TITLE

Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a Danish nation-wide population-based study

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SUMMARY

Background: Estimates of immunity and severity for the SARS-CoV-2 omicron subvariant BA.5 are important to assess the public health impact associated with its rapid global spread despite vaccination. We estimated natural and vaccine immunity and severity of BA.5 relative to BA.2 in Denmark, a country with high mRNA vaccination coverage and free-of-charge RT-PCR testing.

Methods: This was an observational cohort study including residents 18 years or older with an RT-PCR test between 10 April and 20 June, 2022, identified in the national COVID-19 surveillance system database with information since February, 2020, on RT-PCR tests, wholegenome sequencing, vaccinations and hospitalisations with a positive test and COVID-19 as main diagnosis. We calculated the effect of prior omicron infection on the odds ratio (OR) of BA.5 infection among triple-vaccinated individuals (%protection=1-OR). For BA.5 relative to BA.2 we also calculated the OR of triple-vaccination vs none (ie. vaccine effectiveness) and the OR of hospitalisation. ORs were calculated in logistic regression models adjusted for age, time, sex, region, and comorbidities.

Findings: Among 4,809 BA.5 cases and 164,369 test-negative individuals, a prior omicron infection was highly protective against BA.5 (93.6%, 95%CI92.1-94.8; 96 BA.5 and 29,832 test-negative with prior omicron). Among 4,913 BA.5 and 31,874 BA.2 cases, the OR of triple-vaccination was not different (OR1.02, 95%CI0.83-1.26). Although the overall number of hospitalisations due to COVID-19 diagnosis was low and stable during the study period, the proportion of individuals infected with BA.5 increased. In the crude analysis BA.5 was not associated with hospitalisation (OR 1.04 (0.83-1.31) whereas the adjusted OR was 1.65 (1.16-2.34). The adjusted OR was increased in strata of age and calendar period – the two covariates with the largest contribution to confounding of the crude OR.

Interpretation: We found a high protection against BA.5 from prior omicron infection in triple-vaccinated individuals, and similar vaccine effectiveness for BA.5 infection as currently for BA.2. In an analysis adjusted for covariates, BA.5 infection was associated with an increased risk of hospitalisation which needs confirmation and continued surveillance as hospitalisations were low and stable during the study period.

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RESEARCH IN CONTEXT

Evidence before this study: Evidence from peer-reviewed papers were not available and therefore sources for epidemiological data were reports from local public health institutes (e.g. NICD in South Africa and INSA in Portugal). The evidence was collected as part of the routine COVID-19 variant surveillance in Denmark carried out by the authors' institution Statens Serum Institut (SSI). The WHO and ECDC SARS-CoV-2 Variants of concern updates contain assessments on transmissibility and severity of omicron subvariants with study references. The COVID-19 updates on the International Society for Infectious Diseases website (www.promedmail.org) were searched for relevant papers and preprints comparing omicron subvariants. Non-public information has been available via SSI's participation by co-author Dr. Friis in the WHO/Europe biweekly COVID-19 variants update meeting where relevant papers and reports are shared.

Several studies have shown a markedly increased immune escape of BA.4/5 compared to BA.1 and BA.2. In vitro and in vivo animal studies have also highlighted the potential for increased disease severity of BA.4/5 compared to BA.1 and BA.2. However, there is limited real-world evidence on the disease severity of BA.5 and the protection offered against BA.5 by vaccination and/or previous infection. A recent study from South Africa in preprint found that the risk of severe hospitalization and death were similar in the BA.4/5 wave and the preceding BA.1 wave. Previous studies have investigated BA.4 and BA.5 together, but BA.5 have consistently displayed higher growth rates than BA.4 across geographical regions.

Added value of this study: This population-wide study combine data from national registries with results from the extensive national wholegenome sequencing surveillance to estimate the protection offered by triple mRNA-vaccination or previous infection. We also investigated the specific disease severity of the Omicron subvariant BA.5 compared to BA.2. Estimates were adjusted for covariates including vaccination status, time-period, comorbidities and previous SARS-CoV-2 infection. We found a high protection against BA.5 infection among triple mRNA-vaccinated individuals with a previous omicron infection and no evidence of decreased vaccine effectiveness against BA.5 compared to BA.2. Interestingly, and to some extent at odds with available evidence on BA.5 severity, we found that the risk of hospitalization was higher with BA.5 infection compared to BA.2 infection.

Implications of all the available evidence: The available evidence show that previous omicron infection offers significant protection against BA.5 in triple mRNA-vaccinated individuals. Evidence also points to a similar vaccine effectiveness for BA.5 infection compared to BA.2 infection. This suggest that the impact of the current BA.5 wave will be limited in populations with a high degree of hybrid immunity. The increased risk of hospitalization after BA.5 infection found in our study merits further investigation into the disease severity of BA.5. These results may be used to target public health interventions during the ongoing BA.5 wave. This study also highlights how wholegenome sequencing continue to be a cornerstone in the surveillance of the SARS-CoV-2 pandemic.

INTRODUCTION

The BA.5 omicron subvariant is rapidly spreading globally[1] including in Denmark despite high vaccination coverage and a large proportion of the population previously infected with the omicron subvariants BA.1 and BA.2. BA.5 was first observed in South Africa[2] in co-circulation with BA.4 where it caused a fifth wave of infections through April and May 2022. BA.5 have also caused a recent surge in infections in Portugal where by the end of May 2022 it accounted for almost 90% of the tested samples with variant information [3].

BA.5 have acquired characteristic mutations in the spike protein, including the L452R, F486V mutations and a Q493 reversion, all in the receptor-binding domain. The L452R mutation was most notably present in the delta variant, and has been shown to help evade cellular immunity and increase infectivity[4]. Both L452R and F486V enables escape from established humoral immunity, even in individuals with BA.1 breakthrough infection[5]. BA.5 also contains the deletion 69-70 mutation (del69-70) in the S protein encoding gene, which is also present in BA.1, but not BA.2. The del69-70 is known from the Alpha variant (amongst others) and has been shown to increase infectivity[6]. Several studies have highlighted the reduced neutralisation of BA.4/5 compared to BA.1 and BA.2 after vaccination and in sera from individuals with BA.1 or BA.2 breakthrough infections[5,7,8].

While BA.5 is clearly highly transmissible, likely mainly due to immune escape, there is less clear evidence of its virulence relative to other omicron subvariants. Experiences from South Africa do not suggest an increased COVID-19 disease severity compared with BA.1 and BA.2 as measured by the number of hospital admissions and in-hospital deaths during the BA.4/5 wave[9]. A recent situational report from Portugal also found no evidence of increased risk of hospitalisation with BA.5 compared with earlier omicron subvariants (measured as the ratio of hospital admissions per case notification)[10]. In contrast, both South Africa and Portugal have experienced a rise in all-cause excess mortality during the period of BA.5 predominance [10,11]. omicron (B.1.529) replicates most efficiently in the upper parts of the respiratory tract[12,13] and is associated with less severe disease compared to previous variants of concern [14,15]. However, a study published before the emergence of BA.5 showed that the addition of L452R to omicron enhanced its ability to infect lung tissues of humanised ACE2 mice[16].

Another study found that BA.4/5 replicate more efficiently in human lung cells than BA.2 and is more pathogenic than BA.2 in hamsters[17]. A recent risk assessment from Santé Publique in France evaluated syndromic data on 288 BA.4/5 cases and found that the median disease duration was longer for individuals infected with BA.4/5 compared to BA.1 (median duration 7 days ([interquartile range (IQR); 3-10 days) vs. 4 days (IQR 2-7 days)). They also found a significantly higher proportion of BA.4/5-infected individuals suffering from nasal secretion, nausea, diarrhoea, ageusia and anosmia[18]. However, these results were not adjusted e.g. for higher age among the BA.5 cases or differences in vaccinations status.

Given the recent surge in SARS-CoV-2 infections caused by BA.5 it is important to establish whether infection with this subvariant is more likely to lead to serious disease than earlier subvariants, and the extent to which vaccination and previous infection protect against infection with BA.5. A preliminary analysis from the UK[19] found no difference in vaccination status between BA.5 and BA.2 cases in recently vaccinated individuals (<25 weeks since vaccination) compared to individuals vaccinated over 25 weeks prior to infection, indicating that vaccine effectiveness against BA.5 is comparable to that against BA.2.

Using information from wholegenome (WGS) sequencing and national registers in Denmark, we have previously described both vaccine effectiveness, protection of earlier variants against reinfection, and severity of omicron (BA.1 and BA.2), delta, alpha and other previous variants [20-26]. The aims of the

present study were to estimate, (1) the protection of a previous infection conveyed against a new infection with BA.5 among triple vaccinated, (2) the relative vaccine effectiveness against infection with BA.5 relative to BA.2, and (3) the severity of infection with BA.5 relative to BA.2.

METHODS

National test strategy

During 2020-22 of the pandemic, Denmark set up one of the highest reverse transcription Polymerase Chain Reaction (RT-PCR) testing capacities per capita in the world, testing up to one quarter of the population every week [27]. Tests are centrally registered and free-of-charge for all citizens. Since February 2022 testing has been downscaled from around 1.4 million weekly tests at the start of the year to 30.000-100.000 tests per week. Since 10 March, 2022, a PCR test was only recommended if the test-result was expected to inform COVID-19 treatment options, although these were not implemented during the study period. Primarily, recommendation of tests were based on being older than 65 years or belonging to a vulnerable group including being pregnant. Close contacts of infected cases no longer required testing and screening tests was reduced both in the community and health care test systems. As describe elsewhere [23], the test system is divided into a community track with test centres open to citizens and samples analysed at one laboratory site (TestCenter Denmark, TCDK), and a health care track with regional testing at clinics and hospitals and samples processed at 10 hospital laboratories (Departments of Clinical Microbiology).

Vaccination programme

COVID-19 vaccination coverage is high in Denmark. Starting 27 December 2020, vaccinations were offered with priority given to the elderly, those in the healthcare professions or otherwise most at risk of infection or severe disease. By August 2021, all over the age of 12 years had been offered a primary vaccination series. In the autumn of 2021, a booster dose was offered to selected priority groups before being offered more widely from December 2021 to all adults (18+ year-olds) who had completed their primary vaccination series more than 4.5 months earlier. By April 10, 2022 more than 80% of all adults had completed their primary vaccination series and more than 60% had also received a booster dose.[27] A small number of elderly and at-risk individuals received a second booster dose in the first half of 2022.[27] The majority received a primary vaccination series consisting of two mRNA doses with either Cominarty (Pfizer-BioNTech; BNT162b2) (~84%) or Spikevac (Moderna; mRNA-1273; ~12%), while a minority received the adenovector vaccines Vaxzevria (Oxford-AstraZeneca; ChAdOx1; ~3%), or Johnson & Johnson (Ad26.COV2.S JNJ-78436735; VAC31518; ~1%).[23][25]

Genome sequencing strategy and methods

One of the cornerstones of surveillance of SARS-CoV-2 in Denmark has been the extensive use of WGS (www.covid19genomics.dk) with a community track capacity of ~15,000 per week since 2021 and 4,000 since the end of June 2022 through TCDK in addition to samples from clinics and hospitals (the health care track) sequenced regionally at the Departments of Clinical Microbiology. Since the first BA.5 case identified on April 10, 2022, the proportion of isolates subjected to WGS has been >83% of all positive cases of which 85% have produced genomic data on which variants were called. Briefly, at SSI the WGS was performed using the ARTIC v3 amplicon sequencing panel (https://artic.network) with slight modifications including primer spike-ins. Samples were sequenced on either the NextSeq or NovaSeq platforms (Illumina) where consensus sequences were called using an in-house implementation of IVAR with a custom BCFtools

command for consensus calling. From the regional laboratories, consensus sequences were obtained. Subvariants on all genomes were called on the generated consensus sequences containing less than 3,000 missing sites or ambiguous sites using Pangolin with the PangoLEARN assignment algorithm.

Data sources

Data were extracted from the national COVID-19 surveillance system maintained at Statens Serum Institut (SSI; Copenhagen, Denmark) which has been described in detail elsewhere [28]. Briefly, the surveillance system links individual-level information daily between national registers and databases through the unique personal identification number assigned to all residents in the country. This allows centralised surveillance by linking person-level data from various national registers and databases. These include the National Patient Register [29] with person-level information on all inpatient and outpatient diagnoses, admission and discharge dates. From here we obtained data on hospital admissions, COVID-19 diagnosis codes as well as comorbidities based on the International Classification of Diseases 10th revision (ICD-10) diagnosis codes (diabetes, adiposity, haematological and other cancers, neurological diseases, kidney diseases cardiovascular diseases, chronic pulmonary diseases, respiratory diseases, and immune deficiency conditions). Further, from the National Vaccination Registry [30] we obtained data with person-level information on all COVID-19 vaccinations administered, and details of sex, age, vital status and previous and current addresses were obtained from the Civil Registration System [31]. Finally, data were obtained on all SARS-CoV-2 tests conducted by RT-PCR in Denmark since the start of the pandemic from the National Microbiology Database [28].

Study design and statistical methods

The study consisted of three main analyses pertaining to each of the research questions. The first analysis provides an assessment of the protection conveyed against a new omicron infection (studied separately against BA.5 and BA.2) by a previous infection with the omicron, delta or alpha variant in a fully vaccinated population. The second analysis was a comparison of the vaccine protection afforded after three mRNA doses against infection with BA.5 versus that afforded against BA.2. In the third analysis, the virulence of BA.5 was assessed by investigating the relative risk of hospitalisation after infection with BA.5 compared with BA.2.

Study population

The study population in all three analyses was restricted to those who were alive and over 18 years of age by April 10, 2022 and with uninterrupted residency in Denmark since February 2020 to ensure complete SARS-CoV-2 test and vaccination records for all. The designs of investigation in each of the three analyses required further restrictions on the study populations as detailed below. Briefly, analysis 1 involves only (triple) *vaccinated* individuals while analysis 2 and 3 involve only SARS-CoV-2 *infected* individuals.

Analysis 1: Protection against infection

The first analysis was conducted as a test-negative case-control study involving only those with a complete primary vaccination series and a subsequent booster dose, i.e. three mRNA doses in total with either the BNT162b2 or mRNA-1273 (or a combination of the two). Cases tested positive during the outcome period (April 10, 2022 to June 20, 2022) with the BA.5 subvariant identified through WGS, while controls had at least one PCR test during the outcome period but without testing positive for SARS-CoV-2. We then compared the proportion among cases and test-negative controls that had been exposed to a previous omicron infection, i.e. had a positive SARS-CoV-2 PCR test between January 1, 2022 and February 9, 2022, during which period BA.1 and BA.2 accounted for virtually all infections in Denmark. The exposure period

end date was chosen to ensure at least 60 days between a previous infection and a potential new infection during the outcome period as the analysis did not rely on genome sequenced samples from the exposure period. Those with a positive PCR test outside of this exposure period, and before the outcome period, were excluded from the analysis. Furthermore, those without a third mRNA dose by March 27, 2022 (14 days before the start of the outcome period to allow the full effect of vaccination), or with a fourth dose before June 20, 2022, were also excluded from the analysis.

The exposure effect, i.e. the protection from a previous infection, was estimated with a 95% confidence interval in a logistic regression model and expressed as 1 minus the model-derived odds ratio (OR) analogous to the method of estimating vaccine effectiveness. The logistic regression was adjusted for sex, age group (18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, >85 years), geographical area of residency (five-level categorical variable indicating EU NUTS-2 regions),[32] comorbidity count (four-level categorical variable indicating the number of comorbidities: none, one, two, three or more), and time of PCR sampling (categorical variable indicating week number)[31]. Among controls with multiple negative PCR tests during the outcome period, one was randomly selected for inclusion in the analysis. Among the few cases with more than one positive test during the outcome period, only the first positive test was included in the analysis.

Supplementary analyses:

In two extensions of the analysis, estimating instead at protection from a previous delta or alpha infection, the exposure definition was changed from infection during a period when omicron predominated to infection during July 15, 2021 to November 15, 2021 and March 15, 2021 to June 30, 2021, respectively, when the delta and alpha variant predominated. Finally, for comparison all analyses were repeated with cases being those who tested positive during the outcome period with BA.2 rather than BA.5.

Analysis 2: Vaccine protection

This analysis involved only infected participants: those infected with either BA.5, the BA.5-infected cases, or BA.2, the BA.2-infected controls, during the outcome period (April 10, 2022 to June 20, 2022). The analysis then compared vaccination status across the two groups as differences may be interpreted as evidence that the vaccines protect less well against one subvariant compared with the other. Only those with a complete primary vaccination series and a subsequent booster dose by March 27, 2022, i.e. three mRNA doses in total, or those completely unvaccinated against COVID-19 by June 20, 2022, were included in the analysis. The analysis excluded those with a PCR-confirmed SARS-CoV-2 infection prior to April 10, 2022 or with a fourth dose before June 20, 2022. The effect of vaccination on the likelihood of an infection being due to BA.5 rather than BA.2 was analysed in a logistic regression with adjustment as described for the analysis above and expressed as an OR with a 95% confidence interval.

Supplementary analysis:

As only few people remain completely unvaccinated in Denmark (~9% of those aged >18 years), a sensitivity analysis was carried out which did not rely on comparison with this group. In the sensitivity analysis, the reference exposure group was changed to those who had completed their primary vaccination series (2 mRNA doses) more than 4.5 months prior to the start of the outcome period but with no booster dose by June 20, 2022.

Analysis 3: Severity of a BA.5 infection

This analysis also involved only infected participants and compared the proportion of cases hospitalised among those infected with BA.5 during the outcome period from April 10, 2022 to June 20, 2022 with the proportion among those infected with BA.2 during the same period. The effect of subvariant (BA.5 versus BA.2) on the risk of hospitalisation was estimated in a logistic regression with adjustment as described above but with additional adjustment for vaccination status (categorical variable indicating the number of doses received at the time of infection). The analysis included all BA.2 or BA.5 cases in the outcome period, irrespective of COVID-19 vaccination history, and without a previous PCR-confirmed SARS-CoV-2 infection before the outcome period. Hospitalisations included in the analysis were restricted to those that lasted over 12 hours, had associated ICD-10 primary diagnosis codes B342 or B972 and occurred no earlier than two days before and no later than 14 days after a positive PCR-test.

Supplementary analyses:

A large majority of the adult population has received three COVID-19 mRNA doses. We therefore conducted a subgroup analysis in those who had received three mRNA doses prior to March 27, 2022 excluding anyone with a fourth dose before the end of the outcome period. In another supplementary analysis, the main analysis was repeated but with the outcome period extended by advancing the start date to January 1, 2022. Since the delta variant was still in a limited degree in circulation in early 2022 this analysis enabled estimation simultaneously of the effect of BA.5 and the delta variant on hospitalisation using the BA.2 hospitalisation rate as reference.

To evaluate collinearity and contributions to confounding from each of the covariates included in the main model, we subsequently excluded each covariate one at a time in a model always including variant (BA.5 vs BA.2) and keeping the remaining variables in the model. We checked for substantial changes in the parameter estimates or the standard errors when excluding each basic covariate, to evaluate the contribution of each covariate to the model.

Ethical considerations

This study was performed under the authority task of the Danish national infectious disease control institute, which allows Statens Serum Institut to perform analyses on data from existing national COVID-19 surveillance systems. According to Danish law, ethical approval or individual consent is not required for anonymized aggregated register-based studies.

RESULTS

Since the start of 2022 the omicron variant has accounted for virtually all SARS-CoV-2 infections in Denmark (Figure 1). Similar to many other countries, Denmark experienced a massive omicron wave between December 2021 and February 2022 with around 35% of the adult population infected during this three-month period (data not shown). Omicron infections were mainly due to the BA.1 and BA.2 subvariants during December 2021 to January 2022 after which point BA.2 became predominant lasting until the rise of BA.5.

Of the 4,621,974 people over the age of 18 years with residency in Denmark since February 2020, a total of 363,646 were tested by PCR during the outcome period from April 10 to June 20, 2022. Those tested during the outcome period were older, more likely to have comorbidities and without a previous PCR-confirmed

SARS-CoV-2 infection than those not tested during the outcome period (table 1). Of those tested during the outcome period 169,178 were included in Analysis 1, 36,787 were included in Analysis 2 and 41,984 were included in Analysis 3 (Figure 2).

Analysis 1: Protection against reinfection

Of the 4,809 triple-vaccinated cases who tested positive for SARS-CoV-2 with a BA.5 infection during the outcome period (between April 10, 2022 and June 20, 2022), only 98 (2.0%) had also tested positive for SARS-CoV-2 between January 1st and February 9th, 2022, when the BA.1 and BA.2 omicron subvariants accounted for almost all infections (table 2). By contrast, among the 164,369 triple-vaccinated controls who tested negative for SARS-CoV-2 during the outcome period, 29,832 (18.1%) had tested positive for SARS-CoV-2 between January 1 and February 9, 2022. The estimated protection was 93.6% (95% CI: 92.1 to 94.8%) suggesting that a previous omicron infection is highly protective against a new infection with BA.5. in a vaccinated population. By comparison, a previous delta or alpha infection provided much weaker protection of 46.9% (27.0 to 61.3%) and 65.4% (49.8 to 76.2%) respectively, against a new infection with BA.5.

In an additional analysis,estimating protection against BA.2 during the outcome period, a previous omicron infection was even more highly protective against BA.2 than we observed in the above analysis for BA.5, with an estimated protection against BA.2 of 96.3% (95.8 to 96.7%). As in the above analysis of protection against BA.5, a previous infection with the delta or alpha variant protected less well than a previous omicron infection with estimated protection against BA.2 infection of 77.2% (72.2 to 81.3%) and 74.5% (68.7 to 79.2%) respectively.

Analysis 2: Vaccine protection

In the vaccine analysis, which involved only SARS-CoV-2-positive cases during the outcome period from April 10 to June 20, 2022, 95.9% of those with a BA.5 infection and 95.3% of those with a BA.2 infection were vaccinated against COVID-19 with three mRNA doses (table 3). When comparing triple-vaccinated with unvaccinated individuals, the adjusted OR for the effect of the vaccine on the likelihood of an infection being due to BA.5 rather than BA.2, was 1.021 (0.827 to 1.261). When comparing triple-vaccinated individuals with those who had only received two mRNA doses over 4.5 months earlier, the adjusted OR for an infection being due to BA.5 rather than BA.2 was 1.203 (0.964 to 1.503). There was little evidence, therefore, that the mRNA vaccines protect less well against BA.5 than BA.2.

Analysis 3: Severity of a BA.5 infection

Among participants infected with BA.5 during the outcome period from April 10, 2022 to June 20, 2022, 1.4% (87/6,154) were admitted to hospital for COVID-19, as were 1.4% (487/35,830) among those infected with BA.2 during the same period (table 4). After adjustment, however, the OR for hospitalisation was 1.65 (1.16; 2.34) among those infected with BA.5 relative to BA.2. To evaluate to what degree the covariates confounded the crude null association, we excluded each adjustment covariate one at a time; only time and age had a strong confounding effect on the estimate. Further, the estimate did not change substantially when restricting the analysis to include only triple-vaccinated individuals (OR: 1.78; 95% CI: 1.21 to 2.63). When extending the outcome period moving the start date back to January 1, 2022, the OR for hospitalisation remained at 1.65 (1.16 to 2.34) among BA.5 cases relative to BA.2 cases. In the same period, delta cases were substantially more likely to require hospitalisation compared with BA.2 cases with an OR of 2.91 (1.70 to 4.99).

DISCUSSION

In this study we investigated the hazard presented by the BA.5 subvariant in terms of the risk of SARS-CoV-2 infection in a population with hybrid immunity, i.e. a previous infection and vaccine immunity, evidence of reduced vaccine effectiveness, and finally, severity of the infection relative to earlier strains.

Reassuringly, we found that a previous BA.1 or BA.2 omicron infection protected very well against a subsequent infection with BA.5. A previous alpha or delta infection also offered some immune protection although to a much lesser extent – perhaps because of waning immunity or reduced cross-reactive immunity. The level of immune protection of a previous infection was higher against BA.2 in the same period, probably reflecting the increased infectiousness of BA.5 impacting in the period as well as the fact that many of the previous omicron infections were also BA.2.

We found little evidence of poorer vaccine effectiveness against BA.5 infection compared with BA.2 infection. The OR estimates were close to unity both in the analysis using the relatively small population of unvaccinated cases as comparator and in the analysis using the similarly small population of double vaccinated cases as comparator. It is worth noting, however, that even if the vaccine effectiveness is exactly identical for the two subvariants, transmission rates may still be higher with BA.5 than BA.2, including among the vaccinated population, because identical vaccine effectiveness, simply only means that the relative rates of infection comparing vaccinated and unvaccinated remain the same for the two subvariants.

The analysis of severity showed evidence of higher hospitalisation rates among BA.5 infected cases relative to BA.2 cases in an adjusted analysis taking time and age into account. Thanks to the relative rarity of COVID-19 associated hospitalisations, the confidence interval around the OR was quite wide suggesting that the odds of hospitalisation with BA.5 might be anything from 16% higher to over twice as high compared with BA.2.

Importantly with most of the Danish population vaccinated against COVID-19, the subgroup analysis among triple mRNA vaccinated people similarly showed evidence of increased severity with BA.5 in the adjusted analysis. As expected, the analysis also showed increased severity from a delta infection with nearly three times the odds of hospitalisation relative to a BA.2 infection.

The severity of delta variant infections has been confirmed in several previous Danish studies. A recent study found that relative to a BA.1 infection delta was associated with nearly twice the rate of hospitalisations while rates were not different for BA.2 relative to BA.1 [23]. In an earlier study, comparing the severity of infection with delta versus alpha infection, delta was associated with nearly three times the rate of hospitalisations [21].

Studies on the protection of a previous SARS-CoV-2 infection have generally found good protection, around or above 80%, against reinfection, including our own studies, although a lower level of protection has generally been reported of earlier variant infections against a subsequent omicron infection likely due to a combination of waning immunity and lack of cross-immunity between variants [25,26,33,34]. In the present study, we found relatively poor protection of an alpha or delta infection against BA.5, but the protection against BA.2, with estimates in the range 70-80%, was considerably higher than that in our recent cohort analysis of an earlier variant infection against omicron in an *unvaccinated* population (estimates ranging between 19-51%). This may reflect differences in the study designs (cohort versus test-negative case-control analysis), different government guidance and population behaviour with respect to PCR testing

(first versus second quarter of 2022), or because of a genuine hybrid immunity effect in the vaccinated population.

For the vaccine effectiveness results (analysis 2), it is important to note that because the remaining unvaccinated group makes up such a small proportion of the population, we were unable to assess vaccine effectiveness directly as the ratio of infection rates in vaccinated and unvaccinated individuals. Instead, basing the analysis only upon infected individuals, the analysis compares the vaccination status in the BA.5 and BA.2 infected groups, providing a relative measure of vaccine effectiveness against BA.5 relative to BA.2.

In the recent preliminary analysis from the UK Health Security Agency a similar analysis strategy was followed comparing those recently vaccinated with a second, third or fourth dose to a baseline group of those vaccinated with a second or third dose more than 25 weeks prior to infection [19]. Similar to our study, this analysis did not find differences in the vaccination status among those infected with BA.5 versus BA.2 with an OR of 0.83 (0.64 to 1.08), although the report emphasises the need for a formal vaccine effectiveness analysis using a test-negative design. Importantly in this type of analysis, the OR is expected to be one in the absence of vaccine effectiveness against both sub-variants. The analysis therefore relies on there being some level of vaccine protection against infection with BA.2, or the relative measure will be non-informative.

Real-world evidence on the disease severity of BA.5 is sparse. Our analysis showed an increased risk of hospitalization with BA.5 compared to BA.2, however, a recent study (preprint) from South Africa found that the risk of severe hospitalization (i.e. admission to intensive care or mechanical ventilation or oral/intravenous steroid prescription) and death were similar in the BA.4/5 wave and the preceding BA.1 wave [35]. The study also found that infections during both omicron waves had lower risk of severe outcomes than in previous waves which is in line with our findings. In both Portugal and South Africa, the BA.5 wave passed without the COVID-19 hospital admissions and deaths exceeding that of the previous omicron wave, although Portugal reported excess mortality for a few weeks. The impact of a BA.5 wave will likely be determined in large parts by the characteristics of population immunity in each country [9,36].

Limitations and strengths

This analysis was made possible due to the intensive WGS efforts at SSI whereby the majority of isolates from PCR-confirmed cases are sequenced. However not all cases during the outcome period had variant information available, and it is possible that there is some bias in the selection of samples for sequencing as not all sequenced samples are selected at random.

Not all positive cases during the outcome period would have been identified as many are no longer tested. We do not believe this is a major source of bias, however, as analyses 1 employed a test-negative design, thereby conditioning on all individuals having been tested, whereas analysis 2 and 3 included only PCR-confirmed cases (either BA.2 or BA.5), again ensuring that all had been tested.

Finally, infection rates varied considerably throughout the first half of 2022 impacting test rates and the age profile of cases, and in turn the proportion of PCR confirmed cases that were hospitalised. However, alongside other adjustment variables, the severity analysis was adjusted for both age and week number, essentially only comparing rates of hospitalisation for BA.2 and BA.5 within the same week and age band. By evaluating the adjustment variables, we confirmed that age and time was the strongest contributors to confounding of the crude null association between BA.5 and hospitalisation. This may be explained by e.g variations in age of infected cases over time as the test strategy focusing on the elderly (perhaps more

comorbid) and pregnant were carried out while BA.5 became dominant. Importantly, the observation that BA.5 is more severe relative to BA.2 occurred in the context of stable and low absolute numbers of SARS-CoV-2 testpositive hospitalisations in Denmark during the study period.

Conclusion/implications

Our study found that a previous omicron infection offers significant protection against BA.5 in triple mRNA-vaccinated individuals. Evidence also points to comparable vaccine effectiveness against BA.5 infection compared to BA.2 infection. This suggest that the impact of the current BA.5 wave should be limited in populations with a high degree of hybrid immunity, i.e. will be comparable to that of the previous BA.2 wave. The increased risk of hospitalization after BA.5 infection found in our study merits further investigation into the disease severity of BA.5. This study also highlights how WGS continue to be a cornerstone in the surveillance of the SARS-CoV-2 pandemic.

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CONTRIBUTERS

All authors contributed to either the conception and design of the study, acquisition of data, or data analysis and interpretation. All authors had access to the underlying data and CHH and PB verified all data. CHH, NUF, and PB drafted the manuscript and all authors provided critical revisions and final approval for the decision to submit for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA SHARING

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. Data are available now, with no defined end date. For the *Forskerservice* website see https://sundhedsdatastyrelsen.dk/da/forskerservice. Consensus sequences from the Danish WGS surveillance is routinely made available at both GISAID (www.gisaid.org) and ENA (www.ebi.ac.uk/ena/).

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TABLES AND FIGURES

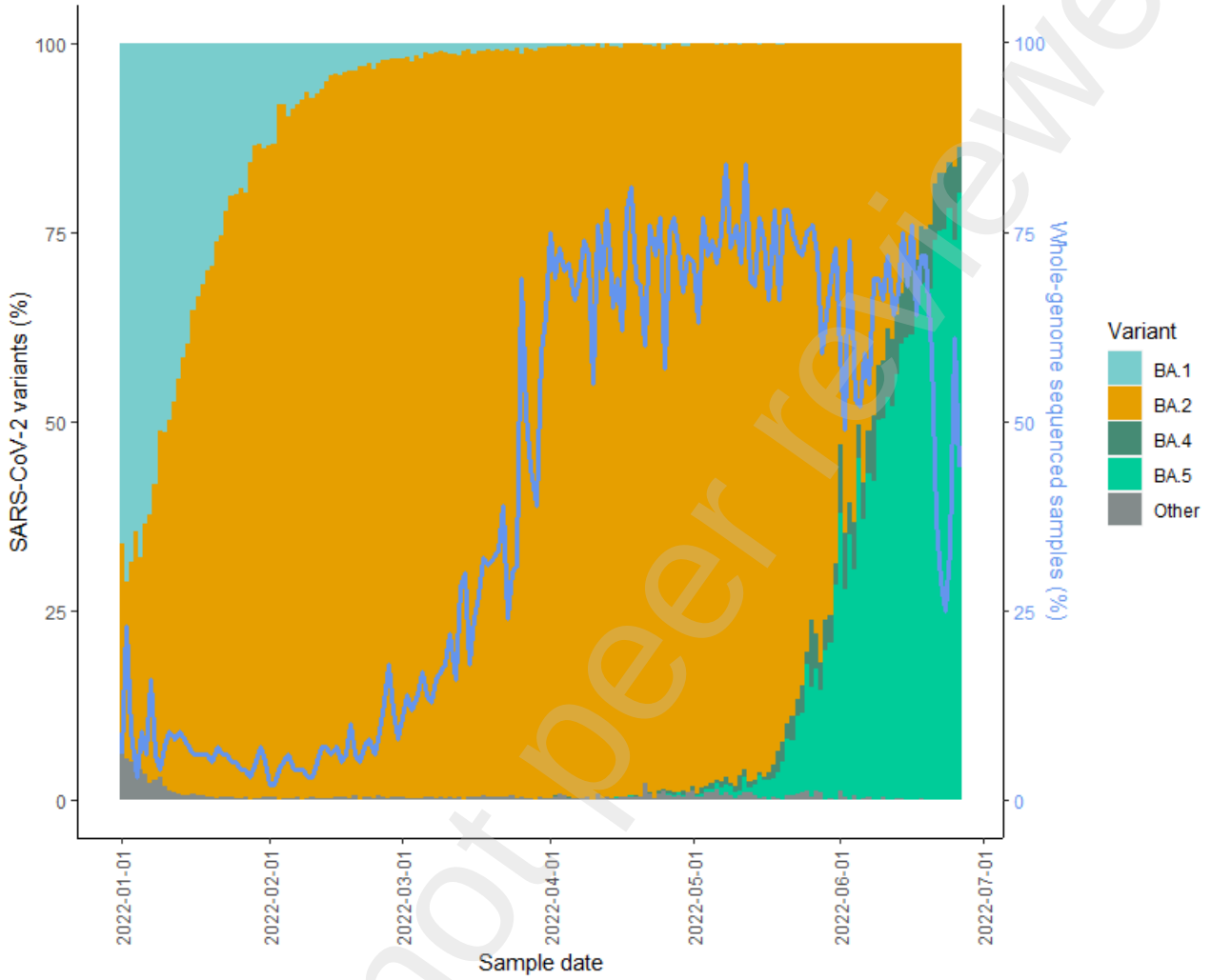

Figure 1 Proportion of cases with wholegenome sequencing and SARS-CoV-2 variants in 2022.

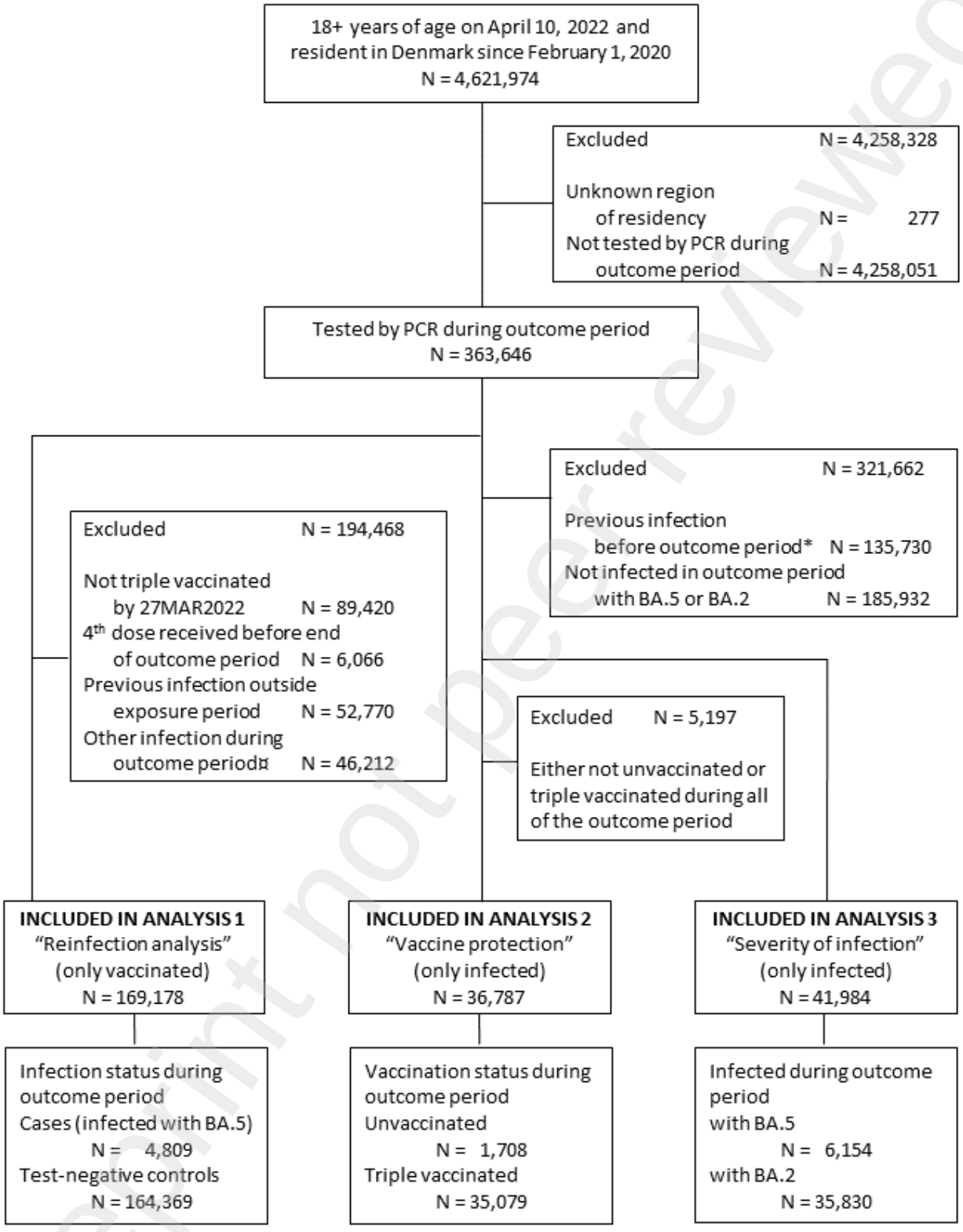

Figure 2 Population included in each of the three main analyses. Outcome period: April 10, 2022 to June 20, 2022. ¤ not shown to be BA.5

Table 1 Characteristics of the study population, 2022, Denmark.

Population: 18+ years of age on April 10, 2022 and resident in Denmark since February 1, 2020	**ALL**		**Tested by PCR during outcome period**	
	Number	*%*	*Number*	*%*
Total	4,621,974	100	363,646	100
Female	2,342,595	50.7	198,906	54.7
Male	2,279,379	49.3	164,740	45.3
Age (years)				
18-24	482,701	10.4	25,916	7.1
25-34	746,865	16.2	51,828	14.3
35-44	663,535	14.4	45,018	12.4
45-54	768,452	16.6	60,331	16.6
55-64	763,952	16.5	69,751	19.2
65-74	624,534	13.5	54,932	15.1
75-84	440,761	9.5	40,265	11.1
85+	131,174	2.8	15,605	4.3
Region of residency	#			
Copenhagen region	1,451,870	31.4	131,958	36.3
Central region	1,052,415	22.8	70,366	19.4
Northern Denmark	472,758	10.2	31,793	8.7
Zealand	673,167	14.6	55,894	15.4
Southern Denmark	971,487	21.0	73,635	20.2
Number of comorbidities*				
None	3,659,692	79.2	260,048	71.5
One	715,355	15.5	70,192	19.3
Two	186,125	4.0	23,515	6.5
Three or more	60,802	1.3	9,891	2.7
COVID-19 vaccinations$				
Unvaccinated	382,352	8.3	27,691	7.6
Only primary vaccination completed – 2 mRNA doses	31,542	0.7	2,982	0.8
Only primary vaccination completed – non-mRNA	4,641	0.1	469	0.1
Primary (mRNA) vaccination + 1 (mRNA) booster dose	3,396,390	73.5	268,711	73.9
Primary (non-mRNA) vaccination + 1 (mRNA) booster dose	147,970	3.2	16,156	4.4
Primary vaccination + 2 booster doses (any type)	36,463	0.8	5,749	1.6
Other¤	622,616	13.5	41,888	11.5
PCR-confirmed SARS-CoV-2 infections‡				
No previous infection	2,457,097	53.2	227,916	62.7
At least 1 previous infection	2,164,877	46.8	135,730	37.3
Infection likely with omicron	1,685,613	(77.9)	94,969	(70.0)
Infection likely with earlier variant	479,264	(22.1)	40,761	(30.0)

$ Vaccinations received by April 10, 2022: mRNA vaccines were either BNT162b2 or mRNA-1273, non-mRNA vaccines included JCOVDEN and ChAdOx1-S. ¤Incomplete primary vaccination or non-mRNA booster doses.*Comorbidities registered in the past 5 years out of the following: diabetes, adiposity, haematological and other cancers, neurological diseases, kidney diseases cardiovascular diseases, chronic pulmonary diseases, respiratory diseases, and immune deficiency conditions. ‡ Infection status by April 10, 2022. Likely omicron infections were those testing positive after December 20, 2021. # residency data missing for 277 individuals.

Table 2 Protection against BA.5 and BA.2 infection after a prior positive SARS-CoV-2 PCR test, April to June, 2022, Denmark.

	Cases	Test-negative controls	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Estimated protection, % (95% CI)
	BA.5 cases				**protection against BA.5**
Exposure: prior omicron infection					
Exposed	96 (2.0)	29,832 (18.1)	0.092 (0.075; 0.112)	0.064 (0.052; 0.079)	93.6 (92.1; 94.8)
Unexposed	4,713 (98.0)	134,537 (81.9)	1	1	
Exposure: prior delta infection					
Exposed	41 (0.8)	2,996 (1.5)	0.554 (0.407; 0.755)	0.531 (0.387; 0.730)	46.9 (27.0; 61.3)
Unexposed	4,962 (99.2)	200,953 (98.5)	1	1	
Exposure: prior alpha infection					
Exposed	30 (0.6)	1,702 (1.2)	0.503 (0.350; 0.723)	0.346 (0.238; 0.502)	65.4 (49.8; 76.2)
Unexposed	4,713 (99.4)	134,537 (98.8)	1	1	
	BA.2 cases				**protection against BA.2**
Exposure: prior omicron infection					
Exposed	249 (0.8)	29,832 (18.1)	0.037 (0.033; 0.042)	0.037 (0.033; 0.042)	96.3 (95.8; 96.7)
Unexposed	30,367 (99.2)	134,537 (81.9)	1	1	
Exposure: prior delta infection					
Exposed	101 (0.3)	2,996 (1.5)	0.215 (0.176; 0.262)	0.228 (0.187; 0.278)	77.2 (72.2; 81.3)
Unexposed	31,512 (99.7)	200,953 (98.5)	1		
Exposure: prior alpha infection					
Exposed	99 (0.3)	1,702 (1.2)	0.258 (0.210; 0.316)	0.255 (0.208; 0.313)	74.5 (68.7; 79.2)
Unexposed	30,367 (99.7)	134,537 (98.8)	1	1	

All participants had received 3 mRNA COVID-19 vaccine doses. Cases were infected with either BA5 or BA.2 during the outcome period from April 10, 2022 to June 20, 2022. OR denotes odds ratio; CI denotes confidence interval. Unexposed individuals had no positive PCR tests before the start of follow-up on April 10, 2022. *adjusted for age group, time (week number), sex, region and comorbidity.

Table 3 Vaccine protection against infection with BA.5 relative to BA.2, April to June, 2022, Denmark.

Exposure (vaccination status)[$]	Type of infection contracted during outcome period: Infected with BA.5	Type of infection contracted during outcome period: Infected with BA.2	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Three doses versus unvaccinated				
Three doses	4,713 (95.9)	30,366 (95.3)	1.17 (1.01; 1.36)	1.02 (0.83; 1.26)
Unvaccinated	200 (4.1)	1,508 (4.7)	1	1
Three versus two doses				
Three doses	4,713 (96.5)	30,366 (95.7)	1.22 (1.04; 1.44)	1.20 (0.96; 1.50)
Two doses	171 (3.5)	1,348 (4.3)	1	1

All participants were infected with either BA.5 or BA.2. The outcome period was between April 10, 2022 and June 20, 2022. The analysis excludes anyone with a previous infection before April 10, 2022. OR denotes odds ratio; CI denotes confidence interval. *Adjusted for age group, time (week number), sex, region and comorbidity. $ Three doses: 3 doses of mRNA-1273 or BNT162b2 before March 27, 2022; two doses: completed primary vaccination series >140 days before the outcome period.

Table 4 Severity of BA.5: risk of hospitalisation after infection, April to June, 2022, Denmark.

Exposure (type of infection)	Hospitalised for COVID-19	Cases not hospitalised¤	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Main analysis				
BA.2	487 (1.4)	35,343 (98.6)	1	1
BA.5	87 (1.4)	6,067 (98.6)	1.04 (0.83; 1.31)	1.65 (1.16; 2.34)
Supplementary analysis 1:				
Subgroup analysis in vaccinated (3x mRNA) $				
BA.2	388 (1.3)	29,909 (98.7)	1	1
BA.5	76 (1.4)	5,209 (98.6)	1.13 (0.88; 1.44)	1.78 (1.21; 2.63)
Supplementary analysis 2:				
Extended outcome period ‡				
BA.2	2,367 (1.5)	159,399 (98.5)	1	1
BA.5	87 (1.4)	6,067 (98.6)	0.97 (0.78; 1.20)	1.65 (1.16; 2.34)
Delta	27 (5.1)	502 (94.9)	3.62 (2.45; 5.35)	2.91 (1.70; 4.99)

All participants were infected with SARS-CoV-2. The main and supplementary analysis 1 included BA.2 and BA.5 infections that occurred during the outcome period between April 10, 2022 and June 20, 2022. The analysis excludes anyone with a previous infection. ‡ Supplementary analysis #2 included BA.2, BA.5 and delta infections that occurred between January 1, 2022 and June 20, 2022. ¤Includes a few cases hospitalised for other reasons. *Adjusted for age group, time (week number) of infection, sex, region, comorbidity and, with the exception of the subgroup analysis, vaccination status. $ Three doses of mRNA-1273 or BNT162b2 before March 27, 2022.