Relative vaccine protection, disease severity and symptoms associated with the SARS-CoV-2 Omicron subvariant BA.2.86 and descendant JN.1: A Danish nationwide observational study

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SUMMARY

Background

Using national electronic health registry data from all regions of Denmark, we investigated whether the SARS-CoV-2 variant BA.2.86, including its descendent JN.1, differed from other circulating variants in terms of ability to escape vaccine protection, risk of infections leading to severe disease, and self-reported symptoms among infected cases.

Methods

We included all Danish residents over 65 years of age with a positive SARS-CoV-2 PCR test and available genomic variant data between October 1, 2023 and December 31, 2023. Data from clinical testing, sentinel and self-sampling-based surveillance were linked with national electronic civil, vaccination and hospitalisation registers. Relative protection of the XBB 1.5 updated COVID-19 vaccine against BA.2.86 infections versus non-BA.2.86 infections, and relative risk of hospitalisation, were analysed in case-control studies adjusted for time, comorbidities, and prior vaccination history among other potential confounders. Prevalence rates of self-reported symptoms were reported separately by variant strain.

Findings

Of the 3,862 COVID-19 cases included in the study, 2,184 (57%) were infected with the BA.2.86 variant, including 1,615 JN.1 infections. Cases who were XBB.1.5 vaccinated and became infected had 1.52 (95% CI 1.25-1.86) the odds of being infected with BA.2.86 than another variant, and 1.60 (95% CI 1.27-2.02) the odds of being infected with JN.1 than another (non-BA.2.86) variant, compared with cases who became infected and had not received the XBB.1.5 vaccine. The severity analysis showed no evidence of association between variant and risk of COVID-19 hospitalisation (OR 1.04, 95% CI 0.86–1.26 for BA.2.86 and OR 1.07, 95% CI 0.85–1.34 for JN.1*). Similarly, we found no evidence of differences in self-reported symptoms by variant strain.

Interpretation

BA.2.86, and the JN.1 sublineage, were less sensitive to vaccine-induced immune protection from the XBB.1.5 updated COVID-19 vaccine, but with no evidence of increased disease severity or different symptom profiles.

Funder

This study was conducted as part of the Danish COVID-19 surveillance with governmental financial support. Additional support was provided within the European Union's EU4Health programme under Grant Agreement Nr 101102733 DURABLE

RESEARCH IN CONTEXT

Evidence before this study

BA.2.86 and in particular it's descendant JN.1 have spread rapidly around the world compatible with greater immune escape as evidenced in virological studies, while vaccine protection against, and the severity of infections with, these new variants remain unclear. We conducted a search on PubMed and medRxiv with the search term ("BA.2.86" OR "JN.1"), with no date or language restrictions. The search was last updated on March 4, 2024, and yielded 115 results. More than half of the results were virological studies, e.g. of neutralising antibodies against BA.2.86 or JN.1, and some were studies of first cases and outbreaks of BA.2.86 in different countries. One study from the Netherlands suggested escape of BA.2.86 infections from immunity induced by recent prior infection and possibly also from XBB.1.5 vaccination (OR 1.6, 95% CI 0.9-2.9), although the number of sequenced JN.1 cases in this study was small (n=314). A study from Qatar suggested immune escape of presumed (nonsequenced) JN.1 infections (n=4828) from immunity induced by recent prior infection. A US study reported reduced vaccine effectiveness against JN.1 (n=258). No further reports were found on vaccine effectiveness and none were reporting evidence on severity of infections or symptoms for the two variants.

Added value of this study

In an epidemiological study based on nationwide electronic healthcare registry data, we found that BA.2.86*, including JN.1*, SARS-COV-2 virus strains are better at escaping protection induced by the XBB.1.5 updated COVID-19 vaccine than the co-circulating non-BA.2.86 strains. However, our case control study only looked at infected people and thus we cannot estimate the absolute vaccine efficacy for protection from infection, only the relative protection from being infected by one variant versus another. There was no evidence, however, that infections with BA.2.86* or JN.1* were associated with more severe COVID-19 disease as the risk of hospitalisation, admission to ICU and the symptoms profiles were similar to those for other circulating lineages.

Implications of all the available evidence

Clear evidence is emerging that the BA.2.86 and JN.1 SARS-CoV-2 variants are less sensitive to immune protection from prior infections as well as the XBB.1.5 updated COVID-19 vaccine. However, there is little evidence that infections with these new variants are more severe or differ in symptoms relative to existing variants.

INTRODUCTION

The SARS-CoV-2 omicron subvariant BA.2.86 was first detected in August 2023 with cases reported in Denmark, Israel, the United States and the United Kingdom followed shortly after by further sporadic cases in several more countries.(1–3) Since then the variant has spread across much of the world, and with the appearance of the JN.1 sublineage is now the fastest growing COVID-19 strain in many places.(4)

The BA.2.86 variant differs notably from previous variants due to its 34 new mutations in the spike protein.(5) Its prevalence over other circulating variants was facilitated by the emergence of the JN.1 descendant, which carries an additional important mutation, L455S. The L455S mutation enhances the virus's ability to bind to the human Angiotensin-converting enzyme 2 (ACE2) receptor, facilitating cell entry. This suggests an evolutionary pattern that may contribute to both altered immune evasion and increased severity of infection.(6) Consequently, WHO reclassified BA.2.86 in November and later JN.1 in December as variants of interest.(7) Further, recent findings in virological studies,(6,8,9) although not all,(10) suggest variants emerging after XBB.1.5, and in particular JN.1, are more resistant to serum neutralization, and thus may have a growth advantage despite the rollout of the latest COVID-19 vaccines that have been updated to target the XBB.1.5 variant.

We recently reported a reduced risk of COVID-19 hospitalisation in Denmark among +65-year-olds who had received the monovalent XBB.1.5 updated seasonal COVID-19 vaccine compared with those who had not yet received it (HR=0.239, 95% CI 0.152, 0.377) in October 2023 when BA.2.86 accounted for only very few cases.(11) The extent to which the new vaccine protects against BA.2.86 therefore remains unclear. The new vaccine has been available in Denmark since October, 2023 coinciding with the appearance and rapid growth of the JN.1 sublineage. To our knowledge, no epidemiological evidence exists from large-scale population-based studies on the vaccine sensitivity of BA.2.86 or JN.1, symptom burden and risk of severe disease.

In this study we used national surveillance data recorded for the period October 1 to December 31, 2023 to investigate whether BA.2.86 and JN.1 differ relative to other circulating variants in terms of 1) their ability to escape vaccine induced immunity from the monovalent XBB.1.5 updated COVID-19 vaccine, 2) risk of infections leading to admission to hospital or intensive care and 3) the symptom burden reported by infected cases.

METHODS

Study design

All study participants were SARS-CoV-2 infected Danish residents with a positive PCR test between October 1, 2023 and December 31, 2023 (the study period), and available whole-genome sequencing data

identifying the SARS-CoV-2 variant that had caused their infection. The analysis of vaccine protection and risk of hospitalisation was restricted to cases aged ≥65 years while the analysis of self-reported symptoms included participants of any age who had enrolled in a nationwide surveillance system for respiratory illness. The study comprises three main analyses: (1) The analysis of relative vaccine protection was designed as a case-control study comparing the proportion of XBB.1.5 vaccinated individuals (the exposure) among those infected with a BA.2.86 infection (the cases) to that among those infected with another SARS-CoV-2 variant (the controls). (2) The relative risk of hospitalisation was similarly analysed in a case-control analysis comparing the proportion of infections that were due to the BA.2.86 strain (the exposure) among those hospitalised for COVID-19 (the cases) to that among those not hospitalised for COVID-19 (the controls). (3) Finally in the analysis of symptoms, prevalence rates based on self-reported questionnaire data of commonly reported COVID-19 symptoms were presented separately by SARS-CoV-2 variant strain.

For the purpose of the analysis, cases were considered hospitalised due to COVID-19 if they were hospitalised for more than 12 h, had associated ICD-10 primary diagnosis codes B342 or B972 (indicating that COVID-19 was the primary reason for hospital admission), and a positive PCR test from two days before to 14 days after their hospital admission date. All other cases, whether hospitalised or not, were categorised as not hospitalised for COVID-19. Below, and unless otherwise stated BA.2.86 and its subvariants are grouped as BA.2.86*, JN.1 and its subvariants are grouped as JN.1*, and all other variants are grouped as “non-BA.2.86”.

Data sources

The study was based on Denmark’s national COVID-19 surveillance system and population-wide registers with individual level data that are updated and linked daily using the unique civil registration number given to all residents. All COVID-19 vaccinations administered in the country were obtained from the National Vaccination Registry.(12) Hospital admission and discharge dates, diagnoses and ICU referrals were obtained from the National Patient Registry.(13) Data on 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) were similarly obtained from the National Patient Registry. Vital status and residency data were obtained from the civil registration system (14) along with other demographic information including sex, age, migration heritage and address history. In adherence to SAGER guidelines for sex and gender reporting, we derived the sex variable from the civil registration numbers assigned at birth or time of entry in Denmark. Persons with an odd numerical value are categorised as male at birth, while those with an equal numerical value are categorized as female. This method aligns with SAGER guidelines, providing a standardized approach to sex assignment in our analysis.

Details of all SARS-CoV-2 PCR tests conducted during the study period were obtained from the Danish Microbiology Database.(15) During the study period all SARS-CoV-2 PCR test results recorded in the national microbiology database originated from one of three sources, namely clinical samples taken on indication,(16) sentinel surveillance through a national system based on ECDC and WHO guidelines,(17) and a recently implemented self-sampling virus monitoring system (*Virus monitoring in Denmark*). The latter began in May 2023, inviting individuals from workplaces and later randomly selected Danish residents to self-sample at home when experiencing respiratory infection symptoms. Samples were analysed at the national reference laboratory at Statens Serum Institut (SSI) using a multiplex PCR-panel for SARS-CoV-2, RSV, Influenza A, and Influenza B. A description of the pilot study preceding this surveillance system has been published.(18) Further details are included in the supplementary material (appendix p 8).

Genomic sequencing

The majority of SARS-CoV-2 positive samples were sequenced at SSI after whole genome amplification using the ARTIC V5.3.2 primer scheme. Samples were sequenced with Illumina technology on a NextSeq instrument after libraries were generated with the COVIDSeq Test Kit according to the manufacturers instructions. Consensus sequences were generated with custom pipeline (19) and lineage designation using Nextclade.(20) A small number of samples were sequenced at the local Departments for Clinical Microbiology. Like SSI, these are part of the Danish COVID-19 Genome Consortium and therefore follow the same requirements for quality control (QC).(21) PCR positive samples are defined by a cycle threshold (CT) value less than 38. All analyses were conducted using validated and approved systems. For participants with ≥2 sequenced samples during the study period, only the first was included in the study.

Vaccinations

The XBB.1.5 updated COVID-19 vaccine was offered to all individuals aged ≥65 years and other at-risk groups from October 1, 2023. Prior to that, the primary COVID-19 vaccinations had been administered to >80% of adults with >60% of all adults given at least one booster dose. Booster doses with the bivalent vaccines targeting both the ancestral strain as well as either Omicron BA.1 or BA.4/5 were offered to all over the age of 50 years during the 2022/23 winter season.

Statistical analysis methods

To assess the relative vaccine protection offered by recent vaccination with the XBB.1.5 updated COVID-19 vaccine against infections with BA.2.86* relative to infections with other SARS-CoV-2 variants, the proportion of XBB.1.5 vaccinated individuals among those with a BA.2.86* infection was compared to that among individuals infected with a non-BA.2.86 variant. The association was analysed in a logistic regression with variant as the modelled outcome and XBB.1.5 vaccination as the main exposure of interest with further adjustment for sex, residency region, age (5-year bands), number of comorbidities (0, 1, 2, ≥3) and prior

vaccination history (four indicator variables capturing whether the primary COVID-19 vaccination schedule was completed, and whether a first, second and third booster dose was given). The regression analysis was also adjusted for the SARS-CoV-2 test date through a restricted cubic spline function with five knots at the 5th, 27.5th, 50th, 72.5th and 95th percentiles. (22) The odds ratio from this analysis for the association between vaccination status and SARS-CoV-2 variant estimates the increase in the likelihood of a BA.2.86 infection escaping vaccine protection relative to that of a non-BA.2.86 infection escaping vaccine protection (for technical details see appendix p9). To assess the relative vaccine protection separately for infections that did and did not require hospitalisation, the analysis was repeated but with separate effects for XBB.1.5 vaccination estimated within the subgroups of those hospitalised for COVID-19 and those who were not. Evidence for differential subgroup effects was assessed using a likelihood ratio test to compare the models with and without interaction by subgroup. Calendar time was strongly associated with both XBB.1.5 vaccination and prevalence of BA.2.86* infection. To assess the adequacy of the calendar time adjustment in the main analysis the model was refitted in a sensitivity analysis with stratification by test date using conditional logistic regression (see appendix p8 for more explanation of this approach). To assess vaccine protection specifically against the JN.1* strain, all above analyses were repeated but restricting the BA.2.86* infections to those caused by JN.1*.

The severity of illness caused by infections with BA.2.86* was assessed by comparing the proportion of BA.2.86* infections among cases hospitalised for COVID-19 with that among individuals not hospitalised for COVID-19. The association between hospitalisation for COVID-19 and variant was analysed in a case-control study and the odds ratio estimated in a logistic regression with hospitalisation for COVID-19 as the modelled outcome, variant as the main exposure and adjustment for all the variables described above for the vaccine protection analysis with additional adjustment for XBB.1.5 vaccination. Assuming that the rates of BA.2.86* infections among cases and controls included in the study reflect those in the population respectively of patients hospitalised for COVID-19 and SARS-CoV-2 positive individuals who are not hospitalised for COVID-19, the odds ratio from this analysis estimates the relative risk of hospitalisation for BA.2.86* relative to that for a non-BA.2.86 variant. As above the model was refitted in a sensitivity analysis with stratification by test date using conditional logistic regression. The controls in this analysis consisted of individuals who were not hospitalised for COVID-19, but many of the PCR tests originated from hospital departments and some individuals in the control group were therefore hospitalised for other reasons. As it is possible that their SARS-CoV-2 infection contributed to their condition, a sensitivity analysis was conducted in which all hospital patients were excluded from the control group. The analysis thus contrasted patients hospitalised for COVID-19 with SARS-CoV-2 infected individuals who were not hospitalised for any reason. As before all analyses were repeated for JN.1.

Finally, the proportion of patients admitted to ICU among cases hospitalised due to BA.2.86* was compared to that among patients hospitalised due to other variants and the contrast analysed using exact conditional logistic regression stratified by PCR test date to control for calendar time.

Participants in *Virus monitoring in Denmark* who reported being symptomatic when registering their swab were asked to indicate which ones, if any, of 20 symptoms they were experiencing. The proportion of respondents during the study period from October 1 to December 31 who reported each symptom was presented separately along with 95% confidence intervals for those infected with BA.2.86*, JN.1*, and non-BA.2.86* infections.

ROLE OF FUNDING SOURCE

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript or the decision to submit it for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

When the first cases of BA.2.86 were identified in August 2023, the SARS-CoV-2 variants circulating in Denmark were almost exclusively EG.5.1* or another XBB.1* variant (Figure 1). BA.2.86* made up a relatively small proportion of infections until the emergence of JN.1* when it began to spread rapidly towards the end of October, 2023 coinciding with the rollout of the new COVID-19 vaccines targeting the XBB.1.5 variant. During the study period from October 1 to December 31, 2023, the proportion of BA.2.86* infections, including JN.1*, grew from around 10% to 90%.

During that same period a total of 7,581 people over 65 years of age tested SARS-CoV-2 positive by PCR. Of these, 5,882 (78%) were eligible for sequencing, and 3,862 (66 %) passed QC and were succesfully sequenced with the variant identified (Figure 2). The 3,719 samples (1,699 + 2,020) that were not sequenced were more likely to originate from the capital region compared with the sequenced samples (Table 1). The majority of the 3,862 included samples originated from hospital departments; 1,406 participants were hospitalised for >12h with a primary diagnosis of COVID-19, while 1,527 participants were hospitalised with another primary diagnosis or hospitalised for any reason but <12h. The remaining 929 participants were not hospitalised in connection with their infection. There were some differences in demographic characteristics across the three groups, notably with the hospitalised cases being older on average and more likely to be male among other differences (appendix, p1, Table S1).

Approximately half of the study participants were female (46%, n=1,780), the median age was 79 years (interquartile range 73-84 years), and 62% (n=2,407) were registered with at least one comorbidity (Table 1).

Nearly all had completed the primary COVID-19 vaccination schedule and 83% (n=3,223) had subsequently received at least two booster doses (not including the new XBB.1.5 updated vaccine). Those infected with BA.2.86* were slightly more likely to be male and to reside in the region of central Denmark than those infected with a non-BA.2.86 variant.

During the study period 2,184 participants were infected with BA.2.86*, including 1,615 JN.1* infections. Of these 1,223 (56.0%) had been vaccinated with the XBB.1.5 updated COVID-19 vaccine at least seven days before the date of their positive SARS-CoV-2 PCR test (Table 2). By comparison, only 367 (21.9%) of the 1,678 non-BA.2.86 cases had received the XBB.1.5 vaccine seven or more days prior to testing positive. The adjusted odds of infection with BA.2.86*, as opposed to a non-BA.2.86 variant, were 1.52 (95% CI 1.25–1.86) times higher among XBB.1.5 vaccinated cases compared to those who had not received the vaccine ≥7 days earlier suggesting that BA.2.86* is 1.52 times more adept at escaping vaccine-induced immunity than the other circulating variants. Similarly, the odds of infection with JN.1*, as opposed to a non-BA.2.86 variant, was 1.60 (1.27–2.02) times higher among XBB.1.5 vaccinated cases. (Note that these results are not suggestive of an increased BA.2.86*/JN.1* infection risk among vaccinated versus unvaccinated individuals, only that the vaccines work less well against these new variants.)

Similar findings were obtained when estimating the effect in cases hospitalised for COVID-19 (OR 1.53, 95% CI 1.11–2.11 for BA.2.86* and OR 1.68, 95% CI 1.15–2.45 for JN.1*), and when estimating the effect in cases not hospitalised for COVID-19 (OR 1.53, 95% CI 1.20–1.93 for BA.2.86* and OR 1.57, 95% CI 1.19–2.07 for JN.1*; appendix, p2, Table S2). Results nearly identical to those in the main analysis were obtained when controlling for calendar time by stratifying on the PCR test date rather than by estimating the effect of time as an adjustment variable in the regression (appendix, page 3, Table S3). The results were also virtually unaffected when excluding from the analysis those who had received the XBB.1.5 vaccine within seven days or within 14 days of testing positive, and when restricting the analysis to individuals with at least two booster doses prior to the study start (appendix, p 3, Table S3).

Throughout the study period the proportion with a BA.2.86* infection was similar among those hospitalised for COVID-19 and those not hospitalised for COVID-19 (appendix, p 4, Figure S1). Overall, BA.2.86* accounted for 54.2% (762/1,406) of infections among those hospitalised for COVID-19, and 57.9% (1,422/2,456) of infections among those who were either not hospitalised or not hospitalised for COVID-19 (Table 3). There was no evidence in the adjusted analysis of an association between variant and risk of hospitalisation for COVID-19 (OR 1.04, 95% CI 0.86–1.26), i.e. there was no evidence that a case infected with BA.2.86* was more likely to require hospitalisation than a case infected with a non-BA.2.86 variant. Similarly, there was no evidence that infection with JN.1* was more likely to lead to hospitalisation for COVID-19 than an infection with a non-BA.2.86 variant (OR 1.07, 95% CI 0.85–1.34). Very similar findings were obtained when the analysis was stratified by PCR sample date (appendix, p 5, Table S4). When all

hospitalisations lasting <12h and those not identified as being due to COVID-19 (n=1,527) were excluded from the analysis, there was still no evidence of an association between BA.2.86* infection and risk of hospitalisation for COVID-19 (OR 1.01, 95% CI 0.78–1.31), nor was there evidence of increased risk of hospitalisation for COVID-19 with JN.1* infections (OR 0.99, 95% CI 0.73–1.35; appendix, page 5, Table S4). Of those hospitalised due to BA.2.86*, 4.6% (35/762) were admitted to an ICU whereas 2.2% (14/644) of those hospitalised due to non-BA.2.86 infections were admitted to ICU. In the adjusted analysis controlling for time there was no evidence of an association. (p=0.37; appendix, page 6, Table S5).

In the study period, 1,247 submitted samples from participants reporting symptoms in *Virus monitoring in Denmark* tested positive for SARS-CoV-2. Of these, whole genome sequencing results were available from 930 (75%) participants. The median age among respondents was 49 years (interquartile range 36-57 years), 46 were aged <18 years and only very few participants (n = 15) were >65 years of age. Most were female (n = 591, 64%). Individual symptoms were reported in similar proportions by participants infected with BA.2.86 strains (excluding JN.1*), JN.1*, and non-BA.2.86 strains respectively (Figure 3). Thus, no apparent differences in symptoms were observed across SARS-CoV-2 variant groups.

DISCUSSION

We found that the XBB.1.5 updated COVID-19 vaccine provides poorer protection against BA.2.86* infections compared to other SARS-CoV-2 lineages. The BA.2.86* strains, including JN.1*, were seen to escape vaccine protection 1.52 times more frequently than other variants. In a recent study we estimated the comparative vaccine effectiveness (compared to people who had received the seasonal booster dose the previous year) to be 76.1% against hospitalisation for COVID-19 shortly after vaccination with the XBB.1.5 vaccine in October 2023 when BA.2.86* accounted for only a small proportion of infections.(11) As a rough approximation, the comparative vaccine effectiveness against disease requiring hospitalisation due to BA.2.86* may therefore be estimated at about 64% (=1-((1-0.761)*1.52)) shortly after vaccination. It is important to note, therefore, that while we have found evidence of reduced vaccine protection against BA.2.86* strains we are certainly not suggesting that XBB.1.5 vaccination is ineffective against these new variants. We also compared the severity of BA.2.86* infections with other variants and found comparable hospitalisation and ICU admission rates in a population aged >65 years. Additionally, in a younger population we found that self-reported symptom profiles among COVID-19 cases were similar for BA.2.86*, JN.1*, and non-BA.2.86 infections.

Prior studies had limited data on JN.1, and did not study hospitalisation risk or specific symptoms. (23) However, a study from the Netherlands suggested a relative immune escape of BA.2.86 infections from recent prior infection, and possibly from XBB.1.5 vaccination (OR 1.6, 95% CI 0.9-2.9) - no separate analysis was reported for the sequenced JN.1 cases (n=314). In support, a study from Qatar suggested

immune escape of presumed (nonsequenced) JN.1 cases (n=4828) from recent prior infection. (24) An early observational study from USA of the XBB.1.5 vaccine reported lower vaccine effectiveness against "likely JN.1" cases, defined by S gene target positive result (n=258), than for those with a negative result (40% vs. 60%). (25) These findings are consistent with the poorer relative vaccine protection we observed for hospitalisation for each of the variants. A likely reason for the success of BA.2.86-descendant lineages, such as observed in the present study, is immune escape in a population where immunity is increasingly derived from infection with or vaccination against XBB lineages. However, the molecular mechanism for this is not fully understood, and several studies report no significant difference in immune evasion from neutralizing antibodies when comparing BA.2.86, or JN.1, to other currently circulating variants like EG.5.1 and XBB.1.5.(10,26) Our findings indicate that the higher level of immune escape is not associated with more severe infection. Over the course of the pandemic, vaccine effectiveness against hospitalisation has mostly been preserved across variants of concern. This is likely due to T cell responses not being focused on the spike receptor-binding domain of the SARS-CoV-2 virus where most mutations have occurred. (27) Hence, altered ACE-2 binding, as observed for JN.1, might have limited impact on severity in the first place.

The analyses presented in this study included only participants who had tested positive for SARS-CoV-2. Many of the potential biases, such as those relating to testing behaviour and differential exposure risks, that are otherwise present in studies that rely on comparisons with non-infected participants were therefore avoided. The case-control design allowed us to compare vaccine protection across variant strains without having to directly estimate vaccine effectiveness. Similarly, we were able to estimate the relative risk of hospitalisation across variant strains without estimating the actual risks of hospitalisation following infection with the relevant variants. While widespread testing of asymptomatic and mildly symptomatic individuals is no longer performed in Denmark, our study includes samples from a population-based surveillance cohort, offering insights on cases with milder symptoms that have not sought contact with the healthcare system. This cohort consisted of mostly younger, working age individuals with only very few participants aged >65 years. It is possible therefore that the symptoms reported in this younger cohort differ from the typical symptoms experienced by COVID-19 cases who are aged over 65 years. Nonetheless, the fact that no differences were observed, even in this younger age group, between the symptoms reported by those with and without a BA.2.86* infection adds to the overall evidence in support of the hypothesis that infections with BA.2.86* are no more severe than infections with other existing variants. Due to the completeness of the Danish electronic health and civil data registries, the study had no or very little missing data in the conventional sense: age, sex and address history (from which residency region was derived) were fully observed. Registration of COVID-19 vaccinations administered in the country is mandatory, however some vaccinations given abroad may not have been registered. As details on comorbidities derive from the national patient registry, some comorbidities that have not been identified in interactions with the hospital service will have been missed in our study data. The vast majority of SARS-CoV-2 infections in the country are no

longer registered and the study was therefore unable to control for or consider interactions with prior infection history. Further,the results of the severity analysis have a degree of uncertainty attached to them as the control group of non-hospitalised participants constitute a very small proportion of all infected cases in the country now that most cases are undetected due to a lack of large-scale testing.

The findings from this population-level epidemiological study suggest that the BA.2.86*, including JN.1*, SARS-COV-2 virus strains are better at escaping protection induced by the XBB.1.5 updated COVID-19 vaccine with BA.2.86* being an estimated 1.52 times more likely to result in a breakthrough infection than the currently circulating non-BA.2.86 infections. Although somewhat less effective against these new variants, vaccination remains protective and reduces the risk of infection and disease from COVID-19. There was no evidence that infections with BA.2.86* or JN.1* were associated with more severe COVID-19 disease as the risk of hospitalisation, admission to ICU and the symptoms profiles were similar to those for other circulating lineages.

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CONTRIBUTORS

All authors contributed to either the conception and design of the study, acquisition of data, or data analysis and interpretation. CH did the statistical analyses for the vaccine protection and severity analyses. TGL analysed the symptoms data. All authors had access to the underlying data and CH and IM verified all data. CH, IM, PB drafted the manuscript with substantial contributions from (TGL, MR, FM, LV) and the corresponding author confirms that 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.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interests.

ACKNOWLEDGEMENTS

This study was conducted as part of the Danish COVID-19 surveillance with governmental financial support. Additional support was provided within the European Union's EU4Health programme under Grant Agreement Nr 101102733 DURABLE. TGL is a fellow of the ECDC Fellowship Programme, supported financially by the European Centre for Disease Prevention and Control. Views and opinions expressed do not necessarily reflect those of the European Union, HaDEA or ECDC. Neither the European Union nor the granting authority can be held responsible for them.

ETHICS STATEMENT

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.

DATA SHARING

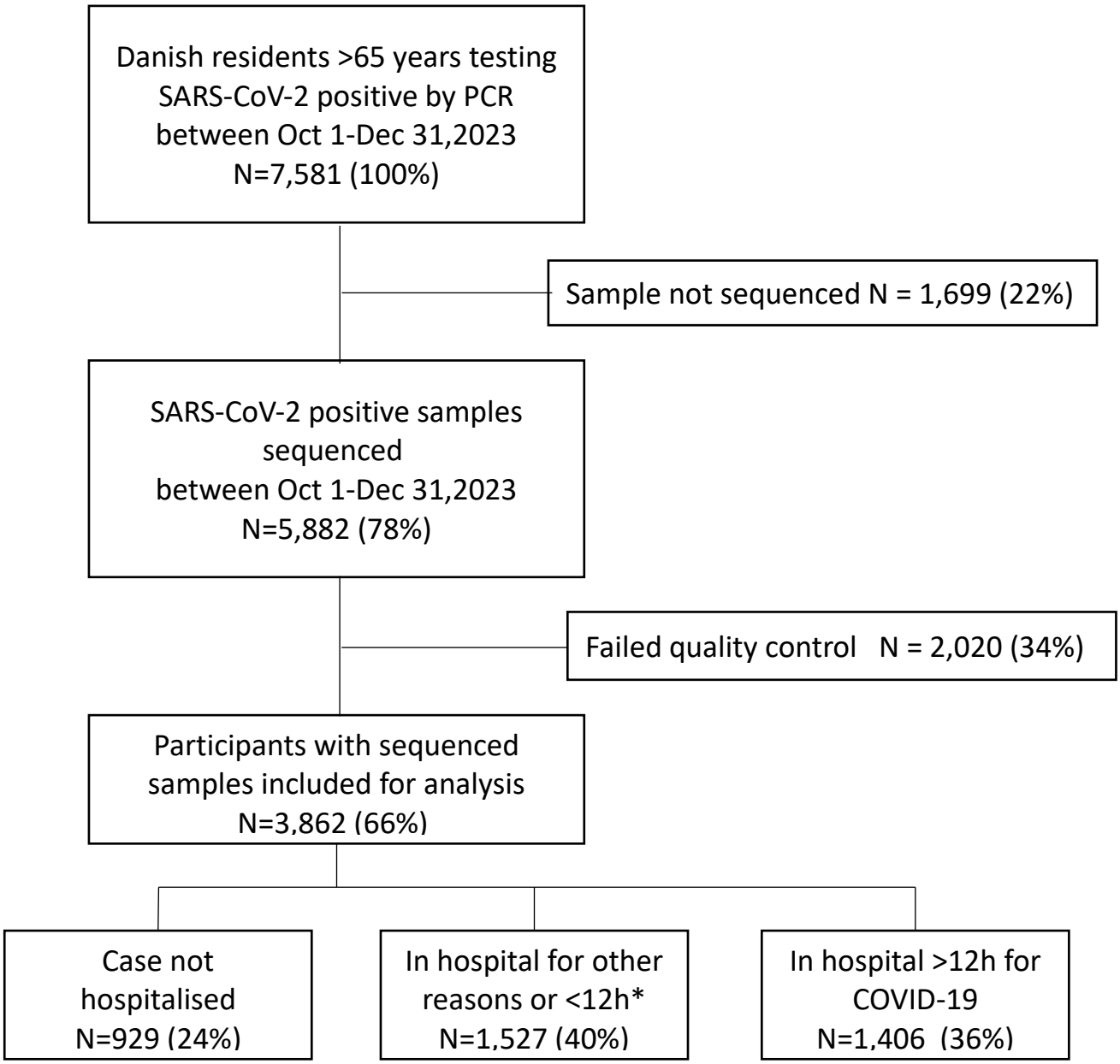
De-identified participant-level data are available for access to members of the scientific and medical community for non-commercial use only. Applications should be submitted to Forskerservice at The Danish Health Data Authority, where they will be reviewed on the basis of relevance and scientific merit.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

FIGURE LEGENDS

Figure 1: Proportion of abundant Pango lineages in Denmark since Aug 28, 2023 (data derived from the Danish Covid-19 Genome Consortium). The study period is between the black vertical lines.

Figure 2 Flow of participants included in the study

Figure 3: Prevalence (and 95% CI) of self-reported symptoms among 701 symptomatic COVID-19 cases participating in *Virus monitoring in Denmark*, reported separately by SARS-CoV-2 variant.



*Hospitalised <12h for any reason, or hospitalised >12h for reasons not primarily due to COVID-19

Figure 2 Flow of participants included in the study

Table 1: Characteristics of the study population and comparison with ineligible participants

	Participants included in study				Excluded from study (sample not sequenced)	
	All	Infected with BA.2.86 variant	Infected with non-BA.2.86 variant	p		p
Total	3,862 (100)	2,184 (100)	1,678 (100)		3,719 (100)	
Sex						
Female	1,780 (46)	969 (44)	811 (48)	0.014	1,804 (49)	0.035
Male	2,082 (54)	1,215 (56)	867 (52)		1,915 (51)	
Age (years)						
65-69	533 (14)	324 (15)	206 (12)	0.115	540 (15)	0.167
70-74	601 (16)	340 (16)	261 (16)		646 (17)	
75-79	987 (26)	561 (26)	426 (25)		924 (25)	
80-85	810 (21)	452 (21)	358 (21)		736 (20)	
85+	931 (24)	504 (23)	427 (25)		873 (23)	
Region of residency						
Capital	1,029 (27)	582 (27)	447 (27)	<0.001	1,718 (46)	<0.001
Central Denmark	698 (18)	446 (20)	252 (15)		446 (12)	
Northern Denmark	454 (12)	227 (10)	227 (14)		308 (8)	
Zealand	768 (20)	409 (19)	359 (21)		594 (16)	
Southern Denmark	913 (24)	520 (24)	393 (23)		653 (18)	
Migration heritage¤						
Denmark	3,589 (93)	2,019 (92)	1,570 (94)	0.351	3,402 (91)	0.093
Other European country	144 (4)	83 (4)	61 (4)		165 (4)	
Middle East and north Africa	74 (2)	49 (2)	25 (1)		79 (2)	
Other	55 (1)	33 (2)	22 (1)		73 (2)	
Number of comorbidities†						
None	1,455 (38)	802 (37)	653 (39)	0.337	1,309 (35)	0.113
One	1,051 (27)	597 (27)	454 (27)		1,019 (27)	
Two	732 (19)	414 (19)	318 (19)		747 (20)	
Three or more	624 (16)	371 (17)	253 (15)		644 (17)	
Primary COVID-19 vaccinations completed by study start						
Yes	3,723 (96)	2,109 (97)	1,614 (96)	0.530	3,552 (96)	0.049
No	139 (4)	75 (3)	64 (4)		167 (4)	
Primary vaccination, completion date*	27 Apr 2021	27 Apr 2021	26 Apr 2021	0.428	25 Apr 2021	0.407
Median	(23 Mar 2021	(23 Mar 2021	(23 Mar 2021		(21 Mar 2021	
(IQR)	15 May 2021)	15 May 2021)	14 May 2021)		15 May 2021)	
COVID-19 booster vaccines received by study start‡						
None	225 (6)	132 (6)	93 (6)	0.292	253 (7)	0.060
One	414 (11)	247 (11)	167 (10)		449 (12)	
Two	2,974 (77)	1,657 (76)	1,317 (78)		2,794 (75)	
Three or more	249 (6)	148 (7)	101 (6)		223 (6)	

Data are number (percent) unless otherwise indicated. P-values are from chi-square tests (unless otherwise indicated) comparing participants with and without a BA.2.86 infection (first column of p-values), or those included versus excluded (second column of p-values). *Date of 2nd dose for 2-dose schedules or 1st dose for 1-dose schedules; p-values from Wilcoxon rank sum tests. †Comorbidities registered during the past 5 years from among (in descending order of prevalence): cardiovascular diseases, chronic pulmonary and respiratory diseases, diabetes, neurological diseases, kidney diseases, adiposity, haematological and other cancers, and immune deficiency conditions. ‡excluding the 2023/24 seasonal booster. ¤Migration heritage was defined by country of birth or, if known, mother's country of birth.

Table 2 Relative vaccine protection of the XBB.1.5 COVID-19 vaccine measured among individuals infected with either BA.2.86 or another SARS-CoV-2 variant

	SARS-CoV-2 variant		OR (95% CI) ‡	p-value
XBB.1.5 COVID-19 vaccinated				
≥7 days prior to infection	**BA.2.86***	**Non-BA.2.86 strain**		
Yes	1,223 (56.0)	367 (21.9)	1.52 (1.25; 1.86)	<0.001
No	961 (44.0)	1,311 (78.1)		
	JN.1*	**Non-BA.2.86 strain**		
Yes	984 (60.9)	367 (21.9)	1.60 (1.27; 2.02)	<0.001
No	631 (39.1)	1,311 (78.1)		

Analysis includes only infected individuals. Data shown indicate frequency (percentage). OR = odds ratio.
CI = confidence interval. * Including sublineages. ‡ OR for the association between vaccination and variant estimated in a logistic regression adjusted for age, sex, comorbidities, residency region, prior vaccination history and SARS-CoV-2 PCR test date.

Table 3 Association between SARS-CoV-2 variant and risk of COVID-19 hospitalisation

	Hospitalised for COVID-19		Not hospitalised/ Not hospitalised for COVID-19 #			
	Number	% with indicated strain	Number	% with indicated strain	OR (95% CI) ‡	p-value
SARS-CoV-2 infection was with						
BA.2.86*	762	54.2	1,422	57.9	1.04 (0.86; 1.26)	0.69
Another (non-BA.2.86) variant	644	45.8	1,034	42.1		
JN.1*	557	46.4	1,058	50.6	1.07 (0.85; 1.34)	0.59
Another (non-BA.2.86) variant	644	53.6	1,034	49.4		

Analysis includes only infected individuals. OR = odds ratio. CI = confidence interval. * Including sublineages. # Includes individuals hospitalised for other reasons, i.e. unrelated to COVID-19. ‡ OR for the association between variant and COVID-19 hospitalisation estimated in a logistic regression adjusted for age, sex, comorbidities, residency region, prior vaccination history, SARS-CoV-2 PCR test date and whether vaccinated with the XBB.1.5 updated COVID-19 vaccine.

1