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# Inhaled corticosteroid treatment and pneumonia in patients with chronic obstructive pulmonary disease – nationwide development from 1998 to 2018

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**ABSTRACT**

**Background:** A decreasing use of inhaled corticosteroids (ICS) in patients with a hospital-registered diagnosis of chronic obstructive pulmonary disease (COPD) has recently been documented in Denmark. ICS treatment is not recommended in patients with high pneumonia risk, and we aimed to assess the development of ICS treatment in relation to pneumonia occurrence.

**Methods:** Annual nationwide register-based cross-sectional studies from 1998 to 2018 including all patients ≥40 years of age with a hospital-registered ICD-10 diagnosis of COPD on the 31st of December each year. We calculated the annual proportion of patients with at least one out-patient pneumonia (redeemed prescription of relevant antibiotics) or pneumonia hospitalization (hospitalization or ER visit), and stratified by ICS dose (No ICS, low dose, medium dose, or high dose).

**Results:** The study population increased from 35,656 patients in 1998 to 99,057 patients in 2018. The annual proportion of patients experiencing a pneumonia decreased from 69.4% to 55.2%. The proportion of patients with at least one outpatient pneumonia, but no hospitalization, decreased (59.2% to 46.2%). The overall proportion of patients with at least one pneumonia hospitalization remained unchanged (10.2% to 9.0%), but this proportion increased in patients in high dose ICS (9.9% to 14.6%). The overall proportion of patients in high dose treatment decreased (12.7% to 5.7%), but not in patients with pneumonia hospitalization (16.5% to 15.1).

**Conclusions:** Our study demonstrates a nationwide decrease from 1998 to 2018 in the proportion of patients who redeemed a prescription for antibiotics used mainly for respiratory tract infections, which may reflect a decrease in the number of outpatient pneumonias. This decrease was largely caused by an increase in the number of patients without pneumonia. No differences over time were seen regarding hospitalization-requiring pneumonia. High dose ICS treatment was unchanged in patients with hospitalization-requiring pneumonia.

## Background

Chronic obstructive pulmonary disease (COPD) is a respiratory disease with obstructive airflow limitation caused by inflammation and destruction of lung tissue [1]. The disease is irreversible, and treatment is primarily focused on relieving symptoms, reducing complications, and delaying the disease progression [1]. Pharmacological treatment is mainly comprised of inhaled medication, which may be divided into bronchodilation therapy and inhaled corticosteroid (ICS) treatment. Many patients with COPD use a combination of both [2,3].

Patients with COPD may experience periods of acute worsening of respiratory symptoms, which are called exacerbations, and ICS treatment has a beneficial preventive effect on these exacerbations. Long-acting bronchodilator therapy has been shown equally effective in the majority of patients, while ICS containing therapy is superior in a proportion of these [2,4–7]. Combined with increasing evidence of negative side effects of ICS treatment [8,9], this has led to increasingly narrow ICS treatment recommendations [10]. An important negative side effect of ICS treatment in COPD is the increased risk of

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pneumonia. Patients with COPD has an increased risk of pneumonia compared to patients without COPD [11], and ICS treatment further increases this risk [12,13]. This is important because hospitalization with pneumonia is more dangerous than hospitalization with non-pneumonic exacerbation [14–16].

Despite a well-documented increase in the overall use of inhaled corticosteroids in Denmark [17], a decrease in the use of ICS per patient in patients with a hospital-registered COPD diagnosis from 1998 to 2018 has recently been documented [10]. The increase in the overall pneumonia incidence in patients with COPD is also well-documented [15], but little is known about how the use of ICS relates to this. As increasingly restricted recommendations for ICS treatment have emerged, and ICS treatment is not recommended in patients with repeated pneumonia events [1], the aim of this current study was to evaluate ICS treatment patterns from 1998 to 2018 in relation to pneumonia occurence.

## Methods

### Data sources

This study was based on data from Danish nationwide registers. Diagnoses were retrieved from the Danish National Patient Registry (DNPR) using International Classification of Diseases 10th revision (ICD-10) codes [18]. Medication data were retrieved from the Danish National Prescription Registry (DNR) using anatomical therapeutical chemical (ATC) codes [19,20]. Age, sex, and socio-economic data were retrieved from various registers within Statistics Denmark (DST) [21,22]. The unique personal identification number assigned to all inhabitants in Denmark was used for linkage across registers on the individual level [23].

### Study design and population

This was an annually repeated cross-sectional study from 1998 to 2018, which included all patients in Denmark with an ICD-10 diagnosis code of COPD (J44) who were alive on the 31st of December each year.

### Setting

Denmark has a tax funded free universal healthcare system, which is divided into a primary and a secondary care sector. Patient access to the secondary sector i.e. hospital admission or hospital-based specialist outpatient clinics, is obtained only through referral from patients' general practitioner (GP), private practice specialist, or other hospital departments. In Denmark, the GPs are responsible for the primary care of COPD. ICD-10 diagnosis codes are registered in the DNPR only upon hospital contact.

### Study variables

Pneumonia was defined as either an outpatient pneumonia (ATC codes from redeemed prescriptions for antibiotics used for pneumonia in COPD) or pneumonia hospitalization (all primary and secondary ICD-10 diagnosis codes of pneumonia from hospitalizations or ER visits). The relevant ATC codes and ICD-10 codes are displayed in Table 1.

The average daily ICS dose was calculated based on the accumulated dose from redeemed prescriptions during a year. Like previous research [10,24], ICS types were converted to standard-particle beclomethasone dipropionate equivalents based on the ICS dose chart from the National Institute for Health and Care excellence [25], and subsequently grouped according to dose: No ICS, low dose (<500 micrograms, medium dose (500–1200 micrograms), and high dose (>1200 micrograms). Prescription is

**Table 1.** Codes used for defining pneumonia.

| Outpatient pneumonia (ATC codes) | Pneumonia hospitalization (ICD-10 codes) |
|---|---|
| ● J01CA04: amoxicillin | ● J12: viral pneumonias |
| ● J01CA02: ampicillin | ● J13–18: bacterial pneumonias |
| ● J01CE02: phenoxymethylpenicillin | ● A481: legionnaires' disease |
| ● J01CR01: ampicillin and beta-lactamase inhibitor | ● A709: ornithosis |
| ● J01CR02: amoxicillin and beta-lactamase inhibitor | ● B012: varicella pneumonia |
| ● J01FA01: erythromycin | |
| ● J01FA06: roxithromycin | |
| ● J01FA09: clarithromycin | |
| ● J01FA10: azithromycin | |

Abbreviations: ATC = anatomical therapeutic chemical. ICD-10 = International Classification of Diseases 10th Revision.

mandatory to collect ICS and antibiotics in Denmark.

Comorbidity was retrieved from the DNPR as ICD-10 diagnosis codes 3 years prior to index date and calculated as the Charlson Comorbidity Index (CCI) according to Quan et al. [26,27].

## Statistical analysis

This was a descriptive study. For categorical variables, the proportion of patients within each group was calculated. Age was the only continuous variable in our study, and we calculated both mean and standard deviation as well as proportions in each 10-year age group (40–49 years, 50–59 years, 60–69 years, 70–79 years, and 80+ years). Short college, medium college, and masters/PhD were summed into one group (college) to account for too few observations in the groups. CCI was grouped into four categories (0, 1, 2, and ≥3). Because ICD-10 code registration in the DNPR is delayed, and we only have access to data until 2018, the last valid CCI is from 2015 [10].

We calculated the proportion of patients who had at least one outpatient pneumonia or pneumonia hospitalization within each year, and we investigated the relationship between pneumonia groups and ICS treatment dose groups. All analyses were performed using SAS 9.4 TS Level 1M5 (SAS, Inc., Cary, NC, USA).

## Results

### Study population

Characteristics of the study populations for the years 1998, 2008, and 2018 are displayed in Table 2. The number of patients with a hospital-registered COPD diagnosis increased from 35,656 in 1998 to 99,057 in 2018. A slightly larger proportion were female, and this was unchanged from 1998 to 2018. Mean age increased from 69 years in 1998 to 72 years in 2018, with an increase in the proportion of patients more than 80 years old (16.1% to 24.5%). More patients were living alone in 2018 (52.5%) compared to 1998 (48.0%). The proportion of patients without ICS treatment increased from 50.6% to 57.6%, while the proportion of patients in both medium and high dose ICS treatment decreased from 21.1% to 18.1% and 17.0% to 9.4%, respectively.

### Pneumonia overall

Figure 1 shows the proportion of patients with at least one outpatient pneumonia or pneumonia hospitalization annually from 1998 to 2018. The underlying data are presented in Appendix A, Table S1. Table 3 shows data on pneumonia in the years 1998, 2008, and 2018, and data for all years are presented in Appendix A, Table S2. The proportion of patients without pneumonia increased from 1998 to 2018 (30.6% to 44.8%), and the proportion of patients with at least one outpatient pneumonia decreased (59.2% to 46.2%). On the other

**Table 2.** Study population characteristics in the years 1998, 2008, and 2018.

|  | 1998 | | 2008 | | 2018 | |
|---|---|---|---|---|---|---|
| Population (N) | 35.565 | | 77.314 | | 99.057 | |
|  | n | % | n | % | N | % |
| **Sex** | | | | | | |
| Male | 16,716 | 47.0 | 35,348 | 45.7 | 45,396 | 45.8 |
| Female | 18,849 | 53.0 | 41,966 | 54.3 | 53,661 | 54.2 |
| **Age, mean (SD)** | 69 | (10.5) | 70 | (10.9) | 72 | (10.4) |
| **Age group** | | | | | | |
| 40–49 | 1,602 | 4.5 | 2,641 | 3.4 | 1,674 | 1.7 |
| 50–59 | 5,090 | 14.3 | 11,125 | 14.4 | 11,239 | 11.3 |
| 60–69 | 10,243 | 28.8 | 21,409 | 27.7 | 26,170 | 26.4 |
| 70–79 | 12,895 | 36.3 | 25,287 | 32.7 | 35,745 | 36.1 |
| ≥80 | 5,735 | 16.1 | 16,852 | 21.8 | 24,229 | 24.5 |
| **Charlson Comorbidity Index** | | | | | | |
| 0 | 25,790 | 72.5 | 59,668 | 77.2 | 72,139* | 73.8* |
| 1 | 5,130 | 14.4 | 7,245 | 9.4 | 9,770* | 10.0* |
| 2 | 3,170 | 8.9 | 7,590 | 9.8 | 11,244* | 11.5* |
| ≥3 | 1,475 | 4.1 | 2,811 | 3.6 | 4,628* | 4.7* |
| **ICS treatment** | | | | | | |
| No ICS | 17,986 | 50.6 | 35,734 | 46.2 | 57,072 | 57.6 |
| Low dose | 4,009 | 11.3 | 14,612 | 18.9 | 14,782 | 14.9 |
| Medium dose | 7,508 | 21.1 | 16,639 | 21.5 | 17,931 | 18.1 |
| High dose | 6,053 | 17.0 | 10,319 | 13.3 | 9,272 | 9.4 |

*Data on comorbidities are from 2015, see explanation in text. Abbreviations: SD, standard deviation. ICS, inhaled corticosteroid.
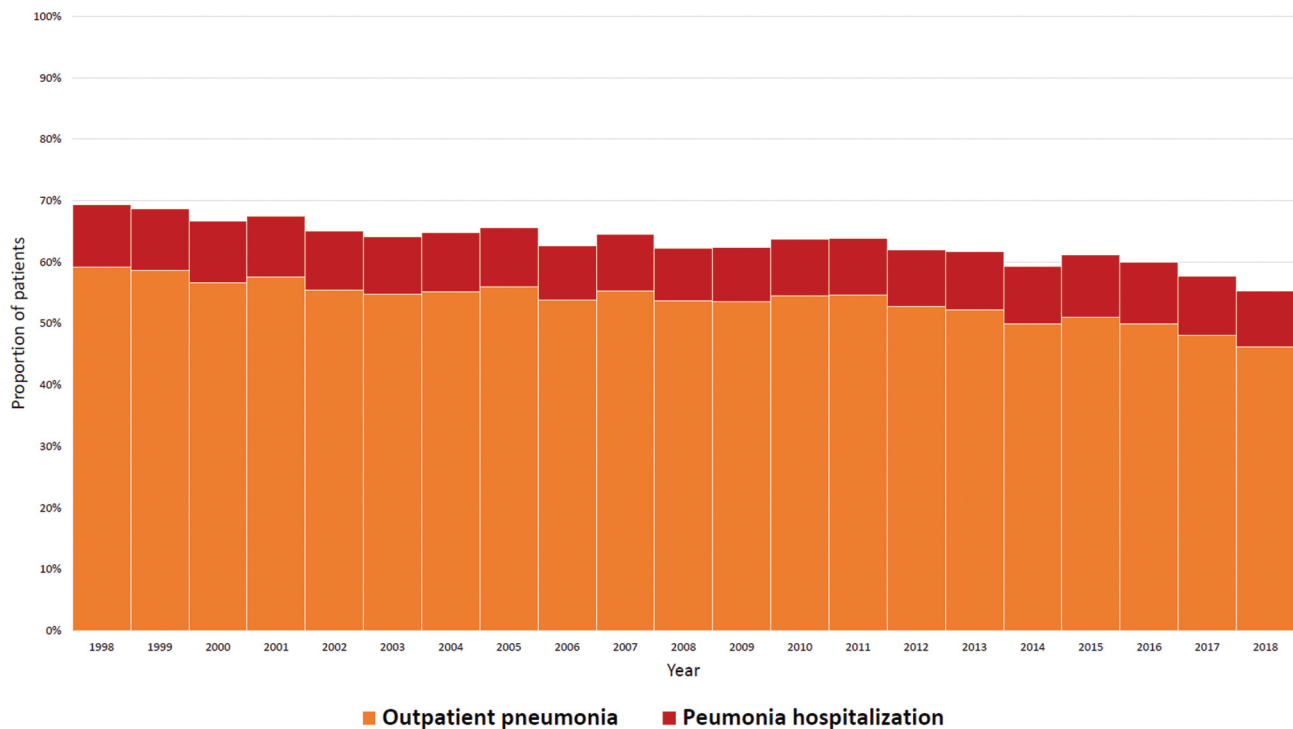
**Figure 1.** Annual proportion of patients with at least one outpatient pneumonia or pneumonia hospitalization from 1998 to 2018.

**Table 3.** Outpatient pneumonias and pneumonia hospitalizations in 1998, 2008, and 2018.

|  | 1998 | | 2008 | | 2018 | |
|---|---|---|---|---|---|---|
| Population (N) | 35,565 | | 77,314 | | 99,057 | |
| **Number of patients in each pneumonia group** | n | % | n | % | n | % |
| No pneumonia | 10,887 | 30.6 | 29,133 | 37.7 | 44,304 | 44.8 |
| At least one outpatient pneumonia, but no hospitalization | 21,050 | 59.2 | 41,553 | 53.7 | 45,807 | 46.2 |
| At least one pneumonia hospitalization | 3,628 | 10.2 | 6,628 | 8.6 | 8,946 | 9.0 |

hand, the proportion of patients who experienced at least one pneumonia hospitalization remained stable (10.2% to 9.0%). An increase was seen from 1998 to 2018 in the total number of patients experiencing both outpatient pneumonia (21,050 to 45,807) and pneumonia hospitalization (3,628 to 8,946).

### Pneumonia in relation to ICS

Figure 2 shows pneumonia groups in relation to inhaled corticosteroid treatment groups from 1998 to 2018. The underlying data can be found in Appendix A, Table S3 and Table S4.

The largest decrease in pneumonia occurrence was seen in patients without ICS treatment, where 54.7% in 1998 experienced pneumonia compared to 40.5% in 2018 (Figure 2(a)). The proportion of patients in this group who experienced at least one outpatient pneumonia decreased from 44.9% to 32.9%, and the proportion with at least one pneumonia hospitalization decreased from 9.8% to 7.5%. In patients in low dose ICS treatment, similar results were seen: 34.7% did not have pneumonia in 1998 compared to 48.7% in 2018, 54.0% compared to 42.5% had at least one outpatient pneumonia, and 11.3% compared to 8.8% had at least one hospitalization. In the group of patients in medium ICS dose treatment, the proportion of patients without pneumonia increased from 32.3% to 41.5%. The proportion with at least one outpatient pneumonia (but no hospitalization) decreased from 56.8% to 47.4%, and the proportion with at least one pneumonia hospitalization was stable at 10.9% to 11.1%. In patients in high dose ICS treatment, the proportion without pneumonia was relatively stable from 28.8% in 1998 to 31.7% in 2018. While the proportion of patients in high dose ICS treatment with at least one outpatient pneumonia decreased from 61.3% to 53,7%, the proportion of patients with at least one pneumonia hospitalization increased from 9.9% to 14.6%.
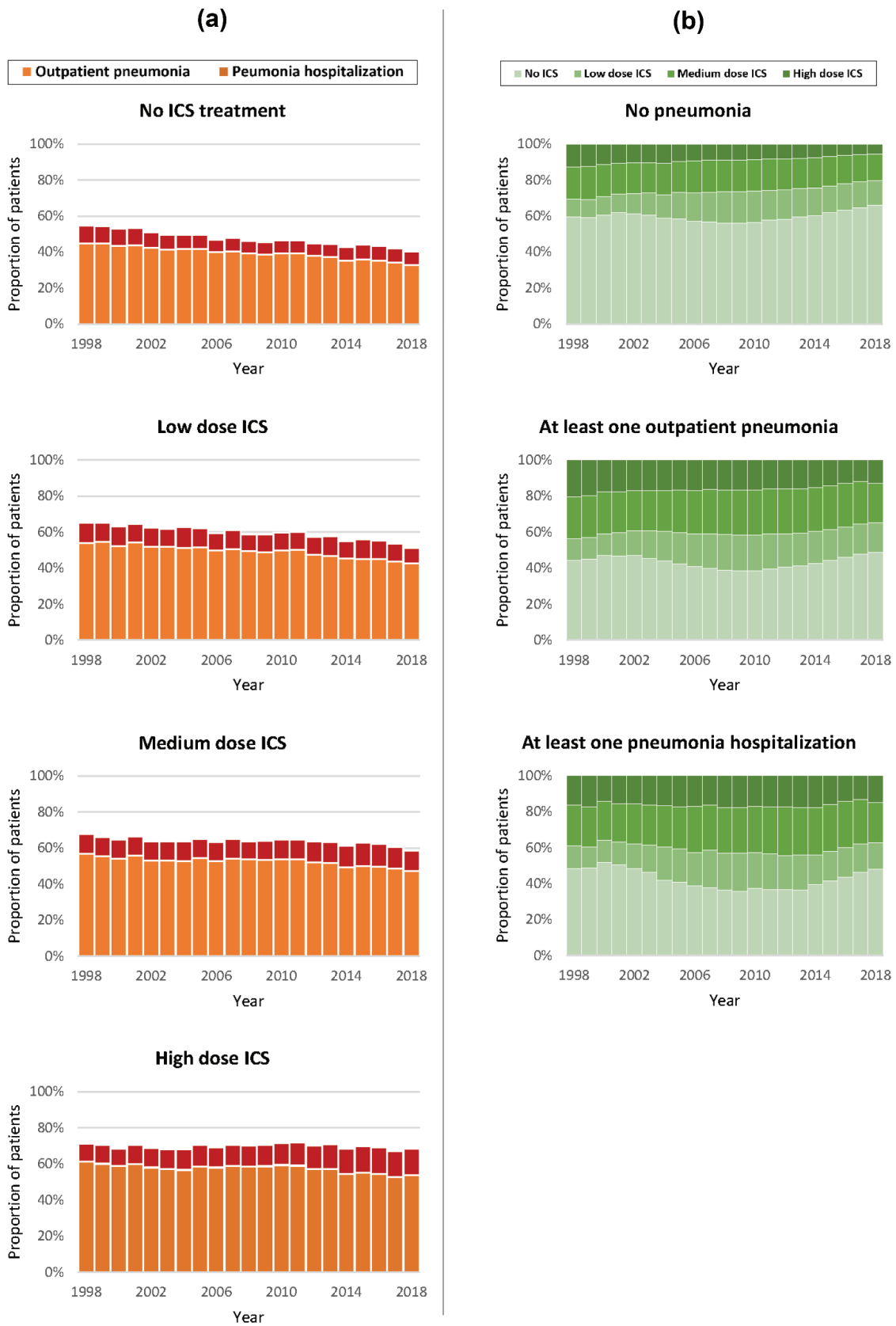
**(a)**

**(b)**



**Figure 2.** Pneumonia in relation to inhaled corticosteroid treatment groups from 1998 to 2018. (a) Annual proportion of patients with at least one outpatient pneumonia or pneumonia hospitalization, grouped by inhaled corticosteroid dose. (b) Annual proportion of patients in inhaled corticosteroid treatment groups, by pneumonia group.

Differences regarding ICS treatment were seen between pneumonia groups (Figure 2(b)). There was a steady decrease in overall ICS use in patients without pneumonia, and especially the proportion of patients in high-dose treatment decreased (12.7% vs 5.7%). In patients with at least one annual pneumonia hospitalization, the proportion of patients without ICS treatment remained unchanged from 48.5% in 1998 to 48.1% in 2018, with a decrease to 35.7% in 2009 and a subsequent increase. On this group, the proportion of patients in high dose ICS treatment remained unchanged through the entire study period (16.5% in 1998, 17.6% in 2009, 15.1% in 2018), and the changes from 2009 to 2018 lied predominantly in the decreasing use of low and medium dose ICS treatment. Overall, an increase in ICS use was seen from 1998 to 2009 with a subsequent decrease, and this pattern was most obvious in the group of patients who experienced at least one pneumonia hospitalization.

## Discussion

We have documented an increase in the annual proportion of patients with a hospital-registered COPD diagnosis who do not experience pneumonia, and a corresponding decrease in the proportion of patients with outpatient pneumonia, but not pneumonia hospitalization.

### Pneumonia in relation to study population

The increasing population size of patients with a hospital-registered COPD diagnosis with a corresponding increase in patients without pneumonia may be a combination of several things. It is possibly the result of an increased focus on diagnosing diseases, including COPD, at an earlier stage of the disease, and an earlier referral from GPs to hospital-based outpatient clinics for specialized assessment. This would lead to an increasing prevalence of hospital-registered COPD diagnosis of patients with milder severity of COPD. Furthermore, the overall prevalence of COPD has been projected to increase substantially until 2050 both worldwide and in Europe [28,29]. These above reasons have been stated as possible causes – along with an aging population combined with overall treatment improvements – of the general increase in chronic diseases and multimorbidity in studies from Sweden and the Netherlands [30–32], which are comparable to Denmark regarding both societal structure and healthcare system. In the case of COPD in particular, an increased focus on the

prevention of pneumonia within COPD could be a contributing factor. Pneumococcal vaccines has a well-documented effect on preventing both pneumonia and exacerbations in COPD [33], and it has been recommended as part of the standard care for patients with COPD in Denmark since 2014 [34]. Preventing pneumonia in COPD has also been a focus with the increasingly narrow ICS treatment recommendations [1], and the observed decline in ICS treatment in our study population may explain our results to some degree. We find it, however, more likely that the reduced ICS use and reduced pneumonia occurrence are both results of an increasing population with less severe disease. Data on this were out of reach for our current study, but future research on the disease severity of first-time referrals from GPs to hospital-based specialized pulmonary outpatient clinics may elucidate this theory.

A decrease was seen particularly in the occurrence of outpatient pneumonias, which were defined as redeemed prescriptions on relevant antibiotics. The use of antibiotics in Denmark is generally restrictive, and Denmark had the 8th lowest use of antibiotics among 25 European countries in 2015 [35]. The report from the Danish Ministry of Health from 2017 also states that 75% of all prescriptions for antibiotics were issued by GPs, and that the use of antibiotics in Denmark increased from 2000 to 2011 and then levelled out [35]. A report from 2021 documents a decrease in general antibiotic use in Denmark from 2012 to 2021, and especially within the primary care sector [36]. The use of both macrolides and penicillin with beta-lactamase inhibitor both decreased in the primary care sector during this period, and this well-documented decrease in the use of antibiotics may be a main reason of our measured decrease in outpatient pneumonias.

No differences were seen from 1998 to 2018 in the proportion of patients with at least one pneumonia hospitalization despite an increasing population of patients with COPD. This agrees with previous Danish epidemiological research, which has shown an increased incidence of pneumonia hospitalization in Denmark within COPD [15] and in general [37].

### Pneumonia in relation to inhaled corticosteroid treatment

We saw an increase in ICS use from 1998 to 2009 with a subsequent decrease, and these fluctuations were larger in patients experiencing pneumonia hospitalization. This may partly be explained by the increased focus on pneumonia risk in the early 2000s: the first

randomized controlled trial to study the risk of pneumonia related to ICS treatment was in 1999, and eight studies were conducted from 2003 to 2009 [9].

A decrease in especially high dose ICS treatment was seen, and this was most evident in patients without pneumonia. This may be caused by the increasingly restricted ICS treatment recommendations with an increasing focus on not prescribing ICS to patients with mild or moderate disease severity. The decreased use of high dose ICS treatment was not seen in patients experiencing pneumonia hospitalization, and the general decrease in the proportion of patients experiencing pneumonia gradually vanished with increasing ICS dose. In fact, an increase in the proportion of patients with at least one pneumonia hospitalization was seen in patients in high dose ICS treatment. In summary, patients in high dose ICS treatment had the highest probability of experiencing pneumonia hospitalization, while patients experiencing pneumonia hospitalization were more likely to be in ICS treatment, and these proportions remained rather constant from 1998 to 2018. This finding may illustrate one of the difficulties in ICS treatment in COPD: ICS treatment is not recommended in patients with frequent pneumonia, and ICS treatment is recommended in patients with frequent exacerbations [1]. There is, however, a considerable overlap between these patient groups, as the risk of both pneumonia and exacerbation is associated with female sex, increased disease severity defined as dyspnea level and airflow limitation, a history of prior exacerbations, and cardiovascular comorbidity [38,39]. Our findings thus highlight the difficult question of whether patients with both frequent exacerbations and a history of pneumonia should be treated with ICS. Although evidence exists of reduced pneumonia risk after withdrawal from ICS treatment [40], data on ICS withdrawal in patients with severe and very severe COPD have been deemed insufficient to draw firm conclusions [41]. Pneumonia is more dangerous than non-pneumonic exacerbations [14], but exacerbations are more frequent, and the benefit-risk profile may ultimately favor ICS treatment [42]. The issue is even further complicated by difficulties in distinguishing between exacerbation and pneumonia clinically [43].

The annual proportion of patients with at least one pneumonia hospitalization was unchanged despite an overall decrease in ICS treatment. This may suggest other and possibly more important determining factors of pneumonia risk in patients with COPD, and this has recently been discussed by Lineros et al. [44]. Some factors are general e.g. sex, age, and socio-economic status, while other factors are specific to COPD e.g.

pulmonary emphysema, severity of airflow obstruction, and concomitant asthma [44]. As such, an increased risk of pneumonia may be seen as a basic condition in COPD, and patient-specific factors including degree of disease severity may be more important than ICS use regarding pneumonia risk. Our study design does not allow for assessment of such causality, and the reasons for our results may therefore only be speculated upon. As we have mentioned earlier, the general decrease in both ICS treatment and redeemed prescription of antibiotics are not necessarily causally connected. This may also be the case regarding ICS use and pneumonia hospitalizations, where the above-mentioned patient-related risk factors for pneumonia may be influential. For instance, the study population got older over time, and pneumonia is related to older age. This could partly explain why no changes in pneumonia hospitalization were seen despite a decrease in ICS treatment.

Despite an increased risk of pneumonia in ICS treatment, there is no evidence of an associated increased pneumonia-related mortality [45]. While ICS treatment is associated with negative side effects, and potential overuse has been documented especially in patients with less severe COPD [2,46], ICS-containing treatment in patients with severe COPD has a well-documented effect on quality of life and exacerbation rate, and it may even reduce mortality [47]. We believe that our results reflect these real-world dilemmas, where the clinical cost–benefit analysis of ICS treatment is difficult. This may be particularly troublesome in patients with both high exacerbation risk and pneumonia risk, and it is further complicated by the often-difficult distinction between exacerbation and pneumonia.

### Strengths and limitations

This study is based on nationwide data of well-documented high quality, which ensures complete follow-up over decades and a general low risk of selection bias [48].

Some limitations must be mentioned. First, we have defined outpatient pneumonias as redeemed prescriptions of antibiotics. This causes a risk of inflated pneumonia numbers by misclassifying exacerbations as pneumonias, especially exacerbations due to suspected bacterial lower respiratory tract infections, which are difficult to distinguish from pneumonia clinically [43]. These events are primarily handled in primary care in Denmark, and GPs have a high clinical predictive value of exacerbation versus pneumonia [49]. Other diseases that are treated with these antibiotics may also be misclassified as pneumonia. This mainly concerns

Ampicillin, which besides respiratory tract infections is recommended for gastroenteritis and gonorrhea, and we do not consider this as a cause of substantial bias. Second, we have included patients with a registered ICD-10 diagnosis code of COPD, and patients with COPD who have never been assessed in a hospital setting have not been included. These patients are likely those with milder disease severity [50,51], and the results of our study may not reflect the entire population of patients with COPD in Denmark. However, this is the closest as possible that we can get to identifying the total population of patients with COPD in this study period in Denmark. Third, as ICS treatment doses have been estimated by average doses through an entire year, it is impossible to tell if a pneumonia preceded ICS treatment initiation or vice versa. However, this study design was necessary to estimate ICS doses. Furthermore, this study was not meant to assess causality between ICS treatment and pneumonia, as this relationship is already well established in studies better designed for this [4,47]. Finally, the lack of data on factors that could influence both ICS treatment and pneumonia is a limitation e.g. adherence to treatment or clinical data such as pulmonary function, dyspnea level, smoking status, or nutritional status. This risk of residual confounding is always present, and in register-based research it is more present, because data are predefined [52].

### Implications and perspectives

We believe that our results reflect the clinical difficulties in risk-benefit calculation of ICS treatment in patients with severe COPD, who are more prone to both frequent exacerbations and pneumonia. Our study thus highlights the need for more research on this topic: should patients with both frequent pneumonia and frequent exacerbation be treated with ICS? Additionally, our results likely reflect the clinical difficulties in distinguishing between a pneumonia and an exacerbation. If clinicians are meant to encourage ICS treatment in patients with frequent exacerbations but discourage ICS treatment in patients with frequent pneumonia, some consensus on the distinction between these events is needed. A consensus of such a distinction in clinical trials has also been advocated for, as only 12 of 36 trials included in a recent systematic review required radiographic confirmation of pneumonia [53]. Finally, our data suggests a healthier study population over time, which may indicate a lower severity threshold for referral from GP to outpatient specialized hospital-based assessment. This should be investigated further, as knowledge on the division of

healthcare burden between primary sector and secondary sector may be of value to health policy makers.

## Conclusions

We have documented a nationwide decrease in the proportion of patients with a hospital-registered COPD diagnosis who redeemed prescriptions of antibiotics used mainly for suspected respiratory tract infections, which may reflect a decrease in the number of outpatient pneumonias. This decrease was largely caused by an increase in the proportion of patients without pneumonia. The annual proportion of patients with at least one hospitalization-requiring pneumonia was unchanged despite an overall decrease in ICS treatment. The proportion of patients with hospitalization-requiring pneumonia in high dose ICS treatment was unchanged from 1998 to 2018 despite an overall decrease in high dose ICS treatment.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Funding

## Data availability statement

Data from Danish national registers are not publicly available. The data supporting the conclusions of this article are available from registers upon approval of access by national authorities.

## Ethics statement

The study was conducted in accordance with the Declaration of Helsinki. All data accessed complied with relevant data protection legislation. Research ethics approval is not required for register-based research according to Danish Law and National Ethics Committee Guidelines.

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