Incidence of community-acquired pneumonia hospitalisation in persons with bronchiectasis during the COVID-19 lockdown in Denmark: a retrospective cohort study

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ABSTRACT
Background Persons with bronchiectasis have a high risk of community-acquired pneumonia. Social distancing measures, implemented to prevent the spreading of SARS-CoV-2, could potentially reduce the incidence of other infectious diseases.

Research question Was the COVID-19 lockdown period, along with accompanying social distancing measures, associated with reduced hospital admissions for community-acquired pneumonia and decreased overall mortality rates among individuals with bronchiectasis?

Methods Social distancing measures were introduced in Denmark by 12 March 2020 and were preserved until 20 May 2020 (social distancing period), after which the measures were gradually dismissed. The study included all adults (≥18 years) with bronchiectasis residing in Denmark. Confirmed cases of SARS-CoV-2 infection were excluded. We retrospectively investigated the incidence of community-acquired pneumonia hospital admission, death of all causes and respiratory antibiotic treatment in the 10-week social distancing period in 2020, compared with the same dates in 2019. 9344 persons were included in the study.

Results In the social distancing period, the incidence rate of pneumonia-hospitalisation per 10 000 person-weeks was 9.2 compared with 13.8 in the reference period. This reduction corresponds to an incidence rate ratio (IRR) of 0.67 (95% CI 0.51 to 0.88, p<0.01). Mortality was unchanged (IRR 0.90, 95% CI 0.61 to 1.32, p=0.58). Fewer persons received respiratory antibiotics (IRR 0.85, 95% CI 0.78 to 0.94, p<0.001).

Conclusion The social distancing period was associated with a lower incidence of community-acquired pneumonia hospitalisations and respiratory antibiotic treatments in persons with bronchiectasis while all-cause mortality remained unchanged.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Persons with bronchiectasis experience frequent respiratory tract infections, which have a significant impact on their overall prognosis and everyday quality of life. It is crucial to develop effective strategies to reduce infections and exacerbations in this population.

WHAT THIS STUDY ADDS
⇒ The period with implemented measures for controlling the spreading of SARS-CoV-2 was associated with a markedly lower risk of severe non-COVID-19 community-acquired pneumonia leading to hospitalisation in persons with bronchiectasis. Milder exacerbations also seemed to decrease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Keeping distance to others could potentially be a tool in infection control for persons with bronchiectasis, especially during seasonal epidemics.

INTRODUCTION
Background Bronchiectasis is a chronic lung disease characterised by bronchial wall thickening due to inflammation, leading to chronic cough, increased sputum production and recurrent respiratory infections.1–3 Ranking as the third most common airway disease today, rates up to 566 per 100 000 persons have been reported, with a prevalence that is still increasing.4 As persons with bronchiectasis have markedly high risk of respiratory tract infections and exacerbation, which significantly impacts their overall prognosis and everyday quality of life,5–9 research in pharmacological and non-pharmacological strategies to reduce the risk...
of pneumonia in persons with bronchiectasis are much warranted.

Current European Respiratory Society (ERS) and British Thoracic Society (BTS) guidelines suggest the use of airway clearance techniques and pulmonary rehabilitation as non-pharmacological self-management strategies; however, ERS guidelines grade these as low quality of evidence and thus only a weak recommendation, and BTS highlights the need for stronger evidence on these interventions.10 11 Frequent exercise combined with pulmonary rehabilitation is however highly encouraged in the ERS guidelines (graded as ‘strong evidence’) for persons with reduced exercise capacity.10 A Cochrane database systematic review concludes that current studies are insufficiently powered and not able to determine if self-management interventions benefit persons with bronchiectasis regarding quality of life and hospitalisations.12 Qualitative studies found that the interviewed persons with bronchiectasis were receptive to self-management strategies.13 14 and social and physical distancing measures could thus be considered possible additional ways of self-managing bronchiectasis.

Following the emerging COVID-19 pandemic, rigorous social distancing measures were implemented in Denmark on 12 March 2019, as an attempt to slow down the pandemic.15 Population-based surveillance studies indicate lower transmission rates of viruses and bacteria associated with respiratory infection during the COVID-19-related lockdown.16 17 Based on both Danish and international data, it has now been shown that the introduction of the social distancing measures have reduced admission rates for respiratory tract infections for chronic obstructive pulmonary disease (COPD) and asthma exacerbations15 18 as well as paediatric admissions with both upper19 and lower respiratory tract infections.20 21 However, it has yet not been evaluated how the implementation of the social distancing measures affected persons with bronchiectasis.

Objectives

The aim of this study was to investigate whether the COVID-19 lockdown and related measures was associated with a reduction of community-acquired pneumonia hospital admission and all-cause mortality in persons diagnosed with bronchiectasis.

METHODS

Design

The study was a retrospective cohort study comparing two 10-week periods using data from the Danish health registers which contain health information on all Danish residents (figure 1). According to Danish law, no consent is required for the retrospective use of registry data and consent cannot be withdrawn; data are only deleted on request if it is wrong or misleading and if it cannot be corrected. Data analyses began on 31 March 2022 after receiving access to data from the national health administrative registries.

Data sources

Health information on Danish residents is divided into different registries dependent on the type of information (ie, vital status, prescriptions and hospital contacts). Public healthcare institutions report data to these individual registries following, for example, hospital discharge, registered death and receipt of laboratory results. All pharmacies report data on the dispensation of prescriptions. At the date of birth or immigration to the country, all Danish residents receive a unique personal identification number in the Civil Registration System.22 We used this personal identification number for exact linkage on an individual level between registers ensuring complete follow-up on registered data.

The following nationwide registries were used in this study:

► The Danish Central Personal Registry contains information on citizens of Denmark. This includes information about sex, date of birth and vital status of the citizens.22

► Danish National Patient Register (DNPR) contains information on all admissions to Danish hospitals since 1977 and hospital outpatient specialist clinic visits since 1995. The admissions are registered with International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes (from 1994). This registry also holds information on dyspnoea and tobacco use for some individuals (ie, if registered during a hospital contact).23

► The National Prescription Registry containing data on dispensed prescriptions, eg, Anatomical Therapeutic Chemical (ATC) codes and date of collection, from pharmacies since year 2004.24

► The Danish register of COVID-19 surveillance data from ‘Statens Serum Institut’ (a national disease control and infectious diseases preparedness institution under the Danish Ministry of Health) contains data on persons tested for SARS-CoV-2.25
The calendar period of social distancing was defined as the 10-week period 12 March 2020–22 May 2020, as this was considered the period with the most extensive law enforced lockdown restrictions in Denmark during the COVID-19 pandemic. No social distancing measures were introduced, or law enforced before 12 March, whereas the period after 22 May 2020 was dominated by alternating social distancing measures and a general reduction in lockdown restrictions. The lockdown measures included physical distance, social gathering avoidance and hygienic measures. Face masks were not mandatory in Denmark during this period and there was no official government recommendation to wear them. The timeline of the introduction of the social distancing measures is presented in table 1.

**Cohort selection**

Persons were included if they were alive by the first day of the reference period (12 March 2019), ≥18 years of age, were registered with a non-cystic fibrosis bronchiectasis diagnosis (ICD-10 code J47.9) in The DNPR from 1 January 2014 to 1 January 2019. According to the Danish national guidelines bronchiectasis is diagnosed by thoracic high-resolution CT scan. Persons with a registered positive PCR laboratory test for SARS-CoV-2 during the study were excluded. No new persons with bronchiectasis were included after 12 March 2019.

**Social distancing period**

The calendar period of social distancing was defined as the 10-week period 12 March 2020–22 May 2020, as this was considered the period with the most extensive law enforced lockdown restrictions in Denmark during the COVID-19 pandemic. No social distancing measures were introduced, or law enforced before 12 March, whereas the period after 22 May 2020 was dominated by alternating social distancing measures and a general reduction in lockdown restrictions. The lockdown measures included physical distance, social gathering avoidance and hygienic measures. Face masks were not mandatory in Denmark during this period and there was no official government recommendation to wear them. The timeline of the introduction of the social distancing measures is presented in table 1.

**Table 1** Lockdown measures during the early COVID-19 pandemic in Denmark

<table>
<thead>
<tr>
<th>Component</th>
<th>Intervention</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assembly ban</td>
<td>Ban of gatherings &gt;100 persons</td>
<td>13 March 2020–18 March 2020</td>
</tr>
<tr>
<td></td>
<td>Ban of gatherings &gt;10 persons</td>
<td>18 March 2020–8 June 2020</td>
</tr>
<tr>
<td>Closure of institutions</td>
<td>Closure of all leisure facilities and indoor cultural institutions</td>
<td>13 March 2020–21 May 2020</td>
</tr>
<tr>
<td>Distance</td>
<td>2 m distance from other people encouraged</td>
<td>12 March 2020–10 May 2020</td>
</tr>
<tr>
<td></td>
<td>1 m distance from other people encouraged. 2 m distance encouraged from people with COVID-19 symptoms or at high risk of complications*</td>
<td>10 May 2020 and throughout the study</td>
</tr>
<tr>
<td>Hygiene</td>
<td>Frequent handwashing or use of hand sanitiser, coughing etiquette and avoidance of handshakes, hugs and kisses as greetings were encouraged. Hand sanitiser facilities in shops and supermarkets were mandatory.</td>
<td>12 March 2020 and throughout the study</td>
</tr>
<tr>
<td>Public transportation</td>
<td>Limited use of public transportation was encouraged, especially during rush hour</td>
<td>12 March 2020 and throughout the study</td>
</tr>
</tbody>
</table>

*Defined by pregnancy, age >65 years, cardiopulmonary diseases (excluding well-treated hypertension, mild and well-treated asthma), chronic renal disease with reduced renal function, chronic liver disease, type 1 and 2 diabetes, rheumatic and neuromuscular diseases with reduced ability to cough, severe obesity with body mass index ≥35 (weight (kg)/height (m)^2), haematological diseases with assessed higher risk of complications, children with chronic disease or sequelae of premature birth and persons with weakened immune system caused by haematological diseases, organ transplantation, immunosuppressive therapy or HIV infection with severe effects on the immune system.

**Outcomes**

We assessed the incidence rates (IRs) of community-acquired pneumonia hospitalisation in the two 10-week periods: the social distancing period compared with the reference period. The primary outcome of the study was community-acquired pneumonia hospitalisation, defined as an admission with a diagnosis of pneumonia (ICD10-codes J12–18.9). Secondary outcomes were death from all causes and respiratory antibiotic cure—defined as collection of respiratory antibiotic prescriptions commonly used to treat mild exacerbations in bronchiectasis (ATC-codes: amoxicillin—J01CA04, amoxicillin/clavulanic acid—J01CR02) from any pharmacy.

**Statistics**

For descriptive statistics, categorical variables were presented as frequencies and proportions while continuous variables were presented as median values with IQR. Baseline Charlson Comorbidity Index Score was calculated using data from DNPR from 1 January 2014 to 1 January 2019. Use of medicine, smoking status and dyspnoea grade was assessed by the newest record containing information on these variables during 1 January 2018 to 1 January 2019. IRs and IR ratios (IRRs) with 95% CIs of community-acquired pneumonia hospitalisation, death and respiratory antibiotic cure were calculated and compared. The statistical analyses were performed by using R V.4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

A total of 9371 persons were registered with bronchiectasis between 1 January 2014 and 1 January 2019. Of these, 27 subjects were excluded due to SARS-CoV-2...
infection during the study period. The final study population consisted of 9344 persons, hereof 3446 males. The median age was 69 years (IQR 59–75). Baseline values can be found in table 2. The population at risk (of all outcomes) was different between the reference period (N=9344) and social distancing period (N=9022) as 322 subjects died before the beginning of social distancing period.

The social distancing intervention was associated with a reduction in pneumonia hospitalisations from 13.8 per 10,000 person-weeks (95% CI 13.5 to 18.7) in the reference period to 9.2 per 10,000 person-weeks (95% CI 8.8 to 13.2) in the social distancing period. This relative reduction in hospitalisation rate corresponds an IRR of 0.67 (95% CI 0.51 to 0.88, p<0.01, table 3). IRs were lower at all times in the social distancing period except during week 5 (figure 2). No difference in mortality between the two periods could be detected (IRR 0.90, 95% CI 0.61 to 1.32, p=0.58, table 3). Respiratory antibiotic cures decreased (IRR 0.85, 95% CI 0.78 to 0.94, p<0.001, table 3).

**DISCUSSION**

Using nationwide health registers, we found a significant decline in the rate of community-acquired pneumonia hospitalisations and respiratory antibiotic cures in the weeks following the implementation of social distancing measures during the COVID-19 pandemic in 2020, compared with the same calendar period in 2019, whereas all-cause mortality was unchanged. Social distancing as an associated parameter could be accountable for this, since community-acquired pneumonia is caused by transmission of viral or bacterial infections, which the social distancing measures were designed to reduce. Despite the substantially lower incidences of pneumonia-hospitalisation and respiratory antibiotic cure in the social distancing period compared with the reference period, the IRs of death did not differ significantly. The total number of deaths was, however, small and may have challenged the statistical power to investigate this outcome.

An observational study from the UK reported a reduction in the number of bronchiectasis exacerbations between March 2020 and March 2021 (1.12 exacerbations per person) compared with the same periods in 2018/2019 (2.08 exacerbations per person) and 2019/2020 (2.01 exacerbations per person) in 147 persons. Since it was a single centre substudy only including patients answering a follow-up questionnaire, and thus prone to selection bias.

**Table 2** Baseline characteristics in the study population by 1 January 2019

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Reference period N=9344</th>
<th>Social distancing period N=9022</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (IQR)</strong></td>
<td>69 (59–76)</td>
<td>68 (59–76)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>3446 (36.9)</td>
<td>3300 (36.6)</td>
</tr>
<tr>
<td><strong>FEV1%, median (IQR)</strong></td>
<td>60 (44–84)</td>
<td>62 (45–85)</td>
</tr>
<tr>
<td><strong>Severity of comorbidities (n=9344) (n=9022)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (CCI 0), n (%)</td>
<td>264 (2.8)</td>
<td>264 (2.9)</td>
</tr>
<tr>
<td>Mild (CCI 1 and 2), n (%)</td>
<td>2444 (26.2)</td>
<td>2433 (27.0)</td>
</tr>
<tr>
<td>Moderate (CCI 3 and 4), n (%)</td>
<td>4470 (47.8)</td>
<td>4365 (48.4)</td>
</tr>
<tr>
<td>Severe (CCI≥5), n (%)</td>
<td>2166 (23.2)</td>
<td>1960 (21.7)</td>
</tr>
<tr>
<td><strong>Dyspnoea (n=445) (n=409)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC grade 1, n (%)</td>
<td>57 (12.8)</td>
<td>56 (13.7)</td>
</tr>
<tr>
<td>MRC grade 2, n (%)</td>
<td>120 (27.0)</td>
<td>118 (28.9)</td>
</tr>
<tr>
<td>MRC grade 3, n (%)</td>
<td>130 (29.2)</td>
<td>122 (29.8)</td>
</tr>
<tr>
<td>MRC grade 4, n (%)</td>
<td>83 (18.7)</td>
<td>70 (17.1)</td>
</tr>
<tr>
<td><strong>Smoking status (n=528) (n=493)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active smoker, n (%)</td>
<td>75 (14.2)</td>
<td>71 (14.4)</td>
</tr>
<tr>
<td>Never-smoker, n (%)</td>
<td>137 (25.9)</td>
<td>135 (27.4)</td>
</tr>
<tr>
<td>Ex-smoker, n (%)</td>
<td>316 (59.9)</td>
<td>287 (58.2)</td>
</tr>
<tr>
<td><strong>Medicine, any dose and length (n=9344) (n=9022)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of azithromycin, n (%)</td>
<td>1691 (18.1)</td>
<td>1628 (18.0)</td>
</tr>
<tr>
<td>Use of ICS, n (%)</td>
<td>1073 (11.5)</td>
<td>1029 (11.4)</td>
</tr>
<tr>
<td>Use of prednisolone, n (%)</td>
<td>1623 (17.4)</td>
<td>1501 (16.6)</td>
</tr>
</tbody>
</table>

CCI, Charlson Comorbidity Index; FEV1%, forced expiratory volume 1 s; ICS, inhaled corticosteroids; MRC, Medical Research Council Dyspnoea Scale.
bias, these results need confirmation. Our current study adds to these findings and provides data from all Danish residents registered with a diagnosis of bronchiectasis. To our knowledge, no further studies investigate the risk of pneumonia hospitalisations in persons with bronchiectasis during periods of social distancing.

Studies on social distancing and exacerbations in other chronic respiratory diseases report similar results. A similar Danish study on patients with severe COPD reported a decrease in incidence of hospital-requiring hospitalisations varying from weekly 5% to 77% in 2020 compared with the reference weeks in 2019 during the weeks corresponding to the 10 weeks investigated in this study.\(^{15}\) Despite failing to report an overall risk estimate for the lockdown period, the mentioned study clearly confirms the tendency of exacerbation risk reduction in a population with severe COPD during periods of distancing measures. This tendency is further confirmed by an American study of 123 individuals comparing year 2020 to the three prior years with an average decrease in exacerbation rate of 54% (74% in frequent exacerbators).\(^{30}\) The CHRONICLE Study investigated 3100 patients with severe asthma and found a decrease of 20%–54% in exacerbation rates through five consecutive months in 2020 compared with 2019.\(^{31}\) This is in line with a Danish study in patients with asthma reporting a decline in the trend for weekly exacerbation rates of −0.75 (hospital-requiring exacerbations) and −12.2 (all exacerbations) during 10 weeks of lockdown.\(^{18}\) Thus, it seems realistic that our findings are not solely due to random fluctuations in infection rates and that pandemic lockdown measures are effective in reducing exacerbation rates in chronic respiratory diseases of different kinds.

Persons with bronchiectasis seem generally willing to change social behaviour, if such a change will result in fewer infections and hospitalisations.\(^{32}\) Hence, it is likely that the persons in our bronchiectasis cohort had high adherence to the social distancing measures, but we did not have data to quantify adherence.

The strengths of the current study include its large population of over 9000 persons with bronchiectasis who met the inclusion criteria. Further, we were able to exclude persons with a microbiologically validated COVID-19 diagnosis via real-time nationwide microbiological data. We wanted to exclude COVID-19 hospitalisations to keep focus on non-COVID-19 causes of community-acquired pneumonia. Danish hospitals did

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**Table 3** Person-week IRs and IRRs for hospital admissions due to community-acquired pneumonia, death of all causes and antibiotic cure corresponding to pneumonia treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Reference period (N=9344)</th>
<th>Social distancing period (N=9022)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia hospitalisations, n (%)</td>
<td>128 (1.37)</td>
<td>83 (0.92)</td>
<td></td>
</tr>
<tr>
<td>IR×10^4</td>
<td>13.8 (13.5 to 18.7)</td>
<td>9.2 (8.8 to 13.2)</td>
<td></td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>Ref.</td>
<td>0.67 (0.51 to 0.88)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Deaths of all causes, n (%)</td>
<td>55 (0.59)</td>
<td>49 (0.54)</td>
<td></td>
</tr>
<tr>
<td>IR×10^4</td>
<td>5.9 (4.3 to 7.7)</td>
<td>5.3 (4.1 to 7.3)</td>
<td></td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>Ref.</td>
<td>0.90 (0.61 to 1.32)</td>
<td>0.58</td>
</tr>
<tr>
<td>Respiratory antibiotic cure, n (%)</td>
<td>1029 (11.01)</td>
<td>848 (9.08)</td>
<td></td>
</tr>
<tr>
<td>IR×10^4</td>
<td>116.0 (109.1 to 123.4)</td>
<td>99.2 (92.6 to 106.1)</td>
<td></td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>Ref.</td>
<td>0.85 (0.78 to 0.94)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IR, incidence rate; IRR, IR ratio.
not exceed capacity during the study period (or any time during the COVID-19 pandemic), and bias due to surpassed capacity can thus be ruled out.

Our study has some limitations. As we compared two 10-week periods in two consecutive years the quantitative values should be interpreted with caution as there might be week-to-week and year-to-year differences unaccounted for. Persons alive at the beginning of the social distancing period may not have been at the same risk of events as those who died before this period commenced, thus inducing survivorship bias. Further, we did not have information on the adherence to the social distancing initiatives in this group of persons. Persons who did not get admitted may in some cases have had community-acquired pneumonia and have preferred not to be admitted or were admitted late—perhaps in fear of contracting COVID-19. Therefore, it cannot be ruled out that the lower incidence of community-acquired pneumonia hospitalisation was caused by a higher threshold for hospital contact rather than a true lower incidence of community-acquired pneumonia. We did, however, also observe a decrease in pharmacy collected respiratory antibiotic cures, indicating less exacerbation was treated in primary care, but this is though with some uncertainty, as the antibiotics investigated could be prescribed on other indications than exacerbation in bronchiectasis. A drop in air pollution in urban areas during the intervention could have decreased the risk of hospitalisation, but we presume this effect does not reliably affect our results; current evidence indicate that the effect of a sudden drop in air pollution on the risk of exacerbations in bronchiectasis is either neutral or weak.33–35

To conclude, the period of social distancing was associated with a reduction in pneumonia hospitalisation rates and a probable reduction in mild exacerbations with no apparent effect on mortality. These results indicate that distancing could be a potential additional self-management strategy in reducing the risk of community-acquired pneumonia hospitalisation in the bronchiectasis population; however, causal studies are needed to further investigate the effects of social distancing measures.

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Contributors Conceptualisation, PS, JE and J-USJ; methodology, PS and JE and J-USJ; data acquisition, PS and JE; formal analysis, VR; writing—original draft preparation, VR and MBF; all authors participated in writing—review and editing; visualisation, VR; supervision, PS and J-USJ; project administration, J-USJ; funding acquisition, J-USJ. J-USJ is the guarantor of the study. All authors have read and agreed to the published version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study has been approved by the Danish Data Protection Agency (Journal no. P-2020-644). In Denmark, retrospective use of registry data does not require ethical approval or patient consent. In Denmark, retrospective use of registry data does not require ethical approval or patient consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. We believe that knowledge sharing increases the quantity and quality of scientific results. Sharing of relevant data will be discussed within the study group on reasonable request.

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