Risk of hospitalisation associated with infection with SARS-CoV-2 lineage B.1.1.7 in Denmark: an observational cohort study

*Peter Bager, Jan Wohlfahrt, Jannik Fonager, Morten Rasmussen, Mads Albertsen, Thomas Yssing Michaelsen, Camilla Holten Møller, Steen Ethelberg, Rebecca Legarth, Mia Sarah Fischer Button, Sophie Gubbels, Marianne Voldstedlund, Kåre Mølbak, Robert Leo Skov, Anders Fomsgaard, Tyra Grove Krause, and The Danish Covid-19 Genome Consortium**

Summary

Background The more infectious SARS-CoV-2 lineage B.1.1.7 rapidly spread in Europe after December, 2020, and a concern that B.1.1.7 could cause more severe disease has been raised. Taking advantage of Denmark's high RT-PCR testing and whole genome sequencing capacities, we used national health register data to assess the risk of COVID-19 hospitalisation in individuals infected with B.1.1.7 compared with those with other SARS-CoV-2 lineages.

Methods We did an observational cohort study of all SARS-CoV-2-positive cases confirmed by RT-PCR in Denmark, sampled between Jan 1 and March 24, 2021, with 14 days of follow-up for COVID-19 hospitalisation. Cases were identified in the national COVID-19 surveillance system database, which includes data from the Danish Microbiology Database (RT-PCR test results), the Danish COVID-19 Genome Consortium, the National Patient Registry, the Civil Registration System, as well as other nationwide registers. Among all cases, COVID-19 hospitalisation was defined as first admission lasting longer than 12 h within 14 days of a sample with a positive RT-PCR result. The study population and main analysis were restricted to the proportion of cases with viral genome data. We calculated the risk ratio (RR) of admission according to infection with B.1.1.7 versus other co-existing lineages with a Poisson regression model with robust SEs, adjusted a priori for sex, age, calendar time, region, and comorbidities. The contribution of each covariate to confounding of the crude RR was evaluated afterwards by a stepwise forward inclusion.

Findings Between Jan 1 and March 24, 2021, 50 958 individuals with a positive SARS-CoV-2 test and at least 14 days of follow-up for hospitalisation were identified; 30 572 (60·0%) had genome data, of whom 10 544 (34·5%) were infected with B.1.1.7. 1944 (6·4%) individuals had a COVID-19 hospitalisation and of these, 571 (29·4%) had a B.1.1.7 infection and 1373 (70·6%) had an infection with other SARS-CoV-2 lineages. Although the overall number of hospitalisations decreased during the study period, the proportion of individuals infected with B.1.1.7 increased from 3·5% to 92·1% per week. B.1.1.7 was associated with a crude RR of hospital admission of 0·79 (95% CI 0·72–0·87; p<0·0001) and an adjusted RR of 1·42 (95% CI 1·25–1·60; p<0·0001). The adjusted RR was increased in all strata of age and calendar period—the two covariates with the largest contribution to confounding of the crude RR.

Interpretation Infection with SARS-CoV-2 lineage B.1.1.7 was associated with an increased risk of hospitalisation compared with that of other lineages in an analysis adjusted for covariates. The overall effect on hospitalisations in Denmark was lessened due to a strict lockdown, but our findings could support hospital preparedness and modelling of the projected impact of the epidemic in countries with uncontrolled spread of B.1.1.7.

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*Collaborators listed in the appendix

Division of Infectious Disease Preparedness (P Bager PhD, C H Møller PhD, S Gubbels PhD, M Voldstedlund PhD, Prof K Mølbak DMSc, R L Skov MD, T G Krause PhD), **Department of Epidemiology Research** (J Wohlfahrt DMSc, P Bager), **Department of Virus & Microbiological Special Diagnostics** (J Fonager PhD, M Rasmussen PhD, A Fomsgaard PhD), **and Infectious Disease Epidemiology & Prevention** (Prof S Ethelberg PhD, R Legarth PhD, M S F Button MD), **Statens Serum Institut, Copenhagen, Denmark; Department of Chemistry and Bioscience, Aalborg University, Aalborg, Denmark** (M Albertsen PhD, T Y Michaelsen MSc); **Department of Veterinary and Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark** (Prof K Mølbak)

Correspondence to:
Dr Peter Bager, Division of Infectious Disease Preparedness, Statens Serum Institut, 2300 Copenhagen, Denmark
pbg@ssi.dk

See Online for appendix

Introduction

On Dec 14, 2020, Denmark was notified through the European Early Warning Response System by the UK health authorities of the occurrence and rapid spread of a new lineage variant of SARS-CoV-2 (B.1.1.7). This lineage is characterised by several mutations in the spike protein of the virus. At the time, Denmark was one of a few countries to have already uploaded B.1.1.7 SARS-CoV-2 genomes to the Global Initiative On Sharing Avian Influenza Data (GISAID), with the first cases identified on Nov 14.[1]

Denmark reached a weekly RT-PCR testing rate of 10 000 tests per 100 000 people in December, 2020.[2] Throughout the epidemic, Denmark increased its capacity for whole genome sequencing (WGS) from fewer than 100 samples to more than 5000 weekly sequenced samples currently, and it has documented a rapid increase in the proportion of B.1.1.7 among sequenced samples, from 0·3% in week 46, 2020, to 93% in week 12, 2021.[3] The relative reproduction number of B.1.1.7, compared with that of all other circulating lineages, has been estimated to be 1·55 (95% CI

Research in context

Evidence before this study

We searched PubMed for articles up to May 3, 2021, containing the search keywords ("B.1.1.7" OR "B117") AND ("admission" OR "hospitalisation") with no language restrictions. Our search yielded 50 articles. Two studies addressed the association between B.1.1.7 and risk of hospitalisation or the clinical course of patients hospitalised with COVID-19. One study found no differences in self-reported symptoms, disease course, or hospitalisation among users of the COVID Symptom Study mobile phone application associated with the geographical B.1.1.7 transmission rate. This study was limited by the ecological design without individual level data on virus lineage and by admissions to hospital being assessed by self reporting. The other study addressed the clinical severity of B.1.1.7 among a cohort of 496 patients hospitalised with COVID-19 and found no evidence of an association between severe disease and death and lineage (B.1.1.7 *vs* non-B.1.1.7). So far, no studies have described the severity of B.1.1.7 infections in terms of risk of hospitalisation in a population-based setting using individual level data.

Added value of this study

We were able to assess the risk of hospitalisation associated with B.1.1.7 using individual-level data from national registers in Denmark, a country with one of Europe´s highest RT-PCR and whole genome sequencing capacities. We were able to adjust for several important confounding factors that can bias the interpretation of complex surveillance data. Our results are in line with previous studies that have found an increased mortality risk associated with B.1.1.7 infections.

Implications of all the available evidence

The consequences of emerging new variants challenge the public health response at the global level. An increased hospitalisation risk associated with B.1.1.7 might have important public health implications in countries with uncontrolled spread of B.1.1.7. Our report complements previous analyses on hospitalisation and mortality risk associated with B.1.1.7 and could support modelling of the effects of the pandemic and support hospital capacity planning.

1·48–1·62) by use of a serial interval of 4·7 days,[4] in line with findings from the London School of Hygiene and Tropical Medicine, which estimated that B.1.1.7 is 43–82% (95% credible interval across three geographical regions 38–106) more transmissible than pre-existing lineages of SARS-CoV-2.[5]

The increase in B.1.1.7 infections occurred while Denmark was in a lockdown implemented on Dec 16, 2020, due to a surge in COVID-19 cases not related to B.1.1.7. In the beginning of January, the Danish Government's strategy was to reduce the case numbers and pressure at the hospitals substantially before mid-February, when B.1.1.7 was estimated to become the dominant SARS-CoV-2 lineage.[6] The lockdown was efficient in reducing case numbers and hospital admissions from January to February, but the relative proportion of COVID-19 cases related to B.1.1.7 increased during the period, and the lineage-specific reproduction number of B.1.1.7 was estimated to be 1·25 on Feb 16.[7]

On Jan 22, 2021, a report was published by the UK New and Emerging Respiratory Virus Threats (NERVTAG) group on the severity of B.1.1.7 compared with other COVID-19 lineages.[8] The report was updated on Feb 11 with additional analyses from different study groups and datasets addressing whether infections with variant of concern B.1.1.7 were associated with an increased risk of hospitalisation and mortality.[9] Until May 6, 2021, two studies on mortality have been published, showing an increased risk (hazard ratio) of mortality related to B.1.1.7 of 64% (95% CI 32–104)[10] and 61% (42–82)[11] compared with other variants. The results regarding the risk of hospitalisations in the NERVTAG report were contradictory. A matched cohort study from Public Health England found no association between B.1.1.7 and hospitalisations in initial analyses, whereas a cohort study from Public Health Scotland suggested an increased risk (hazard ratio) of hospitalisation of 63% (48–80).[9] In two studies with different cohorts of patients hospitalised with COVID-19, no evidence was found of increased mortality or severity in patients with B.1.1.7 compared with those infected with other variants. One of these studies has been published.[12] The NERVTAG report concludes that "it is likely that infection with variant of concern B.1.1.7 is associated with an increased risk of hospitalisation and death compared to infection with non-variant of concern viruses".[9]

It is of urgent public health importance to address whether infection with B.1.1.7 is associated with more severe outcomes in terms of hospitalisation, because the spread of this viral lineage might result in a higher constrain on the health-care systems in the coming months than was modelled before its emergence.

In this study, we linked SARS-CoV-2 genomic data with Danish Health Registers and estimated the risk of hospital admission in individuals with B.1.1.7 compared with those with other SARS-CoV-2 lineages.

Methods

Study design and population

For this observational cohort study, we included all cases of SARS-CoV-2 infection in Denmark confirmed by RT-PCR test of samples from swabs taken between Jan 1 and March 24, 2021, and with 14 days of follow-up for hospitalisation. The study population and main analysis was restricted to the proportion of cases with viral genome data. All analyses were based on updated data

from the national COVID-19 surveillance system database on March 24, 2021. This study was done with use of administrative register data. According to Danish law, ethics approval is not needed for such research.

Information on infection with lineage B.1.1.7 and other lineages of SARS-CoV-2 (ie, viral genome data) was available for individuals with a positive SARS-CoV-2 RT-PCR test for whom WGS resulted in a viral genome with fewer than 3000 undetermined bases, hereafter referred to as samples with a viral genome. The specific lineage was classified by use of the Pangolin COVID-19 Lineage Assigner.[13–15]

Data sources

We obtained data from the Danish Microbiology Database for all individuals tested with SARS-CoV-2 by RT-PCR in Denmark[16–18] and data from other national registers, available in the national COVID-19 surveillance system database at Statens Serum Institut (SSI; Copenhagen, Denmark), described elsewhere.[19] Briefly, the surveillance system links individual-level information daily between national registers and databases by use of the unique personal identification number of all Danish citizens, thereby centralising surveillance information from the National Patient Register (inpatient and outpatient diagnoses, admission, and discharge dates),[20] the Civil Registration System (vital status and previous and current addresses),[21] and viral WGS data from the Danish COVID-19 Genome Consortium,[22] among others.

In Denmark, health-care personnel (who are routinely tested) and individuals with symptoms suggestive of COVID-19 who were seen by a doctor are tested for SARS-CoV-2 by RT-PCR in regional clinics connected with the ten Danish departments of clinical microbiology, which serve public and private hospitals and primary care clinics. This workflow is referred to as the health-care track. Additionally, a centralised high-throughput public COVID-19 test laboratory—the Test Center Denmark (TCDK)—was established by the end of April, 2020, at SSI. TCDK offers free RT-PCR testing to asymptomatic individuals and those with mild symptoms, which is referred to as the community track. All tests are offered as part of a universal tax-funded health-care system and provided free of cost to the citizen. Test slots at TCDK are made publicly available and can be booked online. Information on PCR cycle threshold (Ct) values were available for samples analysed in TCDK, which uses a single laboratory protocol. Information on Ct values in the health-care test track was not available, and many different protocols are used by hospitals. A laboratory-confirmed SARS-CoV-2 case was defined as a person testing positive for SARS-CoV-2 by RT-PCR. Rapid antigen testing has been used increasingly since December, 2020, but, according to national recommendations, a positive rapid antigen test has to be confirmed with a RT-PCR test.

WGS data for SARS-CoV-2 was obtained from the Danish COVID-19 Genome Consortium (DCGC). The DCGC was established in March, 2020, with the purpose of assisting public health authorities by providing rapid genomic monitoring of the spread of SARS-CoV-2. Large-scale SARS-CoV-2 sequencing capacity was initially established at Aalborg University (Aalborg, Denmark) and supported by local sequencing capacity at SSI, Aarhus University Hospital, and Hvidovre Hospital (Hvidovre, Denmark). Since June, 2020, DCGC has included local sequencing nodes across the country to increase the proportion of sequenced samples from the health-care track.

Because of an increased number of cases in the early study period and some initial restrictions in sequencing capacity, some degree of selection of samples by Ct value in both test tracks was required. Therefore, in the community track, samples with Ct values lower than 30 were prioritised from week 53, 2020, to week 3, 2021, and samples with Ct values lower than 35 were prioritised in weeks 4 to 5. Otherwise, samples in this track were picked randomly as they arrived, according to the available workforce at the time of sample arrival and with no deliberate choice taken to pick samples from any particular location, age, or demographic criteria. In the health-care track, hospitals were advised to prioritise samples with Ct value lower than 32, if and when capacity was surpassed in the studied period. However, the degree to which this recommendation was followed for the health-care track is unclear, and Ct values from the health-care track were not available for analysis. All WGS data were centrally stored at Aalborg University and transferred daily to SSI.

Hospitalisation (outcome)

In the Danish national COVID-19 surveillance system, COVID-19 hospitalisations are defined as any visit to a Danish hospital longer than 12 h within 14 days of the first sample with a positive SARS-CoV-2 RT-PCR test or an ongoing hospitalisation. The cutoff of 12 h was chosen as a meaningful way to separate patients with less severe acute COVID-19 (eg, emergency department visits lasting less than 12 h) from those with more severe, treatment-requiring COVID-19 in general, as recommended by the Danish Health Authority.[23] The start of the COVID-19-related hospitalisations were defined in two ways to adjust for COVID-19 cases among patients requiring long-term admission. Patients with a first positive SARS-CoV-2 RT-PCR test before and up to 48 h after admission to a hospital started their COVID-19-related hospitalisation on the admission date to the hospital and were defined as outcome cases for this study. Conversely, patients with a first positive SARS-CoV-2 RT-PCR test taken more than 48 h after admission to a hospital had a COVID-19 related start of hospitalisation based on the sample date and were not defined as outcome cases for this study. The study included data with the latest possible admission for COVID-19 on March 24, 2021.

For the **Danish COVID-19 Genome Consortium** see https://www.covid19genomics.dk/

Covariates

We included possible confounders suspected to be associated with severity of COVID-19 or epidemiologically associated with both SARS-CoV-2 infection and hospitalisation, thus forward denoted basic covariates. These basic covariates included sex, age at sampling, time period (week of the sampling according to ISO 8601 standard, starting Monday; week 53 is a leap week), geographical region of sampling (Capital, Central Denmark, North Denmark, Zealand, Southern Denmark, or missing region name), and comorbidities (diabetes, adiposity, cancer, neurological diseases, nephrological diseases, haematological diseases, cardiac diseases, respiratory disorders, immunological diseases, and other comorbid diseases based on the preceding 5 years of hospital admission diagnoses).[24] Additional covariates were included later in the study and only for sensitivity analyses or to explore effects of B.1.1.7 on admission risk in relevant subgroups; the additional covariates included test track, which was also subdivided by Ct value lower than 30 and equal or higher than 30 in the community track (individuals with missing Ct values were excluded when using this information); ethnicity (second generation [both parents born abroad], Danish-born, or born abroad);[25] comorbidity based on the Register of Selected Chronic Diseases and Severe Mental Disorders (asthma, dementia, type 1 diabetes, type 2 diabetes, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoporosis, schizophrenia),[26] living in a long-term care facility [LTCF] for older people on the basis of the address database of LTCFs for older people (the majority being older than 65 years) and the address at sample date;[27,28] being a health-care worker on the basis of work authorisations in the Danish Register of Healthcare Professionals;[29] and SARS-CoV-2 vaccination status on the basis of the Danish Vaccination Register.[30] Information on intensive care unit treatment was obtained from the National Patient Register.[24]

Statistical analysis

We estimated the associations between SARS-CoV-2 lineage B.1.1.7 and the risk of COVID-19 hospitalisation by calculating risk ratios (RRs) using a Poisson regression model with robust SEs in PROC GENMOD in SAS, version 9.4. We adjusted the RRs for the basic covariates of sex, age (10-year interval groups), calendar period (week 53 from Jan 1, 2021, followed by week 1, week 2, and so on until week 10), region (six levels), and number of comorbidities in the preceding 5 years. To evaluate collinearity and contributions to confounding from each of these a-priori decided basic covariates included in the main model, we subsequently did stepwise forward inclusion in the following manner: each basic covariate was separately included in a model with SARS-CoV-2 lineage (B.1.1.7 or non-B.1.1.7). The basic covariate changing the association between B.1.1.7 and risk of admission the most was included in an updated model. The importance of the remaining basic covariates was then similarly evaluated in the updated model, and this stepwise forward inclusion continued until all basic covariates were included as in the main analysis. As part of the evaluation, we checked for collinearity by inspecting for large changes in the parameter estimates or the SEs when including each basic covariate. To evaluate residual confounding in the main analysis, we used more detailed categories of the basic covariates in sensitivity analyses (eg, 5-year age groups and type of comorbidity). Results of the main analysis are presented stratified in three age groups (0–29 years, 30–59 years, ≥60 years) and four time periods; nevertheless, the presented estimates were adjusted for age in 10-year age groups and for period in week intervals. Associations between SARS-CoV-2 lineage B.1.1.7 and the RR of hospitalisation within strata of covariates (sex, age, period, region, test track, Ct value lower than 30 and equal or higher than 30, LTCF for older people, and COVID-19 vaccination status) were estimated by including interaction terms in the model (in each strata, we used the group with non-B.1.1.7 lineages as reference) and tests for difference between strata categories were done as a test for interaction. In an additional analysis, we evaluated selection bias for COVID-19 hospitalisations in the reference group. Here, we included all cases, with and without viral genome data, and estimated the crude and adjusted RR of hospitalisation among cases without viral genome data relative to the non-B.1.1.7 lineages reference group, while still estimating the RR of hospitalisation among cases of B.1.1.7. All p values from the Poisson regression model with robust SEs were from Score tests. We evaluated differences in proportions using χ^2 test, trends in proportions with the Cochran-Armitage trend test, and the difference in mean Ct value and follow-up time between B.1.1.7 and other lineages with *t* test. Missing values were few and only for name of the region of sampling and Ct value. For region of sampling, the missing group was kept in all analyses to observe if this group was different, and for Ct, missing values were excluded in analyses that included Ct values.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Jan 1 and March 24, 2021, 58 574 individuals tested positive for SARS-CoV-2 by RT-PCR in Denmark. We included in the study 50 958 individuals with up to 14 days of follow-up for COVID-19 hospitalisation. WGS was done for 38 288 (75·1%) individuals and resulted in a viral genome for 30 572 (79·8%) of 38 288 individuals. Therefore, the study population with viral genome data included 30 572 (60·0%) of 50 958 cases of SARS-CoV-2 with 14 days of follow-up, 24735 in the community track and 5837 in the health-care track (appendix p 1). In the

study population, 10 544 (34·5%) individuals were infected with lineage B.1.1.7 and 1944 (6·4%) had a COVID-19 hospitalisation. Of these, 571 (29·4%) had a B.1.1.7 infection (table 1), and the mean follow-up time from date of the positive sample to COVID-19 hospitalisation (within the 14 days of follow-up) was 4·2 days overall (SD 4·0; median 4 days, IQR 0–8) and 5·8 days for B.1.1.7 (4·0; 6 days, 2–9) versus 3·6 days for other lineages (3·9; 2 days, 0–7; p<0·0001). 2·6% of individuals had a first hospital admission within 48 h before a positive SARS-CoV-2 test, thus their follow-up time was set to 0 days in the calculation of follow-up time (to avoid a negative number of days of follow-up of up to 2 days). The proportion of the study population with variants of concern other than B.1.1.7 (34 [0·1%] with B.1.351, and three [<0·1%] with P.1) or with variants of interest (257 [0·8%] with B.1.525) was very low, and proportions for the remaining circulating lineages during the study period (19 734 [64·5%]) are described by DCGC online. Of the 30 572 individuals in the study population, 2031 [6·6%] were health-care workers; of these, 52 were hospitalised with COVID-19, 20 [38·5%] of

	SARS-CoV-2 lineage			Hospitalisations			
	Other lineages (n=20 028)	B.1.1.7 (n=10 544)	p value	All (n=1944)	Other lineages (n=1373)	B.1.1.7 (n=571)	p value
Sex	..	..	<0·0001	..	..	..	0·29
Female	10 513 (52·5%)	5092 (48·3%)	..	942 (48·5%)	676 (49·2%)	266 (46·6%)	..
Male	9515 (47·5%)	5452 (51·7%)	..	1002 (51·5%)	697 (50·8%)	305 (53·4%)	..
Age, years	..	..	<0·0001	..	..	..	<0·0001
0–29	6924 (34·6%)	4679 (44·4%)	..	129 (6·6%)	69 (5·0%)	60 (10·5%)	..
30–59	8515 (42·5%)	4670 (44·3%)	..	592 (30·5%)	347 (25·3%)	245 (42·9%)	..
≥60	4589 (22·9%)	1195 (11·3%)	..	1223 (62·9%)	957 (69·7%)	266 (46·6%)	..
Period	..	..	<0·0001*	..	..	..	0·0012*
Week 53	2340 (11·7%)	40 (0·4%)	..	173 (8·9%)	171 (12·5%)	2 (0·4%)	..
Week 01	3924 (19·6%)	143 (1·4%)	..	345 (17·7%)	330 (24·0%)	15 (2·6%)	..
Week 02	3859 (19·3%)	296 (2·8%)	..	281 (14·5%)	253 (18·4%)	28 (4·9%)	..
Week 03	3181 (15·9%)	466 (4·4%)	..	253 (13·0%)	226 (16·5%)	27 (4·7%)	..
Week 04	2129 (10·6%)	515 (4·9%)	..	152 (7·8%)	122 (8·9%)	30 (5·3%)	..
Week 05	1568 (7·8%)	661 (6·3%)	..	150 (7·7%)	110 (8·0%)	40 (7·0%)	..
Week 06	1032 (5·2%)	921 (8·7%)	..	121 (6·2%)	57 (4·2%)	64 (11·2%)	..
Week 07	825 (4·1%)	1583 (15·0%)	..	126 (6·5%)	40 (2·9%)	86 (15·1%)	..
Week 08	636 (3·2%)	2039 (19·3%)	..	146 (7·5%)	32 (2·3%)	114 (20·0%)	..
Week 09	396 (2·0%)	2270 (21·5%)	..	128 (6·6%)	24 (1·7%)	104 (18·2%)	..
Week 10	138 (0·7%)	1610 (15·3%)	..	69 (3·5%)	8 (0·6%)	61 (10·7%)	..
Region	..	..	<0·0001	..	..	..	<0·0001
Capital	8663 (43·3%)	4591 (43·5%)	..	821 (42·2%)	581 (42·3%)	240 (42·0%)	..
Central Denmark	3094 (15·4%)	1296 (12·3%)	..	282 (14·5%)	220 (16·0%)	62 (10·9%)	..
North Denmark	1843 (9·2%)	284 (2·7%)	..	144 (7·4%)	129 (9·4%)	15 (2·6%)	..
Zealand	3238 (16·2%)	1554 (14·7%)	..	349 (18·0%)	244 (17·8%)	105 (18·4%)	..
Southern Denmark	3028 (15·1%)	2715 (25·7%)	..	337 (17·3%)	192 (14·0%)	145 (25·4%)	..
Missing name of region†	162 (0·8%)	104 (1·0%)	..	11 (0·6%)	7 (0·5%)	4 (0·7%)	..
Number of comorbidities	..	..	<0·0001	..	..	..	<0·0001
0	14 678 (73·3%)	8380 (79·5%)	..	758 (39·0%)	461 (33·6%)	297 (52·0%)	..
≥1	5350 (26·7%)	2164 (20·5%)	..	1186 (61·0%)	912 (66·4%)	274 (48·0%)	..
Test track	..	..	<0·0001	..	..	..	<0·0001
Health-care track	4863 (24·3%)	974 (9·2%)	..	1106 (56·9%)	932 (67·9%)	174 (30·5%)	..
Community track	15 165 (75·7%)	9570 (90·8%)	..	838 (43·1%)	441 (32·1%)	397 (69·5%)	..
Ct values in community track‡	..	..	0·94	..	..	..	0·47
Ct value registered§	14 819 (97·7%)	8990 (93·9%)	..	794 (94·7%)	426 (96·6%)	368 (92·7%)	..
Ct <30	10 360 (69·9%)	6281 (69·9%)	..	575 (72·4%)	304 (71·4%)	271 (73·6%)	..
Ct ≥30	4459 (30·1%)	2709 (30·1%)	..	219 (27·6%)	122 (28·6%)	97 (26·4%)	..

Data are n (%), unless otherwise specified. Ct=cycle threshold. *p_{trend} value. †266 (0·9%) individuals had no sampling region name registered in the COVID-19 surveillance database. ‡Ct values in the health-care track were not available for data analysis. §Proportion of community-track cases (however, Ct values were missing for samples from 926 (3·7%) of 24 735 individuals in this track).

Table 1: **Characteristics of the study population according to SARS-CoV-2 lineage and COVID-19 hospitalisations**

	COVID-19 hospitalisation		COVID-19 hospitalisation RR (95% CI)			
	Yes (n=1944)*	No (n=28 628)*	Crude	p value	Adjusted	p value
Overall Infection with SARS-CoV-2 lineage B.1.1.7	..	..	..	<0·0001	..	<0·0001
No (other co-existing lineages)†	1373 (6·9%)	18 655 (93·1%)	1 (ref)	..	1 (ref)	..
Yes (lineage B.1.1.7)	571 (5·4%)	9973 (94·6%)	0·79 (0·72–0·87)	..	1·42 (1·25–1·60)	..
B.1.1.7 infection by sex	..	..	..	0·52	..	0·87
Male	305 (5·6%)	5147 (94·4%)	0·76 (0·67–0·87)	..	1·41 (1·21–1·63)	..
Female	266 (5·2%)	4826 (94·8%)	0·81 (0·71–0·93)	..	1·43 (1·22–1·67)	..
B.1.1.7 infection by age, years	..	..	..	0·67	..	0·90
0–29	60 (1·3%)	4619 (98·7%)	1·32 (0·93–1·86)	..	1·42 (0·99–2·04)	..
30–59	245 (5·2%)	4425 (94·8%)	1·35 (1·15–1·58)	..	1·46 (1·22–1·74)	..
≥60	266 (22·3%)	929 (77·7%)	1·23 (1·10–1·39)	..	1·39 (1·21–1·60)	..
B.1.1.7 infection by period	..	..	..	0·35	..	0·48
Jan 1–16	42 (9·7%)	393 (90·3%)	1·32 (0·98–1·78)	..	1·49 (1·13–1·98)	..
Jan 17 to Feb 2	78 (6·4%)	1144 (93·6%)	0·98 (0·78–1·24)	..	1·63 (1·30–2·04)	..
Feb 3–19	146 (5·9%)	2316 (94·1%)	1·04 (0·84–1·30)	..	1·33 (1·08–1·63)	..
Feb 20 to March 9	305 (4·7%)	6120 (95·3%)	0·91 (0·70–1·17)	..	1·28 (1·01–1·64)	..
B.1.1.7 infection by region	..	..	..	0·69	..	0·75
Capital	240 (5·2%)	4351 (94·8%)	0·78 (0·67–0·90)	..	1·50 (1·27–1·77)	..
Central Denmark	62 (4·8%)	1234 (95·2%)	0·67 (0·51–0·89)	..	1·32 (1·00–1·74)	..
North Denmark	15 (5·3%)	269 (94·7%)	0·75 (0·45–1·27)	..	1·29 (0·77–2·14)	..
Zealand	105 (6·8%)	1449 (93·2%)	0·90 (0·72–1·12)	..	1·29 (1·04–1·59)	..
Southern Denmark	145 (5·3%)	2570 (94·7%)	0·84 (0·68–1·04)	..	1·53 (1·24–1·89)	..
Missing name of region	4 (3·8%)	100 (96·2%)	0·89 (0·27–2·97)	..	1·13 (0·35–3·65)	..
B.1.1.7 infection by number of comorbidities	..	..	..	<0·0001	..	0·086
0	297 (3·5%)	8083 (96·5%)	1·13 (0·98–1·30)	..	1·56 (1·33–1·84)	..
≥1	274 (12·7%)	1890 (87·3%)	0·74 (0·66–0·84)	..	1·33 (1·15–1·54)	..
B.1.1.7 infection by test track‡	..	..	..	<0·0001	..	0·33
Health-care track	174 (17·9%)	800 (82·1%)	0·93 (0·81–1·08)§	..	1·53 (1·31–1·77)	..
Community track	397 (4·1%)	9173 (95·9%)	1·43 (1·25–1·63)	..	1·67 (1·43–1·95)	..
B.1.1.7 infection by Ct value‡	..	..	..	0·45	..	0·37
Ct <30	271 (4·3%)	6010 (95·7%)	1·47 (1·25–1·73)	..	1·83 (1·49–2·25)	..
Ct ≥30	97 (3·6%)	2612 (96·4%)	1·31 (1·01–1·70)	..	1·59 (1·20–2·12)	..

Data are n (%) or RR (95% CI). p values in the stratified analysis are tests for interaction terms. Adjusted RRs were adjusted for the basic (a priori) covariates sex, age (10-year groups), sample period (calendar week), region (five groups), and comorbidities in the preceding 5 years (none or one or more). RRs in the stratified analysis were adjusted for the remaining basic covariates. However, in strata by age (three age-groups), RR were also adjusted for age in 10-year groups, and in strata by period (four periods), RRs were also adjusted for period in calendar weeks. Ct=cycle threshold. RR=risk ratio. *Percentages are of the total number of individuals with B.1.1.7 infection in each respective category (table 1); to shorten the table, the stratified analyses do not show the number of individuals for the reference group of non-B.1.1.7 infection (table 1). †Percentages are of 20 028 individuals infected with lineages other than B.1.1.7. ‡Ct values were available for the community track alone; in the community track, Ct values were missing for samples from 926 (3·7%) of 24 735 individuals. §Adjusting for age alone (in 5-year age-groups) increased the RR to 1·55 (95% CI 1·36–1·76) in the health-care track and 1·75 (1·53–1·99) in the community track.

Table 2: **Infection with lineage B.1.1.7 and risk of hospitalisation overall and by sex, age, period, region, number of comorbidities, test track, and Ct value**

whom with B.1.1.7 lineage. Of the 24735 individuals in the community track, 926 (3·7%) had missing Ct values and were thus excluded from analyses using Ct value categories (<30 and ≥30).

Overall, the proportion of individuals with and without viral genome data did not differ by sex (59·4% women *vs* 60·7% men; p=0·63), but we observed a minor significant difference by age group (59·0% for age group 0–29 years, 60·8% for 30–59 years, and 60·1% for ≥60 years; p<0·0013). During the first 5 weeks of the study period, the proportion of individuals for whom viral genome data could be obtained increased from 49% to more than 70% (p_{trend} <0·0001; appendix p 1). This initial increase in proportions was also present in each test track for Ct values lower than 30 and equal or higher than 30 and was also observed for WGS proportions (appendix p 2, 3).

Overall, the proportion of individuals with B.1.1.7 increased during the study period (p_{trend} <0·0001, from 143 [3·5%] of 4067 in week 1 to 1610 [92·1%] of 1748 in week 10), including among individuals with COVID-19 hospitalisation (p_{trend}=0·0012). We observed a lower proportion of B.1.1.7 cases in the age group of 60 years or older than in other age groups (p<0·0001), a slightly lower proportion among women than among men (p<0·0001), different proportions between regions (p<0·0001), and a slightly lower proportion in individuals with comorbidities than in those without (p<0·0001). Among individuals who were

hospitalised, we observed a lower proportion of B.1.1.7 cases in the age group of 60 years or older (p<0·0001) and no difference in proportions by sex (p=0·29; table 1).

We observed a higher proportion of individuals with B.1.1.7, also among those with COVID-19 hospitalisations, in the community track than in the health-care track (p<0·0001 for both; table 1). The higher proportion was largely because of the increasing PCR test capacity over time in this track, in parallel with the increased proportion of B.1.1.7 cases. Therefore, the crude RR of having B.1.1.7 in the community track, when compared with that of the health-care track, was 2·32 (95% CI 2·18–2·46) and, after adjusting for period, the RR was reduced to 1·17 (1·12–1·23).

In the community track, in which data on Ct values were available, the proportions of B.1.1.7 cases and those of other lineages remained the same when Ct values were divided into values lower and higher than 30 (p=0·94). Likewise, the proportions of individuals hospitalised remained similar when data were divided by Ct value (p=0·47; table 1). However, individuals with B.1.1.7 had a slightly lower mean Ct value than those infected with other lineages (27·5, SD 4·2, for the 8990 cases of B.1.1.7 *vs* 27·8, 4·0, for the 14 819 cases of other lineages; p<0·0001); however, this difference was not observed in individuals with COVID-19 hospitalisation (26·9, 4·4, for the 368 cases of B.1.1.7 *vs* 27·3, 4·3, for the 426 cases of other lineages; p=0·13).

Overall, in the crude analysis (table 2), we observed an inverse association between infection with lineage B.1.1.7 and hospitalisation (RR 0·79, 95% CI 0·72–0·87, in 571 of 10 544 B.1.1.7 cases) when compared with infection with any other circulating lineages of SARS-CoV-2 virus in Denmark (1373 of 20 028 non-B.1.1.7 cases). However, after adjusting for sex, age, period, region, and number of comorbidities, infection with lineage B.1.1.7 was associated with a 1·4-times increased RR of COVID-19 hospitalisation (1·42, 1·25–1·60) compared with that of other lineages.

To evaluate which of the basic covariates chosen a priori confounded the crude RR of 0·76 to yield the main finding of a RR of 1·42, we did a stepwise forward inclusion. Therefore, when including each covariate (ie, sex, age, period, region, and number of comorbidities) sequentially in the crude analysis, age increased the crude estimate the most, yielding a RR of 1·28 (1·17–1·41). When adding the remaining five covariates one by one, period increased the estimate the most, yielding a RR of 1·39 (1·23–1·57). When adding the remaining four covariates one by one, the number of comorbidities moved the estimate the most, yielding a RR of 1·42 (1·26–1·60). Finally, when adding sex (RR 1·42, 1·26–1·61) or region (1·42, 1·26–1·61) the estimate did not change further.

For most of the strata of age and period, the crude RR for B.1.1.7 hospitalisations was above 1 (table 2). Additionally, for strata of region or number of comorbidities, adjusting for the remaining basic covariates, the RR for B.1.1.7 increased. However, numbers were small for North Denmark and for individuals without a registered region of sampling. When estimates were stratified by test track and Ct values (from the community test track), the adjusted RR for B.1.1.7 hospitalisations was increased in both analyses, although the crude estimate was confounded only in the health-care track (table 2): adjusting for age alone increased the crude RR of 0·93 (0·81–1·08) to 1·55 (1·36–1·76) in this track, whereas in the community track the crude RR was 1·43 (1·25–1·63) and the adjusted RR 1·75 (1·53–1·99). Additionally, in the community test track, further adjusting the estimate for Ct values grouped in intervals of 0–24, 25–27, 28–30, 31–33, and 34 or higher yielded a RR increase of 1·81 (1·47–2·22).

In sensitivity analyses, further adjustment for the additional covariates of ethnicity, type of comorbidity, and higher number of comorbidities (none, one, two, and three or more), or adjusting for age in 5-year groups did not reduce the adjusted main estimate (appendix p 3). Including individuals with fewer than 14 days of observation time, excluding those with samples taken in January (before WGS capacity reached the highest level; appendix p 3), or excluding those with COVID-19 hospitalisations for up to 24 h, also did not change the adjusted main estimate (appendix p 3).

To evaluate a potential selection bias for COVID-19 hospitalisations in the reference group, we did an analysis including all SARS-CoV-2 cases with follow-up during the study period (50 958 individuals). We observed that the RR of hospitalisation among the 20 368 individuals without viral genome data did not differ from the risk in

	B.1.1.7 hospitalisations	Adjusted RR (95% CI)	p value
Main analysis*	571	1·42 (1·25–1·60)	..
Stratification			
Living in a long-term care facility	..	..	0·65
No	561	1·41 (1·24–1·59)	..
Yes, previously	5	1·94 (1·00–3·74)	..
Yes, currently	5	1·22 (0·53–2·78)	..
Health-care worker	..	..	0·011
No	551	1·37 (1·21–1·55)	..
Yes	20	3·29 (1·90–5·69)	..
Vaccinated against SARS-CoV-2†	..	..	0·53
No	513	1·42 (1·24–1·62)	..
Yes, tested positive before vaccination	19	1·14 (0·76–1·70)	..
Yes, tested positive after first vaccination	31	1·66 (1·20–2·31)	..
Yes, tested positive after second vaccination	8	1·35 (0·63–2·89)	..

Data are n or RR (95% CI). RRs adjusted for sex, age (10-year groups), sample period (calendar week), region (five groups), and number of comorbidities in the preceding 5 years (none or one or more). RR=risk ratio. *See table 2. †Vaccinations until March 24, 2021, included the vaccines BNT162b2 (Pfizer–BioNTech [Mainz, Germany], introduced Dec 27, 2020), mRNA-1273 (Moderna [Cambridge, MA, USA], introduced Jan 14, 2021), and ChAdOx1 (AstraZeneca [Cambridge, UK], introduced Feb 8, 2021, and paused or stopped on March 11 to date); the percentage of individuals vaccinated at ages 0–29 years was 3·2%, at 30–59 years was 12·0%, and at 60 years or older was 32·2%.

Table 3: **Infection with lineage B.1.1.7 and risk of hospitalisation in additional stratified analysis of the study population**

the reference group of cases with viral genome data on non-B.1.1.7 lineages when adjusting for sex, age, period, region, and number of comorbidities (crude RR 0·82, 95% CI 0·76–0·88; adjusted RR 0·96, 0·90–1·04). In this analysis, the adjusted RR increase for B.1.1.7 hospitalisation was 1·23 (1·10–1·38, p=0·0002) when compared with that of the reference group; however, after additional adjustment for the interaction between period and availability of viral genome data (as a result of the increase in WGS capacity over time), the RR increase was 1·38 (1·22–1·56; appendix p 2). When changing the reference group to cases without viral genome data, the adjusted B.1.1.7 hospitalisation risk was 1·28 (1·14–1·44, p=0·0002), without adjustment for the aforementioned interaction.

The stratification of the main finding by covariates revealed an even higher risk of hospitalisation among health-care workers infected with lineage B.1.1.7 than among other individuals infected with lineage B.1.1.7 (table 3), whereas the remaining studied covariates (LTCF for older people and COVID-19 vaccination) showed no significant interactions (table 3). The RR of hospitalisation after B.1.1.7 infection when restricting the analysis to individuals not living in an LTCF for older people was 1·41 (1·24–1·59), whereas hospitalisation numbers were small for older people living in LTCF, although LTCF registration for older people in Denmark is close to complete (table 3).

We also had information on intensive care unit (ICU) treatment and observed that 66 (11·6%) of 571 individuals hospitalised with B.1.1.7 infection had been in ICU treatment versus 151 (11·0%) of 1373 individuals hospitalised with non-B.1.1.7 lineage infections. Additional analyses were not done for these data.

Discussion

Our adjusted analyses suggest that individuals infected with lineage B.1.1.7 have an increased risk of hospitalisation of 42% compared with individuals infected with other lineages of SARS-CoV-2. This association was observed within several strata of age, calendar period, and other covariates, and it did not diminish when adjusting for the potential mediators of test track and Ct values.

So far, the concerns related to B.1.1.7 have been mainly about increased transmissibility. According to the NERVTAG report, the UK studies assessing the severity of B.1.1.7 had several limitations.[8,9] Most of the analyses used only community testing data for subsets of the population; therefore, the datasets on mortality only covered 10% of all COVID-19-related deaths.[10,11] Additionally, several confounding factors might not have been adequately adjusted for, such as comorbidity and LTCF stay.

In the crude analyses, we observed a lower risk of hospitalisation in individuals with B.1.1.7 infection than in those infected with other lineages. However, when we adjusted for age and period of sampling, there was a 1·4-times higher risk of hospitalisation after B.1.1.7 infection compared with that of other lineages. Our finding that increased risk of hospital admission was evident in the adjusted analysis alone calls for a careful discussion. First, we found a lower proportion of B.1.1.7 cases in the age group of 60 years or older (11·3%) than in younger age groups (44·3% and 44·4%), by contrast with the proportions of cases with other variants (22·9% for ≥60 years *vs* 42·5% for 30–59 years and 34·6% for 0–29 years). We believe that this difference is due to a later introduction of B.1.1.7 in the older population, who have been reported to be more compliant than young people with self-isolation during the lockdown compared with other age groups.[31] Because age is also strongly associated with hospitalisation, the finding that B.1.1.7 cases were younger than those with other lineages possibly weakened the association between B.1.1.7 and hospitalisation in the crude analysis.

Next to age, period further confounded the crude estimate. During the study period, rates of hospitalisation and infection decreased because of the lockdown, which started on Dec 16, 2020, with closure of shopping centres, followed by closure of kindergartens, schools, and other education centres on Dec 21. Non-essential shops were closed after Dec 25. Kindergartens were opened on Jan 4, 2021, and primary schools after Feb 8. On March 1, shops and secondary schools opened in geographical areas with lowest transmission rates. The number of daily hospital admissions peaked on Dec 28, 2020, and decreased during the study period until the middle of February, 2021. Concomitantly with the lockdown, B.1.1.7 rates increased, becoming the underlying dominant lineage despite the lockdown. Additionally, the national PCR testing capacity increased nearly linearly, from approximately 63 000 daily tests in week 1 to 144 000 in week 12. The increased PCR testing capacity was largely restricted to the community track (whereas the increase in WGS capacity was independent of test track). Thus, more asymptomatic individuals and those with mild disease were probably being detected in the later part of the study period, leading to a reduction in the overall risk of hospitalisation among all confirmed cases by calendar period while the proportion of B.1.1.7 cases increased.

Therefore, our study shows the complexity of analysis and interpretation of surveillance data, for which changes in testing strategy and the effects of non-pharmaceutical interventions need to be considered. Consequently, adjusting for country-specific epidemiological characteristics of B.1.1.7 is very important for a valid discussion of the association between B.1.1.7 and COVID-19 hospitalisation. In line with this reasoning, an analysis (available as a preprint) of the matched cohort study from Public Health England found evidence of increased risk (hazard ratio) only after adjusting for sex, age, period, region, and ethnicity, which changed the estimate

from 1·07 (95% CI, 0·89–1·29) to 1·34 (95% CI 1·07–1·66; for 120 individuals hospitalised with B.1.1.7 infection).[32]

We also observed that, in the test tracks used in Denmark, age and period confounded the B.1.1.7 hospitalisation risk slightly differently. Therefore, because a higher proportion of cases with B.1.1.7 with an age distribution more representative of the population was observed in the community track than in the health-care track, age was not a strong confounder in the community track. In the health-care track, where the proportion with B.1.1.7 was lower than in the community track, mostly individuals who were symptomatic and needed medical evaluation were tested—which, for SARS-CoV-2, is more often older people—and we observed that adjusting for age alone in this track moved the RR of B.1.1.7 hospitalisation from 0·93 to 1·55.

With the increasing WGS capacity reaching 78% in week 5, a risk of selection bias might still have occurred because samples with lower (<30) Ct values initially were selected for WGS to some extent, to increase the chance of obtaining a viral genome. However, for sample selection to hamper the generalisability of the results, the selection should be associated with both exposure (B.1.1.7 infection) and outcome (hospitalisation). We were able to assess the association with hospitalisation, using our complete information on hospitalisations among all SARS-CoV-2 infections in Denmark during the study period, and we did not observe a strong association between having viral genome data and hospitalisation. Therefore, the risk of hospitalisation among individuals with a positive SARS-CoV-2 test without viral genome data was 0·96 (crude risk 0·82) of the risk in the reference group of individuals with non-B.1.1.7 infection with viral genome data, whereas the risk of B.1.1.7 hospitalisation increased relative to the reference group in the same analysis. Additionally, when excluding samples before week 5 when WGS coverage was lowest, the B.1.1.7 hospitalisation risk was similarly increased.

Denmark's efforts in contact tracing and ensuring self-isolation could have led to a possible bias of our findings if B.1.1.7 was detected more frequently among close contacts, and increased focus on B.1.1.7 could have led to more frequent hospitalisation due to concerns related to B.1.1.7. In our study, the time from sampling to hospital admission with B.1.1.7 would then have been expected to be shorter; however, we observed that the time was 2 days longer than that with other lineages. Additionally, a more efficient contact tracing strategy would probably have resulted in the identification of more mild or asymptomatic cases and, if biased towards mild infection with B.1.1.7, case detection would tend to reduce the association with risk of hospitalisation.

Outbreaks of B.1.1.7 at LTCFs for older people might have resulted in an overestimation of the association between B.1.1.7 and hospitalisation, because transmission of B.1.1.7 is increased in populations with very high background risk of hospital admission. Denmark has near-complete national register information on residency status in LTCFs for older people. We stratified our analyses for LTCF residency status, and the association between B.1.1.7 and hospitalisation was similar in the population not living in LTCFs for older people and in the overall adjusted analysis (table 3). Additionally, COVID-19 vaccinations of older people in LTCFs started just before the study period and might have reduced the risk of hospitalisation even in case of outbreaks. Because we also found that health-care workers had an even higher risk of B.1.1.7 hospitalisation than non-health-care workers, we cannot rule out that outbreaks at LTCFs for older people might have exposed, for example, unvaccinated health-care workers at these facilities.

It has been discussed whether the increased mortality observed in the UK in relation to B.1.17 could be explained by a strain on the health-care system, resulting in delayed treatment and increased risk of death.[11] In Denmark's second COVID-19 wave, the number of hospital admissions peaked at the end of 2020. In the Capital region, planned surgeries and hospital treatments were postponed to ensure capacity to accommodate an increasing number of patients, but policy changes were not needed, at any time, regarding admission of acute patients. The fact that our estimates are robust when stratifying for calendar period supports the hypothesis that the increased burden at hospitals at the beginning of the study period was unlikely to have biased our results.

B.1.1.7 is circulating widely in Europe, although insufficiently detailed surveillance with WGS means that its exact prevalence is unclear. The European Centre for Disease Prevention and Control stated in their Feb 15 risk assessment of new variants that unless compliance with non-pharmaceutical interventions is strengthened, a substantial increase in COVID-19 cases and deaths in Europe should be anticipated.[33] Several countries have already experienced overburdened hospitals and excess mortality in connection with the predominance of B.1.1.7, such as the UK, Ireland, Portugal, Spain, and Israel. So far, these surges have mainly been explained by increased transmissibility, but our results corroborate that increased severity in terms of risk of being hospitalised might also, to some degree, play a role.

The available COVID-19 vaccines are expected to be effective against lineage B.1.1.7. Studies addressing the effectiveness of the mRNA vaccines BNT162b2 (Pfizer–BioNTech; Mainz, Germany) and mRNA-1273 (Moderna; Cambridge, MA, USA) found that both infection-induced and vaccine-induced antibodies were effective in neutralising B.1.1.7.[34–36] The clinical efficacy of the ChAdOx1 vaccine (AstraZeneca; Cambridge, UK) against B.1.1.7 was found to be similar to the efficacy of the vaccine against other circulating lineages in the UK, according to a pre-print manuscript.[33,37] The ongoing clinical phase 3 trials of the protein-based vaccine NVX-CoV2373 (Novavax; Gaithersburg, MD, USA)

reported 90% vaccine efficacy against the previous strains of SARS-CoV-2 and more than 85% efficacy against B.1.1.7. These study results were made available in a press release from the manufacturer.[33,38] Finally, observational vaccine studies in countries were the dominant variant was B.1.1.7 have reported efficacy of both BNT162b2 and ChAdOx1 in preventing SARS-CoV-2 infections and hospital admissions for COVID-19 disease.[39–42] On the basis of these findings, a fast rollout of the COVID-19 vaccination programmes is crucial for preventing potential increases in hospitalisation numbers due to B.1.1.7.

We found that the increased risk of B.1.1.7 was also present and consistent in younger age groups, although it was not significantly increased in the age group 0–29 years, in which only 60 B.1.1.7 hospital admissions were included. However, more clinical data are clearly needed to understand if and how B.1.1.7 hospitalisation might represent a severe course of infection associated with intensive care treatment and death in increased numbers, regardless of age. A 2021 study of 496 patients hospitalised with COVID-19 found no evidence of an association between severe disease and death and lineage (B.1.1.7 *vs* non-B.1.1.7).[12]

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The strengths of our study were access to national health registers and SARS-CoV-2 data covering both community testing and health-care track testing and high capacity of WGS data, which allowed us to do thorough epidemiological analyses of the association between B.1.1.7 and COVID-19 hospitalisation in an observational cohort design with both adjustment and stratified analysis of many confounding factors. Additionally, the study covered the period when the prevalence of B.1.1.7 gradually increased, from 1·7% in week 53 to 92% in week 10, which made it possible to have a sufficiently concurrent non-B.1.1.7 comparison group.

The limitations of our study include the short study period during the winter months of January to March, which means that the study cannot be used to make conclusions about B.1.1.7 hospitalisation risk during summer months or other seasons. Additionally, although we adjusted for period, we could not evaluate bias from the pressure on the hospital system that peaked in December, 2020, just before the study period. We did not adjust for socioeconomic status, which could be associated with crowded environments, such as prisons and jails, shelters, and certain occupations or work places, where B.1.1.7 could spread more easily among individuals with an increased risk of severe disease. Finally, the study population was limited by including only 60% of all individuals infected with SARS-CoV-2, and selection bias can thus not be excluded with the observational design that we used.

Our analysis suggested that infection with lineage B.1.1.7 was associated with an increased risk of hospitalisation of 42% compared with that of SARS-CoV-2 lineages other than B.1.1.7. The overall effect on hospitalisations in Denmark was limited because of a strict lockdown, but our findings could support hospital preparedness and modelling of the projected effect of the epidemic in countries with uncontrolled spread of B.1.1.7.

Contributors

All authors contributed to either conception and design of the study, acquisition of data, or analysis and interpretation. All authors had access to the underlying data. PB and JW verified the epidemiological data analysis. MA, TYM, JF, and MR verified the underlying WGS and genome data produced by the Danish Covid-19 Genome Consortium. SG and MV has verified the underlying COVID-19 surveillance system health register data. TGK and PB drafted the manuscript, and all authors provided critical revision of the article and final approval of the version for publication. All authors agreed 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.

Declaration of interests

We declare no competing interests.

Data sharing

The datasets analysed in this study are located in the Danish national COVID-19 surveillance system database at SSI, and the data are becoming or are already available for research upon reasonable request and with permission from the Danish Data Protection Agency and Danish Health and Medicines Authority.

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