.6–84.8%)
						<i>p</i> =0.047*
2–17 years						
No prior infection	687,954	185,296	13,012	70.22	1	-
Previously infected	30,206	3553	47	13.23	0.173 (0.130; 0.230)	82.7% (77.0; 87.0%)
18–29 years						
No prior infection	633,383	193,311	19,655	101.68	1	-
Previously infected	33,154	4628	91	19.66	0.185 (0.150; 0.227)	81.5% (77.3; 85.0%)
30–64 years						
No prior infection	1,480,412	424,381	30,811	72.60	1	-
Previously infected	50,938	8283	101	12.19	0.150 (0.124; 0.183)	85.0% (81.7; 87.6%)
65+ years						
No prior infection	335,911	74,506	3495	46.91	1	-
Previously infected	4,142	974	19	19.51	0.298 (0.190; 0.468)	70.2% (53.2; 81.0%)

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

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.

<sup>§</sup> rate of infection per 1000 person-years of follow-up.

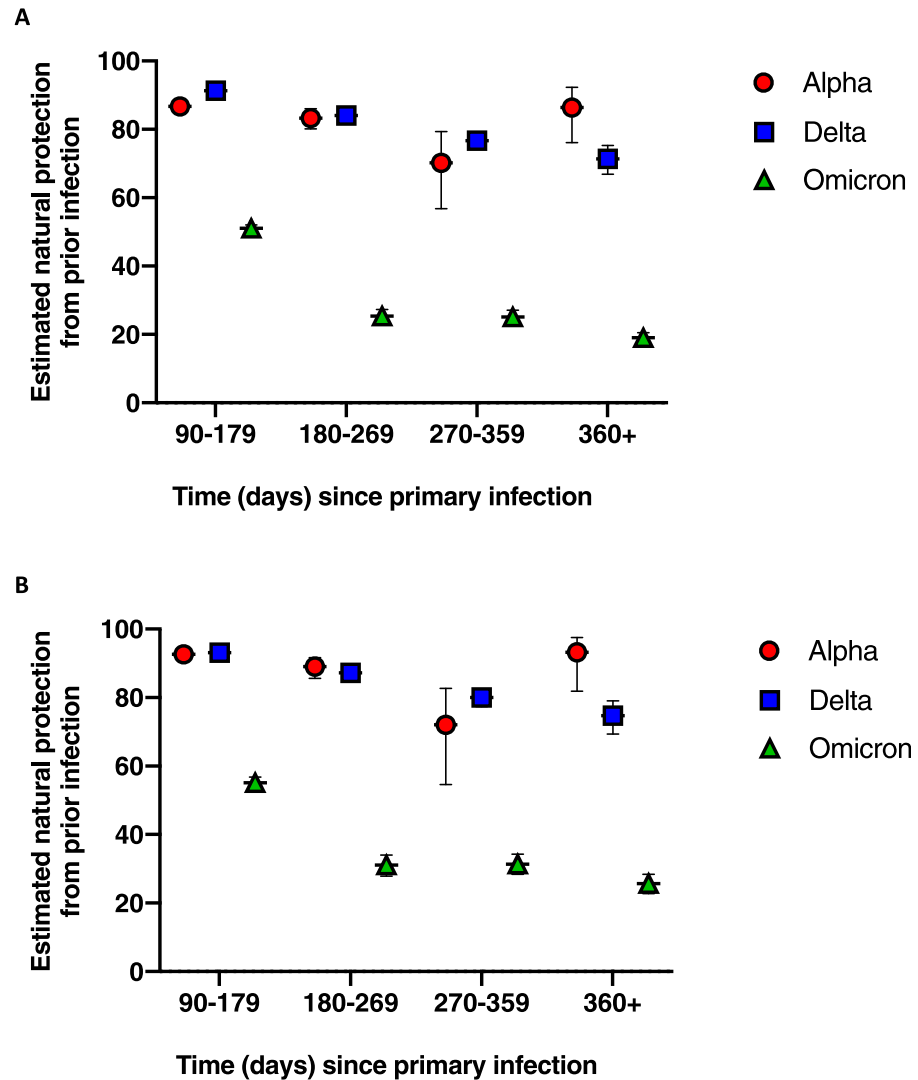
<sup>‡</sup> from a Cox regression model controlling for sex, age group, number of comorbidities and country region.

\* multivariate Wald test for effect heterogeneity across age strata.

however, for the subsequent analyses on protection against infection, which included only very few elderly, non-vaccinated persons, we maintained the 90-days definition.

Among first-time cases, 57.0% (56.8–57.2%) reported that they had experienced symptoms because of their infection whereas 42.1% (39.9–44.3%) reported symptoms as a result of a second infection (Table S2). First-time cases who reported no symptoms were nearly 50% more likely (OR: 1.48; 1.35–1.62) to experience a reinfection compared with symptomatic primary cases (Table S2).

Next, for analysis B, we compared the levels of estimated protection in the time periods in which the main circulating variants, Alpha, Delta and Omicron contributed to 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 S3. Protection against infection during the Alpha period was estimated at 86.7% (84.9–88.3%) and 83.3% (80.1–86.0%), respectively, in months 4–6 and 7–9 after the primary infection. Thereafter, protection appeared initially to wane somewhat and then rebound, although the estimates after nine months



**Figure 3.** (A) Natural protection among unvaccinated individuals against infection with Alpha (red dots), Delta (blue rectangles) or Omicron (green triangles) variants after primary infection with an earlier SARS-CoV-2 variant. (B) Natural protection against symptomatic infection for the same three variants of SARS-CoV-2 following a prior infection. The vertical bars represent the 95% confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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 (Figure 3; Table 2). In a further analysis, we estimated the protection against a SARS-CoV-2 infection leading to hospitalisation. Overall, reinfections associated with hospitalisations occurred only rarely (Table 3). Prior infection was seen to protect against hospitalisation at an estimated level of 86.6% (46.3–96.7%) (Table 3).

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 those who were previously uninfected. The protection was strongest among those with a recent primary infection and ranged from 91.3% (89.7–92.7%) among cases with a first infection 4–6 months earlier to 71.4% (66.9–75.3%) among cases with a first infection over a year earlier (Figure 3; Table 2). Prior infection was also seen to be highly protective against hospitalisation with the Delta variant (estimated protection: 97.2%; 95%CI: 89.0–99.3%) (Table 3).

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 3; Table 2). Those with a primary infection



Category	Population	Person-years of follow-up	Positive SARS-CoV-2 test during follow-up	Infection rate <sup>§</sup> during follow-up	Adjusted hazard ratio (95% CI)	Estimated natural protection from prior infection
<b>Alpha variant<sup>a</sup></b>						
Overall						
Unexposed (no prior infection)	3,182,235	738,207	49,767	67.4	-	-
Exposed (previously infected)	142,259	34,491	405	11.7	0.148 (0.134; 0.163)	85.2% (83.7; 86.6%)
Time since primary infection				<i>p</i> < 0.001*		
90–179 days	126,991	21,900	238	10.9	0.133 (0.117; 0.151)	86.7% (84.9; 88.3%)
180–269 days	105,095	10,153	127	12.5	0.167 (0.140; 0.199)	83.3% (80.1; 86.0%)
270–359 days	16,952	1314	28	21.3	0.298 (0.206; 0.432)	70.2% (56.8; 79.4%)
360+ days	7044	1126	12	10.7	0.136 (0.077; 0.239)	86.4% (76.1; 92.3%)
<b>Delta variant<sup>b</sup></b>						
Overall						
Unexposed (no prior infection)	1,284,431	276,851	53,311	192.6	-	-
Exposed (previously infected)	113,573	27,081	1171	43.2	0.179 (0.169; 0.190)	82.1% (81.0; 83.1%)
Time since primary infection				<i>p</i> < 0.001*		
90–179 days	48,528	7377	131	17.8	0.087 (0.073; 0.103)	91.3% (89.7; 92.7%)
180–269 days	84,474	9872	356	36.1	0.160 (0.144; 0.178)	84.0% (82.2; 85.6%)
270–359 days	51,838	7989	502	62.8	0.233 (0.213; 0.254)	76.7% (74.6; 78.7%)
360+ days	15,917	1844	182	98.7	0.286 (0.247; 0.331)	71.4% (66.9; 75.3%)
<b>Omicron variant<sup>c</sup></b>						
Overall						
Unexposed (no prior infection)	450,714	51,498	238,759	4636.3	-	-
Exposed (previously infected)	101,872	11,411	34,007	2980.1	0.666 (0.658; 0.673)	33.4% (32.7; 34.2%)
Time since primary infection				<i>p</i> < 0.001*		
90–179 days	55,201	4795	10,631	2217.3	0.490 (0.480; 0.499)	51.0% (50.1; 52.0%)
180–269 days	24,306	1718	5540	3223.8	0.746 (0.727; 0.767)	25.4% (23.3; 27.3%)
270–359 days	18,730	1560	5464	3502.8	0.749 (0.729; 0.769)	25.1% (23.1; 27.1%)
360+ days	29,272	3340	12,372	3704.7	0.810 (0.795; 0.828)	19.0% (17.2; 20.5%)

**Table 2: Natural protection among unvaccinated individuals against infection with the Alpha, Delta or Omicron variant following prior infection with an earlier SARS-CoV-2 variant.**

Notes: A reinfection was defined as a new positive PCR test at least 90 days after the primary infection. Participants were aged 2+ years, were COVID-19 unvaccinated and 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 follow-up.

<sup>§</sup> Rate of infection per 1000 person-years of follow-up.

\* Likelihood ratio test for effect heterogeneity.

<sup>‡</sup> From a Cox regression model controlling for sex, age group, residency region and numbers of comorbidity.

<sup>a</sup> Participants were followed up during the period from 15 March to 30 June, 2021, during which the Alpha variant was dominant in Denmark.

<sup>b</sup> Participants were followed up during the period from 15 July to 15 November, 2021, during which the Delta variant was dominant in Denmark.

<sup>c</sup> Participants were followed up during the period from 1 January to 10 March, 2022, during which the Omicron variant was dominant in Denmark.

in the past 3–6 months before the introduction of the Omicron variant were 51.0% (50.1–52.0%) 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 25.4% (23.3–27.3%) or less after six months. In the Omicron period, prior infection was also somewhat less protective against

hospitalisation (69.8%; 51.5–81.2%) than in the Delta variant period (Table 3).

The above analyses were repeated with the outcome event of interest changed to symptomatic infection as opposed to any (symptomatic or asymptomatic) infection using multiple imputation to adjust for missing data. The results from these analyses indicated slightly better protection compared with the level of protection

Analysis period	Population	Person-years of follow-up	SARS-CoV-2 associated admissions during follow-up*	Hospitalisation rate <sup>‡</sup> during follow-up	Adjusted hazard ratio (95% CI)	Estimated natural protection from prior infection
March 15 – June 30, 2021. Dominant variant: Alpha						
No prior infection	2,889,876	549,870	732	1.33	-	-
Previously infected	113,702	12,634	2	0.16	0.134 (0.033; 0.537)	86.6% (46.3; 96.7%)
July 15 – November 15, 2021. Dominant variant: Delta						
No prior infection	1,211,322	249,741	614	2.46	-	-
Previously infected	95,723	19,768	2	0.10	0.028 (0.007; 0.110)	97.2% (89.0; 99.3%)
January 1, 2022 – March 10, 2022. Dominant variant: Omicron						
No prior infection	424,683	48,098	495	10.29	-	-
Previously infected	65,963	7058	18	2.55	0.302 (0.188; 0.485)	69.8% (51.5; 81.2%)

**Table 3: Natural protection among unvaccinated individuals against hospitalisation with a new SARS-CoV-2 infection following a prior infection at least 180 days earlier.**

Participants (aged 2+ years) 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 follow-up.

\* Hospital admission with associated primary ICD-10 diagnosis codes DB342A or DB972A occurring no earlier than two days before, and no later than 14 days after, a positive PCR test.

<sup>‡</sup> Rate of hospitalisations per 1000 person-years of follow-up.

<sup>†</sup> From a Cox regression model controlling for sex, age group, number of comorbidities and country region.

against any infection, but were otherwise very similar (Figure 3, Table S4).

## Discussion

We used person-level data from the Danish integrated COVID-19 surveillance system, including data on tests, vaccines, demographics, self-reported symptoms and hospitalisations to estimate protection against infection following a primary infection with SARS-CoV-2. In an unvaccinated population, we found the overall protection against a secondary infection to be around 83.4%, 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 against reinfection was seen over the period in which the Delta variant was circulating, when Omicron took over, previous infection offered markedly less protection against infection and this protection further diminished over time. Previous infection was also found to offer high protection against serious disease caused by both the Alpha and Delta, and to a lower extent, Omicron variants.

In our Analysis A, covering the epidemic time from the beginning until 1 July 2021, 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 a level of protection after natural infection above 80% and lasting for at least one year.<sup>19-23</sup> 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, between July and November 2021. After the introduction of the Omicron variant into Denmark, protection against SARS-CoV-2 infection 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. It should be noted, that we were not able to estimate the protection of Omicron against a previous Omicron infection, as not enough time had 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<sup>24</sup> while a meta-analysis has showed that levels of protection after either vaccination or natural infection are comparable.<sup>25</sup> A systematic review found protection after vaccination to diminish over the course of six months,<sup>1</sup> and a British study found vaccine-induced protection against infection with the Omicron variant to diminish noticeably over the course of a few months or weeks.<sup>26</sup> Similarly, our recent vaccine effectiveness study using Danish data (in preprint), found protection against Omicron infections to be in the range of 30–40% after two vaccine doses, 40–50% after three doses and declining over the course of a four-month period – though protection against hospitalisation was 80–90% following three vaccine doses.<sup>27</sup> Though difficult to translate the findings directly to this study, they are overall comparable to our findings.

Thus, our study suggests that protection from natural infection against reinfection and serious disease is comparable to vaccine-induced protection in terms of magnitude and duration, but the inference is challenged by the real-life evolution of virus and humoral and cellular immunity which makes it hard to disentangle the different factors of waning immunity.

We assessed protection against serious disease by the number of patients that had been hospitalised due to SARS-CoV-2 infection. Overall, this occurred only rarely. We found significant levels of protection against hospitalisation during the periods when Alpha (87%), Delta (97%) and Omicron (70%) were the predominant viral strains. In other words, infection with a prior SARS-CoV-2 variant would prevent over two-thirds of all hospitalisations otherwise occurring due to Omicron infections. Similar levels of protection against serious disease have been found by others.<sup>3,5</sup> 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 is in line with another study that showed that reinfections were less infectious compared to the primary infection and were less likely to be symptomatic.<sup>5</sup> In part, this is due to pre-existing humoral and cellular immunity.<sup>6,22</sup> However, mild or asymptomatic COVID-19 infections have been found to result in a rapid decline of antibodies within four months after infection.<sup>28</sup> This is in contrast to T cell immunity, which appears to be longer lasting and robust.<sup>10</sup> 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.<sup>29-32</sup>

Among people above the age of 65, we estimated the protection to be around 70% compared with 82–85% among the younger age groups. Based on data from 2020 only, we previously estimated protection among people above the age of 65 to be 47%.<sup>7</sup> 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 more than 3 months, due to the inability to clear virus. We found evidence of this in the data by increasing the time window definition, separating the first from the second infection from 3 months up to 6 months which 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.<sup>12,33,34</sup> 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.<sup>35,36</sup>

In Denmark, test rates have been high and our dataset includes persons tested because they had symptoms and for other reasons. In some other countries, mainly symptomatic individuals are targeted for testing. In order to be able to translate our results to such settings, we performed all analyses in parallel including only reinfections in persons reporting to have had symptoms. Overall, this led to higher estimates of protection against reinfection throughout, and these estimates may be more relevant as a basis of comparison to other studies.

This study has limitations. Importantly, we analysed reinfections only among those not yet vaccinated. With time, this increasingly placed limits on how representative the study population is relative to the source population. In the second half of 2021 and onwards, the unvaccinated population consisted of adults that for unknown reasons choose to opt out of the vaccination program and also 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 Analysis B, including follow-up time after July 2021, focusing on the Delta and in particular the Omicron variants, bias may therefore likely 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 we 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 RT-PCR and transiently RT-PCR positive cases not constituting true reinfections. Repeat PCR positivity for SARS-CoV-2 has been observed in individuals with prolonged viral shedding, while transiently PCR positive test results were observed in individuals who quickly cleared the infection due to pre-existing immunity, due to either vaccination or natural immunity. Either cases are unlikely to be of epidemiological significance as previous studies have shown.<sup>4,37</sup> To examine this further in our study, 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. Finally, a further limitation relates to the symptoms data which were self-reported and incomplete, especially during the Omicron period. Further, 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 whole-genome sequencing programme.<sup>38</sup>

In conclusion, our results imply that the level of protection after natural infection may be comparable to that offered by vaccines, in terms of protection against infection and, possibly, severe disease, with some evidence of lower protection among the elderly but more pronounced protection following symptomatic compared to asymptomatic infections. Reduced protection was increasingly seen with the introduction of new main virus variants, and protection conferred by a previous variant quickly diminished for Omicron infections. This indicates that reduction of protection against reinfection 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.

#### Contributors

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.

#### Data sharing statement

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.

#### Declaration of interests

All authors declare no competing interests.

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#### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.lanepe.2022.100452](https://doi.org/10.1016/j.lanepe.2022.100452).

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