Vaccine effectiveness against infection and COVID-19-associated hospitalisation with the Omicron (B.1.1.529) variant after vaccination with the BNT162b2 or mRNA-1273 vaccine: A nationwide Danish cohort study

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Title: Vaccine effectiveness against infection and COVID-19-associated hospitalisation with the Omicron (B.1.1.529) variant after vaccination with the BNT162b2 or mRNA-1273 vaccine: A nationwide Danish cohort study

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Abstract

Limited evidence exists on the level and longevity of protection afforded by current COVID-19 vaccines against infection and hospitalisation with the Omicron variant. SARS-CoV-2 PCR testing rates in Denmark are exceptionally high. In this nationwide cohort analysis, from December 28, 2021 to February 15, 2022 during which Omicron was the predominant variant, PCR testing data are combined with other national register data with near-complete information on all vaccinations, hospitalisations and comorbidities in the population. Trends over time in vaccine effectiveness after two and three doses with BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) are estimated using Cox regression. Despite relatively poor protection against infection (symptomatic or asymptomatic), vaccine effectiveness against COVID-19-associated hospitalisation was high after the third dose declining from 88.8% (95% CI: 87.3 to 90.1%) to 79.0% (76.5 to 81.3%) for BNT162b2 and 90.2% (87.3 to 92.5%) to 83.6% (77.7 to 88.0%) for mRNA-1273 over the first four months after vaccination.
Introduction

On 26 November, 2021, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant B.1.1.529, named Omicron, was classified as a variant of concern by the World Health Organisation and has since spread rapidly across the globe including in Denmark despite high COVID-19 vaccine coverage.[1-3] Similar to the situation in many other countries, community transmission in Denmark was growing exponentially by the end of 2021 with the Omicron variant accounting for more than 90% of daily cases by December 28, 2021, and more than 99% since mid-January 2022.[4,5]

Meanwhile there is growing evidence that the existing COVID-19 vaccines protect less well against infection with the Omicron variant than against infection with previous variants and that immunity after only two COVID-19 vaccine doses is relatively short-lived, likely due to a combination of immune evasion and waning over time.[6-10]. This has led to an accelerated rollout of additional COVID-19 vaccine doses in many countries. In Denmark, a third dose with either the BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccine has since December 2021 been offered to all adults who received their second dose more than four-and-a-half months earlier. Most people have taken up the offer of a third dose; by 15 February 2022, approximately 3.6 million people (76% of the adult population) had received their third dose.[11] In some countries a fourth dose has also been offered or is being considered, usually with priority given to elderly and other vulnerable or exposed population groups.[12] However, more evidence is needed from large-scale epidemiological studies to better understand the level and longevity of protection after mRNA vaccination against SARS-CoV-2 infection with the Omicron variant, including how well the vaccines protect against severe disease and hospitalisation.

Since 2020, mass testing by polymerase chain reaction (PCR; free of charge and available to all whether symptomatic or not, and without needing referral) has been a central part of Denmark’s COVID-19 surveillance and control strategy.[13] Consequently, the rates of PCR testing in the Danish population are among the highest in the world with around a quarter of the population tested each week during December 2021 and January 2022.[11] Combined with existing centrally-held nationwide individual-level registry data that comprise details on vaccination history, hospital appointments and other clinical and demographic information, the national COVID-19 surveillance data provide a rich source of information for investigation of vaccine effectiveness at population level.
The aim of the present cohort study was to estimate the protection of COVID-19 mRNA vaccines separately by month since vaccination after two or three doses against infection or hospitalisation with the Omicron variant using population-level Danish nationwide register data collected between 28 December, 2021 and 15 February, 2022 when the Omicron variant was the predominant strain in the country.

Results

Unvaccinated participants were more likely to be male than vaccinated participants and to live in or around Copenhagen. Compared with the triple-vaccinated population they were also younger and had fewer comorbidities (Table 1). Those who received mRNA-1273 for their third dose were generally younger with fewer comorbidities and vaccinated a little later than those who received BNT162b2. Many double-vaccinated participants received a third dose during the study period (516,765 of 1,091,397) while some previously unvaccinated participants received a first dose (8,901 of 202,896).

Among the 202,896 participants who contributed unvaccinated time, nearly two-thirds (n=132,102) tested positive by PCR during the study period resulting in a crude infection rate of 7.1 per person-year at risk. The infection rate was similar when restricting the unvaccinated population to the comparison group for the analysis of vaccine protection after three doses, i.e. to those over the age of 18 years (Table 2).

VE against infection

Infection rates were lower in the double-vaccinated population resulting in adjusted vaccine effectiveness estimates of 37.0% (95% confidence interval: 35.6 to 38.3%) and 37.9% (34.4 to 41.2%) 14 to 30 days after vaccination with BNT162b2 and mRNA-1273 respectively (Table 2, Figure 1). For both vaccine types, protection declined gradually thereafter to 27.4% (26.2 to 28.5%) and 23.3% (21.1 to 25.5%) respectively in the fourth month after vaccination. Among those who had received their second dose of BNT162b2 more than 120 days earlier, the median time since the second dose at the end of follow-up was 161 days (interquartile range [IQR]: 148 to 177 days) with a remaining vaccine effectiveness against infection of only 9.8% (9.2 to 10.4%). The median time since vaccination among those who had received their second dose of mRNA-1273 more than 120 days earlier was 149 days (IQR: 142 to 160 days) with a vaccine effectiveness of 13.2% (12.3 to 14.2%).
In the triple-vaccinated population, the vaccine effectiveness against infection was 47.9% (47.4 to 48.3%) and 47.7% (47.0 to 48.3%) for BNT162b2 and mRNA-1273 respectively in the first 14-30 days after vaccination, dropping to 40.5% (38.9 to 42.2%) and 37.9% (33.4 to 42.0%) respectively among those who had received their third dose over 120 days earlier. The median time since vaccination at the end of follow-up was 141 days (IQR: 131-151 days) and 130 days (IQR: 125-140 days) for those who had received a third dose of the BNT162b2 or mRNA-1273 vaccine respectively more than 120 days earlier.

VE against hospitalisation

After two doses, vaccine effectiveness against COVID-19-associated hospital admission was 50.5% (33.9 to 63.0%) in the period 14 to 30 days after vaccination with BNT162b2. The point estimates for the subsequent time periods ranged from 42.6% to 51.6% but with relatively wide confidence intervals providing little evidence of a change over time. Vaccine effectiveness against hospitalisation after two vaccine doses was not estimated for the mRNA-1273 vaccine due to sparse data.

After three doses, vaccine effectiveness against COVID-19-associated hospital admission was 88.8% (87.3 to 90.1%) and 90.2% (87.3 to 92.5%) in the first 14-30 days after vaccination with the BNT162b2 or mRNA-1273 vaccine respectively. The protection against hospitalisation declined gradually thereafter to 79.0% (76.5 to 81.3%) and 83.6% (77.7 to 88.0%) in the fourth month after the third vaccine dose with BNT162b2 or mRNA-1273 respectively. Among those vaccinated with a third dose more than 120 days earlier, the vaccine effectiveness was 66.2% (61.1 to 70.7%) and 77.3% (63.1 to 86.1%), respectively, for the BNT162b2 and mRNA-1273 vaccines.

Discussion

Protection against SARS-CoV-2 infection in the initial period after two mRNA vaccine doses was around 37% with significant waning in the three months thereafter and little remaining protection among those vaccinated more than 121 days ago. Among those vaccinated with a third dose, vaccine protection against infection reached a higher level of around 48% with less waning in the months thereafter. Vaccine effectiveness against COVID-19 related hospitalisation after two doses with the BNT162b2 vaccine ranged from 42.6% to 51.6% although the estimates were relatively imprecise. After three mRNA vaccine doses, however, the level of protection was considerably better with estimates of vaccine effectiveness against COVID-19-associated hospitalisation around 90% in the
initial period, and remaining around 80-90% in the first four months after vaccination with evidence of further waning thereafter.

The vaccine protection against infection in our study, during a period when Omicron was the predominant strain, was markedly lower than that observed against infection with earlier variants such as the SARS-CoV-2 B.1.617.2 (Delta) or B.1.1.7 (Alpha) variants.[14,15] However, the high level of protection against hospitalisation, especially after a third dose, provides reassurance that both mRNA vaccines protect well against serious disease progression with COVID-19.

The vaccine effectiveness estimates were remarkably similar across the two vaccine types, whether modelling infection or hospitalisation, and by time since vaccination. Despite narrow confidence intervals (reflecting the very large sample sizes), the small contrasts that were observed may not reflect genuine differences in the protection afforded by the two vaccine products but may instead be due to small variations in the recipient populations and timing of rollout with the two vaccine products.

Previous studies have investigated the protection afforded by COVID-19 mRNA vaccines against symptomatic infection with the Omicron variant.[6,7] In these, similar or higher estimates were observed after two vaccine doses, while the level of protection after three doses reported in both studies was higher than that observed in our study, but also with evidence of waning. It is worth noting, however, that in both studies vaccine effectiveness was derived from an odds ratio estimate rather than a risk or a rate ratio; the resultant vaccine effectiveness estimate is therefore expected to be higher with the overestimation from logistic regressions accentuated relative to earlier variants by the higher Omicron case rates. Another explanation for the comparably lower estimates in the present study may be that ours estimated vaccine effectiveness against any infection, whether symptomatic or asymptomatic, made possible only by the extremely high levels of PCR testing in the population.

Three studies in hospital populations in the United States have found very similar levels of protection to those in the present study after three mRNA doses against COVID-19-associated hospitalisations during the Omicron period with vaccine effectiveness around 90%.[16-18] One of these stratified the analysis by time since vaccination and found a vaccine effectiveness of 91% (88 to 93%) in the first couple of months after vaccination which decreased to 78% (67 to 85%) after four months. [18] All three studies also found relatively poorer protection after
just two doses. In the United Kingdom, the UK Health Security Agency has reported similar findings on vaccine effectiveness after an mRNA booster dose against hospitalisation following infection with the Omicron variant.[19] Finally, a study from South Africa of members of a healthcare organisation estimated a vaccine effectiveness of 70% (62 to 76%) against hospitalisation for COVID-19 during the Omicron period after two BNT162b2 doses but did not report vaccine protection after three doses or by time since vaccination.[20]. Importantly, irrespective of vaccine protection, infection with the Omicron variant is much less likely to lead to hospital admission compared with the Delta variant.[21]

Limitations

We defined a COVID-19 related hospitalisation as an all-cause hospital admission lasting at least 12 hours and occurring up to 14 days after or two days before a positive SARS-CoV-2 test. Some of the hospitalisations included in our analysis will therefore have been due to causes other than COVID-19. Assuming that the rate of hospitalisation due to other causes is similar in the vaccinated and unvaccinated populations, the lack of specificity around the definition may have resulted in underestimation of the vaccine effectiveness. As with most observational studies of vaccine effectiveness, there are other potential sources of bias too. For instance, differences in behaviour, socio-demographic and clinical characteristics between vaccinated and unvaccinated individuals may have impacted infection exposure or propensity for severe disease beyond what is captured through the existing adjustment variables. Furthermore, cases were identified through PCR testing, and estimates of vaccine effectiveness against infection (but not hospitalisation) rely on participants attending PCR test facilities when feeling unwell or suspecting exposure to infection. Hence, if unvaccinated participants were less prone to PCR testing when feeling unwell, the protective effect of the vaccines would be underestimated. Finally, although the study excluded previous PCR confirmed cases, we were unable to exclude unidentified previous cases, which, if more prevalent among the unvaccinated population would also result in an attenuation of the estimated vaccine effectiveness.

Conclusion

In summary, this nationwide cohort study contributes to growing evidence that the existing COVID-19 mRNA vaccines provide relatively poor protection against any infection (symptomatic or asymptomatic) with the Omicron variant. However, the observed mRNA vaccine effectiveness against COVID-19-associated hospitalisation was
high after a third dose and remained around 80% or higher for both vaccines over the first four months following a third dose. Our findings suggest that third-dose mRNA vaccination is important in order to control hospital admission rates during an era of the highly transmissible Omicron variant.

Methods

Data sources

Person-level data on COVID-19 vaccinations, including dates and products administered, were extracted from the Danish Vaccination Registry which records all administered COVID-19 vaccinations in the country.[22] As part of Denmark’s COVID-19 surveillance and control strategy since 2020, centrally registered, free-of-charge PCR testing is available to all, whether symptomatic or not and without referral.[13] Person-level data on all SARS-CoV-2 infections confirmed by reverse transcription PCR in Denmark were extracted from the Danish Microbiology Database.[23] Hospital admission dates and information on comorbidities were obtained from the Danish National Patient Registry.[24] We defined a COVID-19-associated hospitalisation as any hospital admission lasting at least 12 hours and occurring no earlier than two days before, and no later than 14 days after, a positive PCR test. Information on sex, age, vital status and area of residency (indicating EU NUTS-2 regions) was obtained from the Danish Civil Registration System, and all data sources were linked through the unique civil registry number assigned to all Danish residents. [25-27]

Study population

By August 2021 all residents in Denmark over the age of 12 years had been offered two vaccine doses, and from December 2021 those aged over 18 years who had received their second dose more than four and a half months earlier were offered a third dose.[28] The study included all residents in Denmark aged 12+ years (or 18+ years for the analysis of three doses) on 28 December, 2021 without a previous positive PCR test. Those not tested during the study period were excluded.

Statistical analysis

We analysed time until SARS-CoV-2 infection, or COVID-19-associated hospitalisation, over a seven-week period starting on 28 December, 2021 when the Omicron variant accounted for approximately 90% of all PCR confirmed
cases investigated for Omicron through a variant specific PCR test targeting the 452L mutation, and increasing to
>99% by mid-January 2022. [5,29]

Fitting a separate Cox regression model for each dose level, rates of SARS-CoV-2 infection among participants
who had received two or three doses of either of the two COVID-19 mRNA vaccines that are part of the Danish
vaccination programme, BNT162b2 and mRNA-1273, were compared with the rate of infection in unvaccinated
participants. Rates of COVID-19-associated hospitalisations among vaccinated versus unvaccinated participants
were similarly compared. Vaccine effectiveness against hospitalisation after two vaccine doses was not estimated
for the mRNA-1273 vaccine due to sparse data.

Participant time was included in the analysis from December 28, 2021 or, if later, 14 days after the second (or third
where applicable) dose. Time was included until the earliest of February 15, 2022, a positive SARS-CoV-2 PCR
test (or COVID-19-associated hospitalisation depending on the modelled outcome), emigration, death or
vaccination with any COVID-19 vaccine (first dose for unvaccinated participants and third dose in the analysis
comparing two versus zero doses).

Exposure status was categorised as either unvaccinated or vaccinated with the last dose administered in the past
14-30 days, 31-60 days, 61-90 days, 91-120 days or over 120 days ago. Time falling outside of these categories was
not included in the analysis. Contrasts were estimated for each of the five vaccinated exposure categories versus
unvaccinated time as hazard ratios with 95% confidence intervals in Cox regression models. The models were
adjusted for age (<18, 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, ≥85 years), sex, number of comorbidities
(0, 1, 2, ≥3) and residency region (categorical variable with five levels) with calendar time as the underlying time
scale to control for temporal variations in the overall infection rate. Vaccine effectiveness was calculated as 1 minus
the hazard ratio.

All analyses were done using the SAS Software v9.4. Figures were done in GraphPad Prism v9. According to
Danish law, ethical approval is not required for anonymized aggregated register-based studies.
Data availability

De-identified participant-level data are available for access to members of the scientific and medical community for non-commercial use only. Applications should be submitted to Forskerservice at The Danish Health Data Authority, where they will be reviewed on the basis of relevance and scientific merit. To contact Forskerservice please see https://sundhedsdatastyrelsen.dk/da/forskerservice.


5. Genomic overview of SARS-CoV-2 in Denmark, Danish Covid-19 Genome Consortium, March 03, 2022: https://www.covid19genomics.dk/statistics


28. Everyone aged 18 and over can now get the 3rd booster vaccine dose, the Danish Health Authority, March 03, 2022: https://www.sst.dk/en/English/News/2021/Everyone-aged-18-and-over-can-now-get-the-3rd-booster-vaccine-dose

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Conflict of Interest Disclosures: The authors report no conflicts of interest.

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Table 1. Participant characteristics by vaccination status.

<table>
<thead>
<tr>
<th></th>
<th>Unvaccinated</th>
<th>BNT162b2 (Pfizer-BioNTech)</th>
<th>mRNA-1273 (Moderna)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>2 doses</td>
<td>3 doses</td>
</tr>
<tr>
<td></td>
<td>202,896 (100)</td>
<td>874,421 (100)</td>
<td>1,553,188 (100)</td>
</tr>
<tr>
<td>Female sex</td>
<td>Female sex</td>
<td>102,486 (50.5)</td>
<td>444,038 (50.8)</td>
</tr>
<tr>
<td></td>
<td>Median Age</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>22-42</td>
<td>17-39</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>12-100+</td>
<td>12-100+</td>
</tr>
<tr>
<td>Region</td>
<td>Capital</td>
<td>64,133 (31.6)</td>
<td>252,746 (28.9)</td>
</tr>
<tr>
<td></td>
<td>Central</td>
<td>42,752 (21.1)</td>
<td>213,720 (24.4)</td>
</tr>
<tr>
<td></td>
<td>Northern</td>
<td>19,448 (9.6)</td>
<td>92,620 (10.6)</td>
</tr>
<tr>
<td></td>
<td>Zealand</td>
<td>31,885 (15.7)</td>
<td>121,634 (13.9)</td>
</tr>
<tr>
<td></td>
<td>Southern</td>
<td>44,678 (22.0)</td>
<td>193,701 (22.2)</td>
</tr>
<tr>
<td>Comorbidities‡</td>
<td>0</td>
<td>177,392 (87.4)</td>
<td>781,778 (89.4)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>21,664 (10.7)</td>
<td>79,630 (9.1)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3,093 (1.5)</td>
<td>10,497 (1.2)</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>747 (0.4)</td>
<td>2,516 (0.3)</td>
</tr>
</tbody>
</table>

Data shown are frequencies (percentages) unless otherwise specified. IQR=interquartile range. ‡Number of comorbidities out of the following: diabetes, adiposity, haematological and other cancers, neurological diseases, kidney diseases cardiovascular diseases, chronic pulmonary diseases, respiratory diseases, and immune diseases.

Some participants contributed follow-up time first as unvaccinated and subsequently as vaccinated with 2 doses of BNT162b2 (n=1,232) or mRNA-1273 (n=75). Some participants contributed follow-up time to both the analysis of vaccine effectiveness after 2 and 3 doses after receiving dose 3 during the study with either BNT162b2 (n=321,070) or mRNA-1273 (n=106,758).
Table 2 Protection against infection and hospitalisation with the Omicron SARS-CoV-2 variant after 2 and 3 mRNA vaccine doses in Denmark from December 28, 2021 to February 15, 2022.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Days since vaccination</th>
<th>BNT162b2 (Pfizer-BioNTech)</th>
<th>mRNA-1273 (Moderna)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Population</td>
<td>Person-years</td>
</tr>
<tr>
<td>Protection against infection after 2 doses</td>
<td>Not vaccinated</td>
<td>202,896</td>
<td>18,676</td>
</tr>
<tr>
<td>14-30</td>
<td></td>
<td>59,306</td>
<td>1,995</td>
</tr>
<tr>
<td>31-60</td>
<td></td>
<td>66,925</td>
<td>3,449</td>
</tr>
<tr>
<td>61-90</td>
<td></td>
<td>53,982</td>
<td>2,154</td>
</tr>
<tr>
<td>91-120</td>
<td></td>
<td>122,743</td>
<td>4,091</td>
</tr>
<tr>
<td>121+</td>
<td></td>
<td>772,964</td>
<td>44,463</td>
</tr>
<tr>
<td>Protection against hospitalisation after 2 doses</td>
<td>Not vaccinated</td>
<td>202,896</td>
<td>18,676</td>
</tr>
<tr>
<td>14-30</td>
<td></td>
<td>59,306</td>
<td>1,995</td>
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<td>31-60</td>
<td></td>
<td>66,925</td>
<td>3,449</td>
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<td></td>
<td>53,982</td>
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<td></td>
<td>122,743</td>
<td>4,091</td>
</tr>
<tr>
<td>121+</td>
<td></td>
<td>772,964</td>
<td>44,463</td>
</tr>
<tr>
<td>Protection against infection after 3 doses</td>
<td>Not vaccinated</td>
<td>167,033</td>
<td>15,752</td>
</tr>
<tr>
<td>14-30</td>
<td></td>
<td>1,227,227</td>
<td>49,731</td>
</tr>
<tr>
<td>31-60</td>
<td></td>
<td>1,225,572</td>
<td>69,663</td>
</tr>
<tr>
<td>61-90</td>
<td></td>
<td>573,576</td>
<td>22,520</td>
</tr>
<tr>
<td>91-120</td>
<td></td>
<td>200,520</td>
<td>9,841</td>
</tr>
<tr>
<td>121+</td>
<td></td>
<td>59,085</td>
<td>3,338</td>
</tr>
<tr>
<td>Protection against hospitalisation after 3 doses</td>
<td>Not vaccinated</td>
<td>167,033</td>
<td>15,752</td>
</tr>
<tr>
<td>14-30</td>
<td></td>
<td>1,227,227</td>
<td>49,731</td>
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<td>121+</td>
<td></td>
<td>59,085</td>
<td>3,338</td>
</tr>
</tbody>
</table>

VE denotes vaccine effectiveness. CI denotes confidence interval. VE is calculated as 1 minus the hazard ratio from a Cox regression model adjusted for age, sex, comorbidity count and region of residency. The population included Danish residents aged ≥18 years (or ≥12 years for the analysis of 2 doses) on December 28, 2021 without a previous positive SARS-CoV-2 test and with at least one PCR test during the study period. Participants were able to contribute follow-up time in more than one time category and (if vaccinated during the study period) to both the analysis of VE after 2 and 3 doses.
Figure 1 Protection against infection and hospitalisation with the SARS-CoV-2 Omicron variant after two and three vaccine doses with either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna). VE denotes vaccine effectiveness (%). The vertical bars indicate 95% confidence intervals.