Incidence of positive SARS-CoV-2 PCR after COVID-19 vaccination with up to eight months of follow-up: Real life data from the Capital Region of Denmark

Line Dam Heftdal[a,b], Martin Schultz[c], Theis Lange[d], Andreas Dehlbæk Knudsen[a], Kamille Fogh[e], Rasmus Bo Hasselbalch[e], Christine Borgen Linander[f], Thomas Kallemose[f], Henning Bundgaard[g,h], Kirsten Grønbæk[b,h,i], Palle Valentiner-Branth[j], Kasper Iversen[e,h,k], Susanne Dam Nielsen[a,h,l]

[a]Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [b]Department of Hematology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [c]Department of Internal Medicine, Geriatric Section, Herlev-Gentofte University Hospital, Herlev, Denmark, [d]Department of Public Health, University of Copenhagen, Copenhagen, Denmark [e]Department of Cardiology, Herlev-Gentofte University Hospital, Herlev, Denmark., [f]Department of Clinical Research, Copenhagen University Hospital Amager and Hvidovre, Hvidovre, Denmark; [g]Department of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [h]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [i]Biotech Research and Innovation Centre, University of Copenhagen, Copenhagen, Denmark; [j]Division of Infectious Diseases Preparedness, Statens Serum Institut, Copenhagen, Denmark.; [k]Department of Emergency Medicine, Herlev-Gentofte University Hospital, Herlev, Denmark; [l]Department of Surgical Gastroenterology and Transplantation, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Corresponding author:

Susanne Dam Nielsen

Email: sdn@dadlnet.dk

Summary: In this study of 1,549,488 individuals in the Capital Region of Denmark, of which

1,119,574 were vaccinated against SARS-CoV-2, we found that individuals who received two doses of

a COVID-19 vaccine had very low risk of breakthrough infections with SARS-CoV-2.

Abstract

Background: COVID-19 vaccines are implemented worldwide in efforts to curb the pandemic. **This study** investigates the risk of a positive SARS-CoV-2 RT-PCR test following BNT162b2 vaccination in a large real-life population in Denmark.

Methods: Vaccination status and positive SARS-CoV-2 RT-PCR results **from adults in the Capital Region of Denmark** (n=1,549,488) were obtained from n**ational registries. PCR testing was** free and widely available. The number of positive PCR tests per individual at risk were calculated as weekly rates. Time to positive PCR test was modelled using Kaplan-Meier methods and hazard ratios (HR) were calculated using Cox regression.

Results: 1,119,574 individuals received first dose of BNT162b2 and 1,088,879 received a second dose of BNT162b2. Individuals were followed up to 8.7 months after first dose (median: 5.5 months, IQR:4.1-8.7). Rates of PCR-confirmed SARS-CoV-2 infection two to four months after the second dose were 0.21, 0.33 and 0.36 per 1000 individuals per week at risk for July, August and September, respectively. Four or more months after the second dose, the rates were 0.56, 0.76 and 0.53 per 1000 individuals per week at risk for July, August and September, respectively. HR of SARS-CoV-2 infection after the second dose was 0.2 (95% CI: 0.05-0.48, p=0.001) for individuals with eight months follow-up.

Conclusion: Individuals who received two doses of the BNT162b2 COVID-19 vaccine had a low risk of breakthrough-infection after up to 8 months of follow-up. However, there was a tendency towards higher rates with longer follow-up.

Keywords: SARS-CoV-2, COVID-19, real-life data, vaccination, BNT162b2

Introduction:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of corona virus disease 2019 (COVID-19). The virus has caused a global pandemic with more than 274 million cases and 5.4 million deaths[1]. Efforts to curb the pandemic are highly warranted, and vaccination is the mainstay of such efforts. At present, **five** vaccines **have been approved in the European Union[2]. In Denmark mainly the two mRNA-based vaccines,** BNT162b2 **and** mRNA-1273, are currently in use.

Efficacy of the mRNA vaccines was reported in a phase 2/3 and a phase 3 trial of BNT162b2 **and** mRNA-1273, respectively. **The main outcome was prevention of symptomatic COVID-19 defined as typical COVID-19 symptoms in combination with a positive PCR test within two months of follow-up[3,4].** BNT162b2 had 52% efficacy in preventing symptomatic SARS-CoV-2 infection after the first dose, and 95% efficacy was found seven or more days after the second dose[3]. mRNA-1273 had 95% efficacy after the first dose and 94% efficacy after the second dose[4]. In a recent publication, the manufacturer reports that BNT162b2 is 91.3% effective six months following the second vaccine dose, with a gradual decline in vaccine efficacy over time.[5]

Despite roll-out of the two mRNA vaccines in many countries, only few reports of real-life data have been published. Data from Israel including 4.7 million individuals of all ages vaccinated with BNT162b2 and a median follow-up of 7 weeks, found 95.3% efficacy of BNT162b2 in preventing symptomatic COVID-19 infection after the second dose and 91.5% on asymptomatic infection[6]. Waning immunity with increased risk of breakthrough infections has been observed in early vaccinated individuals compared to individuals vaccinated later[7–9], and a recent study from Israel with one month follow-up after a third dose of BNT162b2 found lower rates of infection in individuals vaccinated thrice[10]. However,

little is known about the incidence of SARS-CoV-2-infection including mild or asymptomatic disease in a vaccinated population[6,7].

In this large, observational study of all individuals in the Capital Region of Denmark between December 27, 2020 and September 14, 2021, **and up to eight months of follow-up,** we aimed **to** determine the rate of breakthrough infections following at least one dose of BNT162b2 COVID-19 vaccine. Furthermore, we present sensitivity analyses of presumed high-risk populations i.e. health care workers (HCW).

Methods

Study design and participants

This is an observational study of all individuals vaccinated against SARS-CoV-2 infection with BNT162b2 between December 27, 2020 and September 14, 2021 in the Capital Region of Denmark. The Danish health care system provides free health care to all Danish citizens, and the Danish vaccination program was organized by the Danish Health Authorities. **HCW were** prioritized for early vaccination in Denmark, along with the elderly population and patients belonging to groups with increased risk of severe COVID-19[12–14]. Testing for SARS-CoV-2 is free-of-charge and widely available in Denmark. All RT-PCR test results for SARS-CoV-2 are registered in the Danish National Registries. HCW in the Capital region of Denmark were recommended weekly **routine RT-PCR tests if not vaccinated with two doses, and both HCW and high-risk groups were recommended RT-PCR tests if symptomatic or after possible exposure to SARS-CoV-2 infected individuals. The l**arge-scale screening pre- and post-enrollment in the COVID-19 vaccination program provides the opportunity to study both symptomatic and asymptomatic SARS-CoV-2 infection after vaccination. We used

surveillance data from the Danish National Registries during the first eight months of the nationwide

vaccination campaign against SARS-CoV-2 in Denmark. All Danish citizens have individual

identification numbers that enables data linkage in the registries. We included all individuals aged 18

years and older, living in the Capital Region of Denmark within the study period. Individuals

vaccinated with other types of COVID-19 vaccines (mRNA-1273, ChAdOx1 or Ad26.COV-s) or with a

positive PCR test before December 27, 2020 were excluded. Individuals who entered the study in the

unvaccinated group and presented a positive test between December 27, 2020 and the date of their

first vaccination were considered events and not subsequently reintroduced in the vaccinated group,

as duration of protection from natural infection is still unknown. For the same reason individuals

with a positive test between their first and second dose were excluded in isolated analyses of the

second dose. Individuals with positive tests in the first week after vaccination were not excluded but

considered events. However, in the sensitivity cox-analyses from 7 days after vaccination, they were

excluded from the analyses.

HCW were identified through regional databases. In order to perform long-term follow-up, two

datasets were combined. The first dataset (December 27, 2020 through May 20, 2021) included

information on all vaccinated individuals as well as negative and positive RT-PCR test results of both

vaccinated and unvaccinated individuals in the Capital Region of Denmark. The second dataset (May

21, 2021 through September 14, 2021) included information on all positive, but not negative, RT-PCR

test results of both vaccinated and unvaccinated individuals as well as time and type of vaccination

in vaccinated individuals in the Capital Region of Denmark.

Statistical analysis:

Baseline variables of the study population are summarized as mean with standard deviation

(SD) or median with interquartile range (IQR) for continues variables and frequencies with

percentages for categorical variables. The rate of infection with SARS-CoV-2 was calculated

as number of positive PCR tests per individual at risk per day and presented as number of

infections per 1000 individuals per week at risk. Since data was only available for unvaccinated individuals who tested positive in the second dataset, non-vaccinated rates could not be calculated beyond May 20, 2021. To show the rate of positive RT-PCR tests changed over the course of the study period, results were stratified according to calendar month. Time to positive SARS-CoV-2 RT-PCR test was modelled using the Kaplan-Meier estimator done separately for the first 3 weeks vaccination was being initiated and the underlying time scale was days since this week. Two groups were compared in each week: group a) vaccinated individuals who had their first vaccine in that week (or similar received their second dose that week) and group b) individuals who were still unvaccinated that week. The study population was defined by individuals from the first dataset, and follow-up throughout the time period of the second dataset. The vaccinated group was followed until positive SARS-CoV-2 RT-PCR test (the event) and censored in case of death. The unvaccinated group was followed until presenting a positive SARS-CoV-2 RT-PCR test (the event) and censored in case of death or vaccination. Hazard ratios were calculated using a Cox regression model and presented with 95% confidence intervals (95% CI); however, the proportional hazards assumption was not met for the models. Hazard ratios were calculated from day of vaccination and as a sensitivity analysis from 7 days after vaccination in which the risk time of unvaccinated controls was also postponed 7 days. Additionally, sub analysis using only HCW were performed. Statistical calculations were performed in R version 3.6.1[15], using R-packages: survival[16],Epi[17] and dplyr[18].

Results

During the study period from December 27, 2020, through September 14, 2021, we included 1,549,488 individuals from the Capital Region of Denmark of which 1,119,574 individuals received at least one dose BNT162b2. By September 14, 2021, a second dose of BNT162b2 was received by 1,088,879 individuals. The dates of vaccine administrations are shown in figure 1. Median follow-up after the first dose was 5.5 months (IQR: 4.1-8.7) and a total of 6,209,550 RT-PCR tests were performed between December 27, 2020 and May 20, 2021. Negative tests were not available after May 20, 2021, however 36,839 positive tests were registered between May 20, 2021 and September 14, 2021. All baseline characteristics are shown in table 1.

The weekly rates of a positive PCR tests for unvaccinated individuals who were tested between December 27, 2020 and May 20, 2021 were 1.9, 0.8, 1.3, 1.6, and 2.2 per week per 1000 individuals at risk in January, February, March, April and May, respectively (Figure 2A and table 2). For individuals vaccinated with the first dose, the rate of RT-PCR-confirmed SARS-CoV-2 infection in January, the first month of the study period, was 5.7 per 1000 individuals per week at risk, compared to 1.9 in unvaccinated individuals (Figure 2A and table 2). The rates of RT-PCR-confirmed SARS-CoV-2 infection after the first dose decreased to 0.57, 0.49, 0.31, 0.88, 0.60, 2.79, 2.32 and 1.73 per week per 1000 individuals at risk in February, March, April, May, June, July, August and September, respectively (Figure 2A).

In the first two months after the second dose, the rates of RT-PCR-confirmed SARS-CoV-2 infection were 0.32, 0.21, 0.12, 0.14, 0.06, 0.47, 0.62 and 0.44 per week per 1000 individuals at risk in February, March, April, May, June, July, August and September respectively (Figure 2A). Between

two and four months after the second dose, the rates of RT-PCR-confirmed SARS-CoV-2 infection were 0.21, 0.55, 0.32, 0.10, 0.21, 0.33 and 0.36 per week per 1000 individuals at risk for March, April, May, June, July, August and September respectively (Figure 2A). Four or more months after the second dose, the rates of RT-PCR-confirmed SARS-CoV-2 infection were 0.45, 0.16, 0.56, 0.76, and 0.53 per week per 1000 individuals at risk for May, June, July, August and September respectively (Figure 2A).

For the 22,893 HCW vaccinated before May 20, the rates of RT-PCR-confirmed SARS-CoV-2 infection after one vaccine dose were 3.76, 0.85, 1.31, 0.48, and 0.83 per week per 1000 individuals at risk in January, February, March, April and May, respectively (Figure 2B). In the first two months after the second dose, the rates of RT-PCR-confirmed SARS-CoV-2 infection were 0.23, 0.36, 0.25, and 0.35 per week per 1000 individuals at risk in February, March, April and May, respectively (Figure 2B). Two or more months after the second vaccine dose, the rates of RT-PCR-confirmed SARS-CoV-2 infection in HCW were 0.61 and 0.59 per week per 1000 individuals at risk for April and May, respectively (Figure 2B).

In a sub-analysis of all 57,312 individuals vaccinated with their first dose in the first 3 weeks of the vaccination program, from December 27, 2020 through January 17, 2021, more individuals of the vaccinated population initially had RT-PCR confirmed SARS-CoV-2 infection compared to the unvaccinated population (Figure 3A+B). The hazard ratio (HR) of having a positive RT-PCR test for individuals vaccinated in the first week of the vaccination program was 5.0 (95% CI: 4.5-5.4, p<0.001) compared to unvaccinated individuals in the same time-period (figure 3A). In HCW, the HR of RT-PCR confirmed SARS-CoV-2 infection for individuals vaccinated in the first week compared to unvaccinated individuals was 2.0 (95% CI: 1.7-2.4, p<0.001) (Figure 3A). Compared to unvaccinated

individuals, the HR of RT-PCR-confirmed SARS-CoV-2 infection after the second vaccine dose was 0.2 (95% CI: 0.05-0.48, p=0.001) for individuals who received their second vaccine dose in the first week of administration of a second dose (Figure 3B). In HCW the corresponding HR was 0.2 (95% CI: 0.03-1.34, p=0.095) (Figure 3B). Similar trends were observed when performing sensitivity analyses 7 days after first and second vaccination respectively. All HRs are summarized in table 3.

Discussion

We present data from a large observational study of all individuals in the Capital Region of Denmark, including 1,119,574 individuals vaccinated with BNT162b2, with up to eight months of follow-up after the first dose. We found low rates of breakthrough SARS-CoV-2 infection in individuals who received two doses of a COVID-19 vaccine, however, there was a tendency towards increasing rates four or more months after the second dose. For individuals who completed the vaccination program in the first week of administration of the second dose, and thus had the longest time to follow-up, we found a HR of 0.2 of RT-PCR confirmed SARS-CoV-2 infection.

As vaccination coverage increases, the implementation of mandatory COVID-19 passports for vaccinated individuals has been suggested to allow for access to public facilities and traveling across borders. Thus, durability of the vaccine induced immunity has become an area of concern. In this study, the rates of RT-PCR-confirmed SARS-CoV-2 breakthrough infection showed a tendency towards increasing in individuals with more than four months since second vaccine dose, suggesting slightly decreasing protection of the vaccine 4 months after completed vaccination. A causal interpretation of the results will require time of vaccination not being dependent on risk of SARS-CoV-2-infection. However, individuals with high risk of severe COVID-19 were prioritized for early

vaccination, and thus time of first vaccination was directly correlated with age and populations considered at increased risk of severe COVID-19. Thus, our results cannot assess the causal effects, and different study design or additional information associated with increased risk of SARS-CoV-2-infection, would be necessary to determine causality.

In the weeks prior to initiation of the vaccine program, Denmark underwent the second nationwide lockdown due to increasing incidence of infection and COVID-19 related hospitalizations[19]. The effect of the lockdown was reflected in the nationwide percentage of positive PCR tests in the following weeks and coincided with the first part of the inclusion period for our study[19]. Thus, the percentage of positive tests also declined during the first three inclusion weeks[19]. In our study, the incidence of SARS-CoV-2 infection was higher in the vaccinated population after administration of the first dose in the first two weeks of the vaccination program compared to the unvaccinated group, reflecting that individuals prioritized for the first doses of vaccine were at very high risk of infection due to either immunosuppression, status of residency at nursing home or employment with high risk of exposure at e.g. designated COVID-19 units. Thus, the increased risk in the vaccinated group in the first weeks after initiation of the vaccination program may reflect the choice of vaccination strategy. However, cases in the HCW only accounted for one fourth of the positive tests, and other mechanisms, including impaired immune function due to age or comorbidities, or potentially fewer protective measures being taken once vaccinated, must also have played a role. At the time of the second vaccination this association had reversed.

So far, few studies outside of Israel have presented real-life data evaluating the risk of SARS-CoV-2 infection after completed vaccination on a population level with more than two months of follow-up[8,9,20–22]. The phase 2/3 study of BNT162b2 did not perform routine tests in asymptomatic

individuals, and it is unknown to what extent BNT162b2 protects against asymptomatic disease[3]. In Denmark, the strongly encouraged, free and widely available testing for all residents, including HCW, provide a near ideal platform for studying the epidemiological effectiveness of COVID-19 vaccination regardless of symptom severity. However, we did not have access to clinical data, including comorbidities or hospitalization, and as such, we cannot provide information about the proportion with symptomatic disease. This may be further challenged by a varying tendency to get tested over the course of the study period. However, we found it reasonable to assume that individuals with symptoms consistent with COVID-19 would get tested regardless of vaccination status, although asymptomatic infections might not have been consistently detected throughout the study period.

The data presented suggest effective protection from virus transmission up to five months after completed vaccination with BNT162b2. However, we did find a tendency towards increasing rates of RT-PCR confirmed SARS-CoV-2 when exceeding 4 months since second vaccination, albeit we cannot draw conclusions on efficacy, as this study is strictly observational. Effects derived from public health interventions in the study environment might influence the result as seen by the decreasing positive percentage over time, but this would likely have affected both vaccinated and un-vaccinated individuals. Behavioral changes such as reduced testing frequency after vaccination or lack of testing due to absence from work are also possible confounders due to the observational nature of the study [6,23]. **Limitations to our study further include that pairing of our data with clinical data or information on comorbidities or hospitalization was not possible, and we cannot distinguish between severe or non-severe SARS-CoV-2 infections.** Additionally, we do not have data on individual variants of concern, however we know from national inventories that the Alpha variant was the predominant strain in Denmark until the middle of June 2020 when the Delta variant took over[24]. SARS-CoV-2 testing in Denmark was free and encouraged as part of contact tracing efforts and for individuals who have symptoms consistent with COVID-19. Though HCW are more exposed,

protection measurements are enforced. Hence, the overall risk is difficult to compare, and we cannot rule out that HCW and groups prioritized for vaccination may have had a higher propensity for testing than the control population.

In conclusion, our data estimates that individuals who received two doses of BNT162b2 had a minimal risk of breakthrough infection with SARS-CoV-2, however, there may be a tendency towards reduction in vaccine effectiveness over time. In the context of containing the current pandemic and preventing additional lockdowns, as winter, a season traditionally associated with higher infection rates, approaches, this is reassuring results. However, more evidence is needed on long term immunogenicity. Importantly, although our data support the findings in the original trials, it is essential to remain rigorous in maintaining transmission preventing precautions until the duration of the effect of the vaccine has been clarified.

NOTES

Conflicts of Interest:

LDH has received a research scholarship from Rigshospitalet, Copenhagen University Hospital. HBU has received honoraria related to Amgen, Bristol-Myers Squibb and MSD, holds IP rights for a heart failure treatment and serves in a fiduciary role in The Danish Heart Foundation, The National Genome Center and PM Heart. KG has received grants from The Danish Cancer Society, The Independent Research Fund Denmark, The Novo Nordisk Foundation, The Danish Cancer Society and the European Hematology Association, and serve in a fiduciary role in the European Hematology Association and Danish Cancer Society. SDN has received unrestricted grants from The Novo Nordisk Foundation, Kirsten and Freddy Johansens Fund and Dr. Sofus Carl Emil Friis and Wife Olga Doris Friis Scholarship. SDN has further received honoraria from Gilead and MSD and has served on advisory boards for Gilead, MSD and GSK.

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Tables:

Table 1 - Baseline Characteristics:

	Combined dataset			Dataset 1 - (December 27, 2020 through May 20, 2021)		Dataset 2 - (May 21, 2021 through September 14, 2021)	
	All	All vaccinated	Vaccinated HCW	All vaccinated	Vaccinated HCW	All vaccinated	Vaccinated HCW
Number, n (%)	1,549,488	1,119,574	30,948	462,262	22,893	657,312	8,055
Mean Age, yr (SD)	41.6 (23.3)	48.4 (20.5)	44.0 (13.4)	66.5 (13.0)	46.2 (13.4)	35.7 (14.2)	37.7 (11.2)
Female, n (%)	788,365 (50.9)	573,620 (51.2)	23,360 (75.5)	252,081 (54.5)	17,349 (75.8)	321,539 (48.9)	6011 (74.6)
Days from 1st to 2nd dose, mean (SD)	N/A	32.3 (7.8)	31.5 (10.3)	29.2 (8.0)	30.6 (11.1)	34.7 (6.8)	34.4 (6.9)
Individuals without SARS-CoV-2 prior to vaccination, n (%)							

- Prior to 1st dose	N/A	1,094,584 (97.8)	30,482 (98.5)	458,127 (99.1)	22,785 (99.5)	636,457 (96.8)	7,697 (95.6)
- Prior to 2nd dose	N/A	1,060,701 (94.7)	29,641 (95.8)	454,194 (98.3)	22,367 (97.7)	606,507 (92.3)	7,274 (90.3)

Table 2 – Weekly rates of positive RT-PCR tests per 1000 individuals:

Weekly rate per 1000 individuals		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep
All	Unvaccinated	1.9	0.8	1.3	1.6	2.2				
	1 vaccine	5.73	0.57	0.49	0.31	0.88	0.60	2.79	2.32	1.73
	< 2months since second vaccine	1.99	0.32	0.21	0.12	0.14	0.06	0.47	0.62	0.44
	2-4 months since second vaccine			0.21	0.55	0.32	0.10	0.21	0.33	0.36
	>4 months since second vaccine					0.45	0.16	0.56	0.76	0.53
HCW	Unvaccinated									
	1 vaccine	3.76	0.85	1.31	0.48	0.83				
	< 2months since second vaccine	1.54	0.23	0.36	0.25	0.35				
	2-4 months since second vaccine				0.61	0.59				

Table 3: Hazard ratios of RT-PCR-confirmed SARS-CoV-2 infection calculated from day of vaccination and from 7 days after vaccination

Hazard ratios (95% confidence interval), p-value		1st dose	7 days after 1st dose	2nd dose	7 days after 2nd dose
All	Week 1	5.0 (4.5-5.4), p<0.001	4.2 (3.7-4.8), p<0.001	0.2 (0.05-0.48), p=0.001	0.2 (0.05-0.51), p=0.002
	Week 2	5.7 (5.2-6.1),p<0.001	4.8 (4.3-5.4), p<0.001	0.3 (0.3-0.4), p<0.001	0.2 (0.2-0.3), p<0.001
	Week 3	1.7 (1.4-2.0), p<0.001	1.4 (1.2-1.8), p=0.001	0.2 (0.2-0.2), p<0.001	0.2 (0.1-0.2), p<0.001
HCW	Week 1	2.0 (1.7-2.4), p<0.001	1.3 (1.0-1.6), p=0.063	0.2 (0.03-1.34), p=0.095	0.2 (0.03-1.48), p=0.116
	Week 2	1.2 (1.0-1.6), p=0.077	1.1 (0.8-1.5), p=0.616	0.3 (0.2-0.5), p<0.01	0.3 (0.2-0.4), p<0.001
	Week 3	0.9 (0.7-1.2), p=0.564	0.8 (0.5-1.1), p=0.156	0.3 (0.2-0.4), p<0.001	0.3 (0.2-0.4), p<0.001

Figure legends:

Figure 1: Distribution of BNT162b2 COVID-19 vaccine administration in the Capital Region of Denmark between December 27, 2020 and September 14, 2021, according to date. Only individuals without a positive SARS-CoV-2 test prior to vaccination are included. Dark grey: Administration of first dose. Light grey: administration of second dose.

Figure 2: Weekly risk rates of positive RT-PCR for SARS-CoV-2 in individuals vaccinated with one dose of BNT162b2 COVID-19 vaccine (grey), individuals with less than two months since receiving the second vaccine dose (red), individuals with two to four months after the first vaccine dose (dark blue) or more than 4 months after the second vaccine dose (light blue), stratified by calendar month. **A:** All individuals in the Capital Region of Denmark **B:** All health care workers (HCW) in the Capital Region of Denmark.

Figure 3: Kaplan-Meier plots of time to presenting a positive SARS-CoV-2 RT-PCR test modelled separately for each of the first three weeks vaccination was being initiated. Underlying time scale is days since this week. Two groups were compared in each week: Red: vaccinated individuals without a positive SARS-CoV-2 PCR test prior to vaccination, who had their first vaccine in that week (or similar received their second dose that week) and Black: individuals who were still unvaccinated that week. The vaccinated group was followed until presenting a positive SARS-CoV-2 RT-PCR test (the event) and censored in case of death. The unvaccinated group was followed until presenting a positive SARS-CoV-2 RT-PCR test (the event) and censored in case of death or vaccination. **A:** The first three weeks of BNT162b2 COVID-19 vaccine administration in the Capital Region of Denmark. **B:** The first three weeks of administration of a second BNT162b2 COVID-19 vaccine dose to individuals who had already received their first dose.

Upper level plots represent all individuals, lower level plots represent health care workers.
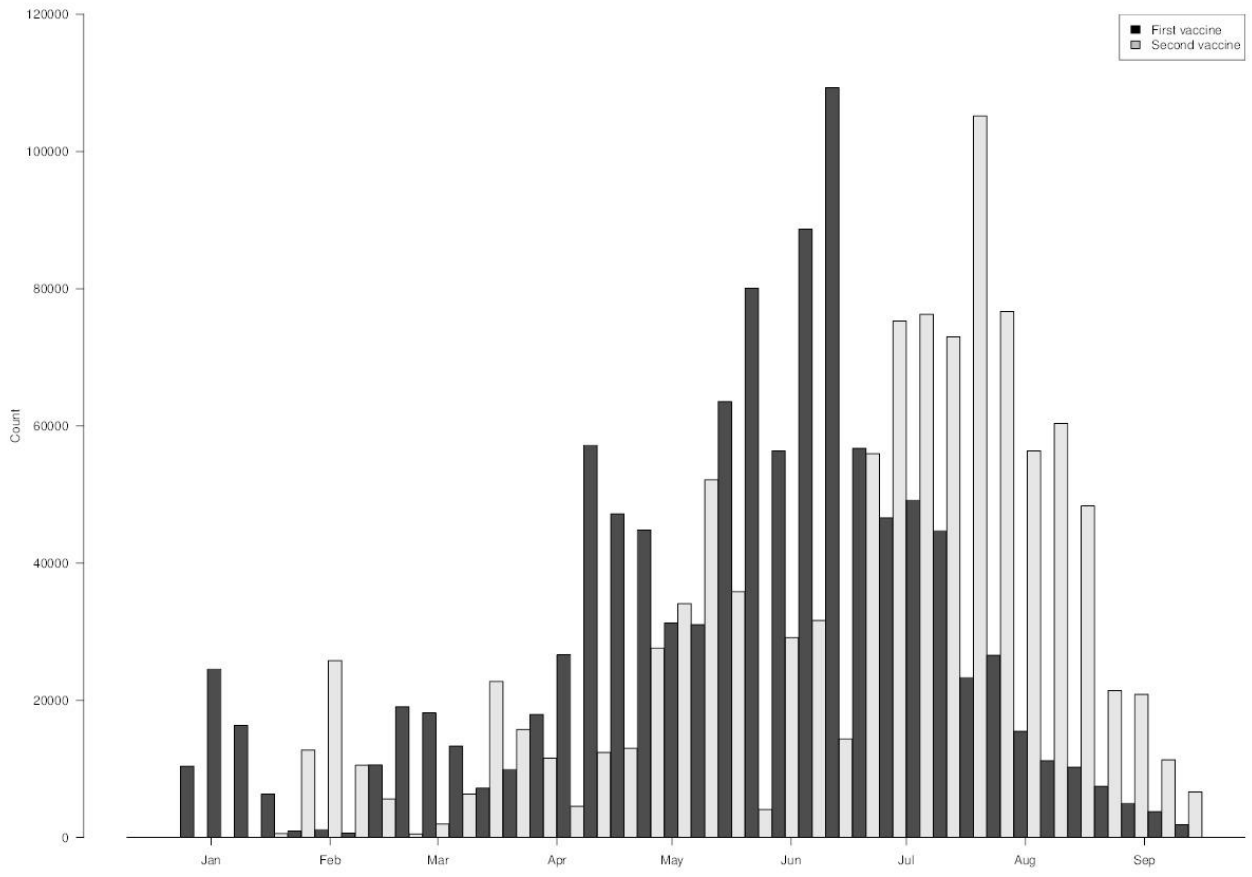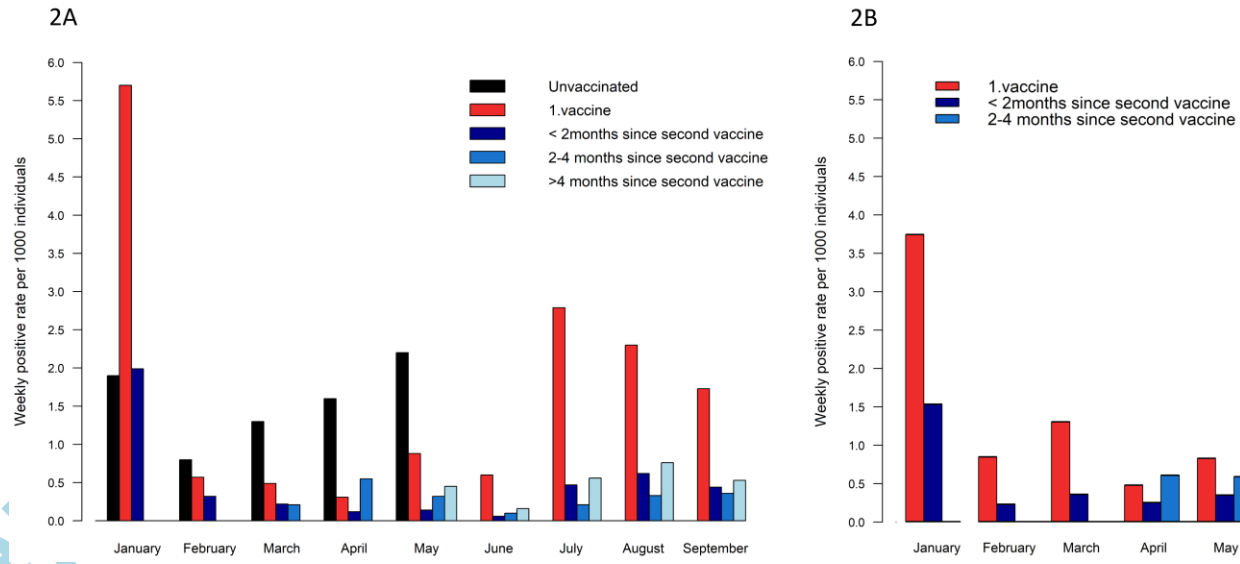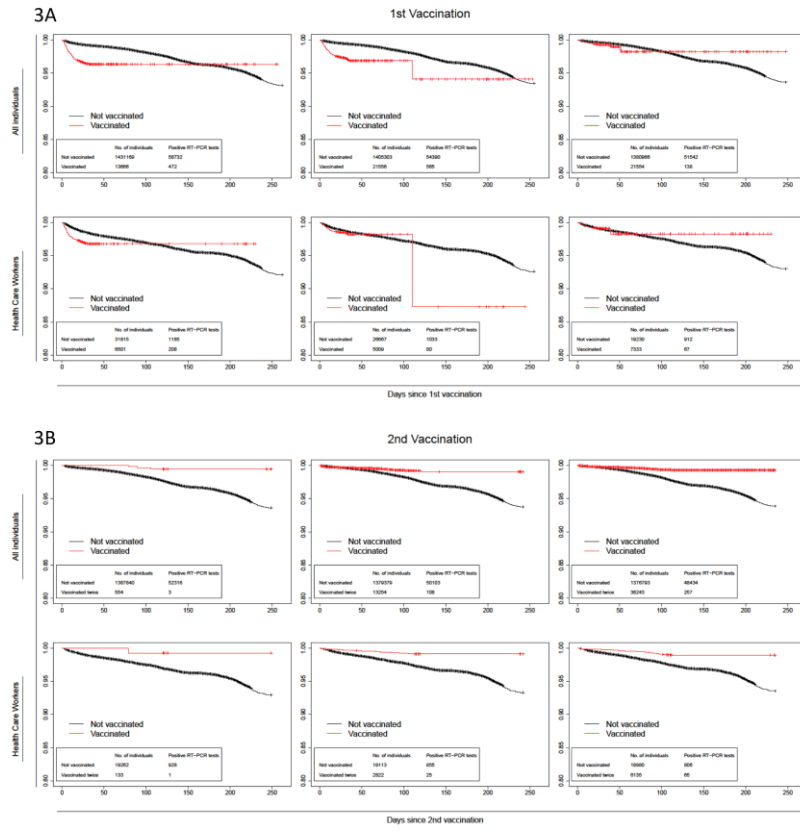
Figure 1

Figure 2

2A

2B

Figure 3

3A — 1st Vaccination

3B — 2nd Vaccination