Title: Increased risk of hospitalisation associated with infection with SARS-CoV-2 lineage B.1.1.7 in Denmark

Authors: Peter Bager[1], Jan Wohlfahrt[2], Jannik Fonager[3], Morten Rasmussen[3], Mads Albertsen[4], Thomas Yssing Michaelsen[4], Camilla Holten Møller[1], Steen Ethelberg[5], Rebecca Legarth[5], Mia Sarah Fischer Button[5], Sophie Gubbels[1], Marianne Voldstedlund[1], Kåre Mølbak[1], Robert Leo Skov[1], Anders Fomsgaard[3], Tyra Grove Krause[1].

[1]Division of Infectious Disease Preparedness, Statens Serum Institut, Copenhagen, Denmark
[2]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark
[3]Department of Virus & Microbiological Special Diagnostics, Statens Serum Institut, Copenhagen, Denmark
[4]Center for Microbial Communities, Department of Chemistry and Bioscience, Aalborg University, Denmark
[5]Infectious Disease Epidemiology & Prevention, Statens Serum Institut, Copenhagen, Denmark

Corresponding author: Peter Bager; Division of Infectious Disease Preparedness, Statens Serum Institut, Copenhagen, Denmark; Artillerivej 5, 2300 Copenhagen S, Denmark; Phone: +45 32688327; Email: pbg@ssi.dk

Data availability statement: The datasets analysed during the current study are located in the Danish national COVID-19 surveillance system database at Statens Serum Institut, 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.

Author Contributions: All authors contributed to either conception and design of the study, acquisition of data, or analysis and interpretation; P.B. and J.W. has veryfied the epidemiological data analysis; M.A., T.Y.M., J.F., and M.R. has veryfied the underlying WGS and genome data; S.G. and M.V. has verified the underlying COVID-19 surveillance system health register data; T.G.V. and P.B. drafted the manuscript and all authors provided critical revision of the article, and final approval of the version to publish; 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.

Conflict of interest disclosure statement: The authors declare that they have no competing interest.

Word count: Manuscript 3307; abstract **333/**250

ABSTRACT

Background:

The more infectious SARS-CoV-2 virus lineage B.1.1.7, rapidly spread in Europe after December 2020, and a concern of B.1.1.7 causing more severe disease has been raised. Denmark has one of Europe´s highest capacities per capita of SARS-CoV-2 reverse transcription polymerase chain reaction (RT PCR) test and whole genome sequencing (WGS). We used national health register-data to explore whether B.1.1.7 increases the risk of COVID-19 hospitalisation.

Methods and Findings:

In an observational cohort study we included all SARS-CoV-2 RT PCR test-positive individuals in Denmark sampled between the 1st January and until the 9th February, 2021, identified in the national COVID-19 surveillance system. The surveillance system includes national individual RT PCR test results and viral WGS analyses and data from national health registers including COVID-19 related hospital admissions defined as first admission within 14 days of the test-positive swab. The odds ratio (OR) of admission according to infection with B.1.1.7, vs other co-existing lineages, was calculated in a logistic regression model adjusted for sex, age, period, follow-up time less than 14 days, region, and comorbidities. A total of 35,887 test-positive individuals were identified, 23,057 (64%) had WGS performed, of whom 18,499 (80%) resulted in a viral genome and a total of 2,155 of these were lineage B.1.1.7. The proportion of individuals with B.1.1.7 increased from 4% in early January to 45% in early February. Among the individuals with viral genome data, B.1.1.7 was associated with a crude OR of admission of 0.87 (95%CI, 0.72-1.05) and an adjusted OR of 1.64 (95%CI, 1.32-2.04) based on 128 admissions after B.1.1.7 infection and 1,107 admissions after infection with other lineages. The adjusted OR was increased in all strata of age and calendar time - the two most important confounders of the crude OR.

Conclusions:

Infection with lineage B.1.1.7 was associated with an increased risk of hospitalisation compared with other lineages. This finding may have serious public health impact in countries with spread of B.1.1.7 and can support hospital preparedness and modelling of projected impact of the epidemic.

INTRODUCTION

On the 14th December 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 of SARS-CoV-2 (B.1.1.7). The lineage is characterised by several mutations in the spike protein. At the time of notification Denmark had, as one of few countries, already uploaded B.1.1.7 SARS-CoV-2 genomes to GISAID, with the first cases identified dating back to the 14th of November.

Denmark has one of the highest SARS-CoV-2 PCR testing capacities in the world reaching a weekly testing rate of 10,000 tests/100.000 population in December 2020. Furthermore, throughout the epidemic Denmark has increased its capacity for whole genome sequencing (WGS) of test-positive cases and almost 25% of all positive samples have been whole genome sequenced throughout the epidemic. With more than 5.000 weekly sequenced samples presently, we have been able to document a rapid increase in the proportion of B.1.1.7 among sequenced samples from 0.3% in week 46, 2020, to 47% in week 6, 2021. The relative reproductive number of B.1.1.7 compared with all other circulating lineages has been estimated to 1.55 (95% confidence interval 1.48-1.62) which is in line with findings from London School of Hygiene and Tropical Medicines which estimated that B.1.1.7 is 43-82% more transmissible (95% credible interval across three regions 38-106%) than preexisting lineages of SARS-CoV-2 [1, 2].

The increase in B.1.1.7 occurred while Denmark was in a lock-down implemented on the 16th of December due to a surge in cases not related to B.1.1.7. When the threat of B.1.1.7 became apparent, the 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. The lock-down has been efficient in reducing case numbers and the burden at the hospitals but nevertheless B.1.1.7 has increased during the period and the lineage-specific reproduction number of B.1.1.7 has been estimated to 1.25 on the 16th of February in spite of the lock-down.

On the 22nd January a report was published by NERVTAG (New and Emerging Respiratory Virus Threats) presenting results from UK on the severity of B.1.1.7 compared with other lineages [3]. The report was updated on the 11th February with additional analyses from different study groups and datasets addressing whether infections with Variant of Concern (VOC) B.1.1.7 was associated with a higher risk of hospitalisation and mortality [4]. The report concludes that "it is likely that infection with VOC B.1.1.7 is associated with an increased risk of hospitalisation and death compared to infection with non-VOC viruses". So far, only one of the studies that estimated an increased mortality of 35% has been published in a preprint paper [5].

It is of urgent public health importance to address whether infection with B.1.1.7 is associated with more severe outcomes, because the inevitable spread of this viral lineage may result in a higher constrain on the health care systems in the coming months than previously modelled.

In this study, we linked SARS-CoV-2 genomic data with Danish Health Registers and estimated the risk of hospitalisation among cases with B.1.1.7 compared with cases detected with other SARS-CoV-2 lineages.

METHODS

Data sources

Data on all individuals tested with SARS-CoV-2 RT-PCR were obtained from the Danish Microbiology Database [6-8], and data from other national registers were available in the national COVID-19 surveillance system database at Statens Serum Institut (SSI), described elsewhere [9, 10]. Briefly, the surveillance system links individual-level information daily between registers and databases using the unique personal identification number of all Danes, and thereby centralize surveillance information from e.g. the National Patient Register (in- and outpatient diagnoses, admission and discharge dates) [11], the Civil Registration System (vital status, addresses) [12], as well as viral WGS data from the Danish COVID-19 Genome Consortium [13].

Data sources on SARS-CoV-2 test results in Denmark

Individuals with symptoms suggestive of COVID-19 seen by a doctor as well as health care personnel are tested by RT PCR in regional clinics connected with the ten Danish departments of clinical microbiology serving public and private hospitals and primary care. This workflow is referred to as the "Health care track". In addition, a centralised high throughput public COVID-19 test-laboratory, Test Center Denmark (TCDK), was established by the end of April 2020. TCDK offers free RT PCR testing to asymptomatic persons and persons with mild symptoms, and is referred to as the "Community track". All tests are payed by the Danish government and is free of cost for the citizen. Test slots at the TCDK are made publicly available and can be booked online (at https://www.coronaprover.dk/). 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.

The Danish COVID-19 Genome Consortium (DCGC)

WGS data for SARS-CoV-2 virus was obtained from the 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 and

supported by local sequencing capacity at Statens Serum Institute and Hvidovre Hospital. Since June 2020, the consortium has included local sequencing nodes across the country to increase the proportion of sequenced samples from the health care track. Restrictions in sequencing capacity, mainly in the community track (TCDK), has required a selection of samples for sequencing. When capacity was surpassed in the community track before 11th January, 2021, samples with Ct values <30 were selected, but with increasing capacity the cut-off was raised to samples with Ct values <32 or <35. All WGS data are kept centralised at Aalborg University and transferred daily to SSI.

Study population

The study population included all confirmed cases of SARS-CoV-2 infection with RT PCR test-positive pharyngeal swabs sampled since January 1, 2021 and until the sampling date of the most recent B.1.1.7 sample, which was February 9, 2021. Statistical analysis included updated data from the national COVID-19 surveillance system database on 14th February, 2021.

Exposure to B.1.1.7

Information on infection with lineage B.1.1.7 and other lineages of SARS-CoV-2 virus was available for test-positive individuals where WGS resulted in a viral genome with less than 3000 undetermined bases, hereafter referred to as samples with a viral genome. The specific lineage was classified using pangolin [14, 15].

Hospitalisation (outcome)

The outcome was COVID-19 hospitalisation, which was defined as the first admission within 14 days after a positive SARS-CoV-2 RT PCR test, or first admission within 48 hours before a positive test. Only admissions with lengths of stay above 12 hours were included. This definition is the same used for national surveillance of COVID-19 related admissions in Denmark. The study population included data with the latest admission for COVID-19 on 14th February, 2021.

Co-variates

Basic co-variates included sex, age at sampling, period (week of the swab sampling, ISO 8601 standard starting Monday. Week 53 is a leap week), geographical region of sampling (Capital, Central Denmark, North Jutland, Zealand, Southern Denmark, Missing), and comorbidities (diabetes, adiposity, cancer, neurological diseases, nephrological diseases, haematological diseases, cardiac diseases, respiratory disorder, immunological diseases, other comorbid diseases based on the last 5 years of admission diagnoses) [16]. Additional co-variates included test-track (also subdivided by Ct value below and above 27 in community

track, or by regional Department of Clinical Microbiology performing the RT PCR test in the health care track), ethnicity (2nd generation, Danish born, born abroad), comorbidity based on the registry of chronic diseases (asthma, dementia, diabetes type 1, diabetes type 2, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, osteoporosis, schizophrenia) [17], living in a long-term care facility (LTCF) [18, 19], occupation type for health care workers [20], and SARS-CoV-2 vaccination status [21].

Statistical methods

Associations between SARS-CoV-2 lineage B.1.1.7 and the risk of hospital admission were estimated by calculating odds ratios (OR) using logistic regression in PROC GENMOD in SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). We adjusted the ORs for sex, age (10-year groups), calendar period (week 53 from January 1st, week 1, 2, …,6), region (6 levels), and comorbidities the past 5 years (0, 1+). To take into account that some individuals did not yet have 14 days of follow-up for admission, we further adjusted the analyses for days of follow-up (1-4, 5, 6, …, 14, >14 days). Note that results are presented stratified in four age-groups (0-29, 30-59, 60+ year) and four periods, nevertheless estimates are still adjusted in 10-year groups and week-intervals. Interactions between SARS-CoV-2 lineages and covariates in the analysis of admission were evaluated by including interaction terms in the model. All p-values from the logistic regression analysis of ORs were from Wald-tests. The difference in mean Ct value between B.1.1.7 and other lineages were evaluated using the t-test.

Ethics

This study was conducted on administrative register data. According to Danish law, ethics approval is not needed for such research.

Role of funding sources

The authors received no specific funding for this work.

RESULTS

The study population included 35,887 individuals who tested RT PCR positive for SARS-CoV-2 in samples taken between 1st January and 9th February, 2021, and with data until 14th February, 2021. WGS were performed for 23,057 individuals (64%), and resulted in a viral genome for 18,499 (80%) of the 23,057 individuals. Among individuals with a viral genome, a total of 2,155 (11.6%) had been infected with lineage B.1.1.7.

Table 1 shows characteristics of the study population. From week number 53, 2020, to week 05, 2021, the proportion of test-positive individuals with WGS data increased (58%, 45%, 68%, 83%, 91%, 82%) while WGS data for week 6 was not fully updated (33%). The proportion of individuals with B.1.1.7 infection increased during the same period (1.9%, 3.7%, 7.2%, 12.9%, 19.9%, 30.9%, and 45.1%).

The proportion of test-positive individuals with WGS data were higher in some regions than others (Capital, 64.8%; Central Denmark, 59.7%; North Jutland, 56.1%; Zealand, 69.4%; Southern Denmark, 66.6%; Missing data on region, 67.5%) whereas there was no difference in relation to comorbidities (66.4%, vs. 63.5%), and whether sampled at health care (68.5%) or community test track (62.9%). In the community track, where Ct values were present, WGS was more frequently undertaken among individuals with lower Ct values (Ct<32, 69%; Ct>=32, 49%); from week 2 and onwards, more than 80% of individuals with Ct<32 had WGS undertaken. (Table 1). Among individuals with COVID-19 hospitalisations, the proportion who had WGS undertaken was slightly different than among individuals not admitted for COVID-19 (69.7% vs. 63.9%).

There was a lower proportion of B.1.1.7 cases in the age group 60+ years (6.8%) compared to the other age groups (0-29 years, 14.0%; 30-59 years, 12.2%) (p<0.01), a lower proportion among females compared to males (10.9% vs. 12.5%, p<0.01), and a lower proportion with B.1.1.7 in the health care track (6.3%) than in the community track (13.3%) (p<0.01). In the community track, where data on Ct values were available, the proportion of B.1.1.7 cases was the same among individuals with Ct values below and above 32 (13.2% and 12.6%, p=0.45). (Table 1). However, B.1.1.7 cases had a slightly lower mean Ct value than cases infected with other lineages (27.4, SD 4.1, for the 1811 cases of B.1.1.7; vs. 27.7, SD 4.0, for the 12,028 cases of other lineages; p<0.01).

Table 2 shows the association between infection with lineage B.1.1.7 and the OR of hospitalisation among individuals with WGS data. Overall, in the crude analysis there was no association between infection with lineage B.1.1.7 and hospitalisation (OR 0.87, 95%CI, 0.72-1.05), when compared with infection with any other current lineages of SARS-CoV-2 virus. However, after adjusting for sex, age, period, region, and comorbidities, infection with lineage B.1.1.7 was associated with a 1.6-fold increased OR of admission (OR 1.64, 95%CI, 1.32-2.04) compared with other lineages. Table 2 also shows the estimates stratified by the two most important confounders; age and period. For several of the strata hereof, the crude OR for B.1.1.7 hospital admission was increased. In addition, estimates in Table 2 are shown stratified by test track and Ct values (from the community test track), and in both analyses the adjusted OR for B.1.1.7 hospital admission was increased. In addition, in the community test track, adjusting the estimate further for Ct values grouped in intervals of 0-24, 25-27, 28-30, 31-33, and 34+, yielded an OR of 2.19 (95%CI, 1.65-2.91)

(data not shown in Table 2).

Further adjustment of the main finding for co-variates did not reduce the estimate, e.g. adjusting for 5-year age-grouping (OR 1.62, 95%CI 1.31-2.01). Excluding individuals with less than 14 days observation time, or extending analysis to include all SARS-CoV-2 RT PCR test-positive individuals also did not change the estimate (Table S1). Stratifications by basic co-variates, living in a LTCF, and being a health care worker, did not reveal that any of these exhibited significant interactions with the effect of B.1.1.7 on hospitalisation. The OR of admission after B.1.1.7 when not living in an LTCF was 1.65 (95% CI, 1.32-2.06) while numbers were small for individuals living in LTCF. (Table S2).

We also had information on intensive care unit treatment, however, numbers were too small to be conclusive on the association with B.1.1.7 (13 ICU among 128 B.1.1.7 admissions versus 115 ICU among 1090 admissions after infection with other lineages).

DISCUSSION

The present analyses suggest that individuals infected with lineage B.1.1.7 have an increased risk of hospitalisation of an estimated 64% compared with individuals infected with other lineages of SARS-CoV-2 virus. The association was observed within several strata of age, calendar period and of other covariates. The association did not diminish, but rather slightly enhanced, when adjusting for the potential mediators test track and Ct value.

Hitherto, the concerns related to B.1.1.7 has mainly been due to the increased transmissibility and not increased severity following infection. According to the NERVTAG report there were several limitations with the UK studies assessing the severity of B.1.1.7. The majority of the analyses were limited to community testing data for subsets of the population; therefore the datasets on mortality only covers 10% of all deaths. In addition, there may be several confounding factors not adequately adjusted for such as comorbidity and LTCF stay. In the present study, we have had access to national data covering both community testing and healthcare track testing with high capacity on WGS data, and we were able to adjust for and perform stratified analyses on several possible confounding factors including age, period, comorbidity, and LTCF stay. In the crude analyses, we found a similar risk of hospitalisation among B.1.1.7 cases and cases with other lineages. When we adjusted for age at sample date and period there was a 1.6-fold higher risk of hospitalisation after B.1.1.7 infection compared with other lineages. The fact that the increased risk of hospital admissions was evident in adjusted analysis only calls for a careful discussion. First, age confounded

the crude estimate as the age-group 60+ years were less likely to be B.1.1.7 positive although they have a high risk of hospitalisation. Next to age, period further confounded the crude estimate, as there was a general tendency of reduced rates of hospitalisation as the epidemic progressed concomitantly with an increase in B.1.1.7. Thus, our study shows that 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.

With the increasing WGS capacity, reaching 65% in week 5, our results become generalisable but there might be a potential risk of selection bias as samples with lower Ct values to some extent were selected to increase the chance of obtaining a viral genome. For this to hamper generalisability of the results, the selection should, however, be associated with both exposure and outcome, i.e. B.1.1.7 infection (exposure) and hospitalisation (outcome). Using our complete information on hospitalisation, we did, however, not observe a strong association with between being sequenced and hospitalisation among all test-positive.

Two mechanisms for the increased transmissibility has been suggested 1) a higher ACE- 2 receptor binding affinity 2) a higher viral load (which might generally result in lower Ct values) [22, 23]. Our study cannot address the first hypothesis but lower Ct values for B.1.1.7 has been described in the NERVTAG report from the 23rd December [24]. One could argue that a higher viral load may strain the immune system and result in more severe outcomes. However, this mechanism is not supported by our result. First, the association between B.1.1.7 and hospitalisation was not weakened by adjustment for the Ct level. Secondly, the difference in Ct level between B.1.1.7 and other variants was minor.

Due to the increased public health concern of B.1.1.7, Denmark has put an extra effort in contact tracing and ensuring self-isolation. This could lead to a possible bias of our finding if B.1.1.7 is detected more frequently among close contacts, and increased focus on B.1.1.7 could lead to more frequent hospitalisation due to concerns of finding B.1.1.7. On the other hand, a more efficient contact tracing strategy would likely result in the identification of more milder or asymptomatic cases. But an increased detection of mild cases of B.1.1.7 compared to other SARS-CoV-2 lineages would tend to underestimate the association between B.1.1.7 and hospital admission. Thus, we think that an improved contact tracing around cases with lineage B.1.1.7 would rather underestimate our finding of an increased risk of hospitalisation after infection with B.1.1.7

On the other hand outbreaks of B.1.1.7 at LTCF may result in an overestimation of the association between B.1.1.7 and hospitalisation as B.1.1.7 results in increased transmission in a population with a very high "background risk" of admission. We were able to stratify for LTCF and the association between B.1.1.7 was

similar in the population not living in LTCF (OR 1.65, table S2) as in the overall adjusted analysis (OR 1.64), which supports that B.1.1.7 outbreaks at LTCF could not explain the increased risk of hospitalisation for B.1.1.7 cases.

Currently B.1.1.7 seems to be circulating widely in Europe although lack of proper surveillance using WGS blurs the picture. ECDC states in the most recent risk assessment related to the spread of new SARS-CoV-2 variants that unless Non-pharmaceutical interventions (NPI) are strengthened in terms of compliance in the coming months a significant increase in COVID-19 cases and deaths in Europe should be anticipated [25]. Several countries have already experienced overburdened hospital and excess mortality in connection with the predominance of B.1.1.7, such as in the UK, Ireland, Portugal, Spain and Israel. So far, these surges has mainly been explained by an increased transmissibility, but our corroborates that an increased severity may also play a role.

On the positive side, the current COVID-19 vaccines are expected to be effective against lineage B.1.1.7. A study addressing the effectiveness of the Moderna mRNA vaccine found both infection- and vaccine-induced antibodies were effective at neutralising the SARS-CoV-2 B.1.1.7 [26]. According to the European Centre for Disease Prevention and Control's (ECDC) risk assessment, similar results have been shown for the Corminaty vaccine, although they have not yet been published. The clinical efficacy of the AstraZeneca vaccine against B.1.1.7 is similar to the efficacy of the vaccine against other circulating lineages in the UK, according to a pre-print manuscript [25, 27].The ongoing clinical phase 3 trials of the protein-based vaccine Novavax 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 have been available in a press release from the manufacturer [25, 28]. Based on these findings a fast roll out of the COVID-19 vaccination programs is crucial for preventing an increased burden at hospitals due to B.1.1.7.

We have shown that infection with lineage B.1.1.7 is associated with a considerable increased risk of hospitalisation of 64% as compared with other SARS-CoV-2 lineages. This finding may have serious public health impact in countries with spread of B.1.1.7 and can support hospital preparedness and modelling of projected impact of the epidemic.

REFERENCES

1. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday J, et al. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England. medRxiv 2020.12.24.20248822 [Preprint]. 2020 [cited 2021 February 22]. Available from: https://www.medrxiv.org/content/10.1101/2020.12.24.20248822v1 doi: 10.1101/2020.12.24.20248822. 2020.
2. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday J, et al. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England. medRxiv: 2020.12.24.20248822 [Preprint]. 2021 [cited 2021 Feb 22] Available from: http://medrxiv.org/content/early/2021/02/07/2020.12.24.20248822.abstract doi: 10.1101/2020.12.24.20248822. 2021.
3. Horby P, Huntley C, Davies N, Edmunds J, Ferguson N, Medley G, et al. NERVTAG note on B.1.1.7 severity for SAGE 77. New & Emerging Respiratory Threats Advisory Group, 2021. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961037/NERVTAG_note_on_B.1.1.7_severity_for_SAGE_77__1_.pdf.
4. New & Emerging Respiratory Threats Advisory Group. NERVTAG update note on B.1.1.7 severity. 2021. Available from: https://www.gov.uk/government/publications/nervtag-update-note-on-b117-severity-11-february-2021.
5. Davies NG, Jarvis CI, Edmunds WJ, Jewell NP, Diaz-Ordaz K, Keogh RH. Increased hazard of death in community-tested cases of SARS-CoV-2 Variant of Concern 202012/01 [Preprint]. 2021 [cited 2021 Feb 19]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33564794 doi: 10.1101/2021.02.01.21250959. Epub 2021/02/11. PubMed PMID: 33564794; PubMed Central PMCID: PMCPMC7872389.
6. Voldstedlund M, Haarh M, Mølbak K, the MiBa Board of Representatives. The Danish Microbiology Database (MiBa) 2010 to 2013. Eurosurveillance. 2014;19(1):20667. doi: https://doi.org/10.2807/1560-7917.ES2014.19.1.20667.
7. Statens Serum Institute. MiBa, HAIBA og det digitale infektionsberedskab. [Cited 2021 Feb 22]. Available from: https://miba.ssi.dk/.
8. Jepsen MT, Trebbien R, Emborg HD, Krause TG, Schønning K, Voldstedlund M, et al. Incidence and seasonality of respiratory syncytial virus hospitalisations in young children in Denmark, 2010 to 2015. Eurosurveillance. 2018;23(3):17-00163. doi: https://doi.org/10.2807/1560-7917.ES.2018.23.3.17-00163.
9. Reilev M, Kristensen KB, Pottegard A, Lund LC, Hallas J, Ernst MT, et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. Int J Epidemiol. 2020;49(5):1468-81. Epub 2020/09/06. doi: 10.1093/ije/dyaa140. PubMed PMID: 32887982; PubMed Central PMCID: PMCPMC7499657.
10. Statens Serum Institute. COVID-19. [Cited 2021 Feb 19]. Available from: https://covid19.ssi.dk/.
11. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scandinavian Journal of Public Health. 2011;39(7_suppl):30-3. doi: 10.1177/1403494811401482.
12. Pedersen CB. The Danish Civil Registration System. Scandinavian Journal of Public Health. 2011;39(7_suppl):22-5. doi: 10.1177/1403494810387965.
13. Statens Serum Institute. COVID-19: SARS-CoV-2-virusvarianter. [Cited 2021 Feb 19]. Available from: https://covid19.ssi.dk/virusvarianter.
14. Lo SW, Jamrozy D. Genomics and epidemiological surveillance. Nature Reviews Microbiology. 2020;18(9):478-. doi: 10.1038/s41579-020-0421-0.
15. Pangolin COVID-19 Lineage Assigner. Available from: https://pangolin.cog-uk.io/.
16. Emborg HD, Krause TG, Nielsen L, Thomsen MK, Christiansen CB, Skov MN, et al. Influenza vaccine effectiveness in adults 65 years and older, Denmark, 2015/16 – a rapid epidemiological and virological assessment. Eurosurveillance. 2016;21(14):30189. doi: https://doi.org/10.2807/1560-7917.ES.2016.21.14.30189.

17. Danish Health Data Authority. Selected Chronic Diseases and severe mental disorders. [Cited 2021 Feb 19]. Available from: https://www.danishhealthdata.com/find-health-data/Udvalgte-kroniske-sygdomme-og-Svaere-Psykiske-Lidelser.
18. Statens Serum Institute. COVID-19: Ugentlige opgørelser med overvågningsdata. [Cited 2021 Feb 19]. Available from: https://covid19.ssi.dk/overvagningsdata/ugentlige-opgorelser-med-overvaagningsdata.
19. Sundhedsdatastyrelsen. Plejehjem og plejehjemsbeboere. [Cited 2021 Feb 19]. Available from: https://sundhedsdatastyrelsen.dk/da/tal-og-analyser/analyser-og-rapporter/sundhedsvaesenet/plejehjem.
20. Statens Serum Institute. COVID-19: Branchefordelte opgørelser over covid-19-testede og -positive. [Cited 2021 Feb 19]. Available from: https://covid19.ssi.dk/overvagningsdata/branchefordelte-opgoerelser.
21. Statens Serum Institute. COVID-19: Vaccinationstilslutning til covid-19. [Cited 2021 Feb 19]. Available from: https://covid19.ssi.dk/overvagningsdata/vaccinationstilslutning.
22. Leung K, Shum MH, Leung GM, Lam TT, Wu JT. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. Euro Surveill. 2021;26(1):2002106. doi: 10.2807/1560-7917.ES.2020.26.1.2002106. PubMed PMID: 33413740.
23. Kissler S, Fauver JR, Mack C, Tai CG, Breban MI, Watkins AE, et al. Densely sampled viral trajectories suggest longer duration of acute infection with B.1.1.7 variant relative to non-B.1.1.7 SARS-CoV-2. [Preprint]. 2021 [cited 2021 Feb 20]. Available from: https://dash.harvard.edu/handle/1/37366884

24. New and Emerging Respiratory Virus Threats Advisory Group. NERVTAG meeting on SARS-CoV-2 variant under investigation VUI-202012/01. 2020. Available from: https://app.box.com/s/3lkcbxepqixkg4mv640dpvvg978ixjtf/file/756963730457.
25. European Centre for Disease Prevention and Control. SARS-CoV-2 - increased circulation of variants of concern and vaccine rollout in the EA/EEA, 14th update - 15 February 2021. ECDC: Stockholm, 2021. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/RRA-covid-19-14th-update-15-feb-2021.pdf.
26. Edara VV, Floyd K, Lai L, Gardner M, Hudson W, Piantadosi A, et al. Infection and mRNA-1273 vaccine antibodies neutralize SARS-CoV-2 UK variant. medRxiv: 2021.02.02.21250799. 2021 [cited 2021 Feb 21]. Available from http://medrxiv.org/content/early/2021/02/05/2021.02.02.21250799.abstract. doi: 10.1101/2021.02.02.21250799.
27. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus BJ, Bibi S ea. Efficacy of ChAdOx1 nCoV-19 (AZD1222) Vaccine Against SARS-CoV-2 VOC 202012/01 (B.1.1.7). The Lancet [Preprint]. 2021 [cited 2021 Feb 19] Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160#references-widget.
28. Novavax. Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial. 2021 Jan 28 Available from: https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccinedemonstrates-893-efficacy-uk-phase-3.

Table 1. Characteristics of the study population of 35,887 confirmed cases of SARS-CoV-2 virus infection (RT PCR test-positive) by WGS data, genome data, B.1.1.7 cases, and hospitalisations, 1st January to 14th February, 2021, Denmark.

		WGS of SARS-CoV-2 virus							
				Genome		B.1.1.7		Hospitalisation	
Characteristic	All confirmed cases of infection	WGS (sequenced)	% of all	N	% of all	n	% of genome	n	% of all
All	35887	23057	64.2	18499	51.5	2155	11.6	2269	6.3
Sex									
Females	18874	12058	63.9	9600	50.9	1043	10.9	1088	5.8
Males	17013	10999	64.7	8899	52.3	1112	12.5	1181	6.9
			P=.13		*P<.01*		*P<.01*		*P<.01*
Age									
0-29	13060	8117	62.2	6456	49.4	904	14.0	145	1.1
30-59	15252	9912	65.0	8010	52.5	977	12.2	607	4.0
60+	7575	5028	66.4	4033	53.2	274	6.8	1517	20.0
			P<.01		*P<.01*		*P<.01*		*P<.01*
Period									
week 53	4932	2839	57.6	2373	48.1	46	1.9	298	6.0
week 01	11183	5036	45.0	3941	35.2	147	3.7	670	6.0
week 02	6891	4703	68.2	3832	55.6	275	7.2	470	6.8
week 03	5295	4373	82.6	3564	67.3	459	12.9	373	7.0
week 04	3606	3288	91.2	2566	71.2	510	19.9	225	6.2
week 05	3080	2524	81.9	1999	64.9	617	30.9	190	6.2
week 06	900	294	32.7	224	24.9	101	45.1	43	4.8
			P<.01		*P<.01*		*P<.01*		*P=.03*
Test track									
Health care track	8676	5942	68.5	4355	50.2	273	6.3	1590	18.3
Community track	27211	17115	62.9	14144	52.0	1882	13.3	679	2.5
			P<.01		*P<.01*		*P<.0001*		*P<.0001*
Ct values in community track*									
Ct value registered	26553	16752	63.1	13839	52.1	1811	13.1	660	2.5
Ct value>=32	8182	4019	49.1	2286	27.9	288	12.6	152	1.9
Ct value<32	18371	12733	69.3	11553	62.9	1523	13.2	508	2.8
			P<.01		*P<.01*		*P=.45*		*P<.01*

WGS, viral Whole Genome Sequencing; P-values are from Chi-square test.

*Ct values in the health care track were not available for data analysis.

Table 2. Infection with lineage B.1.1.7 and risk of hospitalisation overall and by age, period, test track, and Ct value, among 18,499 confirmed cases of SARS-CoV-2 virus infection (RT PCR test-positive) with viral genome data, 1st January to 14th February, 2021, Denmark.

	Admission within 14 days of test-positive sample date				
Infection with SARS-CoV-2 lineage B.1.1.7	**Yes**	**%**	**No**	Crude* OR (95% CI)	Adjusted** OR (95% CI)
Overall					
No (other co-existing lineages)	1107	6.8	15237	1 (ref)	1 (ref)
Yes (lineage B.1.1.7)	128	5.9	2027	0.87 (0.72-1.05)	1.64 (1.32-2.04)
				P=.14	*P <.01*
By age					
0-29	14	1.5	890	1.57 (0.87-2.84)	1.84 (1.01-3.35)
30-59	50	5.1	927	1.36 (1.00-1.85)	1.62 (1.18-2.23)
60+	64	23.4	210	1.30 (0.96-1.76)	1.61 (1.16-2.23)
				P=.51	*P= .92*
By period					
1-9 January	15	9.1	150	1.17 (0.68-2.00)	1.66 (0.92-3.01)
10-19 January	36	8.3	397	1.24 (0.87-1.78)	1.78 (1.20-2.66)
20-25 January	24	5.8	390	0.88 (0.56-1.37)	1.71 (1.06-2.76)
26 January - (9 February)	24	5.6	401	0.98 (0.61-1.55)	1.50 (0.91-2.47)
<14 days follow-up for admission	29	4.0	689	1.12 (0.71-1.76)	1.49 (0.90-2.45)
				P=.52	*P=.98*
By test track* **					
Health care track	46	16.8	227	0.88 (0.63-1.22)	1.67 (1.14-2.44)
Community track	82	4.4	1800	1.59 (1.25-2.04)	1.98 (1.51-2.58)
Ct <27	44	4.9	852	1.65 (1.17-2.32)	2.19 (1.46-3.27)
Ct >=27	35	3.6	924	1.53 (1.06-2.22)	2.18 (1.50-3.18)
				P=.77	*P=.99*

OR, odds ratio; CI, confidence intervals

*All estimates stratified by sample period in the 5 groups shown are adjusted for sample period in detail (calendar week) and days of follow-up for admission if <14 days. Those stratified by age are adjusted for age in detail (10-year groups).

** Adjusted for sex, age (10-year groups), sample period (calendar week) and days of follow-up for admission if <14 days, region (5 groups), and comorbidities last 5 years (0, 1+). In a forward elimination analysis, shown in order of most to least important confounders yielded ORs 1.36 (1.11-1.67) adjusted for age, 1.60 (1.29-1.98) adding period, 1.64 (1.32-2.04) adding comorbidities, 1.64 (1.32-2.04) adding sex, and 1.64 (1.32-2.04) adding region.

*** Ct values were available for the community track only. In the community track, Ct values were missing for 305 individuals (2%, see table 1). The Ct cut-off 27 were chosen as the floor of the median. P-values for the interaction with test track were P=.01 in crude, and P=.47 in the adjusted analysis.

Table S1. Infection with lineage B.1.1.7 and risk of hospitalisation using additional adjustment and exclusions/extensions, among 18,499 confirmed cases of SARS-CoV-2 virus infection (RT PCR test-positive) with WGS data, 1st January to 14th February, 2021, Denmark.

Hospitalisations after infection with B.1.1.7		Adjusted OR* (95% CI)
Main analysis (see Table 2)	128	1.64 (1.32-2.04)
Additional adjustment		
Adjusted for ethnicity	128	1.58 (1.27-1.97)
Adjusted for age in 5-year groups	128	1.63 (1.31-2.02)
Adjusted for each comorbidity (10 disease groups)**	128	1.67 (1.34-2.09)
Adjusted fine for number of comorbidities (1, 2, 3+)	128	1.67 (1.34-2.08)
Adjusted for each RUKS comorbidity (8 diseases)**	128	1.62 (1.31-2.02)
Adjusted fine for number of RUKS comorbidities (1, 2, 3+)	128	1.61 (1.30-2.00)
Adjusted fine for number of comorbidities incl. RUKS (1, 2, 3+)	128	1.65 (1.33-2.06)
Exclusion/extensions		
Excluding persons with <14 days follow-up for hospitalisation	99	1.68 (1.32-2.14)
Extending analysis to all test-positive (N=35,887)		
Not adjusted for period X WGS data interaction	128	1.37 (1.11-1.69)
Adjusted for period X WGS data interaction	128	1.56 (1.26-1.94)

OR, odds ratio; CI, confidence intervals

* Adjusted for sex, age (10-year groups), sample period in detail (calendar week) and follow-up time <14 days, region (5 groups), and comorbidities last 5 years (0, 1+)

**Hospital patient diagnosis the latest 5 years before the sample date: Diabetes, adiposity, cancer, neurological diseases, nephrological diseases, haematological diseases, cardiac diseases, respiratory disorder, immunological disaseses, other comorbid diseases. Data obtained from the National Patient Registry.

** Chronic diseases: RUKS comorbidities include asthma, dementia, diabetes type 1, diabetes type 2, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, osteoporosis, scizophrenia. Data obtained from the register of chronic diseases (RUKS) which is created based on data from the National Patient Register, the Prescription Register, and the Health Service register.

Table S2. Infection with lineage B.1.1.7 and risk of hospitalisation in additional stratified analysis, among 23,057 18,499 confirmed cases of SARS-CoV-2 virus infection (RT PCR test-positive) with WGS data, 1st January to 14th February, 2021, Denmark.

	B.1.1.7 hospitalisations	Adjusted OR (95% CI)*
Main analysis (see Table 2)	128	1.64 (1.32-2.04)
Stratification		
Living in a long-term care facility (LTCF)		
No	121	1.64 (1.31-2.05)
Yes, previously	4	6.32 (0.64-62.4)
Yes, currently	3	1.07 (0.29-3.90)
		P=0.39
Health care worker		
No	124	1.62 (1.30-2.03)
Yes	4	1.79 (0.61-5.26)
		P=0.86
Sex		
Male	70	1.63 (1.22-2.18)
Female	58	1.65 (1.22-2.25)
		P=0.94
Region		
Capital	47	1.89 (1.35-2.65)
Central Denmark	15	2.13 (1.19-3.82)
North Jutland	4	1.74 (0.59-5.15)
Zealand	43	1.65 (1.11-2.45)
Southern Denmark	18	1.11 (0.65-1.88)
Missing region**	1	0.45 (0.05-3.75)
		P=0.02
Vaccinated against SARS-CoV-2***		
No	114	1.60 (1.27-2.02)
Yes, test-positive before vaccination	13	6.72 (0.51-87.8)
Yes, test-positive after vaccination	1	1.85 (0.92-3.69)
		P=0.63

OR, odds ratio; CI, confidence intervals

* Adjusted for sex, age (10-year groups), sample period in detail (calendar week) and follow-up time <14 days, region (5 groups), and comorbidities last 5 years (0, 1+)

** The RT PCR sample of 162 of 18,499 individuals (0.8%) were not registered with a region in the COVID-19 surveillance database.

***Vaccinations until 14th February, 2021, included the vaccines Corminaty® (Pfizer-BioNTech), COVID-19 vaccine Moderna®, and AstraZeneca. Vaccinated individuals were grouped into test-positive after 1st or 2nd dose, and before 1st dose.