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This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

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ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
BMI	Body Mass Index
CAP	Community Acquired Pneumonia
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSC	Fluticasone Propionate/Salmeterol Combination
FEV_1	Forced Expiratory Volume in One Second
FF	Fluticasone Furoate
GERD	Gastroesophageal reflux disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
CPRD-GOLD	GP OnLine Database
GP	General Practitioner
GSK	GlaxoSmithKline
HAP	Hospital-Acquired Pneumonia
HES	Hospital Episode Statistics
ICS	Inhaled Corticosteroid
ICD	International Classification of Diseases
IPTW	Inverse Probability of Treatment Weighting
LABA	Long Acting Beta Agonist
LAMA	Long-Acting Anti-Muscarinic
LABD	Long-Acting Bronchodilator
MRC	Medical Research Council
OCS	Oral Corticosteroids
PS	Propensity Score
SABA	Short-Acting Beta-Agonist
SABD	Short- Acting Bronchodilator
SAL	Salmeterol
THIN	The Health Improvement Network
QOF	Quality Outcomes Framework
UK	United Kingdom
VI	Vilanterol

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1. INTRODUCTION

1.1. Background

An association has been observed between pneumonia and currently marketed ICS-containing medications relative to non-steroid containing medications among patients with COPD [Ernst, 2007, Crim, 2009; Drummond, 2008; Spencer, 2011; Singh, 2010]. The risk factors for development of pneumonia, including severe pneumonia requiring hospitalization, have been well-characterized in clinical and observational studies and include older age, current smoking, low BMI, certain chronic comorbid conditions (e.g. dementia), higher levels of dyspnea, and markers of COPD disease severity [Calverley, 2011; Crim, 2009; Mannino, 2009; Müllerova, 2012].

In studies within the ICS/LABA medications, there was approximately a 1.5 to 2-fold increase in the risk of serious pneumonia among the ICS-containing medication treatment group as compared to long-acting beta-agonist (LABA) monotherapy (30 vs. 55 pneumonia episodes per 1,000 person years for 500/50 fluticasone propionate / salmeterol combination [FSC] and 50 salmeterol, respectively [Crim, 2009]. There was no increase in the risk of pneumonia fatality, and results suggested a reduction in mortality in patients taking FSC relative to placebo, but the reduction did not achieve statistical significance [Calverley, 2007]. A similar two-fold increase in risk was seen in the two, one-year long studies of FSC vs. SAL studies (data not shown).

Fluticasone furoate (FF)/vilanterol (VI) is a once-daily ICS/LABA fixed dose combination for the long-term, maintenance treatment of COPD. In clinical trials of fluticasone furoate (FF)/vilanterol (VI), serious pneumonia was defined as any pneumonia (pre-specified set of preferred terms) that resulted in death, immediate risk of death (investigator judgment), or hospitalization or prolonged existing hospitalization. An increased incidence of pneumonia, including serious pneumonia was observed with the use of FF/VI compared with VI monotherapy in two one-year-long exacerbation studies (study HZC102970 and study HZC102871). The proportion of patients reporting pneumonia were 3.3%, 5.9%, 6.3%, and 6.8% in 25 VI, 50/25 FF/VI, 100/25 FF/VI, and 200/25 FF/VI [Dransfield , 2013]. In the integrated safety summary, the risk of serious pneumonia was almost three-fold greater for the FF/VI relative to the VI treatment groups (34.9, 37.0, and 33.6 per 1,000 person years for 50/250, 100/25, and 200/25 FF/VI versus 12.1 per 1,000 person years in 25 VI). Inconsistencies in incidence of fatal pneumonia events between the two FF/VI exacerbation studies were noted; however, the low absolute number of fatal events precludes an accurate assessment of the risk or an evaluation of a dose response relationship due to low precision.

1.2. Rationale

Based on the increased risk of serious pneumonia observed in patients randomized to FF/VI, GSK sought to gain a better understanding of the rates and risk factors for severe pneumonia in patients with COPD using retrospective observational studies of the class of inhaled corticosteroid (ICS)-containing medications.

In addition to quantifying the magnitude of association between ICS and severe pneumonia, this study aimed to provide additional information to the previous studies of COPD and pneumonia through examination of risk factors for pneumonia requiring hospitalization (e.g. body mass index [BMI], lung function, current smoking status, dyspnea) not measured in previous observational data sources. Further, it evaluated statistical interaction between ICS and other risk factors for severe pneumonia. Finally, it evaluated characteristics of patients with pneumonia who were more likely to be admitted to hospital.

The results may be used to identify patients at greater risk of pneumonia requiring hospitalization and may identify where risk minimization and/or medical recommendations may be appropriate to prevent pneumonia or improve pneumonia treatment leading to reduced morbidity and mortality.

2. STUDY OBJECTIVE(S)

The overall objectives of this retrospective observational COPD cohort study were:

- To estimate the magnitude of association between risk factors and pneumonia requiring hospitalization, including treatment with ICS-containing medications
- To evaluate if ICS-containing medications modify the effect of risk factors for severe pneumonia (i.e. evaluate statistical interaction between ICS × other risk factors)
- To evaluate any differences in clinical characteristics between patients who develop pneumonia or severe pneumonia vs. those who do not develop pneumonia in the one year period following new user cohort entry

3. TARGET AUDIENCE

This study may be used by GSK, clinicians, and regulatory agencies to inform on risk factors for pneumonia in patients with COPD for the purposes of risk minimization. The results will be disseminated in a form of manuscripts and scientific presentations. The results will be provided to the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

4. METHODOLOGY

4.1. Preliminary Feasibility Assessment

Prior to conducting this study, two feasibility assessments were conducted to support the study objectives including a preliminary feasibility assessment and more refined assessment following cohort selection. The feasibility informs on the number of patients in each pre-defined group of new users of respiratory medications and the number of patients meeting different definitions of pneumonia. These figures allowed for an assessment of the available statistical precision to examine treatment group differences.

Mannino and colleagues found a rate of pneumonia requiring hospitalization to be 22.7 per 1,000 person years among patients with advanced disease (GOLD stage airflow limitation III or IV) [Mannino, 2009]. A previous study of community-acquired pneumonia (CAP) in a primary care population of patients with COPD in the GPRD [Müllerova, 2012], there were approximately 40,000 patients with prevalent COPD in Clinical Practice Research Datalink's CPRD-GOLD between 1996-2006 with ~8% experiencing pneumonia (CAP without restricting to those requiring hospitalization) during the study period with a CAP rate of 22.4 per 1000 person years. The authors included a highly sensitive definition of pneumonia, resulting in 1,469 cases of CAP in their case-control study.

Initial feasibility results on the 2005-2010 study period included approximately 12,000 new users and 185 pneumonia events. When expanded to include the study period 2002-2010 to achieve greater sample size, there were a total of 18,742 new users of ICS-containing medications (n=12,065) or long-acting bronchodilators (n=6,677) (LABD) with the required CPRD-GOLD linkage to HES (Table 1) and included 283 pneumonia events. These totals of new users and pneumonia events included the application of all inclusion/exclusion criteria; however, additional subjects were excluded in the final analysis based on censoring for on-going pneumonia at the time of cohort entry, and missing data on selected covariates.

Table 1 Feasibility Results: New User Cohort

Number of New Users	Year of Cohort Entry									Total
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
LABD	354	513	703	765	715	723	972	938	994	6,677
ICS-containing[a]	1,828	1,499	1,633	1,369	1,310	1,207	1,244	1,100	875	12,065
Total by Year	2,182	2,012	2,336	2,134	2,025	1,930	2,216	2,038	1,869	18,742

a. ICS-Containing=inhaled corticosteroid-containing medications, LABA=long-acting beta-agonists, LAMA=long-acting antimuscarinics

During creation of the final analysis database, a formatting issue with the ICD-10 catalog was noted, which had resulted in under-counting of hospitalized pneumonia in the database. Upon adjustment, final feasibility prior to any programming demonstrated 751 pneumonia events.

The final feasibility following the adjustment to the ICD-10 coding library is presented in Table 2. There were 751 pneumonias, 652 severe CAP, and 43 HAP. Due to concerns about the ability to distinguish HAP from hospitalized CAP and the low number of potential HAP, the hospitalized events were combined for this study per protocol amendment.

Table 2 Count of First Pneumonia Events Including Adjustments for Episodes: New User Cohort

Pneumonia Events	Year of Cohort Entry									Total New Users
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode										
HAP	5	4	7	7	5	7	3	3	2	43
Severe CAP	88	79	78	86	98	64	72	56	31	652
Non-severe CAP	9	9	9	7	5	4	7	5	1	56
All Pneumonia	102	92	94	100	108	75	82	64	34	751

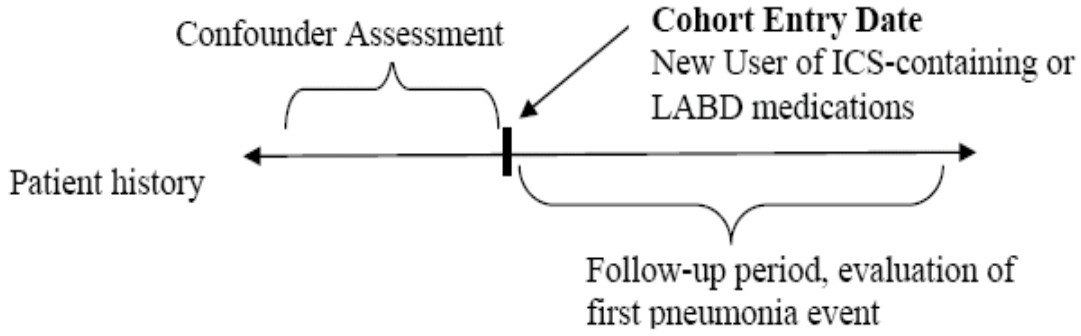
4.2. Study Design

This was a retrospective cohort design.

CPRD-GOLD data was used to identify a 'new-user' COPD cohort to evaluate a relationship between an exposure to respiratory medications, long-acting bronchodilators (LABD) or ICS-containing medications and the first episode of the pneumonia types of interest.

New users of ICS-containing medications or long-acting bronchodilator (LABD) were evaluated in a cohort design for the occurrence of pneumonia following their designation as new users. Specific medications are described in Section 4.4. To adjust for anticipated differences in confounding by severity between the two treatment groups, important patient characteristics relating to COPD severity and pneumonia were evaluated in the patient history in the period prior to and including the new user date. Propensity scores (PS) were generated using these characteristics. The study schematic is presented in Figure 1.

Figure 1 Study Schematic: New User Cohort Design 2002-2010



4.3. Data

This study used the Clinical Practice Research Datalink's (CPRD)-GP OnLine Database (GOLD), a primary care research database in the United Kingdom. The study utilized CPRD-GOLD data available through December 22, 2011.

CPRD-GOLD data were formally referred to as the General Practice Research Database (GPRD). To prevent confusion between the database and the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which characterize COPD severity and treatment guidelines, the study report refers to the database as CPRD-GOLD. CPRD-GOLD contains computerized health care information entered by General Practitioners in the United Kingdom (UK). More than 600 General Practices have been contributing medical history data since 1987, with more than 6 million patients in the database. The database contains longitudinal data recorded by the GP on patient demographic and clinical characteristics, medical history including records of referrals to consultants and hospitalizations, primary care utilization, and prescription medication history over a period of up to 15 years. Descriptive and pharmacoepidemiological studies of patients with COPD have been conducted in CPRD-GOLD, including validation of physician-recorded COPD diagnosis [Soriano, 2001] and evaluation of COPD co-morbidities [Soriano, 2005]. Studies of pneumonia have also been conducted, including a study of CAP in CPRD-GOLD [Müllerova, 2012] and a validation study of CAP requiring hospitalization in The Health Improvement Network (THIN), which uses the same software as CPRD to capture primary care information [Meropol, 2012].

We also included the following data with linkages to CPRD-GOLD:

- Hospital Episode Statistics through November 30, 2010 (http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=289)
- Office of National Statistics Mortality File or CPRD mortality information through January 15, 2012 (http://www.ons.gov.uk/ons/rel/subnational-health1/the-21st-century-mortality-files/2010/index.html)
- Townsend Deprivation Scores (http://www.communities.gov.uk/documents/communities/pdf/733520.pdf)

The database linkages are important to capture hospitalization information and mortality. In CPRD-GOLD, the GP enters information about hospitalizations, including severe pneumonia, from the discharge summary materials sent to their practice. HES includes hospitalization information for the majority of practices in the CPRD-GOLD. These data provide more information about the cause of hospitalization and length of stay than are otherwise available in the primary care record. Finally, we used the Office of National Statistics linkage to mortality information. Mortality is an important competing risk for any COPD study, as patients are older and have co-morbid diseases due to aging and smoking history.

4.4. Study Population

Based on the treatment guidelines, we expected the potential for differences in COPD severity between treatment groups that would require adjustment in the analysis. For the treatment of COPD, there is a consensus document on the treatment paradigm for patients with COPD [GOLD, 2009]. A LABD is recommended as an initial maintenance treatment in patients with COPD, including long-acting antimuscarinics (LAMA) or long-acting beta-agonists (LABA). If the disease severity warrants, adding additional therapy (a second bronchodilator or ICS) is recommended. However, an internal unpublished analysis estimated that ~10% of patients at COPD diagnosis were prescribed triple therapy (LABA, LAMA, ICS) during the period 2008 -2009.

CPRD-GOLD data were available through December 22, 2011. HES data were available through November 30, 2010. Therefore, patients were examined to identify new users between January 2002 and December 31, 2010 to allow for time in the cohort after being identified as a new user and prior to censoring of available data. Initially, the study was planned to evaluate new users identified between January 2005 and December 31, 2010, but the new user identification period was expanded, based on the feasibility assessment.

The **Baseline Period** was the one-year period prior to Cohort Entry Period to confirm new user status and evaluate patient characteristics of interest.

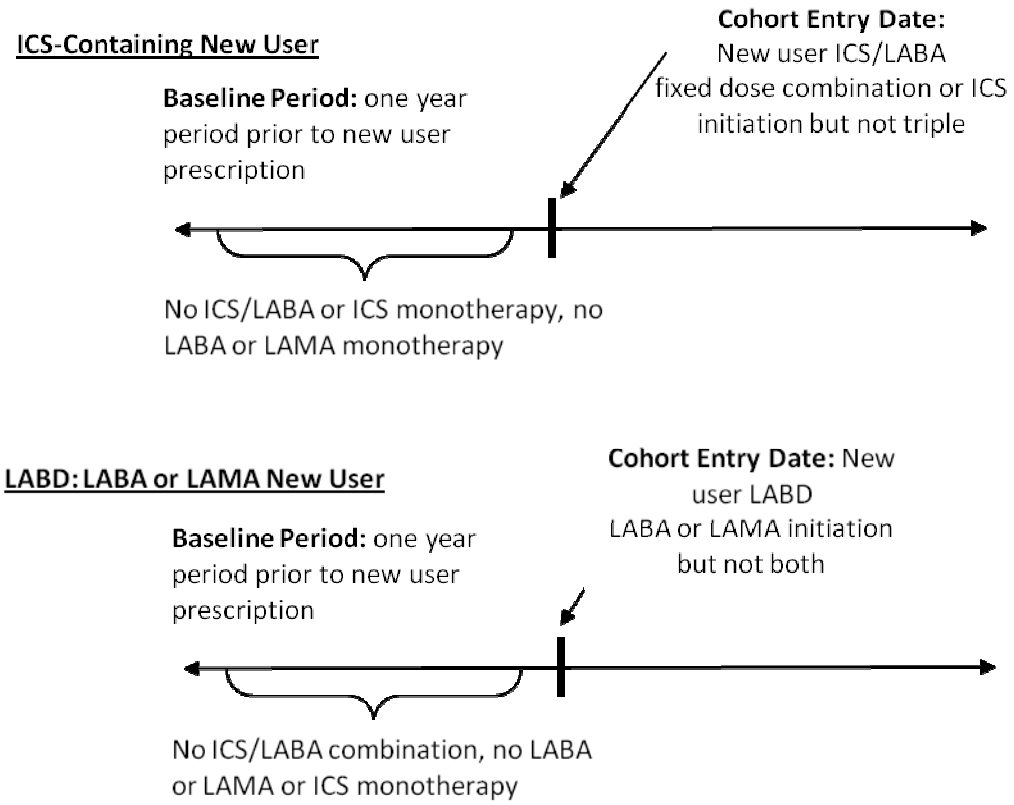
The date when patients become new users of LABD or ICS-containing medications was considered the **Cohort Entry Date**.

Identifying New Users
For the purposes of this study, a new user was defined as someone who had not used medications of interest (ICS-containing or LABD medications) in the year prior to a new prescription of a medication of interest (ICS-containing or LABD). The one-year period of no use was referred to as a washout period rather than requiring no use of these medications ever in the patient's history. New users of ICS-containing medications and new users of LABD were identified separately, and are described in Figure 2.

The following patients were not considered new users:

- New users of triple therapy (LABA/LAMA/ICS) in three single inhalers or ICS/LABA inhaler plus LAMA.
- Patients who stepped up from LABD to ICS/LABA combination therapy in a single device (based on definition of a new user, they had LABD in the history).

Figure 2 Identification of New Users



ICS New Users- Patients had to have at least one prescription for ICS-containing medications from January 2002 (the earliest use) until December 2010 preceded by a year of no use of ICS-containing medications (ICS monotherapy or ICS/LABA fixed dose combination or ICS/SABA) or LABA or LAMA prior to the new user prescription. At Cohort Entry, patients who were new users of ICS monotherapy or ICS+LABA or ICS+LAMA in separate inhalers could be included as new users. However, patients prescribed new use of triple therapy (ICS, LAMA, LABA) were excluded from this analysis.

LABD New Users- Patients had to have at least one prescription for LABA or LAMA (but not both) from January 2002 (the earliest use) until December 2010 preceded by a year of no use of ICS-containing medications (ICS monotherapy or ICS/LABA fixed dose combination or ICS/SABA) or LABA or LAMA prior to the new user prescription. By definition, patients prescribed new use of triple therapy (ICS, LAMA, LABA) were excluded from this analysis.

Algorithm to Identify New Users. To identify new users, the following algorithm was employed. First, patients were evaluated to identify their first prescription of LABD in the analysis period (2002 through 2010). Next patients were evaluated to see if they were new users of ICS-containing medications in a similar manner. Patients were included in the analysis only once. As patients could conceivably qualify as new users more than

once during the study period or be on more than one medication during the study period, the first prescription defining a patient as eligible for the study (either as new user of LABD or new user of ICS) during the study period only was evaluated. As patients generally tend to fill multiple prescriptions for COPD in a year and add therapies rather than switch therapies in COPD, subsequent prescriptions were not evaluated for new use moving forward to the end of available data, as this was expected to yield few patients. In the case of data anomalies where a patient was prescribed ICS/LABA fixed dose combination with either LABA or ICS monotherapy, the patient was considered as having an ICS/LABA new user prescription.

4.4.1. Inclusion/Exclusion Criteria

Inclusion Criteria

Patients were required to:

1. Have CPRD-GOLD data of acceptable research quality according to CPRD standards.
2. Be new users of LABD or ICS-containing medications from January 2002-December 2010.
3. Have a COPD diagnosis at any time in the period prior to and including the Cohort Entry Date (to eliminate any patients with asthma only).
4. Have at least one year of data prior to Cohort Entry Date.
5. Be at least 45 years of age at Cohort Entry Date.
6. Have GPRD-HES linkage. (Individuals without this linkage were retained for basic demographics but were not part of the new user cohort).
7. Have HES coverage one year prior to the Cohort Entry Date

Exclusion Criteria

1. Patients with an occurrence of a code for a medical condition incompatible with COPD diagnosis any time in their history. This list contained conditions that are a related to lung or bronchial developmental anomalies, degenerative processes (cystic fibrosis, pulmonary fibrosis), bronchiectasis, pulmonary resection or other significant respiratory disorders other than COPD (but not including cancer) that can interfere with clinical COPD diagnosis or substantially change the natural history of the disease.
2. Patients with an asthma diagnosis were not excluded.

4.5. Outcome Definition and Measures

Pneumonia is difficult to define in database studies, and preliminary work was performed to better understand the number of pneumonias and coding trends in CPRD-GOLD and HES. Most diagnoses of pneumonia in CPRD-GOLD did not assign an organism or cause.

4.5.1. Considerations in Defining Pneumonia

No single definition of pneumonia severity would meet all needs [Brown, 2011]. In addition, there were challenges in accurately distinguishing the types and severity of pneumonia in the GP and hospital records without the confirmation of chest x-ray results, analysis of sputum sample for type of bacterial infection, etc. However, this information may not be collected depending on the healthcare setting and clinical presentation; on the other hand, COPD exacerbations can be associated with the identification of organisms in sputa without presence of pneumonia. The type of pneumonia and underlying organism may be critical to determining appropriate treatment and prognosis [Brown, 2011].

There are additional difficulties in identifying CAP using primary care, particularly using primary care databases. Several scenarios can occur to further complicate CAP diagnosis in primary care, e.g. (1) CAP will be diagnosed later than the real disease start and recorded only after the medical investigation confirms the working medical diagnosis; (2) CAP will be a consequence or a complication of a previous infectious disease or a COPD exacerbation, (3) CAP will be later rejected by further clinical evidence or (4) health-care acquired pneumonia, including HAP, could be misdiagnosed as CAP, particularly in patients who seek healthcare frequently. It is not possible to fully address these caveats in a primary care database, but these were considered when defining the CAP diagnosis and episode. A validation study of CAP showed requiring hospitalization [Meropol, 2012] and the availability of the CPRD-GOLD linkage to HES improves the ability to identify severe pneumonia (e.g., involving hospitalization).

Each pneumonia was classified as an episode, with a start date and end date based on the type of pneumonia. In the case of CAP, treatment could precede diagnosis by up to 3 days. Defining the episode allowed distinction between pneumonia episodes that occur in the baseline period (prior to Cohort Entry Date) versus following cohort entry. Recurrent episodes were not calculated in the study.

4.5.2. Pneumonia Definitions

Several pneumonia outcomes were defined for this study based on what is recorded in HES and/or the GP record. Distinctions were made between episodes of severe and non-severe pneumonia events as follows:

- Non-Severe CAP
- Severe pneumonia
  - Severe CAP (CAP requiring hospitalization or resulting in death)
  - Hospital-acquired pneumonia (HAP)

These are defined below. The above categories identify three main classification categories of pneumonia that differ in etiology, severity, and prognosis.

CAP episodes were identified and classified as severe (requiring hospitalization or resulting in death) or non-severe.

CAP was based on definitions used previously in CPRD-GOLD [Müllerova, 2012] and those published by others [Meropol, 2012], which have undergone extensive review and evaluation. We allowed a slightly more sensitive definition for the study; however, most pneumonia events were recorded using only a few codes as shown in APPENDIX 1, and varied the sensitivity and specificity of the pneumonia definition based on where it was recorded in a hospital episode (e.g., first episode vs. any episode of care, primary reason vs. not primary reason for episode).

Non-Severe CAP was classified as an episode of pneumonia that was treated in the community and did not result in hospitalization or death. It was tabulated based on examining pneumonia episodes and subtracting away any severe CAP or HAP.

Severe CAP was classified based on hospitalization or death due to pneumonia during the CAP episode. The following CAP was considered as severe:

- Pneumonia episode that did not involve hospitalization and patient died during the episode (CPRD-GOLD) OR
- Pneumonia episode that resulted in hospitalization, where pneumonia was recorded prior to hospitalization (CPRD-GOLD) or within the first 2 days of admission to hospital (HES). If recorded in HES, pneumonia could be recorded on any episode within a spell in any position (e.g., primary or secondary).

We varied the sensitivity and specificity of the pneumonia definition based on where it was recorded in a hospital episode (e.g., first episode vs. any episode of care, primary reason vs. not primary reason for episode).

In HES, spells represent an admission to the hospital and are comprised of a series of care episodes. Each care episode has a primary diagnosis and secondary diagnosis, where the secondary diagnoses are a series of significant co-morbid conditions. Most hospital admissions (>90%) have only one episode of care. Based on the nature of the care received, each spell has a healthcare related group (HRG) assigned to it that corresponds to the highest level of care needed.

Hospital-acquired pneumonia or HAP was classified as a pneumonia episode that was not acquired in the community but was acquired in the hospital (based on HES). Typically, HAP is diagnosed in the hospital >2 days following admission. Pneumonia diagnosed within the first 2 days of hospitalization would be considered severe CAP.

For the purposes of pneumonia outcomes, we examined all episodes of pneumonia within a spell. Pneumonia diagnoses that occur during any episode within a spell 3 or more days following admission were considered HAP.

Unfortunately, there were too few HAP identified during the subsequent feasibility analysis prior to study conduct based on the date that pneumonia was recorded in the hospital. This raises concern about the ability to distinguish HAP from severe CAP in databases. Given the limited number of HAP, it could not be evaluated separately in the analyses and was combined with severe CAP.

Algorithms were evaluated to prevent from double counting a single episode as one type of pneumonia. Pneumonia episodes were classified first as HAP, then severe CAP, and the remaining were considered CAP based on their relative severity and risk of mortality. It is acknowledged that coding anomalies may exist but be relatively infrequent, for example, there will be pneumonia episodes that may have codes suggested as CAP prior to hospital admission, but an individual patient may be diagnosed with HAP based on their HES information instead of CAP.

4.5.3. Pneumonia Episodes

As pneumonia could be recorded during the baseline period and/or following the Cohort Entry Date and last for a significant period of time, pneumonia was identified using episodes in a similar manner to COPD exacerbations episodes (start and end dates). We based the assumptions on the definition of pneumonia episodes on prior work [Müllerova, 2012], and prior consultation regarding pneumonia clinical course and resolution patterns. We made one adjustment to the previously applied algorithm, allowing the antibiotics to start within 3 days (rather than 14 days) of the pneumonia diagnosis based on feedback from physicians consulting on the study.

Although the focus in this study did not involve measuring recurrence as an endpoint, definitions of pneumonia episodes are important to distinguish between those that were in the baseline period (prior to being classified as a new user), on-going at the Cohort Entry Date, or in the cohort follow-up period. In addition, the number of prior pneumonia episodes in the baseline period could be an important factor relating to the risk of pneumonia in the analysis. Patients with on-going pneumonia episodes during cohort entry or with pneumonia that ended within 14 days of the cohort entry date were excluded from the analysis. During the follow-up period, only the **FIRST** episode of pneumonia per person was characterized Note: The entire first episode was examined to distinguish between non-severe CAP, severe CAP, and HAP. Patients with a non-severe pneumonia event could have a subsequent severe CAP or HAP and be included in the severe outcome. This decision was made in the event that a prior CAP was a risk factor for a severe pneumonia.

In a prior CAP study conducted by GSK using CPRD-GOLD [Müllerova, 2012], a pneumonia definition was postulated based on a prior consultation with Dr. Mark Woodhead. The pneumonia episode length was estimated to last approximately 10 weeks (70 days) based on the following assumptions: 77% of COPD patients are expected to be managed at home to recover from CAP back to baseline clinical status within 42 days (6 weeks). Furthermore, it is expected that radiological changes would take longer, with 88% of patients exhibiting return to baseline chest X-ray by ten weeks following the CAP episode start. Therefore, an episode of pneumonia was considered to last up to 70 days or longer (see below).

The **CAP pneumonia episodes** are defined as follows:

Start Date for CAP Episodes:

Non-severe CAP and severe CAP in the baseline period were recorded as indicator variables (yes/no) and the number of events based on the one-year period prior to Cohort Entry Date. The start of the first CAP episode was the 1st pneumonia event (diagnosis

or antibiotics within 3 days prior to diagnosis) in the year prior to Cohort Entry Date. If antibiotics were provided in the 3 days prior to the pneumonia diagnosis, the start date was the date of antibiotics prescription. The pneumonia end date was at least 70 days with some exceptions (see below).

For all CAP episodes, we looked back to confirm if an episode was at least 14 days after the end of any prior pneumonia episode. In the follow-up period (after Cohort Entry), patients with CAP or HAP that had not ended at least 14 days prior to the Cohort entry Date were excluded from the analysis.

End Date for CAP Episodes:

Applying to all CAP episodes, the **end of episode** was defined as 70 days after the start of the episode with some exceptions. The end date could shift under these scenarios: 1) if hospital discharge date for pneumonia CAP was after 70 days, end of the event was set to the discharge date 2) if the patient died or available data in HES or CPRD-GOLD ended prior to 70 days, end date was set to date of death or data end date, or 3) if there was another pneumonia diagnosis or antibiotic prescribed 14 days following the 70-day end date, the end date was set to the date of antibiotics prescription or 4) if there was hospitalization for pneumonia within the 14-day period after the 70 days, the end date was set to the hospital discharge date,

This check was repeated until a period of 14 days was found, free of a pneumonia event and antibiotics prescription.

CAP episodes were then classified based on severity (e.g., resulted in hospitalization) during the episode.

The **HAP pneumonia episodes** are defined as follows:

Start Date for HAP Episodes:

HAP in the baseline period was recorded as indicator variables (yes/no) and the number of events based on the one-year period prior to Cohort Entry Date. The start of the first HAP episode was the 1st non-CAP pneumonia event where pneumonia was diagnosed >2 days following admission to hospital. The pneumonia end date was at least 70 days with some exceptions (see below).

For all HAP episodes, we looked back to confirm if the start of an episode was at least 14 days after the end of any prior pneumonia episode. In the follow-up period (after Cohort Entry), patients with CAP or HAP that had not ended at least 14 days prior to the Cohort entry Date were excluded from the analysis.

End Date for HAP Episodes:

Applying to all HAP episodes, the **end of episode** was defined as 70 days after the start of the episode with some exceptions. The end date could shift under these scenarios: 1) if hospital discharge date for pneumonia CAP was after 70 days, end of the event was set to the discharge date 2) if the patient died or available data in HES or CPRD-GOLD

ended prior to 70 days, end date was set to date of death or data end, or 3) if there was another pneumonia diagnosis or antibiotic prescribed 14 days following the 70-day end date the end date was set to the end date of antibiotics prescription, or 4) if there was hospitalization for pneumonia within the 14-day period after the 70 days, the end date was set to the hospital discharge date.

This check was repeated until a period of 14 days was found free of a pneumonia event and antibiotics events.

4.6. Exposure

The primary exposure of interest was ICS, evaluated in a new user cohort of ICS-containing medications. The comparator exposure group of interest was LABD.

To account for poor adherence to respiratory medications, patients were classified as exposed to study medication for the duration of prescribed therapy plus 30 days. When the duration of prescribed therapy could not be determined due to missing information, it was assumed to be a 30-day supply to correspond to the amount of medications in a single inhaler. In the case of a single inhaler, patients were allowed for gaps of up to 90 days between prescriptions.

To identify a study population of long-term users, we conducted a secondary analyses restricted to patients on treatment for greater than 6 months. The long-term users allowed for examination of cumulative doses. Gaps between each dispensing of up to 90 days were allowed. A patient dispensed a single inhaler on the Cohort Entry Date was censored at 90 days if they did not have another prescription. A patient dispensed a second prescription of a single inhaler on day 40 would experience 99 days of coverage (i.e., 39 days of coverage for the first inhaler and 90 days for the second inhaler).

The strength of the new user prescribed ICS medication on the Cohort Entry Date was categorized into equipotent doses of low, medium, and high-dose ICS based on classification according to Figure 3-1 presented in the Global Initiative for Asthma (GINA) guidelines [GINA, 2011]. The strength of the new user prescription was entered into the Cox model primary outcome models as low, medium, and high relative to LABD (e.g. dummy variables). The strength of the medication was tabulated based on the prescription on the Cohort Entry Date.

The use of other medications during the one-year **Baseline Period** was included in the model as a marker of disease severity.

Prescriptions (Yes/No) during the Baseline Period indicative of disease severity. In addition, the number of prescriptions (except oxygen use) for the following was collected:

- short-acting bronchodilators (short-acting anticholinergics or short-acting beta-agonists, including combination inhalers)
- long-term oral corticosteroid use (>4 Rx in 12 months)
- oral steroid use

- theophyllines
- oxygen use, when recorded (changes in reimbursement censor this information during part of the analysis period, but we captured what information was available)
- nebulized therapy (associated with severity / frailty)
- Daxas (roflumilast) was to be included; however, no Daxas prescriptions were identified (approved in June 2010)

Exposure "counts" of medications were categorized during analysis (e.g., tabular summaries, propensity score creation, Cox modeling).

4.7. Confounders

Key risk factors for pneumonia that may also relate to treatment were measured in the one-year Baseline Period. For the purposes of general comorbidity assessment and vaccination for pneumonia, a longer history was examined. Although patients may have varying periods of history, this was not expected to be differentially recorded by treatment (which could result in information bias). A longer look back period was needed to identify co-morbidities given they may not be recorded in the Baseline Period.

Confounders evaluated included:

- Age at Cohort Entry
- Gender
- Body Mass Index (BMI) ever in patient history
- Smoking status ever in patient history
- Overall Social Deprivation Scores for England
- Townsend Scores
- Charlson Co-morbidity index and individual chapters ever in patient history (prior to Cohort Entry Date)
- Depression, Anxiety, Asthma, GERD ever in patient history (prior to Cohort entry Date)
- Co-Medications of Interest associated previously with CAP in Baseline Period (Statins, ACE-inhibitors, and Immunosuppressive treatment including antiretroviral medications)
- COPD severity during Baseline Period (1-year prior to and 3 months following Cohort Entry Date)
- Number of GP visits in the 1-year Baseline Period
- Number of Moderate and Number of Severe COPD Exacerbations in the 1-year Baseline Period
- Number of Emergency Hospitalizations in the 1-year Baseline Period
- Number of Non-Emergency Hospitalizations in the 1-year Baseline Period

- Number of non-severe CAP Baseline Period (no hospitalization or death)
- Number of severe CAP in the Baseline Period
- Number of HAP in the Baseline period
- Prior vaccination for influenza in the Baseline Period
- Prior vaccination for pneumonia in past 5-years
- Medical Research Council (MRC) dyspnea scale
- Calendar year of Cohort Entry

Confounders that were based on "counts" of healthcare encounters and exacerbation were categorized during analysis (e.g., tabular summaries, propensity score creation, Cox modeling).

4.8. Data Analysis

4.8.1. New User Cohort

Patients in the cohort were described according to their COPD disease severity, treatment patterns, demographic characteristics, and comorbidities. Treatment guidelines for COPD consider long-acting bronchodilators as monotherapy as being prescribed for patients that have less severe COPD than those who would be given an ICS as add-on to a long-acting bronchodilator.

For the primary objective, patients were required to be new users of ICS-containing medications or LABD after a one-year period of non-use. ICS are add-on therapy for LABD; therefore, new users of ICS could have ICS monotherapy or ICS/LABA as fixed dose inhaler in the one year prior to **Cohort Entry Date**.

The primary pneumonia outcomes were severe pneumonias, which were severe CAP and HAP. Due to small numbers and lack of validation of the outcome, severe CAP and HAP were combined. The secondary outcome was all pneumonias combined. The protocol was amended to evaluate all pneumonia and severe pneumonia (resulting in hospitalization or death within the pneumonia episode).

Confounders were selected for inclusion in the analysis based on clinical importance and are described in Section 4.7 and respiratory medications in Section 4.6. Additional information about the modeling strategy is addressed in a statistical analysis plan.

4.8.2. Patient Follow-up Time from Cohort Entry

Patients were followed from the date of their first eligible prescription (New User entry date) until the earliest of the following:

- date of treatment end (up to 90-day gap allowed for each inhaler),
- date of study end point (first pneumonia event of interest)
- date of transfer to a new practice / practice stops participating or CPRD ends,

- date of ICS initiation (among LABD new users)
- death or
- HES data ends (last available HES data)

As part of the primary analysis, patients were examined for their first pneumonia (severe CAP, HAP, or non-severe CAP). Patients with severe pneumonia (resulting in hospitalization or death) could have experienced a prior non-severe pneumonia and were not censored, in the event that non-severe pneumonia was a risk factor for severe pneumonia.

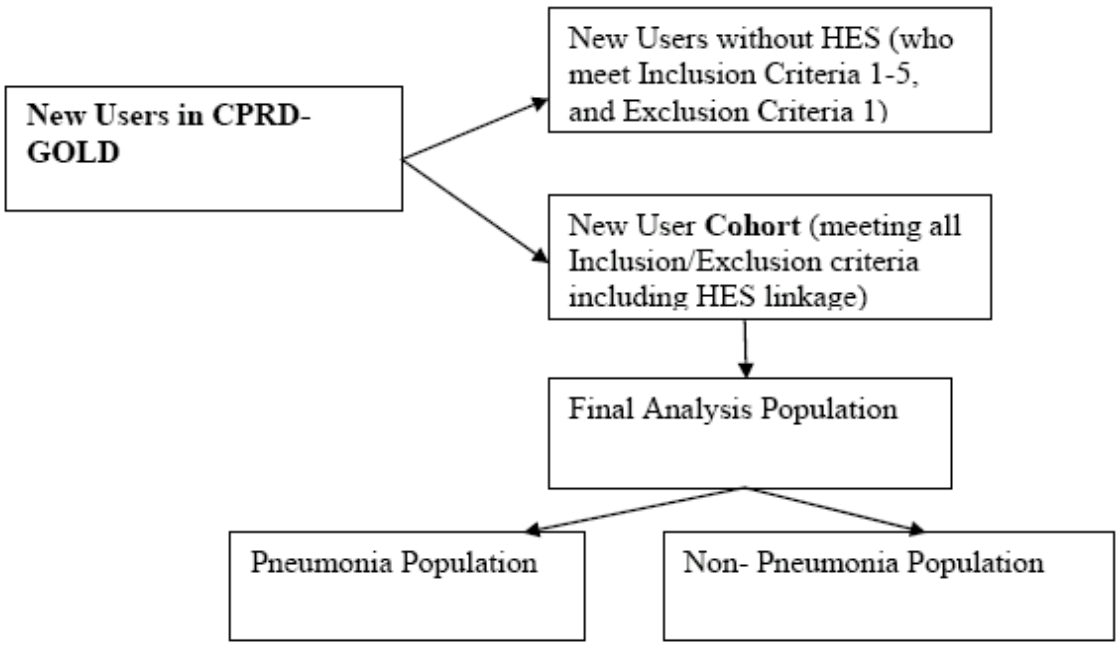
Each patient had a time and "censoring" variable, which was an indicator variable (yes/no) that indicated if they had the event of interest or if they were censored. Time was calculated as the date of the event or censoring minus the cohort entry date plus 1.

Incidence rates of the pneumonia outcomes were calculated as the number of patients experiencing an event divided by the person-years at risk. Incidence rate ratios were calculated as the incidence rate in the ICS-containing group divided by the incidence rate in the LABD group. Precision of effect estimates were evaluated from the width of the 95% CIs.

4.8.3. Analysis Populations

There were a few analysis populations of interest in this study for tabular summaries and/or modeling. Patient populations are described below and presented graphically in Figure 3 to illustrate subsets.

Figure 3 Summary of Populations



New User Cohort: These patients met the inclusion/exclusion criteria in the protocol regarding being classified as new users of ICS-containing medications or LABD with HES linkage.

New Users without HES Linkage: These patients met the inclusion criteria 1-5 and exclusion criteria 1 except for the fact that they were missing the HES linkage (e.g., they fail inclusion criteria 6, 7). These individuals were described to compare to the New User Cohort group in the study who had the HES linkage.

New User Cohort Free of Pneumonia at Index Date: These patients were a subset of new users that were at risk of pneumonia at the time of their new use. Patients in the new user cohort who were experiencing an episode of pneumonia that was on-going or had not been resolved for at least 14 days prior to their index date were excluded from this cohort.

New Users with HES Linkage Excluded from Final Analysis: These patients met all inclusion/exclusion criteria except were excluded for having an influential propensity score weight or on-going pneumonia or at the time of entry into the New User Cohort.

Final Analysis Population: These patients were a subset of the New User cohort who have propensity scores within an acceptable range, were not experiencing a pneumonia episode at the time of their Cohort Entry Date, and had HES and CPRD data during the period following the Cohort Entry Date.

Pneumonia Population: These patients were a subset of the New User Cohort free of pneumonia at index date and had experienced at least one pneumonia event in the year following Cohort Entry, regardless of censoring status in the Cox modeling. The first pneumonia event was tabulated as either HAP (most severe), severe HAP (less severe), or non-severe CAP (least severe) to count patients in one category. These patients were compared to those new users free of pneumonia at the Cohort Entry Date who did not develop pneumonia in the year following Cohort Entry.

4.8.4. Multivariable Modeling

Multivariable analysis was performed using Cox proportional hazard model with adjustment for confounders and exposures in Section 4.7 and Section 4.6.

The following outcomes were examined:

- Severe pneumonia events (HAP and Severe CAP combined)
- All pneumonia events

Severe pneumonia events were examined as the primary outcome. As a secondary outcome, all pneumonia events were analyzed. The number of confounders that could be supported in the modeling was based on the total number of severe pneumonia and all pneumonia events and their distribution by treatment.

To adjust for differences confounding by severity due to differences in prescribing between ICS-containing medications and LABD, propensity scores (PS) were utilized. The propensity score was estimated to model the probability that a chance of a patient

receiving ICS-containing medications compared with receiving LABD given a patient's observed set of baseline covariates. The logistic models used to calculate the propensity scores, all available variables in Section 4.6 (exposures) and in Section 4.7 (confounders) were entered into the model. Propensity scores were produced.

The PS in both groups were evaluated for overlap, and patients with scores in the tails of the distribution that were not represented in both groups were eliminated from the analysis. Patients with extreme PS weights (values >10) were to be removed from the analysis as their contribution would be influential and affect the model. Patients eliminated from the analysis were described.

Multivariable analysis was performed using Cox proportional hazard model with adjustment for the propensity score using inverse probability of treatment weighting (IPTW) [Robins, 1998; Robins, 1999; Robins, 2000]. This approach is more appropriate then propensity score matching when there may be effect measure modification [Stürmer, 2006]. Because of the cohort design, it was possible to adjust for confounders in the PS approach as well as include them as main effects in the model; however, it has been demonstrated that the addition of confounders with propensity scores does not contribute appreciably to the model [Rubin, 2000; Stürmer, 2006].

Parameterization of the explanatory variables in the propensity score generation and subsequent modeling was based on determining the most appropriate measure (e.g., number of moderate exacerbations may be collapsed into ordinal categories). Imputation, removal of outliers, and parameterization of variables for the model are described in the analysis plan and were determined prior to fitting final outcome models.

For the primary analyses (severe CAP and HAP combined), patients were followed using a Cox proportional hazards model until they experienced the first of the following events or censoring: (1) pneumonia event of interest (based on their first pneumonia episode following Cohort Entry), or censoring for (2) death (competing cause), (3) other pneumonia event of interest prior to severe event (competing cause) (4) cohort exit / transfer, practice stopped participating, or end of CPRD follow-up, (5) new user treatment ended, (6) LABD new user was prescribed an ICS, or (7) end of HES follow-up. Each patient had a time and "censoring" variable, which was an indicator variable (yes/no) that indicates if they have had the event of interest or if they were censored.

For the analysis of all pneumonia, patients were followed using a Cox proportional hazards model until they experience any pneumonia event (as their first pneumonia episode) or censoring.

To test proportionality of the hazard functions, model diagnostics were evaluated by including time-dependent covariates in the Cox model. The primary outcome was severe pneumonia, (defined as severe CAP and HAP). As a secondary analysis, all pneumonia was examined.

If one of the explanatory variables was not proportional, we considered alternatives (time-dependent variable for the non-proportional predictors or stratification on the non-proportional predictors).

Interactions between explanatory variables were determined based on available theory and include ICS/LABD medication use by known risk factors for pneumonia (BMI, age, GOLD stage III/IV, MRC ≥4, history of pneumonia, current smoking status, deprivation quintiles).

Additional analysis or adjustments to the analytic or modeling strategy were performed as the data warranted. A more detailed modeling strategy, including generation of the propensity scores and Cox modeling, are provided in an analysis plan.

4.8.5. Additional Multivariable Analyses

All pneumonia events were combined as a secondary pneumonia outcome. Multivariable modeling was employed on this outcome (all pneumonia) in the same manner as applied to the primary severe pneumonia outcome.

To examine a potential dose-response relationship with ICS-containing medications, the strength of the prescribed ICS medication on the Cohort Entry Date was categorized into equipotent doses of low, medium, and high-dose ICS based on classification according to Figure 3-1 presented in the Global Initiative for Asthma (GINA) guidelines [GINA, 2011]. The strength of the new user prescription was entered into the Cox model primary outcome models as low, medium, and high relative to LABD (e.g. dummy variables).

To identify more persistent users, the primary endpoint (severe pneumonia) was evaluated restricting to patients who were prescribed treatment for greater than 6 months (allowing for 90-day gaps between treatments as each inhaler can last up to 90 days).

As there may be differential drop out over time, ICS-containing vs. LABD new users who continue taking medications for at least 6 months may not be clinically similar. Therefore, additional confounders were identified in the 6-month period to account for any events that would affect censoring or outcomes (e.g., COPD exacerbations, emergency and non-emergency hospitalization, primary care visits). The PS were regenerated among the more persistent group to include updated confounders measured in the 6-mo period of persistent use as the new analysis “start”. Patients who had an unresolved episode of pneumonia after 6 months of persistent use were excluded from the persistent analysis. Patients were required to have at least 14 days between their last pneumonia episode and the persistent analysis “start” date.

All analyses were performed using SAS [Cary, NC].

MRC dyspnea score was included as a confounder in the primary model (collected as part of QOF for 2009 onwards) as part of secondary analyses.

To examine potential differences in patient groups, demographic characteristics of patients with HES linkage vs. those without HES linkage were compared. It was not expected that there would be clinically significant differences between these groups.

The number of deaths in each treatment group was described.

4.8.6. Comparisons of Patient Characteristics by Pneumonia Status

To evaluate the third objective comparing patients developing severe pneumonia vs. non-severe pneumonia, a Pneumonia Population was identified. The first pneumonia (or no pneumonia) within one year following the Cohort Entry Date was included regardless of censoring in the proportional hazards model. Patients who did not experience pneumonia within the first year were included in this analysis and counted as having no pneumonia.

As it was also of interest to compare patients who get pneumonia versus those who did not get pneumonia during this period, descriptive summaries included all three categories: severe pneumonia (severe CAP and HAP combined), non-severe pneumonia, and no pneumonia. To assess differences between pneumonia groups, clinical and patient characteristics were compared using descriptive statistics

Characteristics of patients experiencing any pneumonia or pneumonia resulting in hospitalization on first episode within a spell within the year following Cohort Entry were compared to those individuals that did not develop an episode of pneumonia using multiple logistic regression modeling in an exploratory fashion in the new user cohort, irrespective of treatment and censoring. Based on the number of events, the number of confounders included in the model was selected using a backward variable reduction strategy with default settings in SAS described in the analysis plan. Treatment was not be included in the logistic regression modeling, as the model focused on patient characteristics and did not account for treatment discontinuation.

4.9. Protocol Amendment(s)

As specified in the protocol, feasibility was conducted prior to analysis to determine precision of the pre-specified study design. The event rate and number of pneumonia events was lower than expected based on feasibility and prior work. As a result, most of the following adjustments were made to the protocol to improve precision regarding estimates of pneumonia. The protocol was amended with an effective date of 26-Nov-2012.

- The protocol feasibility sections were updated following selection of the new user cohort and development of algorithms to identify episodes of pneumonia and censoring periods. Preliminary feasibility had not adjusted for the protocol inclusion/exclusion criteria or analysis requirements.
- The analysis period was expanded from 2005-2010 to 2002-2010 to increase precision to examine pneumonia via identification of additional new users and pneumonia events.
- Severe pneumonia events, hospital-acquired pneumonia (HAP) and severe community-acquired pneumonia (CAP), were combined rather than analyzed separately due to the low number of HAP events.
- The primary endpoints for modeling were clarified to be severe pneumonia events (HAP and severe CAP combined) and all pneumonia events combined rather than HAP, severe CAP and non-severe CAP separately. These individual endpoints needed to be defined in order to evaluate pneumonia by severity; however, there is

more efficiency in combining all events together and then subsetting by severe events than analyzing separately.

- The secondary analysis comparing severe and non-severe CAP was adjusted to include comparisons of patients with pneumonia versus patients without pneumonia on demographics, COPD history, and co-morbid conditions. The original objective was to compare between severe and non-severe pneumonia, however, the small number of events limited the ability to perform multiple logistic regression of severe and non-severe pneumonia.
- Minor clarification on table shell populations and analyses to improve clarity.

4.10. Changes to Planned Analyses

Changes to the planned analysis were performed in order to better understand results or adjust based on data distributions.

- Most pneumonia events in the final analysis cohort (90%, 631 of 702) resulted in hospitalization (pneumonia as primary or secondary cause), which was discovered following protocol amendment and feasibility analyses. Therefore, additional pneumonia endpoints relating to pneumonia were added prior to modeling to include more specific pneumonia hospitalization outcomes.
  - Any pneumonia - planned
  - Severe pneumonia, resulting in pneumonia hospitalization or death during the episode - planned
  - Pneumonia hospitalization (primary outcome on any episode)- added post hoc
  - Pneumonia hospitalization (primary outcomes on the first episode within a spell) – added post hoc
- Benzodiazapines and non-benzodiazapine sedatives that bind to the same receptor were added to the propensity score modeling due to recent evidence that suggests they are associated with pneumonia [Obiora, 2013].
- An evaluation of the initial time period (2005-2010) following the discovery of the undercounting of pneumonia events in feasibility that resulted in expansion to the broader time period of 2002-2010.
- The IPTW approach to propensity scores was planned in this study. To evaluate robustness of the results, alternative methods including quintiles, deciles, and 1:1 matching were produced and presented in the report.
- The comparison of ICS/LABA vs. ICS had been performed previously in the literature, including a 2008 meta-analysis of randomized controlled trials [Drummond, 2008]. This post hoc analysis was performed to help understand pneumonia trends potentially confounded by time, formulation, and dose.
- Most pneumonia events in this study were associated with hospitalization; therefore, the differences in patient characteristics were examined by comparing those patients with pneumonia as the primary reason on the FIRST episode within a hospital spell, other pneumonia, pneumonia not meeting that criteria (no hospitalization, not primary reason on first episode), and those who were not diagnosed with pneumonia.

5. RESULTS

5.1. Organization of Results

All pneumonia outcomes examined in this study followed the same process to evaluate an association with ICS-containing vs. LABD use, including:

- Generation of propensity scores from propensity score model, with comparison of patient characteristics before and after balancing.
- Evaluation of the distribution of propensity scores, potential outliers, overlap between groups
- Fit final model of time to first pneumonia with IPTW propensity score weighting

These results include four pneumonia endpoints to fully evaluate sensitive and specific definitions of pneumonia. The pneumonia outcome was defined as overall pneumonia, severe pneumonia (resulting in a hospitalization or death during a pneumonia episode), hospitalized pneumonia (resulting in hospitalization where pneumonia was a primary reason on **any** HES episode), and hospitalized pneumonia with pneumonia as the primary reason on the **first** episode. The number of events for the primary model is presented in Table 4.

Lag in exposure was examined to investigate the potential for channeling bias (within 30 days of new use) and persistent use of six months.

Additional analyses were conducted to examine dose based on budesonide dipropionate units.

The results section provides descriptive summaries for each step; however, tabular summaries of the interim steps are provided in the POST-TEXT TABLES AND FIGURES for most endpoints. Due to the number of endpoints, lag time, dose evaluation, etc., all results are consolidated into Table 22, with individual output from the propensity score generation, modeling, etc. provided in the POST-TEXT TABLES AND FIGURES.

The final analysis population is the primary population for the study report, which included new users of ICS-containing and LABD medications meeting the inclusion/exclusion criteria, free of pneumonia at the index date, with sufficient data on covariates and linked data with HES. The demographics of the final analysis population are presented in the results (section 5.3.1). New users meeting the inclusion/exclusion criteria but without HES linkage were not part of the final analysis population, but the demographics of these new users are presented in the post-text tables (section 8.1.3).

Results evaluating an association with ICS vs. LABD use are presented in the following sections:

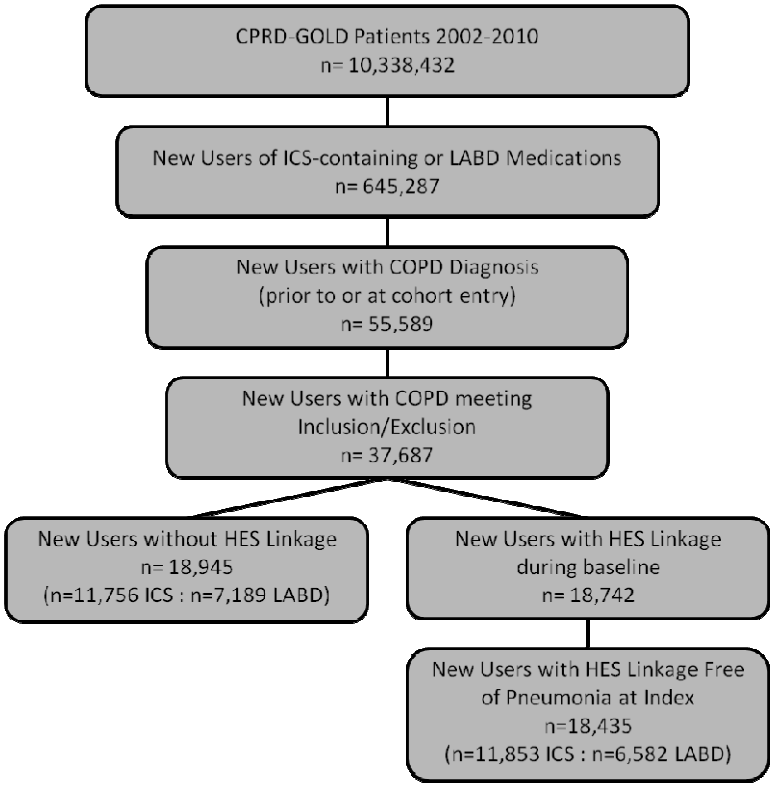
- Primary analysis (full final analysis new user population) - Section 5.3
- Persistent new users (new users with ≥6 months of treatment)- Section 5.6

- New users by Dose- Section 5.7
- Persistent new users by dose- Section 5.8
- New user cohort from 2005-2010- Section 5.9
- New use of at least 30 days- Section 5.10
- New users by device (ICS monotherapy vs ICS/LABA fixed dose combination)- Section 5.11

5.2. New User Cohort

Figure 4 shows the generation of the new user cohort. Among new users with COPD meeting the inclusion/exclusion criteria, 18,742 (n=12,065 ICS; n=6,677 LABD) patients had HES linkage and were included in the study, and 18,945 patients met all of the inclusion/exclusion criteria except linkage with HES data. Among the patients included in the study, 18,435 were free of pneumonia at index, including 11,853 new ICS-containing users and 6,582 new LABD users.

Figure 4 New User Cohort Generation



Data on the feasibility of the new user cohort are presented in the post-text tables including estimates of the number of new users (Post-Text Table 1) and persistent new users (Post-Text Table 2) meeting the inclusion/exclusion criteria by cohort entry year with HES linkage. Among new ICS users (n=12,065), 41% (n=4,947) initiated ICS-containing fixed dose combinations and 58% (n=7,7107) initiated ICS monotherapy. Five percent (5%) of the ICS monotherapy group also had a script for a LAMA or LABA on

the initiation date, while 18% of the ICS monotherapy group added a LAMA or LABA during the study. The majority of the ICS- fixed dose use was fluticasone propionate/salmeterol (72%) and the majority of the ICS monotherapy was beclomethasone dipropionate (89%). ICS monotherapy doses tend to be lower than ICS doses in the fixed dose combination based on the GINA estimated equipotent daily doses of ICS, as show in Table 3.

Data on the number of first pneumonia events by type in the new user cohort regardless of censoring (Post-Text Table 3) and causing censoring (Post-Text Table 4) are presented. Though a spectrum of ICD-10 HES codes (Appendix Table 3) and GPRD codes (Appendix Table 4) were used to identify pneumonia, most pneumonia events in this study were identified by a small number of codes used most frequently (Appendix Table 1, Appendix Table 2).

Table 3 New Users of ICS-containing Products by Dose

	Too Low	Low	Med	High	Too High
ICS Monotherapy Group n (%)	22 0.3%	4067 **57.2%**	2518 35.43	472 6.6%	28 0.4%
Fixed Dose Combinations n (%)	9 0.2%	966 19.5%	2186 **44.2%**	1780 **36.0%**	6 0.1%

5.2.1. Characteristics of new user cohort of patients without pneumonia at index date are presented in New User Cohort Demographics

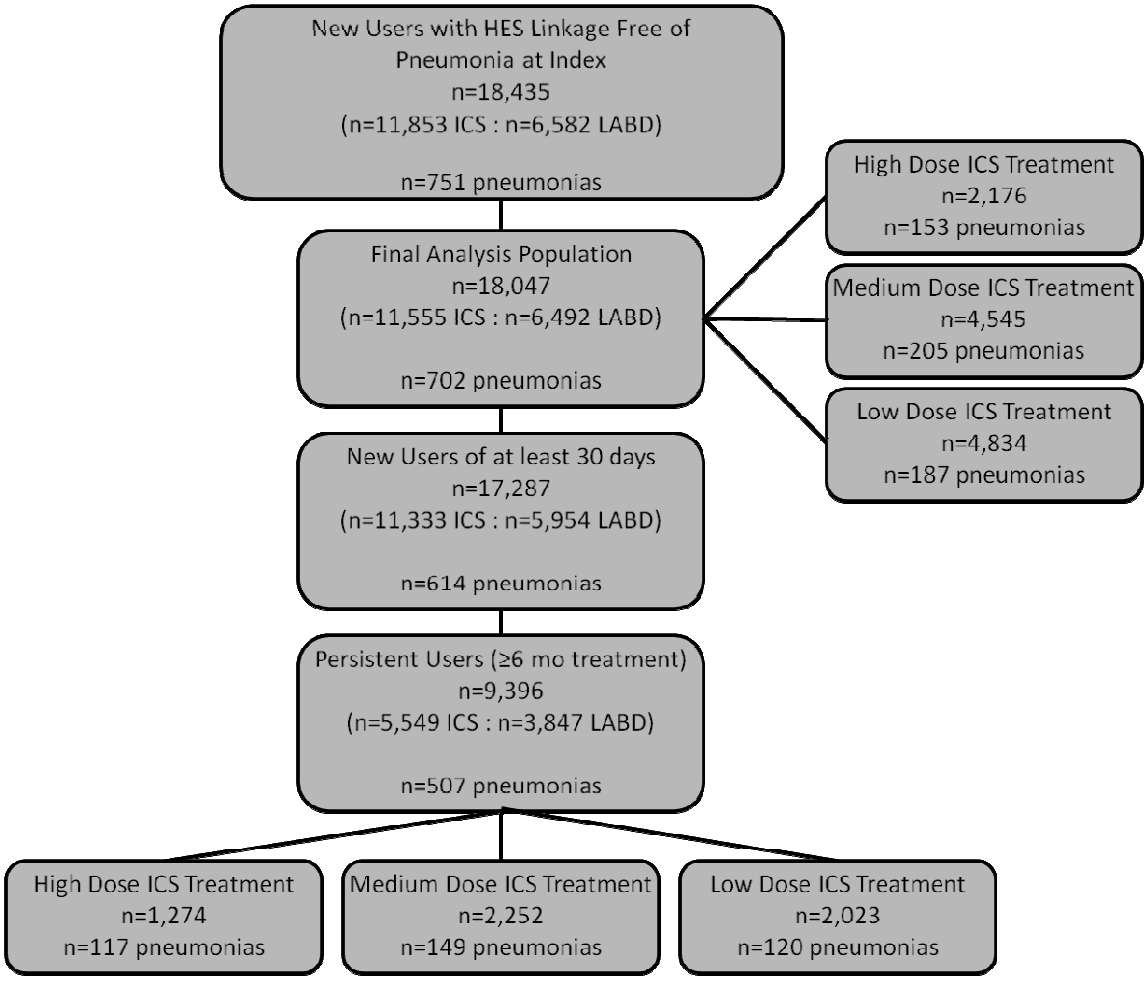
Post-Text Table 5 of the post-text tables by exposure cohort (ICS-containing vs. LABD). Post-Text Table 6 summarizes the co-morbidities of the new user cohort with patient medications used and healthcare utilization at baseline summarized in Post-Text Table 7. The number of first pneumonia events and reasons for censoring in the new user cohort without pneumonia at index date are presented Post-Text Table 11, along with the time until event or censoring (Post-Text Table 12).

New users of ICS-containing and LABD drugs who did not have HES linkage were excluded from the final analysis cohort and composed approximately half of all new user patients in CPRD-GOLD. The descriptive characteristics, co-morbidities, and medications/healthcare utilization of the new users excluded due to lack of a HES linkage are presented in the post-text tables (Post-Text Table 8, Post-Text Table 9, Post-Text Table 10 respectively), but were similar to the new user cohort without pneumonia at index date.

5.3. Final Analysis Cohort

The final analysis cohort contained 18,047 new users including 11,555 new users of ICS-containing products and 6,492 LABD new users. The final analysis cohort excluded new users with HES linkage that were free of pneumonia at index but were missing data on smoking status and deprivation indices. Figure 5 shows the number of patients and number of pneumonia events observed in the patient populations of the analysis dataset.

Figure 5 Patient Populations in Analyses



Data on the feasibility of the final analysis population before propensity score balancing are presented in the post-text tables including estimates of the number of new users meeting inclusion/exclusion criterion by cohort entry year (Post-Text Table 13), the number of first pneumonia events by type regardless of censoring (Post-Text Table 14), and the number of events causing censoring (Post-Text Table 15). Among the new user cohort with HES linkage, there were 751 pneumonia events that caused a patient to be censored. After patients in the new user cohort missing data on smoking status and deprivation score (IMD and/or Townsend) were excluded for the final analysis cohort, 702 pneumonia events caused a patient to be censored. Table 4 shows the number of pneumonia events according to the 4 pneumonia endpoints in this study for the primary analysis.

Table 4 Pneumonia Events by Endpoint in Primary Analysis

Pneumonia Event	ICS-Containing (n=11,555)	LABD (n=6,492)	Total (n=18,047)
Overall Pneumonia	545	157	702
Severe Pneumonia (hospitalized pneumonia or death on episode)	513	147	660
Hospitalized Pneumonia (primary cause, any episode)	319	90	409
Hospitalized with Pneumonia on the First Episode (primary cause)	252	70	322

5.3.1. Final Cohort Demographics before PS Balancing

Characteristics of final analysis cohort before propensity score balancing are presented in Table 5 by exposure cohort (ICS-containing vs. LABD). The ICS-containing cohort contained a higher percentage of patients with an unknown COPD severity, who were non-smokers, and had an asthma diagnosis prior to cohort entry date. The LABD cohort had more new users with clinically significant dyspnea and ex-smokers. Both cohorts had similar percentages of current smokers.

Table 5 Descriptive Characteristics from the Baseline Period (year before cohort entry)/Patient History for the Final Analysis Cohort before PS Balancing

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=11,555	%	n=6,492	%	
Male	6,332	54.8	3,778	58.2	<0.01
Age at cohort entry date					
45-64 yrs	3,835	33.2	1,938	29.9	<0.01
65-79 yrs	5,521	47.8	3,316	51.1	.
>=80 yrs	2,199	19.0	1,238	19.1	.
Smoking status prior to cohort entry date					
No	815	7.1	278	4.3	<0.01
Yes	5,160	44.7	2,899	44.7	.
Ex	5,580	48.3	3,315	51.1	.
COPD severity					
COPD Dx but spirometry conflicts	284	2.5	164	2.5	<0.01
Restrictive COPD	761	6.6	485	7.5	.
GOLD I	338	2.9	225	3.5	.
GOLD II	1,862	16.1	1,537	23.7	.
GOLD III	1,277	11.1	915	14.1	.
GOLD IV	253	2.2	170	2.6	.

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=11,555	%	n=6,492	%	
Unknown	6,780	58.7	2,996	46.1	.
Clinically significant dyspnea diagnosis	948	8.2	1,084	16.7	<0.01
Asthma diagnosis prior to cohort entry date	2,186	18.9	776	12.0	<0.01
Pneumonia episode in baseline period	232	2.0	121	1.9	0.50
Number of non-severe CAP episodes in baseline period					
0	11,503	99.5	6,468	99.6	0.26
1	52	<1	23	<1	.
2	0	<1	1	<1	.
Number of severe CAP episodes in baseline period					
0	11,376	98.5	6,396	98.5	0.85
1	175	1.5	93	1.4	.
2	4	<1	3	<1	.
Number of HAP pneumonia episodes in baseline period					
0	11,547	99.9	6,489	100.0	0.55
1	8	<1	3	<1	.
Townsend Deprivation quintile (Year 2001)					
Quintile 1 (Least deprived)	1,735	15.0	970	14.9	0.05
Quintile 2	2,265	19.6	1,218	18.8	.
Quintile 3	2,578	22.3	1,362	21.0	.
Quintile 4	2,793	24.2	1,656	25.5	.
Quintile 5 (Most deprived)	2,184	18.9	1,286	19.8	.
IMD Deprivation quintile closest to cohort entry date					
Quintile 1(Least deprived)	1,696	14.7	894	13.8	0.20
Quintile 2	2,225	19.3	1,210	18.6	.
Quintile 3	2,327	20.1	1,327	20.4	.
Quintile 4	2,704	23.4	1,520	23.4	.
Quintile 5 (Most deprived)	2,603	22.5	1,541	23.7	.

Table 6 summarizes the co-morbidities of the final analysis cohort before propensity score balancing. The two cohorts were similar regarding most co-morbidities, though new users of LABD drugs tended to have higher vaccination (influenza and pneumococcal) coverage than new users of ICS-containing drugs.

Table 6 Patient Co-morbidities in the Baseline Period (year before cohort entry)/Patient History for the Final Analysis Cohort before PS Balancing

Variable	Cohort				
	ICS-Containing Medications		LABD Medications		
	n=11,555	%	n=6,492	%	p-value
Influenza Vaccination in baseline period	7,573	65.5	4,526	69.7	<0.01
Pneumococcal Vaccination in (up to) 5 years prior to cohort entry date	4,298	37.2	2,681	41.3	<0.01
BMI status					
No recording	1,115	9.6	476	7.3	<0.01
Underweight (0< - <18.5)	574	5.0	356	5.5	.
Low Normal (18.5 - <21)	1,139	9.9	672	10.4	.
High Normal (21 - <25)	2,901	25.1	1,672	25.8	.
Overweight (25 - <30)	3,452	29.9	1,891	29.1	.
Obese (≥30)	2,374	20.5	1,425	22.0	.
MI diagnosis	950	8.2	590	9.1	0.05
CHF diagnosis	959	8.3	568	8.7	0.30
CVD diagnosis	918	7.9	495	7.6	0.44
Dementia diagnosis	95	<1	36	<1	0.04
GERD diagnosis or GERD prescription	5,467	47.3	3,247	50.0	<0.01
Peptic Ulcer diagnosis	890	7.7	552	8.5	0.06
Peripheral Vascular Disease diagnosis	989	8.6	638	9.8	<0.01
Mild Liver Disease diagnosis	78	<1	44	<1	0.98
Moderate Liver Disease diagnosis	10	<1	8	<1	0.45
Connective Tissue Disorder diagnosis	582	5.0	354	5.5	0.23
Hemiplagia/Paraplegia diagnosis	41	<1	15	<1	0.15
Diabetes diagnosis	1,174	10.2	705	10.9	0.14
Diabetes (with complications)	219	1.9	144	2.2	0.14
Anxiety diagnosis or Anxiety prescription	3,353	29.0	1,846	28.4	0.41
Depression diagnosis or Depression prescription	5,188	44.9	2,900	44.7	0.77
Cancer (non-metastatic solid tumours) diagnosis	967	8.4	570	8.8	0.34
Cancer (Metastatic solid tumours) diagnosis	27	<1	20	<1	0.35
Renal Diseases diagnosis	876	7.6	703	10.8	<0.01

1. Variables recorded in patient history "prior to cohort entry date" unless otherwise specified

Patient medications used and healthcare utilization at baseline in the final analysis cohort before propensity score balancing are summarized in Table 7. Patients newly initiating LABD drugs had greater use of statins, ACE-inhibitors, and SABD during the baseline period, while patients initiating ICS-containing drugs had more emergency hospital admissions during the baseline period. ICS and LABD new users were similar regarding other measures of medication and healthcare use.

Table 7 Patient Medications Used and Healthcare Utilization in the Baseline Period (year before cohort entry) for the Final Analysis Cohort before PS Balancing

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=11,555	%	n=6,492	%	
Oral Corticosteroids (>4 Rx)	335	2.9	218	3.4	0.09
Oxygen	189	1.6	84	1.3	0.07
Nebulized therapy	396	3.4	162	2.5	<0.01
SABD	8,066	69.8	4,738	73.0	<0.01
Theophylline	279	2.4	126	1.9	0.04
ACE-inhibitors	2,785	24.1	1,742	26.8	<0.01
Statins	3,351	29.0	2,372	36.5	<0.01
Immunosuppresants	144	1.2	99	1.5	0.12
Count of GP visits					
0	159	1.4	43	<1	<0.01
1-5	2,803	24.3	1,537	23.7	.
6-10	3,703	32.0	2,108	32.5	.
11-15	2,405	20.8	1,332	20.5	.
15-20	1,205	10.4	741	11.4	.
≥21	1,280	11.1	731	11.3	.
Count of emergency hospital admissions					
0	9,008	78.0	5,365	82.6	<0.01
1-2	2,297	19.9	1,028	15.8	.
≥3	250	2.2	99	1.5	.
Count of non-emergency hospital admissions					
0	9,416	81.5	5,168	79.6	<0.01
1-2	1,887	16.3	1,174	18.1	.
≥3	252	2.2	150	2.3	.
Count of moderate COPD exacerbations					
0	7,180	62.1	4,272	65.8	<0.01
1	3,063	26.5	1,598	24.6	.
≥2	1,312	11.4	622	9.6	.
Count of COPD hospitalizations					
0	10,855	93.9	6,126	94.4	0.25
1	638	5.5	325	5.0	.
≥2	62	<1	41	<1	.

1. Variables recorded in baseline period unless otherwise specified

5.3.2. Incidence before Propensity Score Balancing

The crude incidence rate of first pneumonia (either severe or non-severe) by exposure cohort and key covariates among the final analysis population before PS balancing were analyzed to confirm consistency with the literature and are presented in Post-Text Table 16. The crude incidence rate of pneumonia was 48.7 per 1000 person years (PY) among

the ICS-containing cohort and 30.9 per 1000 PY among the LABD cohort. The trends in the incidence among the new user cohort were consistent with known risk factors for pneumonia.

5.3.3. Censoring

Table 8 presents the reasons for censoring among the final analysis cohort with the time until censoring presented in Table 9. New users in the final analysis cohort remained in the cohort for relatively short periods of time, averaging approximately 9 months among LABD new users and 1 year among ICS new users before a censoring event. The median time in the cohort for both the ICS and LABD new users was approximately 5 months. Censoring occurred at the first occurrence of a censoring event; therefore censoring groups are mutually exclusive. Pneumonia was the cause of censoring among 702 of the 18,047 new users of either ICS- or LABD drugs (545 of 11,555 ICS users and 157 of 6,492 LABD users). Among new users of LABDs, nearly 30% were censored according to our analysis plan due to the addition of an ICS or ICS/LABA.

Table 8 First Pneumonia Events and Censoring Information among the Final Analysis Cohort before PS Balancing

Event or Censoring	Cohort				Total Number of New Users
	ICS-Containing Medications		LABD Medications		
	n	%	n	%	N
Reason for censoring					
Pneumonia event	545	4.7	157	2.4	702
Death	586	5.1	204	3.1	790
Discontinuation of new use of therapy	8,630	74.7	2,999	46.2	11,629
Initiation of ICS or ICS/LABA	.	.	1,916	29.5	1,916
End of follow up in GPRD	312	2.7	123	1.9	435
End of follow up in HES	1,482	12.8	1,093	16.8	2,575
All	11,555	100.0	6,492	100.0	18,047

Table 9 Summary Statistics for Time until Event or Censoring among the Final Analysis Cohort before PS Balancing

Cohort	Variable	Statistic	Number of days	Number of years
ICS Containing Drugs	Time at risk	Mean	353.40	0.97
		Std Deviation	472.44	1.29
		Median	155.00	0.42
		Min	1.00	0.00
		Max	3,229.00	8.84
LABD Containing Drugs	Time at risk	Mean	285.79	0.78
		Std Deviation	352.57	0.97
		Median	145.00	0.40
		Min	1.00	0.00
		Max	3,116.00	8.53

5.4. Propensity Score Model

5.4.1. Effect of Covariates on Treatment

The propensity score model predicts the likelihood of being prescribed an ICS based on a patient's characteristics and is used to control for confounding by severity. The estimates of effect and maximum likelihood estimates of covariates on treatment used for propensity score generation are presented in Post-Text Table 17 and Post-Text Table 18, respectively. The most significant covariates in the propensity score model for the final analysis cohort ($p<0.1$ in Post-Text Table 18) included: age at cohort entry; male gender; cohort entry year; BMI (≥25-30); asthma or CHF diagnosis prior to cohort entry; influenza vaccination in baseline, SABD, statin, oxygen, or non-benzodiazepine use in baseline; dyspnea grade(Grade 2, 3, and 4); COPD severity (GOLD 0, I, III, and unknown); smoking status prior to cohort entry; number of emergency and non-emergency hospital admissions (1-2 admissions); and oral corticosteroid use.

The odds ratio estimates of the effect of covariates (descriptive characteristics; co-morbidities; medications and healthcare utilization) on ICS treatment utilized in propensity score generation are presented in Table 10, Table 11, and Table 12.

Table 10 Odds Ratio Estimates of Effects of the Descriptive Characteristics on Treatment for PS Model

Odds Ratio Estimates of Effect	Point Estimate	95% Wald Confidence Limits	
Age at Cohort Entry Date	0.992	0.988	0.996
Dyspnea			
Grade1	1.020	0.876	1.188
Grade2	0.828	0.743	0.921
Grade3	0.630	0.386	1.026
Grade4	0.637	0.397	1.023
Grade5	1.039	0.577	1.869
Clinically significant dyspnea diagnosis	1.080	0.654	1.782
Male vs. Female	0.909	0.849	0.973
Cohort Entry Year			
2003 vs. 2002	0.600	0.511	0.704
2004 vs. 2002	0.501	0.430	0.584
2005 vs. 2002	0.417	0.358	0.487
2006 vs. 2002	0.436	0.373	0.510
2007 vs. 2002	0.414	0.353	0.486
2008 vs. 2002	0.320	0.274	0.374
2009 vs. 2002	0.314	0.267	0.370
2010 vs. 2002	0.248	0.209	0.295
Smoking status prior to cohort entry date			
Ex vs. No	0.691	0.594	0.803
Yes vs. No	0.661	0.566	0.772
COPD severity			
Gold Stage 0 vs. 2	1.161	1.012	1.332

Odds Ratio Estimates of Effect		Point Estimate	95% Wald Confidence Limits	
Gold Stage	1 vs. 2	1.171	0.971	1.412
Gold Stage	3 vs. 2	1.113	0.994	1.246
Gold Stage	4 vs. 2	1.095	0.884	1.357
Gold Stage	Unknown vs. 2	1.367	1.254	1.491
BMI status prior to cohort entry date				
<18.5 vs. ≥18.5-25		0.903	0.778	1.047
≥25-30 vs. ≥18.5-25		1.133	1.045	1.228
≥30 vs. ≥18.5-25		1.061	0.968	1.163
No recording vs. 0		1.053	0.930	1.194
Townsend Deprivation quintile (Year 2001)				
Quintile	2 vs. 1	1.081	0.959	1.218
Quintile	3 vs. 1	1.098	0.958	1.258
Quintile	4 vs. 1	0.916	0.780	1.075
Quintile	5 vs. 1	0.918	0.754	1.117
IMD Deprivation quintile closest to cohort entry date				
Quintile	2 vs. 1	0.972	0.863	1.096
Quintile	3 vs. 1	0.899	0.784	1.031
Quintile	4 vs. 1	0.991	0.845	1.163
Quintile	5 vs. 1	0.994	0.820	1.205

Table 11 Odds Ratio Estimates of Effects of the Patient Co-morbidities on Treatment for PS Model

Odds Ratio Estimates of Effect	Point Estimate	95% Wald Confidence Limits	
Asthma diagnosis	1.394	1.269	1.531
Pneumonia episode in baseline period	0.920	0.561	1.509
Influenza Vaccination in baseline period	0.920	0.851	0.995
Pneumococcal Vaccination in (up to) 5 years	0.965	0.899	1.034
MI diagnosis	0.978	0.866	1.104
CHF diagnosis	0.822	0.727	0.930
CVD diagnosis	1.037	0.917	1.174
Dementia diagnosis	1.369	0.914	2.050
Peptic Ulcer diagnosis	0.926	0.822	1.044
Peripheral Vascular Disease diagnosis	0.982	0.877	1.099
Mild Liver Disease diagnosis	0.998	0.667	1.493
Moderate Liver Disease diagnosis	0.683	0.247	1.887
Connective Tissue Disorder diagnosis	0.966	0.824	1.133
Hemiplagia/Paraplegia diagnosis	1.572	0.849	2.911
Diabetes diagnosis	1.058	0.937	1.194
Diabetes (with complications) diagnosis	0.960	0.752	1.225
Cancer (non-metastatic solid tumours) diagnosis	1.011	0.901	1.136
Cancer (Metastatic solid tumours diagnosis) diagnosis	0.655	0.354	1.211
Renal Diseases diagnosis	1.018	0.906	1.144
Anxiety diagnosis or Anxiety prescription	1.046	0.965	1.134

Odds Ratio Estimates of Effect	Point Estimate	95% Wald Confidence Limits	
Depression diagnosis or Depression prescription	1.017	0.945	1.094
GERD diagnosis or GERD prescription	0.971	0.890	1.058
GERD diagnosis or GERD prescription in baseline period	1.055	0.961	1.159

1. Variables recorded in patient history "prior to cohort entry date" unless otherwise specified

Table 12 Odds Ratio Estimates of Effects of the Patient Medications Used and Healthcare Utilization on Treatment for PS Model

Odds Ratio Estimates of Effect	Point Estimate	95% Wald Confidence Limits	
Oxygen	0.762	0.574	1.012
Nebulized therapy	0.971	0.787	1.199
SABD	0.811	0.754	0.872
Theophylline	0.897	0.714	1.128
ACE-inhibitors	0.993	0.915	1.077
Statins	0.884	0.816	0.958
Immunosuppresants	0.961	0.719	1.285
Benzodiazepine	0.950	0.847	1.066
Non- benzodiazepine	0.871	0.748	1.014
Number of severe CAP episodes 1 vs 0	0.937	0.536	1.639
Count of GP visits			
1 vs. 0	1.002	0.918	1.094
2 vs. 0	1.045	0.945	1.156
3 vs. 0	0.962	0.851	1.087
4 vs. 0	1.024	0.902	1.162
Count of emergency hospital admissions			
1-2 vs. 0	1.321	1.204	1.448
>2 vs. 0	1.578	1.219	2.043
Count of non-emergency hospital admissions			
1-2 vs. 0	0.893	0.819	0.974
>2 vs. 0	0.965	0.776	1.201
Count of moderate COPD exacerbations			
1 vs. 0	1.034	0.958	1.117
≥2 vs. 0	1.067	0.875	1.301
Count of COPD hospitalizations ≥1 vs. 0	1.075	0.930	1.243
Oral Corticosteroid Use (Rx) ≥1 vs. 0	1.324	1.213	1.447
Oral Corticosteroid Use (>4 Rx)	0.579	0.470	0.714

1. Variables recorded in baseline period unless otherwise specified

The association of predicted probabilities and observed responses for the covariates are presented in Post-Text Table 19.

5.4.2. Hazard Ratios: Time to Pneumonia for Modeling

The hazard ratios for time to first pneumonia event (severe or non-severe) for the propensity score modeling by quintiles are presented in post-text Post-Text Table 20. The

hazard ratios for time to first severe hospitalized pneumonia event, defined as a severe pneumonia episode due to a HES episode (hospitalization) with pneumonia as a primary diagnosis during an episode of care within the HES episode and not censored for other reasons during the severe pneumonia episode before the primary diagnosis, by propensity score quintiles are presented in Post-Text Table 21. The hazard ratios for the severe (death or hospitalization) endpoint not censoring for prior non-severe pneumonia are presented in Post-Text Table 22. The hazard ratios for all pneumonia, severe pneumonia, and severe hospitalized pneumonia by propensity score strata and deciles were additionally calculated [data not shown].

5.4.3. Propensity Score Distribution and Weighting Graphs

The distribution of propensity scores by exposure (not exposed or exposed to an ICS) and the combined propensity score weights are presented in Post-Text Table 23. Figure 6 graphically represents the distribution of the propensity scores. The distribution of the ICS exposed patients is shifted right, as would be expected, with a greater percentage of individuals with higher propensity scores.

Figure 6 PS Distribution for Final Analysis Before PS Balancing

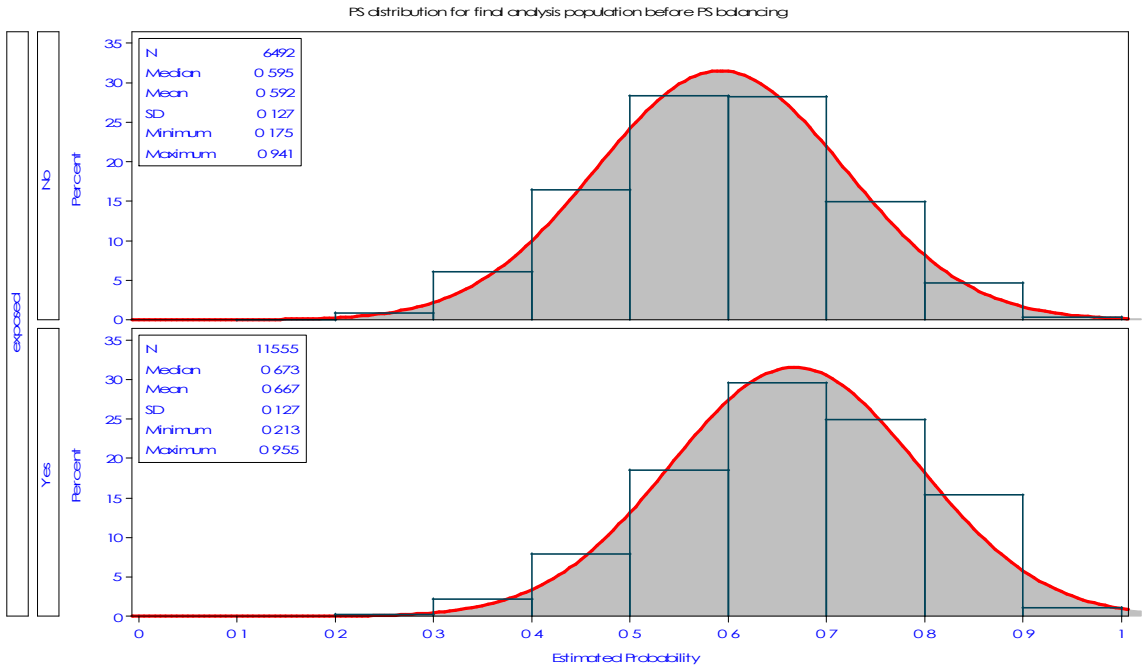
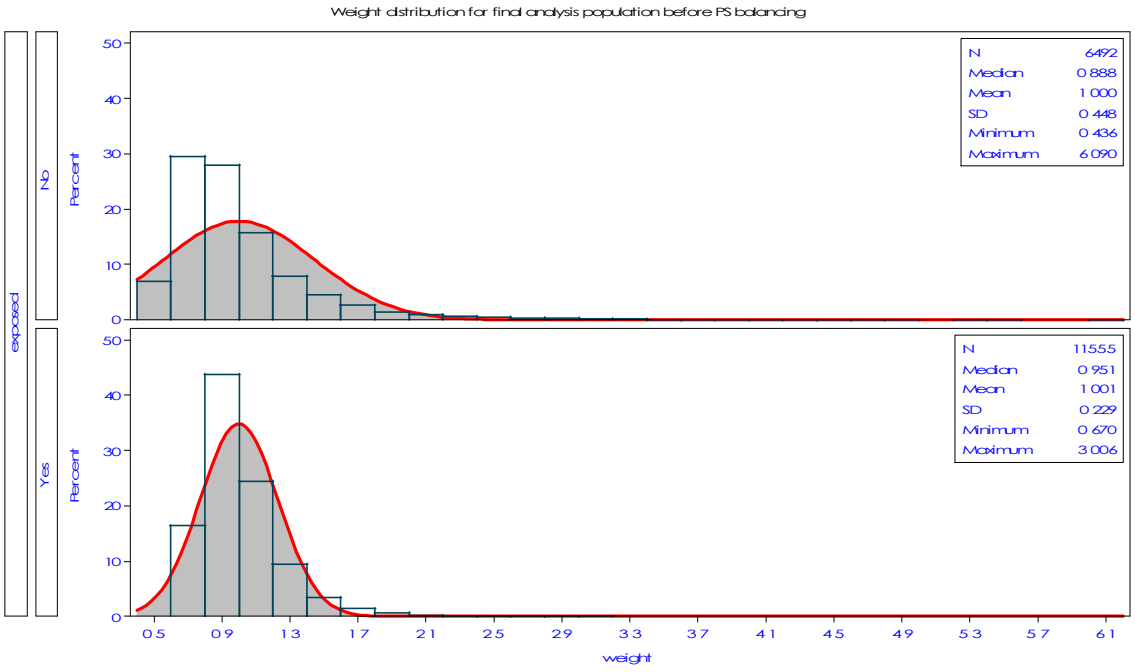


Figure 7 represents the distribution of the propensity score weights. There were no patients with scores in the tails of the distribution that were not represented in both groups, therefore no patients were eliminated from the analysis due to outlier propensity scores.

Figure 7 Weight Distribution for Final Analysis Before PS Balancing



5.5. Final Analysis Cohort after Propensity Score Balancing

One analysis method matches patients in the exposure cohorts based on propensity score. New users were matched 1:1 based on propensity score. Data on the feasibility of the matched analysis cohort after propensity score balancing are presented in the post-text tables including estimates of the number of new users meeting inclusion/exclusion criterion by cohort entry year (Post-Text Table 24), number of first pneumonia events by type regardless of censoring (Post-Text Table 25), and number of events causing censoring (Post-Text Table 26).

5.5.1. Matched Cohort Demographics after Propensity Score Balancing

Propensity score matching results in smaller cohorts of patients (n=6,201 new users for each ICS-containing and LABD), but eliminates covariate imbalances between the cohorts. Characteristics of matched cohort of COPD patients after propensity score balancing are presented in Table 13. After matching, imbalances in covariates such as asthma diagnosis, clinically significant dyspnea, and smoking status were no longer present.

Table 13 Descriptive Characteristics from the Baseline Period (year before cohort entry)/Patient History for the Matched Cohort after Propensity Score Balancing

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=6,201	%	n=6,201	%	
Male	3,633	58.6	3,589	57.9	0.42
Age at cohort entry date					
45-64 yrs	1,897	30.6	1,889	30.5	0.10
65-79 yrs	3,061	49.4	3,155	50.9	.
>=80 yrs	1,243	20.0	1,157	18.7	.
Smoking status prior to cohort entry date					
No	283	4.6	278	4.5	0.96
Yes	2,750	44.3	2,763	44.6	.
Ex	3,168	51.1	3,160	51.0	.
COPD severity					
COPD Dx but spirometry conflicts	154	2.5	163	2.6	1.00
Restrictive COPD	475	7.7	469	7.6	.
GOLD I	213	3.4	214	3.5	.
GOLD II	1,381	22.3	1,382	22.3	.
GOLD III	883	14.2	864	13.9	.
GOLD IV	163	2.6	167	2.7	.
Unknown	2,932	47.3	2,942	47.4	.
Clinically significant dyspnea diagnosis	865	13.9	894	14.4	0.46
Asthma diagnosis prior to cohort entry date	770	12.4	769	12.4	0.98
Pneumonia episode in baseline period	110	1.8	114	1.8	0.79
Number of non-severe CAP episodes in baseline period					
0	6,177	99.6	6,178	99.6	0.58
1	24	<1	22	<1	.
2	0	<1	1	<1	.
Number of severe CAP episodes in baseline period					
0	6,112	98.6	6,111	98.5	0.90
1	87	1.4	87	1.4	.
2	2	<1	3	<1	.
Number of HAP pneumonia episodes in baseline period					
0	6,200	100.0	6,198	100.0	0.32
1	1	<1	3	<1	.
Townsend Deprivation quintile (Year 2001)					
Quintile 1(Least deprived)	932	15.0	927	14.9	0.79
Quintile 2	1,215	19.6	1,181	19.0	.
Quintile 3	1,323	21.3	1,319	21.3	.
Quintile 4	1,501	24.2	1,559	25.1	.
Quintile 5 (Most deprived)	1,230	19.8	1,215	19.6	.

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=6,201	%	n=6,201	%	
IMD Deprivation quintile closest to cohort entry date					
Quintile 1(Least deprived)	875	14.1	858	13.8	0.88
Quintile 2	1,210	19.5	1,174	18.9	.
Quintile 3	1,257	20.3	1,271	20.5	.
Quintile 4	1,413	22.8	1,447	23.3	.
Quintile 5 (Most deprived)	1,446	23.3	1,451	23.4	.

Table 14 summarizes the co-morbidities of the final analysis cohort after propensity score balancing. The ICS and LABD users were similar regarding vaccination status in the matched cohort.

Table 14 Patient Co-morbidities in the Baseline Period (year before cohort entry)/Patient History for the Final Analysis Cohort after PS Balancing

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=6,201	%	n=6,201	%	
Influenza Vaccination in baseline period	4,321	69.7	4,284	69.1	0.47
Pneumococcal Vaccination in (up to) 5 years prior to cohort entry date	2,565	41.4	2,532	40.8	0.55
BMI status					
No recording	472	7.6	467	7.5	0.90
Underweight (0< - <18.5)	343	5.5	341	5.5	.
Low Normal (18.5 - <21)	616	9.9	638	10.3	.
High Normal (21 - <25)	1,650	26.6	1,595	25.7	.
Overweight (25 - <30)	1,797	29.0	1,813	29.2	.
Obese (≥30)	1,323	21.3	1,347	21.7	.
MI diagnosis	532	8.6	548	8.8	0.61
CHF diagnosis	540	8.7	531	8.6	0.77
CVD diagnosis	483	7.8	474	7.6	0.76
Dementia diagnosis	39	<1	36	<1	0.73
GERD diagnosis or GERD prescription	3,062	49.4	3,083	49.7	0.71
Peptic Ulcer diagnosis	512	8.3	518	8.4	0.85
Peripheral Vascular Disease diagnosis	598	9.6	590	9.5	0.81
Mild Liver Disease diagnosis	39	<1	42	<1	0.74
Moderate Liver Disease diagnosis	9	<1	8	<1	0.81
Connective Tissue Disorder diagnosis	330	5.3	331	5.3	0.97
Hemiplagia/Paraplegia diagnosis	16	<1	15	<1	0.86
Diabetes diagnosis	673	10.9	669	10.8	0.91
Diabetes (with complications) diagnosis	132	2.1	138	2.2	0.71

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=6,201	%	n=6,201	%	
Anxiety diagnosis or Anxiety prescription	1,781	28.7	1,776	28.6	0.92
Depression diagnosis or Depression prescription	2,744	44.3	2,768	44.6	0.66
Cancer (non-metastatic solid tumours) diagnosis	541	8.7	550	8.9	0.78
Cancer (Metastatic solid tumours) diagnosis	15	<1	18	<1	0.60
Renal Diseases diagnosis	628	10.1	639	10.3	0.74

1. Variables recorded in patient history "prior to cohort entry date" unless otherwise specified

Patient medications used and healthcare utilization at baseline in the matched final analysis cohort after propensity score balancing are summarized in Table 15.

Table 15 Patient Medications Used and Healthcare Utilization in the Baseline Period (year before cohort entry) for the Final Analysis Cohort after PS Balancing

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=6,201	%	n=6,201	%	
Oral Corticosteroids (>4 Rx)	206	3.3	202	3.3	0.84
Oxygen	90	1.5	84	1.4	0.65
Nebulized therapy	176	2.8	159	2.6	0.35
SABD	4,534	73.1	4,488	72.4	0.35
Theophylline	134	2.2	126	2.0	0.62
ACE-inhibitors	1,654	26.7	1,643	26.5	0.82
Statins	2,185	35.2	2,207	35.6	0.68
Immunosuppresants	93	1.5	88	1.4	0.71
Count of GP visits					
0	66	1.1	43	<1	0.26
1-5	1,426	23.0	1,464	23.6	.
6-10	1,986	32.0	2,012	32.4	.
11-15	1,269	20.5	1,279	20.6	.
15-20	729	11.8	705	11.4	.
≥21	725	11.7	698	11.3	.
Count of emergency hospital admissions					
0	5,098	82.2	5,100	82.2	0.98
1-2	1,003	16.2	1,004	16.2	.
≥3	100	1.6	97	1.6	.
Count of non-emergency hospital admissions					
0	4,956	79.9	4,950	79.8	0.61
1-2	1,117	18.0	1,107	17.9	.
≥3	128	2.1	144	2.3	.
Count of moderate COPD exacerbations					
0	4,032	65.0	4,052	65.3	0.93
1	1,562	25.2	1,545	24.9	.

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=6,201	%	n=6,201	%	
≥2	607	9.8	604	9.7	.
Count of COPD hospitalizations					
0	5,845	94.3	5,850	94.3	0.85
1	319	5.1	310	5.0	.
≥2	37	<1	41	<1	.

1. Variables recorded in baseline period unless otherwise specified

5.5.2. Incidence after Propensity Score Balancing

The adjusted incidence rate of first pneumonia episode (either sever or non-severe) by exposure cohort and key covariates among the matched cohort after propensity score balancing are presented in Post-Text Table 27.

5.5.3. Censoring

Table 16 and Post-Text Table 28 present the number of censoring events and time till censoring among the matched final analysis cohort. The mean and median time till censoring for each exposure cohort in the matched final analysis population was similar to before propensity score balancing. 436 pneumonia events were observed among the 12,402 new users in the matched final analysis population.

Table 16 First Pneumonia Events and Censoring Information among the Final Analysis Cohort after PS Balancing

Event or Censoring	Cohort				Total Number of New Users
	ICS Containing Medications		LABD Containing Medications		
	n	%	n	%	n
Reason for censoring					
Pneumonia event	286	4.6	150	2.4	436
Death	323	5.2	199	3.2	522
Discontinuation of new use of therapy	4,323	69.7	2,902	46.8	7,225
Initiation of ICS or ICSLABA	.	.	1,870	30.2	1,870
End of follow up in GPRD	168	2.7	117	1.9	285
End of follow up in HES	1,101	17.8	963	15.5	2,064
All	6,201	100.0	6,201	100.0	12,402

5.5.4. Hazard Ratio: Time to First and First Severe Pneumonia

The hazard of time to first pneumonia, first severe hospitalized pneumonia, and first severe pneumonia were calculated utilizing four propensity score modeling methods: inverse probability of treatment weights (IPTW), propensity scoring by deciles, propensity scoring by quintiles, and matched propensity scores. The hazard ratios

utilizing the IPTW, quintiles, and deciles methods are presented in Table 22 and based on the matched method in Table 23.

Based on the IPTW, an increased, statistically significant hazard was observed for time to first pneumonia event (HR=1.49, 95% CI: 1.22-1.83), first severe pneumonia [death or hospitalization, not censoring for prior non-severe pneumonia(s)] (HR=1.57, 95% CI: 1.28-1.92), first hospitalized pneumonia (HR=1.52, 95% CI: 1.16-1.98), and first hospitalized pneumonia with pneumonia as the primary cause on the first episode of care (HR=1.55, 95% CI:1.14-2.10). These increased hazards were observed across propensity score methods. Figure 8, Figure 9, and Figure 10 are the survival plots for first pneumonia, first hospitalized pneumonia, and first severe pneumonia respectively. The survival plots show the time to first pneumonia event by LABD vs. ICS-containing cohorts. As exposure time increases more subjects in the ICS exposed cohort experience pneumonia events as compared to the LABD cohort. Initiation of ICS or ICS/LABA was a censoring event in this study, therefore patients that began ICS or ICS/LABA therapy would be censored before any potential pneumonia events and are not represented in these plots.

Figure 8 Survival Plot: Time to First Pneumonia

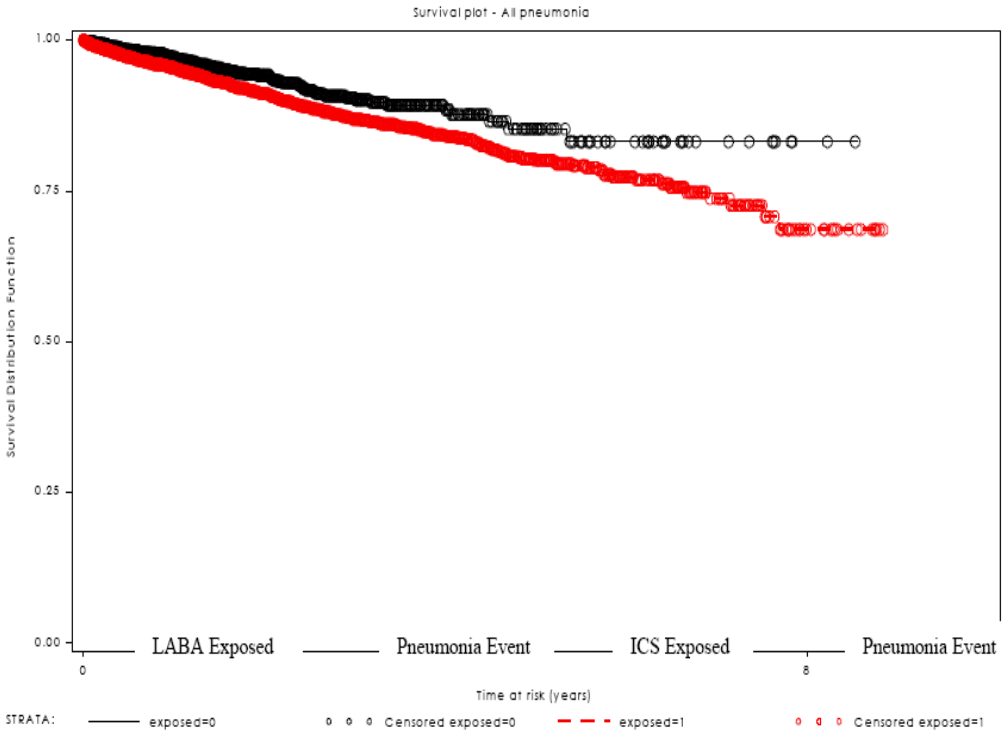


Figure 9 Survival Plot: Time to First Hospitalized Pneumonia

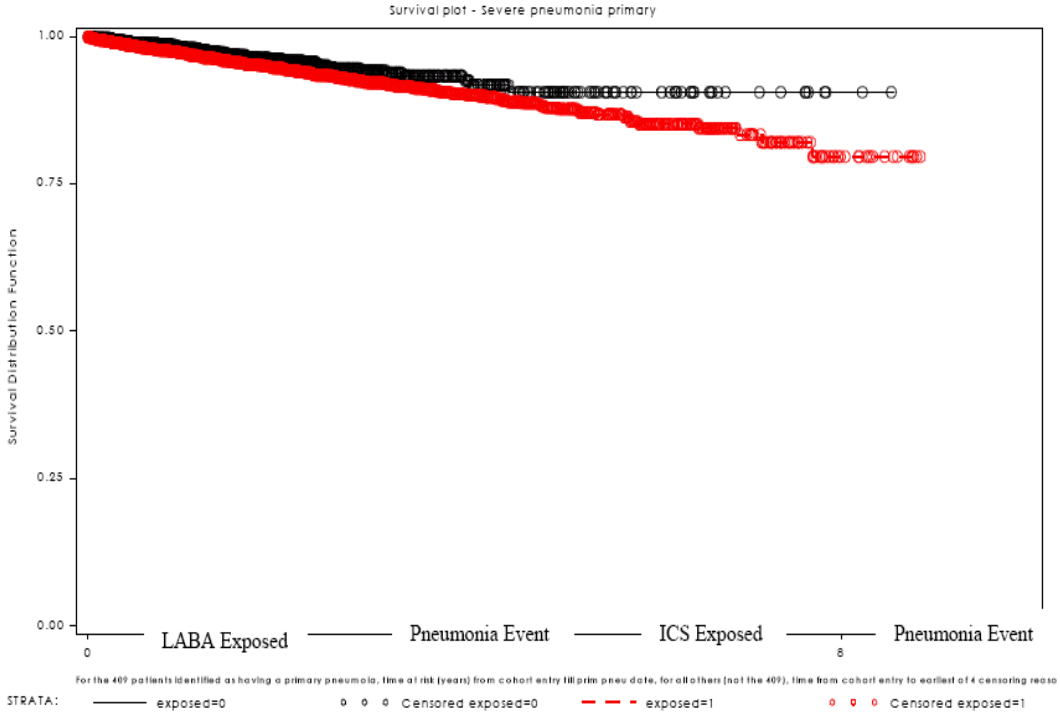
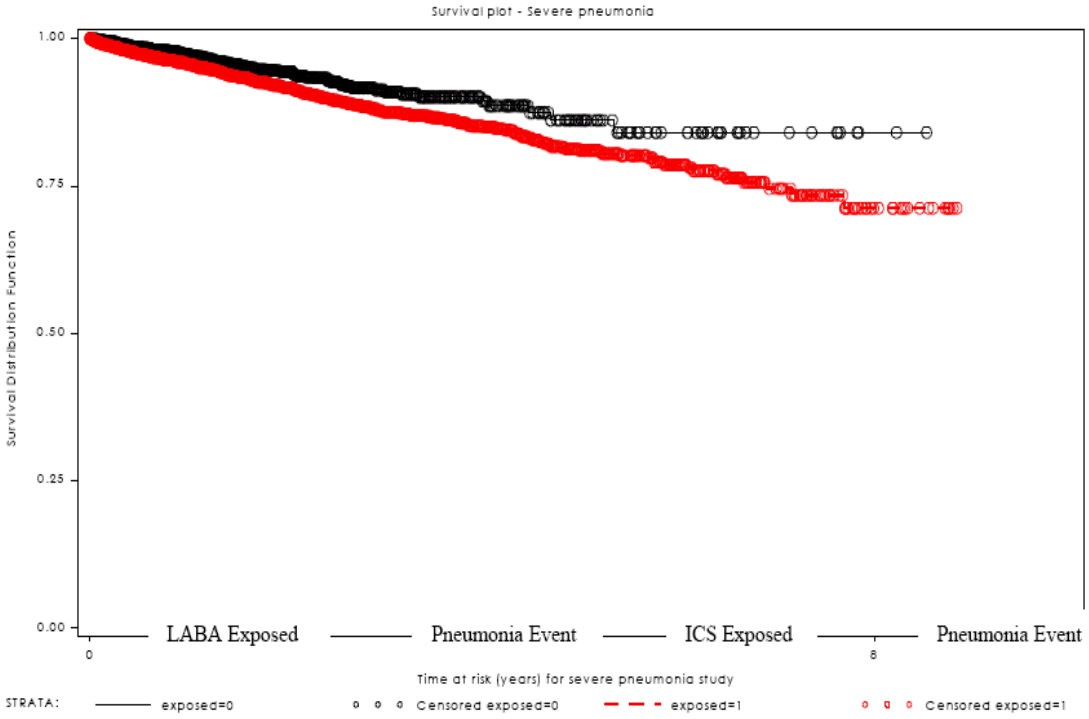


Figure 10 Survival Plot: Time to First Severe Pneumonia



5.6. Persistent New Users Treated for 6 Months or More

Data on the feasibility of the final analysis cohort of persistent new users prescribed treatment for greater than 6 months (allowing for 90-day gaps between treatments as each inhaler can last up to 90 days) before propensity score balancing are presented in the post-text tables including estimates of the number of new users meeting inclusion/exclusion criterion by cohort entry year (Post-Text Table 29). 9,396 new users in the final analysis cohort were prescribed treatment for 6 months or longer, including 5,549 new ICS users and 3,847 new LABD users. Additionally, data on the number of first pneumonia events by type before propensity score balancing regardless of censoring (Post-Text Table 30) and causing censoring (Post-Text Table 31) are presented in the post-text tables.

5.6.1. Persistent User Cohort Demographics before PS Balancing

Characteristics of final analysis cohort of persistent users before propensity score balancing are presented in Table 17 by exposure cohort. The imbalances between the exposure cohorts regarding smoking status, clinically significant dyspnea, COPD severity, and asthma diagnosis that were present in the whole final analysis population remained in the persistent user population.

Table 17 Descriptive Characteristics from the Baseline Period (year before cohort entry)/Patient History for the Final Analysis Cohort of Persistent Users before PS Balancing

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=5,549	%	n=3,847	%	
Male	3,071	55.3	2,219	57.7	0.02
Age at cohort entry date					
45-64 yrs	1,757	31.7	1,133	29.5	0.02
65-79 yrs	2,756	49.7	2,017	52.4	.
>=80 yrs	1,036	18.7	697	18.1	.
Smoking status prior to cohort entry date					
No	328	5.9	144	3.7	<0.01
Yes	2,482	44.7	1,690	43.9	.
Ex	2,739	49.4	2,013	52.3	.
COPD severity					
COPD Dx but spirometry conflicts	127	2.3	90	2.3	<0.01
Restrictive COPD	380	6.8	267	6.9	.
GOLD I	154	2.8	124	3.2	.
GOLD II	955	17.2	918	23.9	.
GOLD III	749	13.5	622	16.2	.
GOLD IV	161	2.9	117	3.0	.
Unknown	3,023	54.5	1,709	44.4	.
Clinically significant dyspnea diagnosis	553	10.0	701	18.2	<0.01
Asthma diagnosis prior to cohort entry date	893	16.1	431	11.2	<0.01

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=5,549	%	n=3,847	%	
Pneumonia episode in baseline period	112	2.0	62	1.6	0.15
Number of non-severe CAP episodes in baseline period					
0	5,529	99.6	3,832	99.6	0.82
1	20	<1	15	<1	.
Number of severe CAP episodes in baseline period					
0	5,455	98.3	3,801	98.8	0.15
1	92	1.7	45	1.2	.
2	2	<1	1	<1	.
Number of HAP episodes in baseline period					
0	5,548	100.0	3,845	99.9	0.36
1	1	<1	2	<1	.
Townsend Deprivation quintile (Year 2001)					
Quintile 1(Least deprived)	840	15.1	604	15.7	0.04
Quintile 2	1,129	20.3	726	18.9	.
Quintile 3	1,225	22.1	782	20.3	.
Quintile 4	1,315	23.7	981	25.5	.
Quintile 5 (Most deprived)	1,040	18.7	754	19.6	.
IMD Deprivation quintile closest to cohort entry date					
Quintile 1(Least deprived)	776	14.0	524	13.6	0.68
Quintile 2	1,113	20.1	732	19.0	.
Quintile 3	1,112	20.0	797	20.7	.
Quintile 4	1,274	23.0	889	23.1	.
Quintile 5 (Most deprived)	1,274	23.0	905	23.5	.

Table 18 summarizes the co-morbidities of the persistent user cohort before propensity score balancing. As in the full final analysis population, persistent new users of LABD drugs tended to have higher vaccination rates.

Table 18 Patient Co-morbidities in the Baseline Period (year before cohort entry)/Patient History for the Final Analysis Cohort of Persistent Users before PS Balancing

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=5,549	%	n=3,847	%	
Influenza Vaccination in baseline period	3,759	67.7	2,738	71.2	<0.01
Pneumococcal Vaccination in (up to) 5 years prior to cohort entry date	2,139	38.5	1,630	42.4	<0.01
BMI status					
No recording	501	9.0	272	7.1	<0.01
Underweight (0< - <18.5)	274	4.9	202	5.3	.
Low Normal (18.5 - <21)	562	10.1	373	9.7	.
High Normal (21 - <25)	1,418	25.6	1,007	26.2	.
Overweight (25 - <30)	1,663	30.0	1,129	29.3	.
Obese (≥30)	1,131	20.4	864	22.5	.
MI diagnosis	444	8.0	338	8.8	0.18
CHF diagnosis	444	8.0	315	8.2	0.74
CVD diagnosis	445	8.0	284	7.4	0.26
Dementia diagnosis	50	<1	17	<1	<0.01
GERD diagnosis or GERD prescription	2,592	46.7	1,892	49.2	0.02
Peptic Ulcer diagnosis	424	7.6	325	8.4	0.16
Peripheral Vascular Disease diagnosis	480	8.7	375	9.7	0.07
Mild Liver Disease diagnosis	39	<1	26	<1	0.88
Moderate Liver Disease diagnosis	3	<1	3	<1	0.65
Connective Tissue Disorder diagnosis	274	4.9	205	5.3	0.40
Hemiplagia/Paraplegia diagnosis	22	<1	10	<1	0.26
Diabetes diagnosis	550	9.9	419	10.9	0.12
Diabetes (with complications) diagnosis	108	1.9	87	2.3	0.29
Anxiety diagnosis or Anxiety prescription	1,561	28.1	1,090	28.3	0.83
Depression diagnosis or Depression prescription	2,427	43.7	1,703	44.3	0.61
Cancer (non-metastatic solid tumours) diagnosis	411	7.4	305	7.9	0.35
Cancer (Metastatic solid tumours) diagnosis	8	<1	11	<1	0.13
Renal Diseases diagnosis	474	8.5	429	11.2	<0.01

1. Variables recorded in patient history "prior to cohort entry date" unless otherwise specified

Patient medications and healthcare utilization at baseline in the persistent user cohort before propensity score balancing are summarized in Table 19, with trends similar to the full final analysis population.

Table 19 Patient Medications Used and Healthcare Utilization Baseline Period (year before cohort entry) for the Persistent User Cohort before PS Balancing

Variable	Cohort				p-value
	ICS-Containing Medications		LABD Medications		
	n=5,549	%	n=3,847	%	
Oral Corticosteroids (>4 Rx)	160	2.9	120	3.1	0.51
Oxygen	81	1.5	47	1.2	0.33
Nebulized therapy	204	3.7	88	2.3	<0.01
SABD	4,078	73.5	2,884	75.0	0.11
Theophylline	129	2.3	79	2.1	0.38
ACE-inhibitors	1,449	26.1	1,084	28.2	0.03
Statins	1,726	31.1	1,458	37.9	<0.01
Immunosuppresants	55	<1	58	1.5	0.02
Count of GP visits					
0	55	<1	27	<1	0.23
1-5	1,243	22.4	925	24.0	.
6-10	1,829	33.0	1,272	33.1	.
11-15	1,216	21.9	801	20.8	.
15-20	597	10.8	422	11.0	.
≥21	609	11.0	400	10.4	.
Count of emergency hospital admissions					
0	4,228	76.2	3,220	83.7	<0.01
1-2	1,219	22.0	582	15.1	.
≥3	102	1.8	45	1.2	.
Count of non-emergency hospital admissions					
0	4,551	82.0	3,093	80.4	0.13
1-2	888	16.0	676	17.6	.
≥3	110	2.0	78	2.0	.
Count of moderate COPD exacerbations					
0	3,378	60.9	2,548	66.2	<0.01
1	1,484	26.7	942	24.5	.
≥2	687	12.4	357	9.3	.
Count of COPD hospitalizations					
0	5,171	93.2	3,637	94.5	<0.01
1	349	6.3	185	4.8	.
≥2	29	<1	25	<1	.

1. Variables recorded in baseline period unless otherwise specified

5.6.2. Censoring before PS Balancing

507 pneumonia events occurred among the persistent new users and 38% of the patients initiating LABD drugs were censored due to the initiation of ICS or ICS/LABA therapy (Table 20). Compared to the full final analysis population, the persistent new users remained in the cohort longer (mean time at risk), approximately 1 year and 9 months

among persistent new ICS users, and 1 year and 2 months among persistent new LABD users, with medians of approximately 1 year and 1 month, and 10 months respectively, before censoring (Table 21).

Table 20 First Pneumonia Events and Censoring Information among the Persistent User Cohort before PS Balancing

Event or Censoring	Cohort				Total Number of New Users
	ICS Containing Medications		LABD Containing Medications		
	n	%	N	%	n
Reason for censoring (hierarchically applied, one reason per patient)					
Pneumonia event	386	7.0	121	3.1	507
Death	390	7.0	123	3.2	513
Discontinuation of new use of therapy	3,182	57.3	1,088	28.3	4,270
Initiation of ICS or ICS/LABA	.	.	1,462	38.0	1,462
End of follow up in GPRD	221	4.0	86	2.2	307
End of follow up in HES	1,370	24.7	967	25.1	2,337
All	5,549	100.0	3,847	100.0	9,396

Table 21 Summary Statistics for Time until Event or Censoring among the Final Analysis Cohort before PS Balancing

Cohort	Variable	Statistic	Number of days	Number of years
ICS Containing Drugs	Time at risk	Mean	623.16	1.71
		Std Deviation	568.95	1.56
		Median	401.00	1.10
		Min	1.00	0.00
		Max	3,229.00	8.84
LABD Containing Drugs	Time at risk	Mean	418.50	1.15
		Std Deviation	406.82	1.11
		Median	294.00	0.80
		Min	1.00	0.00
		Max	3,116.00	8.53

5.6.3. Propensity Score Generation

Propensity scores were generated for the persistent user cohort utilizing the same methodology as the primary analysis [data not shown]. The hazard ratios for time to first pneumonia event (severe or non-severe) for modelling by propensity score quintiles among persistent users are presented in Post-Text Table 32 and for first hospitalized pneumonia event by propensity score quintiles in Post-Text Table 33. The hazard ratios for the severe (death or hospitalization) endpoint not censoring for prior non-severe pneumonia are presented in Post-Text Table 34. The hazard ratios for all pneumonia, severe pneumonia, and hospitalized pneumonia by strata and deciles were additionally calculated [data not shown].

5.6.4. Matched Persistent User Cohort after Propensity Score Balancing

Data on the feasibility of the matched analysis cohort (n=6,674 new users matched 1:1) of persistent users after propensity score balancing are presented in the post-text tables including estimates of the number of new users meeting inclusion/exclusion criterion by cohort entry year (Post-Text Table 35), number of first pneumonia events by type regardless of censoring (Post-Text Table 36), and number of events causing censoring (Post-Text Table 37).

Characteristics, co-morbidities, and patient medications/ healthcare used of the matched cohort of persistent users after propensity score balancing are presented in Post-Text Table 38, Post-Text Table 39, and Post-Text Table 40, respectively.

5.6.5. Censoring after Propensity Score Balancing

The matched cohort of persistent users included 6,674 new users (matched 1:1) with 319 pneumonia events causing censoring and 40% of LABD new users initiating ICS or ICS/LABA resulting in censoring (Post-Text Table 41). The time to censoring event among the matched persistent user cohort was similar to the full persistent user cohort (Post-Text Table 42).

5.6.6. Hazard Ratio: Time to First and First Severe Pneumonia among Persistent Users

The hazard of time to first pneumonia, first severe hospitalized pneumonia, and first severe pneumonia were calculated utilizing the inverse probability of treatment weights (IPTW), propensity scoring by deciles, propensity scoring by quintiles, and matched propensity scores. The hazard ratios utilizing the IPTW, quintiles, and deciles methods are presented in Table 22 and based on the matched method in Table 23. Increased hazards of time to first pneumonia (HR=1.19, 95% CI: 0.93-1.52), severe pneumonia (HR=1.22, 95% CI: 0.97-1.55), hospitalized pneumonia (HR=1.24, 95% CI: 0.93-1.65), and first hospitalized pneumonia with pneumonia as the primary cause on the first episode of care (HR=1.23, 95% CI:0.89-1.72) were observed, through smaller increased hazards compared to the primary analysis and not consistently statistically significant across propensity score methodologies.

5.7. New Users by Dose

The new user final analysis population (n=11,555 ICS; n=6,492 LABD) was additionally examined based on dose. The strength of the new user prescribed ICS medication on the Cohort Entry Date was categorized into equipotent doses of low, medium, and high-dose ICS based on classification according to Figure 3-1 presented in the Global Initiative for Asthma (GINA) guidelines [GINA, 2011]. The strength of the new user prescription was entered into the Cox model primary outcome models as low, medium, and high relative to LABD (e.g. dummy variables). The strength of the medication was tabulated based on the prescription on the Cohort Entry Date. Approximately 20% of new ICS users initiated

high dose ICS therapy (n=2,176), with equal proportions 40% each initiating medium dose (n=4,545) and low dose (n=4,834) therapy.

5.7.1. Propensity Score Generation

Propensity scores were generated for the new user final analysis cohort by dose utilizing the same methodology as the primary analysis [data not shown]. The hazard ratios by propensity score quintile for time to first pneumonia event (severe or non-severe) for the model of high, not high, medium, and low dose among the final analysis cohort are presented in Post-Text Table 43, Post-Text Table 44, Post-Text Table 45, and Post-Text Table 46, respectively, The hazard ratios for all pneumonia by strata and deciles for each of the exposure dose levels were additionally calculated by strata and deciles [data not shown]. Hazard ratios for hospitalized and severe pneumonia by propensity score quintiles, deciles, and strata were calculated for modelling [data not shown].

5.7.2. Hazard Ratio: Time to First Pneumonia by Dose among New Users

The hazards of time to first pneumonia among new users in the final analysis cohort by dose at cohort entry date were calculated utilizing the IPTW, propensity scoring by deciles, propensity scoring by quintiles, and matched propensity scores methods. The hazard ratios for time to first pneumonia, severe pneumonia, hospitalized pneumonia and hospitalized pneumonia with pneumonia as the primary cause on the first episode of care utilizing the IPTW, quintiles, and deciles methods are presented in Table 22 and based on the matched method in Table 23. Increased hazard of pneumonia was observed in a potential dose related trend for first pneumonia, along with first hospitalized (both definitions) and severe pneumonia.

5.8. Persistent Users by Dose

The persistent user cohort (n=5,549 ICS; n=6,492 LABD) was also examined based on dose. The strength of the persistent user prescribed ICS medication on the Cohort Entry Date was categorized into equipotent doses of low, medium, and high-dose ICS based relative to LABD, as described in section 5.7. The distribution of ICS dose among persistent users was similar to the distribution among the full analysis cohort. Approximately 23% of new ICS users initiated high dose ICS therapy (n=1,247), 41% initiated medium dose therapy (n=2,252) and 36% low dose therapy (n=2,023).

5.8.1. Propensity Score Generation

Propensity scores were generated for the persistent user cohort [data not shown] by dose utilizing the same methodology as the primary analysis. The hazard ratios by quintile for time to first pneumonia event (severe or non-severe) for the propensity score model of high, not high, medium, and low dose among the persistent user cohort are presented in Post-Text Table 47, Post-Text Table 48, Post-Text Table 49, and Post-Text Table 50, respectively. The hazard ratios for all pneumonia by strata and deciles for each of the exposure dose levels were additionally calculated by strata and deciles [data not shown].

Hazard ratios for hospitalized and severe pneumonia by propensity score quintiles, deciles, and strata were calculated for modelling [data not shown].

5.8.2. Hazard Ratio: Time to Pneumonia among Persistent Users by Dose

The hazards of time to first pneumonia, first hospitalized pneumonia (both definitions), and first severe pneumonia among persistent new users by dose at cohort entry date were calculated utilizing the four methods described previously. The hazard ratios utilizing the IPTW, quintiles, and deciles methods are presented in Table 22 and utilizing the matched method in Table 23. Hazard ratios increased with dose for first, severe, and hospitalized (both definitions) pneumonia among the persistent user cohort, though not statistically significant and with smaller magnitudes as compared to the dose analysis among the full new user population.

5.9. New User Cohort: 2005-2010

The original analysis period was set to begin in 2005 since reimbursement for of lung function testing began in the UK in 2005 and ADVAIR was approved for a COPD indication by this date. Considering these time trends and the originally proposed analysis, the primary propensity score model was run utilizing the data from 2005-2010, including 6,937 new ICS users and 5,000 new LABD users.

5.9.1. Propensity Score Generation

Propensity scores were generated for the new user final analysis cohort [data not shown] restricted to new users between 2005 and 2010 utilizing the same methodology as the primary analysis. The hazard ratios by propensity score quintiles for time to first pneumonia event (severe or non-severe) among 2005-2010 new users are presented in Post-Text Table 51. The hazard ratios for all pneumonia by strata and deciles were additionally calculated [data not shown]. Hazard ratios for hospitalized and severe pneumonia by propensity score quintiles, deciles, and strata were calculated for modelling [data not shown].

5.9.2. Hazard Ratio: Time to First and First Severe Pneumonia among New Users from 2005-2010

As with the primary analysis, time to first pneumonia, first hospitalized (both definitions) pneumonia, and first severe pneumonia among 2005-2010 new users was calculated using four propensity scoring methods. The hazard ratios utilizing the IPTW, quintiles, and deciles methods are presented in Table 22 and based on the matched method in Table 23. Increased hazard of time to first pneumonia, first hospitalized pneumonia (both definitions), and first severe pneumonia were observed.

5.10. New Users of at least 30 Days

New use of an ICS-containing or LABD medication could be an indication of a patient's declining health and a pneumonia occurring within 30 days of therapy initiation may not be related to therapy, therefore new users with at least 30 days of therapy were analyzed. Requiring at least 30 days of use reduced the number of new users by ~2% to 11,333 from 11,555 and the number of overall pneumonia events (severe or non-severe) by ~13% to 472 from 545.

5.10.1. Propensity Score Generation

Propensity scores were generated for the new user final analysis with at least 30 days of therapy [data not shown] utilizing the same methodology as the primary analysis. The hazard ratios for time to first pneumonia event (severe or non-severe) by propensity score quintiles are presented in Post-Text Table 54. The hazard ratios for all pneumonia by strata and deciles were additionally calculated [data not shown]. Hazard ratios for hospitalized and severe pneumonia by propensity score quintiles, deciles, and strata were calculated for modelling [data not shown].

5.10.2. Hazard Ratio: Time to First and First Severe Pneumonia among New Users of at least 30 Days

The hazards of time to first, first hospitalized (both definitions), and first severe pneumonia among new users by device were calculated utilizing the four propensity scoring methods. The hazard ratios utilizing the IPTW, quintiles, and deciles methods are presented in Table 22 and based on the matched method in Table 23. Statistically significant increased hazards in the time to first pneumonia, first hospitalized pneumonia (both definitions), and first severe pneumonia were observed, though the magnitudes of the hazards were smaller than the primary analysis.

5.11. New User Cohort by Device

The new user final analysis population (n=11,555 ICS; n=6,492 LABD) was additionally examined based on device. New users of ICS were categorized as initiating ICS monotherapy or ICS combination therapy within a single device, ICS/LABA patients. Approximately 40% (n=4,744) of new ICS users initiated ICS monotherapy and 60% (n=6,811) initiated ICS/LABA in a fixed dose combination.

5.11.1. Propensity Score Generation

Propensity scores were generated for the new user final analysis cohort by device [data not shown] utilizing the same methodology as the primary analysis. The hazard ratios for time to first pneumonia event (severe or non-severe) for the propensity score model by quintile among patients initiating ICS monotherapy and ICS/LABA combination therapy are presented in Post-Text Table 52 and Post-Text Table 53, respectively. The hazard ratios for all pneumonia for both ICS monotherapy and ICS combination therapy new users by strata and deciles were additionally calculated [data not shown]. Hazard ratios

for hospitalized and severe pneumonia by propensity score quintiles, deciles, and strata were calculated for modelling [data not shown].

5.11.2. Hazard Ratio: Time to First and First Severe Pneumonia among New Users by Device

The hazards of time to first pneumonia among new users by device were calculated utilizing the four propensity scoring methods. The hazard ratios utilizing the IPTW, quintiles, and deciles methods are presented in Table 22 and based on the matched method in Table 23. Increased hazard in the time to first pneumonia, first hospitalized pneumonia (both definitions), and first severe pneumonia were observed for both ICS monotherapy and ICS combination therapy new users across propensity scoring methods. For all pneumonia outcomes, the hazards were greater for new users exposed to ICS/LABA at baseline as compared to ICS monotherapy.

5.12. Hazard Ratio Summary: Time to First, First Hospitalized, and First Severe Pneumonia Associated with initiating ICS-containing vs LABD Medication

Table 22 Hazard Ratio and 95% CI on the Association between First Pneumonia and Medication Use Utilizing IPTW, PS Deciles, and PS Quintiles

Endpoint	ICS-Containing New Users	LABD New Users	Pneumonia Events		IPTW[3]			PS[4] Deciles			PS[4] Quintile		
	N=	N=	ICS	LABD	HR	LL	UL	HR	LL	UL	HR	LL	UL
Primary Model													
Overall Pneumonia	11,555	6,492	545	157	**1.49**	1.22	1.83	**1.60**	1.33	1.93	**1.61**	1.34	1.94
Severe Pneumonia[2]	11,555	6,492	513	147	**1.57**	1.28	1.92	**--**	--	--	**1.63**	1.35	1.97
Hospitalized Pneumonia[1]	11,555	6,492	319	90	**1.52**	1.16	1.98	**--**	--	--	**1.66**	1.30	2.12
Hospitalized with Pneumonia on the First Episode	11,555	6,492	252	70	**1.55**	1.14	2.10	**--**	--	--	**1.70**	1.29	2.24
New Use of at least 30 days													
Overall Pneumonia	11,333	5,954	472	142	**1.39**	1.12	1.72	**1.50**	1.23	1.82	**1.52**	1.25	1.85
Severe Pneumonia[2]	11,333	5,954	444	133	**1.46**	1.17	1.82	**--**	--	--	**1.53**	1.26	1.87
Hospitalized Pneumonia[1]	11,333	5,954	278	84	**1.41**	1.07	1.86	**--**	--	--	**1.54**	1.19	1.98
Hospitalized with Pneumonia on the First Episode	11,333	5,954	220	67	**1.40**	1.02	1.92	**--**	--	--	**1.54**	1.16	2.04
Persistent User (≥6 mo)													
Overall Pneumonia	5,549	3,847	386	121	**1.19**	0.93	1.52	**1.28**	1.03	1.58	**1.29**	1.04	1.60
Severe Pneumonia[2]	5,549	3,847	360	115	**1.22**	0.97	1.55	**--**	--	--	**1.25**	1.01	1.56
Hospitalized Pneumonia[1]	5,549	3,847	237	74	**1.24**	0.93	1.65	**--**	--	--	**1.27**	0.97	1.68
Hospitalized with Pneumonia on the First Episode	5,549	3,847	186	57	**1.23**	0.89	1.72	**--**	--	--	**1.28**	0.93	1.75
By ICS Dose													

Endpoint	ICS-Containing New Users	LABD New Users	Pneumonia Events		IPTW[3]			PS[4] Deciles			PS[4] Quintile		
	N=	N=	ICS	LABD	HR	LL	UL	HR	LL	UL	HR	LL	UL
Overall Pneumonia													
High	2,176	6,492	153	157	**1.86**	1.47	2.35	**1.84**	1.44	2.35	**1.86**	1.46	2.36
Not High	9,379	6,492	392	157	**1.40**	1.13	1.74	**1.51**	1.25	1.84	**1.51**	1.24	1.83
Medium	4,545	6,492	205	157	**1.49**	1.19	1.86	**1.55**	1.25	1.93	**1.55**	1.25	1.93
Low	4,834	6,492	187	157	**1.37**	1.07	1.76	**1.39**	1.10	1.75	**1.41**	1.12	1.77
Severe Pneumonia[2]													
High	2,176	6,492	149	147	**1.97**	1.55	2.49	**--**	--	--	**1.97**	1.54	2.51
Not High	9,379	6,492	364	147	**1.45**	1.17	1.80	**--**	--	--	**1.50**	1.23	1.83
Medium	4,545	6,492	188	147	**1.49**	1.18	1.88	**--**	--	--	**1.53**	1.22	1.92
Low	4,834	6,492	176	147	**1.42**	1.10	1.83	**--**	--	--	**1.42**	1.13	1.80
Hospitalized Pneumonia[1]													
High	2,176	6,492	99	90	**2.17**	1.61	2.93	**--**	--	--	**2.15**	1.57	2.95
Not High	9,379	6,492	220	90	**1.35**	1.02	1.80	**--**	--	--	**1.46**	1.13	1.89
Medium	4,545	6,492	121	90	**1.50**	1.11	2.02	**--**	--	--	**1.56**	1.17	2.08
Low	4,834	6,492	99	90	**1.25**	0.91	1.72	**--**	--	--	**1.30**	0.95	1.78
Hospitalized with Pneumonia on the First Episode													
High	2,176	6,492	78	70	**2.22**	1.58	3.12	**--**	--	--	**2.19**	1.53	3.14
Not High	9,379	6,492	174	70	**1.39**	1.01	1.92	**--**	--	--	**1.51**	1.13	2.02
Medium	4,545	6,492	97	70	**1.57**	1.13	2.20	**--**	--	--	**1.62**	1.17	2.24
Low	4,834	6,492	77	70	**1.21**	0.84	1.72	**--**	--	--	**1.29**	0.91	1.84
Persistent User (≥6 mo) by ICS Dose													
Overall Pneumonia													
High	1,274	3,847	117	121	**1.61**	1.22	2.12	**1.50**	1.13	1.99	**1.52**	1.15	2.01
Not High	4,275	3,847	269	121	**1.08**	0.83	1.40	**1.21**	0.96	1.52	**1.22**	0.97	1.53
Medium	2,252	3,847	149	121	**1.18**	0.91	1.53	**1.27**	0.98	1.64	**1.27**	0.99	1.64

Endpoint	ICS-Containing New Users	LABD New Users	Pneumonia Events		IPTW[3]			PS[4] Deciles			PS[4] Quintile		
	N=	N=	ICS	LABD	HR	LL	UL	HR	LL	UL	HR	LL	UL
Low	2,023	3,847	120	121	**1.01**	0.75	1.37	**1.12**	0.84	1.51	**1.13**	0.85	1.51
Severe Pneumonia[2]													
High	1,274	3,847	113	115	**1.68**	1.28	2.22	**--**	--	--	**1.56**	1.17	2.07
Not High	4,275	3,847	247	115	**1.08**	0.84	1.40	**--**	--	--	**1.16**	0.92	1.47
Medium	2,252	3,847	135	115	**1.15**	0.88	1.49	**--**	--	--	**1.20**	0.93	1.56
Low	2,023	3,847	115	115	**0.99**	0.73	1.34	**--**	--	--	**1.11**	0.83	1.49
Hospitalized Pneumonia[1]													
High	1,274	3,847	78	74	**1.81**	1.29	2.54	**--**	--	--	**1.70**	1.20	2.42
Not High	4,275	3,847	159	74	**1.08**	0.79	1.46	**--**	--	--	**1.14**	0.85	1.54
Medium	2,252	3,847	89	74	**1.14**	0.82	1.58	**--**	--	--	**1.16**	0.84	1.61
Low	2,023	3,847	70	74	**1.02**	0.70	1.49	**--**	--	--	**1.09**	0.75	1.58
Hospitalized with Pneumonia on the First Episode													
High	1,274	3,847	61	57	**1.81**	1.22	2.67	**--**	--	--	**1.74**	1.17	2.59
Not High	4,275	3,847	125	57	**1.08**	0.76	1.53	**--**	--	--	**1.15**	0.82	1.62
Medium	2,252	3,847	73	57	**1.21**	0.84	1.73	**--**	--	--	**1.24**	0.86	1.79
Low	2,023	3,847	52	57	**0.91**	0.60	1.38	**--**	--	--	**1.04**	0.67	1.59
Original Time Period (2005-2010)													
Overall Pneumonia	6,937	5,000	326	114	**1.63**	1.31	2.04	**1.63**	1.31	2.03	**1.63**	1.31	2.03
Severe Pneumonia[2]	6,937	5,000	307	109	**1.61**	1.29	2.03	**--**	--	--	**1.62**	1.29	2.02
Hospitalized Pneumonia[1]	6,937	5,000	207	67	**1.70**	1.27	2.27	**--**	--	--	**1.73**	1.30	2.31
Hospitalized with Pneumonia on the First Episode	6,937	5,000	155	53	**1.62**	1.16	2.25	**--**	--	--	**1.68**	1.21	2.33
By device													
Overall Pneumonia													
ICS/LABA fixed dose combination	4,744	6,492	278	157	**1.61**	1.31	1.96	**1.61**	1.32	1.98	**1.62**	1.32	1.98

Endpoint	ICS-Containing New Users	LABD New Users	Pneumonia Events		IPTW[3]			PS[4] Deciles			PS[4] Quintile		
	N=	N=	ICS	LABD	HR	LL	UL	HR	LL	UL	HR	LL	UL
ICS monotherapy	6,811	6,492	267	157	**1.41**	1.11	1.79	**1.52**	1.22	1.89	**1.51**	1.22	1.88
Severe Pneumonia[2]													
ICS/LABA fixed dose combination	4,744	6,492	264	147	**1.62**	1.32	2.00	**--**	--	--	**1.64**	1.33	2.02
ICS monotherapy	6,811	6,492	249	147	**1.49**	1.17	1.90	**--**	--	--	**1.53**	1.23	1.91
Hospitalized Pneumonia[1]													
ICS/LABA fixed dose combination	4,744	6,492	173	90	**1.67**	1.29	2.18	**--**	--	--	**1.67**	1.28	2.18
ICS monotherapy	6,811	6,492	146	90	**1.40**	1.02	1.92	**--**	--	--	**1.48**	1.10	1.98
Hospitalized with Pneumonia on the First Episode													
ICS/LABA fixed dose combination	4,744	6,492	138	70	**1.74**	1.29	2.34	**--**	--	--	**1.73**	1.29	2.34
ICS monotherapy	6,811	6,492	114	70	**1.38**	0.97	1.99	**--**	--	--	**1.47**	1.06	2.05

1. Patients with a severe pneumonia episode due to a HES episode (hospitalization) with pneumonia as a primary diagnosis during an episode of care within the HES episode and not censored for other reasons during the severe pneumonia episode before the primary diagnosis
2. Patients with a severe pneumonia episode due to hospitalization or death during the pneumonia episode not censoring for prior non-severe pneumonia episode(s)
3. inverse probability of treatment weights method
4. Propensity score

Table 23 Hazard Ratio and 95% CI on the Association between Pneumonia and Medication Use Utilizing PS Matching

Endpoint	ICS-Containing New Users	LABD New Users	Pneumonia Events		PS Matching		
	N=	N=	ICS	LABD	HR	LL	UL
Primary Model							
Overall Pneumonia	6,201	6,201	286	150	**1.64**	1.35	2.00
Severe Pneumonia[2]	6,201	6,201	272	140	**1.67**	1.36	2.05
Hospitalized Pneumonia[1]	6,201	6,201	170	87	**1.69**	1.30	2.19
Hospitalized with Pneumonia on the First Episode	6,201	6,201	135	69	**1.70**	1.27	2.27
New Use of at least 30 days							
Overall Pneumonia	5,713	5,713	241	137	**1.61**	1.30	1.98
Severe Pneumonia[2]	5,713	5,713	228	128	**1.63**	1.31	2.02
Hospitalized Pneumonia[1]	5,713	5,713	145	82	**1.61**	1.23	2.11
Hospitalized with Pneumonia on the First Episode					**1.57**	1.16	2.13
Persistent User (≥6 mo)							
Overall Pneumonia	3,337	3,337	206	113	**1.31**	1.04	1.65
Severe Pneumonia[2]	3,337	3,337	191	170	**1.28**	1.01	1.62
Hospitalized Pneumonia[1]	3,337	3,337	132	69	**1.36**	1.02	1.82
Hospitalized with Pneumonia on the First Episode	3,337	3,337	101	52	**1.39**	0.99	1.94
By ICS Dose							
Overall Pneumonia							
High	2,170	2,170	153	59	**1.88**	1.39	2.55
Not High	5,616	5,616	235	142	**1.49**	1.21	1.83
Medium	4,081	4,081	184	107	**1.44**	1.13	1.82
Low	3,677	3,677	140	101	**1.31**	1.02	1.70
Severe Pneumonia[2]							
High	2,170	2,170	149	53	**2.05**	1.49	2.82
Not High	5,616	5,616	218	132	**1.47**	1.19	1.83

Endpoint	ICS-Containing New Users	LABD New Users	Pneumonia Events		PS Matching		
	N=	N=	ICS	LABD	HR	LL	UL
Medium	4,081	4,081	169	98	**1.44**	1.12	1.84
Low	3,677	3,677	131	93	**1.33**	1.02	1.73
Hospitalized Pneumonia[1]							
High	2,170	2,170	99	35	**2.02**	1.37	3.00
Not High	5,616	5,616	139	85	**1.45**	1.11	1.90
Medium	4,081	4,081	110	62	**1.47**	1.08	2.01
Low	3,677	3,677	74	61	**1.14**	0.81	1.59
Hospitalized with Pneumonia on the First Episode							
High	2,170	2,170	78	25	**2.26**	1.43	3.57
Not High	5,616	5,616	110	68	**1.44**	1.06	1.95
Medium	4,081	4,081	89	51	**1.44**	1.02	2.04
Low	3,677	3,677	57	47	**1.15**	0.78	1.69
Persistent User (≥6 mo) by ICS Dose							
Overall Pneumonia							
High	1,236	1,236	110	36	**1.96**	1.34	2.86
Not High	2,848	2,848	157	99	**1.14**	0.88	1.46
Medium	1,663	1,663	91	58	**1.36**	1.01	1.84
Low	2,026	2,026	132	67	**1.16**	0.83	1.61
Severe Pneumonia[2]							
High	1,236	1,236	107	34	**2.04**	1.39	3.01
Not High	2,848	2,848	142	95	**1.06**	0.82	1.38
Medium	1,663	1,663	121	64	**1.31**	0.96	1.77
Low	2,026	2,026	85	56	**1.12**	0.80	1.57
Hospitalized Pneumonia[1]							
High	1,236	1,236	74	19	**2.49**	1.50	4.14
Not High	2,848	2,848	95	63	**1.07**	0.78	1.48

Endpoint	ICS-Containing New Users	LABD New Users	Pneumonia Events		PS Matching		
	N=	N=	ICS	LABD	HR	LL	UL
Medium	1,663	1,663	80	47	**1.20**	0.83	1.72
Low	2,026	2,026	57	39	**1.07**	0.71	1.60
Hospitalized with Pneumonia on the First Episode							
High	1,236	1,236	58	17	**2.21**	1.28	3.82
Not High	2,848	2,848	77	48	**1.15**	0.81	1.66
Medium	1,663	1,663	66	35	**1.32**	0.87	1.99
Low	2,026	2,026	39	30	**0.97**	0.60	1.55
Original Time Period (2005-2010)							
Overall Pneumonia	4,669	4,669	190	109	**1.50**	1.18	1.90
Severe Pneumonia[2]	4,669	4,669	181	104	**1.50**	1.18	1.92
Hospitalized Pneumonia[1]	4,669	4,669	122	66	**1.58**	1.17	2.14
Hospitalized with Pneumonia on the First Episode	4,669	4,669	94	53	**1.53**	1.09	2.15
By device							
Overall Pneumonia							
ICS/LABA fixed dose combination	4,478	4,478	261	113	**1.69**	1.35	2.11
ICS monotherapy	4,416	4,416	168	111	**1.50**	1.18	1.90
Severe Pneumonia[2]							
ICS/LABA fixed dose combination	4,478	4,478	248	106	**1.71**	1.36	2.15
ICS monotherapy	4,416	4,416	158	102	**1.53**	1.19	1.96
Hospitalized Pneumonia[1]							
ICS/LABA fixed dose combination	4,478	4,478	162	72	**1.62**	1.22	2.15
ICS monotherapy	4,416	4,416	95	68	**1.38**	1.01	1.87
Hospitalized with Pneumonia on the First Episode							
ICS/LABA fixed dose combination	4,478	4,478	128	54	**1.73**	1.26	2.39
ICS monotherapy	4,416	4,416	75	52	**1.43**	1.01	2.03

Endpoint	ICS-Containing New Users	LABD New Users	Pneumonia Events		PS Matching		
	N=	N=	ICS	LABD	HR	LL	UL

1. Patients with a severe pneumonia episode due to a HES episode (hospitalization) with pneumonia as a primary diagnosis during an episode of care within the HES episode and not censored for other reasons during the severe pneumonia episode before the primary diagnosis
2. Patients with a severe pneumonia episode due to hospitalization or death during the pneumonia episode not censoring for prior non-severe pneumonia episode(s)

5.13. Logistic Regression

Logistic regression was conducted to identify patient factors associated with diagnosis of pneumonia. All covariates were included in the modeling using a backward elimination variable selection strategy. The end points of any pneumonia, severe pneumonia, and hospitalized pneumonia in the year following cohort entry were evaluated. Exposure to ICS-containing or LABD medication was not included in the model. Table 24 shows the adjusted odds ratios for any pneumonia in the year after cohort entry. The odds ratio with greatest magnitude on pneumonia diagnosis endpoint was observed for 2 or more emergency hospital admissions (for any reason) during baseline (OR=3.2, 95% CI: 2.3-4.4).

Table 24 Adjusted Odds Ratios for Any Pneumonia in the Year following Cohort Entry

Wald Confidence Interval for Adjusted Odds Ratios			
Effect	**Odds Ratio**	**95% Confidence Limits**	
Age at Cohort Entry	1.043	1.034	1.052
Baseline Pneumonia	2.289	1.646	3.183
CHF in baseline	1.255	1.003	1.570
CVD in Baseline	1.294	1.018	1.644
Peripheral vascular disease	1.295	1.030	1.629
Hemiplagia/Paraplegia diagnosis prior to cohort entry date	2.314	1.007	5.320
Diabetes	1.414	1.112	1.799
Cancer, Non-metastatic	1.436	1.149	1.794
Anxiety diagnosis or Anxiety prescription prior to cohort entry date	1.243	1.046	1.476
SABD in Baseline Period	1.211	1.009	1.452
Statins in Baseline Period	0.767	0.635	0.927
Gender : Male vs Female	1.414	1.201	1.665
Cohort Entry Year 2003 vs 2002	1.099	0.805	1.500
Cohort Entry Year 2004 vs 2002	0.944	0.686	1.299
Cohort Entry Year 2005 vs 2002	1.213	0.887	1.661
Cohort Entry Year 2006 vs 2002	1.313	0.953	1.809
Cohort Entry Year 2007 vs 2002	1.189	0.848	1.667
Cohort Entry Year 2008 vs 2002	1.250	0.903	1.731
Cohort Entry Year 2009 vs 2002	1.435	1.037	1.987
Cohort Entry Year 2010 vs 2002	0.759	0.510	1.130
GOLD Stage 0 vs 2	1.142	0.740	1.760
GOLD Stage 1 vs 2	0.594	0.271	1.304
GOLD Stage 3 vs 2	1.284	0.908	1.816
GOLD Stage 4 vs 2	1.360	0.739	2.504
GOLD Stage Unknown vs 2	1.924	1.484	2.494
BMI <18.5 vs. ≥18.5-21	1.565	1.162	2.107
BMI 21 - <25 vs ≥18.5-21	0.822	0.674	1.002
BMI 25 - <30 vs ≥18.5-25	0.770	0.607	0.977
BMI Unknown vs ≥18.5-25	1.138	0.877	1.477
GERD Diagnosis or Medication in Baseline	1.210	1.024	1.429
Count of emergency hospital admissions in the baseline period 1 vs 0	1.432	1.185	1.731
Count of emergency hospital admissions in the baseline period 2 vs 0	3.153	2.256	4.406
Count of moderate COPD exacerbations during baseline period 1 vs 0	1.202	1.019	1.418
Count of moderate COPD exacerbations during baseline period 2 vs 0	2.130	1.541	2.945
Number of severe exacerbations in baseline period 1 vs 0	1.357	1.046	1.759

Table 25 shows the adjusted odds ratios for severe pneumonia in the year after cohort entry. The similar pattern was observed as for severe pneumonia, such that 2 or more emergency hospital admissions during baseline had the highest magnitude (OR=3.7, 95% CI: 2.6-5.1).

Table 25 Adjusted Odds Ratios for Severe Pneumonia in the Year following Cohort Entry

Wald Confidence Interval for Adjusted Odds Ratios			
Effect	**Odds Ratio**	**95% Confidence Limits**	
Age at Cohort Entry	1.046	1.036	1.055
Baseline Pneumonia	2.282	1.628	3.200
CHF in baseline	1.280	1.017	1.612
CVD in Baseline	1.381	1.086	1.758
Diabetes	1.502	1.173	1.921
Cancer, Non-metastatic	1.413	1.121	1.781
Anxiety diagnosis or Anxiety prescription prior to cohort entry date	1.258	1.053	1.504
SABD in Baseline Period	1.244	1.031	1.502
Statins in Baseline Period	0.795	0.655	0.965
Gender : Male vs Female	1.404	1.187	1.661
Cohort Entry Year 2003 vs 2002	1.108	0.802	1.530
Cohort Entry Year 2004 vs 2002	0.976	0.701	1.358
Cohort Entry Year 2005 vs 2002	1.215	0.876	1.684
Cohort Entry Year 2006 vs 2002	1.399	1.007	1.945
Cohort Entry Year 2007 vs 2002	1.193	0.838	1.698
Cohort Entry Year 2008 vs 2002	1.239	0.882	1.741
Cohort Entry Year 2009 vs 2002	1.517	1.084	2.122
Cohort Entry Year 2010 vs 2002	0.813	0.540	1.224
GOLD Stage 0 vs 2	1.270	0.813	1.984
GOLD Stage 1 vs 2	0.566	0.243	1.320
GOLD Stage 3 vs 2	1.278	0.884	1.849
GOLD Stage 4 vs 2	1.464	0.776	2.763
GOLD Stage Unknown vs 2	2.050	1.557	2.699
BMI <18.5 vs. ≥18.5-21	1.658	1.225	2.244
BMI 21 - <25 vs ≥18.5-21	0.801	0.651	0.984
BMI 25 - <30 vs ≥18.5-25	0.734	0.572	0.942
BMI Unknown vs ≥18.5-25	1.169	0.895	1.526
GERD Diagnosis or Medication in Baseline	1.225	1.031	1.456
Count of emergency hospital admissions in the baseline period 1 vs 0	1.534	1.271	1.852
Count of emergency hospital admissions in the baseline period 2 vs 0	3.660	2.642	5.070
Count of moderate COPD exacerbations during baseline period 1 vs 0	1.155	0.973	1.371
Count of moderate COPD exacerbations during baseline period 2 vs 0	2.066	1.480	2.885

Table 26 shows the adjusted odds ratios for hospitalized pneumonia in the year after cohort entry. The highest odds of hospitalized pneumonia were observed for metastatic cancer (OR=3.7, 95% CI: 1.1-12.4).

Table 26 Adjusted Odds Ratios for Hospitalized Pneumonia in the Year following Cohort Entry

Wald Confidence Interval for Adjusted Odds Ratios			
Effect	**Odds Ratio**	**95% Confidence Limits**	
Age at Cohort Entry	1.064	1.049	1.079
Baseline Pneumonia	2.581	1.564	4.261
CVD in Baseline	1.486	1.036	2.133
Dementia	2.107	1.046	4.243
Cancer, metastatic	3.703	1.106	12.394
Anxiety diagnosis or Anxiety prescription prior to cohort entry date	1.393	1.050	1.848
SABD in Baseline Period	1.437	1.048	1.971
Gender : Male vs Female	1.452	1.109	1.901
Cohort Entry Year 2003 vs 2002	1.408	0.800	2.479
Cohort Entry Year 2004 vs 2002	0.942	0.508	1.745
Cohort Entry Year 2005 vs 2002	2.125	1.242	3.635
Cohort Entry Year 2006 vs 2002	1.824	1.039	3.201
Cohort Entry Year 2007 vs 2002	1.910	1.075	3.391
Cohort Entry Year 2008 vs 2002	1.560	0.873	2.788
Cohort Entry Year 2009 vs 2002	1.959	1.109	3.461
Cohort Entry Year 2010 vs 2002	1.159	0.598	2.245
GOLD Stage 0 vs 2	1.135	0.518	2.485
GOLD Stage 1 vs 2	0.560	0.131	2.399
GOLD Stage 3 vs 2	1.814	1.021	3.223
GOLD Stage 4 vs 2	1.607	0.546	4.729
GOLD Stage Unknown vs 2	2.417	1.529	3.820
Count of emergency hospital admissions in the baseline period 1 vs 0	1.568	1.166	2.109
Count of emergency hospital admissions in the baseline period 2 vs 0	3.349	2.003	5.600
Count of moderate COPD exacerbations during baseline period 1 vs 0	1.509	1.151	1.978
Count of moderate COPD exacerbations during baseline period 2 vs 0	2.431	1.444	4.093

Table 27, Table 28, and Table 29 compare the characteristics, co-morbidities, and medication use/healthcare utilization between patients who developed hospitalized pneumonia where pneumonia was the primary cause on the first HES episode, all other pneumonia, or no pneumonia in the year after cohort entry.

Table 27 Characteristics of Patients with Hospitalized Pneumonia (primary cause on first episode), Any Other Pneumonia, and No Pneumonia in the year after cohort entry

	Population					
	Primary pneumonia cause on first HES episode		Any other pneumonia		No pneumonia	
Variable	n= 209	%	N=412	%	N=15,835	%
Male	134	64.1	260	63.1	8,773	55.4
Age at cohort entry date						
45-64 yrs	23	11.0	73	17.7	5,160	32.6
65-79 yrs	101	48.3	200	48.5	7,857	49.6
>=80 yrs	85	40.7	139	33.7	2,818	17.8
Year of cohort entry						
2002	16	7.7	52	12.6	1,613	10.2
2003	23	11.0	50	12.1	1,561	9.9
2004	17	8.1	55	13.3	1,897	12.0
2005	35	16.7	43	10.4	1,755	11.1
2006	28	13.4	49	11.9	1,724	10.9
2007	27	12.9	39	9.5	1,717	10.8
2008	23	11.0	51	12.4	1,999	12.6
2009	25	12.0	50	12.1	1,836	11.6
2010	15	7.2	23	5.6	1,733	10.9
Smoking status prior to cohort entry date						
No	14	6.7	39	9.5	907	5.7
Ex	121	57.9	207	50.2	7,922	50.0
Yes	74	35.4	166	40.3	7,006	44.2
COPD severity						
COPD Dx but spirometry conflicts	3	1.4	9	2.2	407	2.6
Restrictive COPD	8	3.8	21	5.1	1,156	7.3
GOLD I	2	1.0	5	1.2	531	3.4
GOLD II	22	10.5	48	11.7	3,149	19.9
GOLD III	24	11.5	34	8.3	1,986	12.5
GOLD IV	4	1.9	8	1.9	367	2.3
Unknown	146	69.9	287	69.7	8,239	52.0
Clinically significant dyspnea diagnosis	18	8.6	45	10.9	1,857	11.7
Asthma diagnosis prior to cohort entry date	31	14.8	74	18.0	2,587	16.3
Pneumonia episode in baseline period	16	7.7	28	6.8	270	1.7
Number of severe CAP episodes in baseline period						
0	197	94.3	392	95.1	15,625	98.7
1	11	5.3	19	4.6	207	1.3
2	1	0.5	1	0.2	3	0.0
Townsend Deprivation quintile (Year 2001)						
Least deprived (quintile 1)	33	15.8	69	16.7	2,363	14.9
Quintile 2	29	13.9	75	18.2	3,096	19.6
Quintile 3	52	24.9	82	19.9	3,434	21.7
Quintile 4	50	23.9	110	26.7	3,903	24.6
Most deprived (Quintile 5)	45	21.5	76	18.4	3,039	19.2
IMD Deprivation quintile closest to cohort entry date						
Least deprived (Quintile 1)	31	14.8	59	14.3	2,275	14.4
Quintile 2	33	15.8	78	18.9	3,004	19.0
Quintile 3	44	21.1	82	19.9	3,186	20.1
Quintile 4	48	23.0	106	25.7	3,719	23.5
Most deprived (Quintile 5)	53	25.4	87	21.1	3,651	23.1

1. Baseline period includes the year before cohort entry

Table 28 Co-morbidities of Patients with Hospitalized Pneumonia (primary cause on first episode), Any Other Pneumonia, and No Pneumonia in the year after cohort entry

	Population					
	Primary pneumonia cause on first HES episode		Any other pneumonia		No pneumonia	
Variable	n= 209	%	N=412	%	N=15,835	%
Flu Vaccination in baseline	165	78.9	296	71.8	10,764	68.0
Pneumococcal Vaccination in (up to) 5 years prior to cohort entry	97	46.4	164	39.8	6,239	39.4
BMI						
Underweight (0<-<18.5)	17	8.1	45	10.9	868	5.5
Low Normal (18.5-<21)	28	13.4	57	13.8	1,726	10.9
High Normal (21-<25)	62	29.7	117	28.4	4,394	27.7
Overweight (25-<30)	63	30.1	120	29.1	5,160	32.6
Obese (>=30)	39	18.7	73	17.7	3,687	23.3
MI diagnosis	26	12.4	53	12.9	1,372	8.7
CHF diagnosis	32	15.3	64	15.5	1,289	8.1
CVD diagnosis	32	15.3	47	11.4	1,224	7.7
Dementia diagnosis	8	3.8	6	1.5	92	0.6
GERD diagnosis or GERD prescription	114	54.5	230	55.8	7,731	48.8
GERD diagnosis or GERD prescription in baseline	75	35.9	151	36.7	4,540	28.7
Peptic Ulcer diagnosis	16	7.7	41	10.0	1,277	8.1
Peripheral Vascular Disease diagnosis	32	15.3	57	13.8	1,429	9.0
Mild Liver Disease diagnosis	.	.	6	1.5	101	0.6
Moderate Liver Disease diagnosis	.	.	1	0.2	16	0.1
Connective Tissue Disorder diagnosis	16	7.7	20	4.9	830	5.2
Hemiplagia/Paraplegia diagnosis	1	0.5	4	1.0	43	0.3
Diabetes diagnosis	35	16.7	61	14.8	1,752	11.1
Diabetes (with complications) diagnosis	7	3.3	19	4.6	336	2.1
Anxiety diagnosis or Anxiety prescription	67	32.1	130	31.6	4,638	29.3
Depression diagnosis or Depression prescription	82	39.2	207	50.2	7,184	45.4
Cancer (non-metastatic solid tumours) diagnosis	31	14.8	64	15.5	1,321	8.3
Cancer (Metastatic solid tumours) diagnosis	2	1.0	1	0.2	40	0.3
Renal Diseases diagnosis	27	12.9	50	12.1	1,453	9.2

1. Variables recorded in patient history “prior to cohort entry date” unless otherwise specified

Table 29 Medications Used and Healthcare Utilization of Patients with Hospitalized Pneumonia (primary cause on first episode), Any Other Pneumonia, and No Pneumonia in the year after cohort entry

	Population					
	Primary pneumonia cause on first HES episode		Any other pneumonia		No pneumonia	
Variable	n= 209	%	N=412	%	N=15,835	%
OCS use	69	33.0	122	29.6	4,118	26.0
Oxygen	5	2.4	17	4.1	204	1.3
Nebulized therapy	14	6.7	21	5.1	451	2.8
SABD	163	78.0	306	74.3	11,272	71.2
Theophylline	5	2.4	12	2.9	330	2.1
ACE-Inhibitor	61	29.2	118	28.6	4,078	25.8
Statins	65	31.1	130	31.6	5,316	33.6
Immunosuppressant	4	1.9	5	1.2	219	1.4
Benzodiazepine prescription	24	11.5	54	13.1	1,553	9.8
Non-Benzodiazepine sedative prescription	6	2.9	34	8.3	738	4.7
Count of GP visits						
0	.	.	4	1.0	157	1.0
1-5	35	16.7	75	18.2	3,672	23.2
6-10	55	26.3	124	30.1	5,133	32.4
11-15	53	25.4	89	21.6	3,354	21.2
15-20	26	12.4	47	11.4	1,744	11.0
≥21	40	19.1	73	17.7	1,775	11.2
Count of emergency hospital admissions						
0	129	61.7	255	61.9	12,778	80.7
1-2	64	30.6	126	30.6	2,810	17.7
≥3	16	7.7	31	7.5	247	1.6
Count of non emergency hospital admissions						
0	155	74.2	295	71.6	12,772	80.7
1-2	46	22.0	102	24.8	2,707	17.1
≥3	8	3.8	15	3.6	356	2.2
Count of Moderate COPD exacerbations						
0	102	48.8	242	58.7	10,152	64.1
1	63	30.1	112	27.2	4,058	25.6
≥2	44	21.1	58	14.1	1,625	10.3
Count of Severe COPD exacerbations						
0	185	88.5	358	86.9	14,950	94.4
1	22	10.5	44	10.7	803	5.1
≥2	2	1.0	10	2.4	82	0.5

1. Variables recorded in baseline period unless otherwise specified

6. DISCUSSION AND CONCLUSIONS

6.1. Discussion

New use of ICS-containing mediations was associated with an increased risk of pneumonia relative to LABD (HR=1.49, 95% CI: 1.22, 1.83). The excess ICS risk was attenuated somewhat when requiring ≥30 days of new use (HR=1.39, 95% CI: 1.12, 1.72) or persistent use (HR=1.19, 95% CI: 0.93, 1.52), but the results were robust and did not vary appreciably when examining more sensitive or more specific pneumonia hospitalization and severity outcomes (e.g., pneumonia hospitalization, pneumonia as primary reason in any episode, pneumonia as a primary reason on the first episode of care). There was an apparent dose response, with an increase in risk of pneumonia observed with increasing doses of ICS; however, the confidence intervals between doses overlapped and residual confounding by severity cannot be ruled out as contributing to this trend. The association was observed utilizing various propensity scoring methods (IPTW, matching, PS deciles, and PS quintiles), though not always statistically significant. Among new users of ICS, factors associated with pneumonia within the first year independent of treatment included known risk factors such as low BMI, advanced age, severe exacerbation, and co-morbidities. The strongest risk factor for pneumonia was 2 or more emergency hospital admissions in the prior year (OR=3.2, 95% CI: 2.3-4.4).

A strength of the new-user cohort design is that patient follow-up starts with the initial medication prescription written by the healthcare provider similarly for all treatment groups and avoids potential biases that result from examining prevalent users relating to survivor bias and changes in their covariates based on exposure to treatment [Ray, 2003].

Evidence generated from this observational study is complementary to the observations noted in previous studies of ICS-containing treatment for COPD and to analyses from the FF/VI clinical development program. A strength of the primary care database (CPRD-GOLD) is the ability to examine and adjust for risk factors for pneumonia (e.g., BMI, lung function, smoking history, MRC dyspnea score) included in the UK Quality Outcomes Framework (QOF) for COPD that are not collected routinely in most other observational data sources (e.g. healthcare insurance claims). This design permits an increased specificity of COPD diagnosis relative to other healthcare databases enabled by the routinely collected lung function and QOF protocol. The new-user design may minimize biases that can be caused by comparing events between prevalent user groups (e.g., survivor bias, covariates altered by exposure which cannot be resolved through statistical adjustment). However, a disadvantage of the new-user approach is a smaller sample size relative to alternative designs that include prevalent users and potentially a loss in generalizability of the results.

As a result of the subsequent feasibility prior to the conduct of the study, this protocol was amended to improve precision. The study period was expanded to include more patients and pneumonia events, though there are time trends to be considered with the expanded time period. In May 2003, ICS/LABA was indicated for COPD in the UK and in May 2007, the indication expanded to the COPD population with <60% predicted FEV1. GOLD guidelines during the early years of this study also indicated ICS

monotherapy for COPD treatment. Additionally, during around 2005 spirometry and QoF became reimbursable activities in the UK having a potential effect upon the number of COPD diagnoses.

There are also known limitations of non-randomized database analyses of medication safety, including the potential for confounding by severity. ICS-containing medications may have been dispensed to patients who have more severe COPD or those at higher risk for exacerbation than patients who are receiving long-acting bronchodilators alone per treatment guidelines. In this study, we adjusted for disease severity in the year prior to initiation using propensity scores, including adjustments for several confounders relating to the assignment to treatment (e.g., lung function, exacerbation history, pneumonia history, smoking status, and rescue medication use). Co-morbidities were also accounted for in the propensity score analysis using the entire patient record. We did note channelling of more severe patients to ICS medications, as requiring 30 days of treatment and 6 months of treatment attenuated the observed HRs (ICS vs. LABD), though pneumonia was still associated with ICS exposure. In addition, there were higher rates of pneumonia observed among those patents prescribed the highest doses of ICS. Most of the prescribed high-dose ICS was fixed dose combination whereas low-dose was ICS-monotherapy, which could also reflect channelling of more severe patients to higher dose ICS.

There may be some differences in this observational study relative to clinical trials in terms of the diagnosis of pneumonia. When identifying pneumonia in databases, definitions are based upon existing information collected in routine healthcare which may not include all details measured in clinical trials. In addition, there is lack of agreement between pneumonia classification in the absence of chest x-rays, sputum, etc. Our definitions were based on using HES for hospitalization and built upon prior work (including validation of severe CAP). There may be some confusion between diagnoses of pneumonia versus influenza-related morbidity. However, most pneumonia events in the study were associated with an inpatient hospital admission where pneumonia was recorded as a primary or non-primary cause (95%, 631 of 702 pneumonia events). Therefore, it is likely that pneumonia was more rigorously diagnosed than pneumonia diagnosed in the primary care setting where chest x-rays may not be ordered.

In our final propensity score model, we evaluated known risk factors for pneumonia as main effects and included interaction terms between ICS; however, none were significant. A limitation of using propensity score modeling is that these additional main effects in the model do not contribute appreciably, as differences between groups in individual confounders are adjusted for with the propensity score [Rubin, 2000; Stürmer, 2006].

Additional limitations of the observational study design include that only diagnosed diseases including COPD are recorded in CPRD-GOLD. Medication use in CPRD-GOLD is based on prescribed medications recorded by the GP, which might not have been dispensed at the pharmacy or ultimately utilized by the patient. This study does not include the investigational combination inhaled medication FF/VI, but rather can only examine approved ICS-containing medications in this retrospective cohort design.

Despite the limitations, this large observational study provides insights into risk factors for all pneumonias and severe pneumonia, including ICS-containing medications, in well

characterized COPD patients treated in clinical practice. The results identified patient groups that are at greatest risk of pneumonia and where risk minimization and/or medical recommendations may be appropriate (e.g., those with exacerbation history, low BMI, pneumonia history, and multiple co-morbidities).

6.2. Conclusions

- Among new users, factors associated with pneumonia within the first year independent of treatment included known risk factors such as low BMI, advanced age, severe exacerbation, and co-morbidities. The strongest risk factor for pneumonia was 2 or more emergency hospital admissions in the prior year (during baseline (OR=3.2, 95% CI: 2.3-4.4).
- The results of this new-user cohort study design are consistent with published findings that ICS use is associated with increased risk of pneumonia and hospitalized pneumonia in COPD patients treated in the UK.
- New use of ICS-containing mediations was associated with an increased risk of pneumonia relative to LABD (n=18,047 at risk, n=702 events; HR=1.49, 95% CI: 1.22, 1.83)
- Excess ICS risk was attenuated somewhat when requiring ≥30 days of new use (n=17,287, n=614 events; HR=1.39, 95% CI: 1.12, 1.72) or persistent use (≥6 months; n= 9,396; n=507 events, HR=1.19, 95% CI: 0.93, 1.52);
- Results were robust and did not vary appreciably when examining more sensitive or more specific pneumonia hospitalization outcomes (e.g., pneumonia hospitalization, pneumonia as primary reason in any episode, pneumonia as a primary reason on the first episode of care)
- There was an apparent dose response, with an increase in risk of pneumonia observed with increasing doses of ICS; however, the confidence intervals between doses overlapped and residual confounding by severity cannot be ruled out as contributing to this trend.
- This risk must be weighed against the benefits when prescribing ICS to patients with COPD.

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8. POST-TEXT TABLES AND FIGURES

8.1. New User Cohort

8.1.1. New User Cohort Feasibility

Post-Text Table 1 New User Feasibility (New User Cohort): Estimates of New Users by Year Meeting Inclusion/Exclusion

		Year of Cohort Entry									Total Number of New Users
		2002	2003	2004	2005	2006	2007	2008	2009	2010	
New Use Drug	Subcategory										
ICS Containing Drugs	ICS monotherapy	1,617	1,156	997	753	663	530	546	481	364	7,107
	ICS-Containing fixed dose combination	203	340	636	616	647	677	698	619	511	4,947
	ICS-SABA	8	3	.	.	.	.	.	.	.	11
	Total	1,828	1,499	1,633	1,369	1,310	1,207	1,244	1,100	875	12,065
LABD Containing Drugs	Subcategory										
	LABA	338	294	338	295	246	202	209	174	147	2,243
	LAMA	16	219	365	470	469	521	763	764	847	4,434
	Total	354	513	703	765	715	723	972	938	994	6,677
Total Number of New Users		2,182	2,012	2,336	2,134	2,025	1,930	2,216	2,038	1,869	18,742

Post-Text Table 2 New User Feasibility (New User Cohort): Estimates of Persistent New Users by Year Meeting Inclusion/Exclusion

Number of Persistent New Users (>=180 days of treatment)		Year of Cohort Entry									Total Number of Persistent Patients
		2002	2003	2004	2005	2006	2007	2008	2009	2010	
New Use Drug	Subcategory										
ICS Containing Drugs	ICS monotherapy	567	416	442	335	296	226	212	199	168	2,861
	ICS-Containing fixed dose combination	95	184	374	371	391	425	411	352	314	2,917
	ICS-SABA	2	1	.	.	.	.	.	.	.	3
	Total	664	601	816	706	687	651	623	551	482	5,781
LABD Containing Drugs	Subcategory										
	LABA	167	141	173	158	120	106	120	92	74	1,151
	LAMA	9	143	244	286	288	300	506	470	547	2,793
	Total	176	284	417	444	408	406	626	562	621	3,944

Number of Persistent New Users (>=180 days of treatment)	Year of Cohort Entry									Total Number of Persistent Patients
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Total Number of Persistent New Users	840	885	1,233	1,150	1,095	1,057	1,249	1,113	1,103	9,725

Post-Text Table 3 New User Feasibility (New User Cohort): First Pneumonia Events by Type

Pneumonia Events	Year of Cohort Entry									Total Number of New Users
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode										
HAP	32	29	29	28	25	21	10	9	3	186
Severe CAP	416	377	390	325	268	192	160	95	39	2,262
Non-severe CAP	43	41	28	29	11	14	17	7	2	192
All Pneumonia	491	447	447	382	304	227	187	111	44	2,640

1. All first pneumonia events occurring after or equal cohort entry date
2. Pneumonia event may occur after the patient is censored

Post-Text Table 4 New User Feasibility (New User Cohort): First Pneumonia Events by Type that Cause the Patient to be Censored

Pneumonia Events	Year of Cohort Entry									Total Number of New Users
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode										
HAP	5	4	7	7	5	7	3	3	2	43
Severe CAP	88	79	78	86	98	64	72	56	31	652
Non-severe CAP	9	9	9	7	5	4	7	5	1	56
All Pneumonia	102	92	94	100	108	75	82	64	34	751

1. All first pneumonia events occurring after or equal cohort entry date

8.1.2. New User Cohort Demographics

Post-Text Table 5 Descriptive Characteristics from the Baseline Period (year before cohort entry)/Patient History for the New User COPD Cohort Free of Pneumonia at Index Date

Variable	Cohort				p-value
	ICS-Containing Drugs		LABD Drugs		
	n=11,853	%	n=6,582	%	
Male	6,488	54.7	3,828	58.2	<0.01
Age at cohort entry date					
45-64 yrs	3,901	32.9	1,951	29.6	<0.01
65-79 yrs	5,658	47.7	3,366	51.1	.
>=80 yrs	2,294	19.4	1,265	19.2	.
Smoking status prior to cohort entry date					
No	818	6.9	279	4.2	<0.01
Yes	5,176	43.7	2,908	44.2	.
No recording	259	2.2	74	1.1	.
Ex	5,600	47.2	3,321	50.5	.
COPD severity					
COPD Dx but spirometry conflicts	288	2.4	164	2.5	<0.01
Restrictive COPD	765	6.5	488	7.4	.
GOLD I	341	2.9	225	3.4	.
GOLD II	1,876	15.8	1,554	23.6	.
GOLD III	1,292	10.9	922	14.0	.
GOLD IV	255	2.2	170	2.6	.
Unknown	7,036	59.4	3,059	46.5	.
Clinically significant dyspnea diagnosis	952	8.0	1,090	16.6	<0.01
Asthma diagnosis prior to cohort entry date	2,241	18.9	791	12.0	<0.01
Pneumonia episode in baseline period	238	2.0	123	1.9	0.51
Number of non-severe CAP episodes in baseline period					
0	11,801	99.6	6,558	99.6	0.27
1	52	<1	23	<1	.
2	0	<1	1	<1	.
Number of severe CAP episodes in baseline period					
0	11,668	98.4	6,484	98.5	0.84
1	181	1.5	95	1.4	.
2	4	<1	3	<1	.
Number of HAP pneumonia episodes in baseline period					
0	11,845	99.9	6,579	100.0	0.56
1	8	<1	3	<1	.
Townsend Deprivation quintile (Year 2001)					
No recording	40	<1	17	<1	0.05
Quintile 1(Least deprived)	1,769	14.9	981	14.9	.
Quintile 2	2,319	19.6	1,233	18.7	.
Quintile 3	2,642	22.3	1,379	21.0	.
Quintile 4	2,849	24.0	1,673	25.4	.
Quintile 5 (Most deprived)	2,234	18.8	1,299	19.7	.
IMD Deprivation quintile closest to cohort entry date					
No recording	40	<1	17	<1	0.20
Quintile 1(Least deprived)	1,732	14.6	900	13.7	.
Quintile 2	2,273	19.2	1,222	18.6	.
Quintile 3	2,382	20.1	1,348	20.5	.
Quintile 4	2,768	23.4	1,540	23.4	.
Quintile 5 (Most deprived)	2,658	22.4	1,555	23.6	.

Post-Text Table 6 Patient Co-morbidities in the Baseline Period (year before cohort entry)/Patient History for the New User Cohort Free of Pneumonia at Index Date

Variable	Cohort				
	ICS-Containing Drugs		LABD Drugs		
	n=11,853	%	n=6,582	%	p-value
Influenza Vaccination in baseline period	7,749	65.4	4,591	69.8	<0.01
Pneumococcal Vaccination in (up to) 5 years prior to cohort entry date	4,377	36.9	2,708	41.1	<0.01
BMI status					
No recording	1,316	11.1	531	8.1	<0.01
Underweight (0< - <18.5)	579	4.9	359	5.5	.
Low Normal (18.5 - <21)	1,141	9.6	672	10.2	.
High Normal (21 - <25)	2,929	24.7	1,679	25.5	.
Overweight (25 - <30)	3,481	29.4	1,903	28.9	.
Obese (≥30)	2,407	20.3	1,438	21.8	.
MI diagnosis	968	8.2	595	9.0	0.04
CHF diagnosis	1,000	8.4	582	8.8	0.35
CVD diagnosis	944	8.0	502	7.6	0.41
Dementia diagnosis	98	<1	36	<1	0.03
GERD diagnosis or GERD prescription	5,573	47.0	3,286	49.9	<0.01
Peptic Ulcer diagnosis	902	7.6	557	8.5	0.04
Peripheral Vascular Disease diagnosis	1,006	8.5	651	9.9	<0.01
Mild Liver Disease diagnosis	80	<1	45	<1	0.94
Moderate Liver Disease diagnosis	11	<1	8	<1	0.56
Connective Tissue Disorder diagnosis	587	5.0	360	5.5	0.13
Hemiplagia/Paraplegia diagnosis	43	<1	15	<1	0.12
Diabetes diagnosis	1,184	10.0	713	10.8	0.07
Diabetes (with complications) diagnosis	220	1.9	145	2.2	0.11
Anxiety diagnosis or Anxiety prescription	3,413	28.8	1,866	28.4	0.52
Depression diagnosis or Depression prescription	5,286	44.6	2,934	44.6	0.98
Cancer (non-metastatic solid tumours) diagnosis	988	8.3	578	8.8	0.30
Cancer (Metastatic solid tumours diagnosis) diagnosis	29	<1	20	<1	0.45
Renal Diseases diagnosis	879	7.4	709	10.8	<0.01

1. Variables recorded in patient history “prior to cohort entry date” unless otherwise specified

Post-Text Table 7 Patient Medications Used and Healthcare Utilization in the Baseline Period (year before cohort entry) for the New User Cohort Free of Pneumonia at Index Date

Variable	Cohort				p-value
	ICS-Containing Drugs		LABD Drugs		
	n=11,853	%	n=6,582	%	
Oral Corticosteroids (>4 Rx)	348	2.9	222	3.4	0.10
Oxygen	201	1.7	90	1.4	0.09
Nebulized therapy	417	3.5	172	2.6	<0.01
SABD	8,252	69.6	4,804	73.0	<0.01
Theophylline	294	2.5	132	2.0	0.04
ACE-inhibitors	2,836	23.9	1,764	26.8	<0.01
Statins	3,381	28.5	2,389	36.3	<0.01
Immunosuppresants	145	1.2	100	1.5	0.09
Count of GP visits					
0	171	1.4	46	<1	<0.01
1-5	2,915	24.6	1,559	23.7	.
6-10	3,794	32.0	2,130	32.4	.
11-15	2,441	20.6	1,350	20.5	.
15-20	1,225	10.3	753	11.4	.
≥21	1,307	11.0	744	11.3	.
Count of emergency hospital admissions					
0	9,226	77.8	5,429	82.5	<0.01
1-2	2,373	20.0	1,053	16.0	.
≥3	254	2.1	100	1.5	.
Count of non-emergency hospital admissions					
0	9,670	81.6	5,238	79.6	<0.01
1-2	1,927	16.3	1,193	18.1	.
≥3	256	2.2	151	2.3	.
Count of moderate COPD exacerbations					
0	7,388	62.3	4,335	65.9	<0.01
1	3,133	26.4	1,614	24.5	.
≥2	1,332	11.2	633	9.6	.
Count of COPD hospitalizations					
0	11,146	94.0	6,209	94.3	0.33
1	644	5.4	331	5.0	.
≥2	63	<1	42	<1	.

1. Variables recorded in baseline period unless otherwise specified

8.1.3. New User Cohort Excluded due to Lack of HES Linkage Demographics

Post-Text Table 8 Descriptive Characteristics from Baseline Period (year before cohort entry)/Patient History of the New Users Free of Pneumonia at Index Date Excluded from Final Analysis due to Lack of HES Linkage

Variable	Cohort				
	ICS Containing Drugs		LABD Containing Drugs		
	n=11,756	%	n=7,189	%	p-value
Male	6,368	54.2	4,132	57.5	<0.01
Age at cohort entry date					
45-64 yrs	3,903	33.2	2,269	31.6	<0.01
65-79 yrs	5,631	47.9	3,734	51.9	.
>=80 yrs	2,222	18.9	1,186	16.5	.
Smoking status prior to cohort entry date					
No	792	6.7	272	3.8	<0.01
Yes	5,313	45.2	3,530	49.1	.
No recording	364	3.1	94	1.3	.
Ex	5,287	45.0	3,293	45.8	.
COPD severity					
COPD Dx but spirometry conflicts	313	2.7	131	1.8	<0.01
Restrictive COPD	728	6.2	488	6.8	.
GOLD I	279	2.4	224	3.1	.
GOLD II	1,741	14.8	1,687	23.5	.
GOLD III	1,261	10.7	933	13.0	.
GOLD IV	237	2.0	158	2.2	.
Unknown	7,197	61.2	3,568	49.6	.
Clinically significant dyspnea diagnosis	851	7.2	1,046	14.6	<0.01
Asthma diagnosis prior to cohort entry date	2,202	18.7	710	9.9	<0.01
Townsend Deprivation quintile (Year 2001)					
No recording	9,566	81.4	5,882	81.8	0.25
Quintile 1(Least deprived)	306	2.6	206	2.9	.
Quintile 2	444	3.8	231	3.2	.
Quintile 3	479	4.1	277	3.9	.
Quintile 4	542	4.6	321	4.5	.
Quintile 5 (Most deprived)	419	3.6	272	3.8	.
IMD Deprivation quintile closest to cohort entry date					
No recording	9,566	81.4	5,882	81.8	0.30
Quintile 1(Least deprived)	312	2.7	184	2.6	.
Quintile 2	431	3.7	245	3.4	.
Quintile 3	442	3.8	257	3.6	.
Quintile 4	580	4.9	325	4.5	.
Quintile 5 (Most deprived)	425	3.6	296	4.1	.

1. This cohort meets all inclusion/exclusion criteria to be classified as New Users except that they either do not have HES Linkage or they do have HES Linkage but it does not cover the baseline period.
2. Descriptive characteristics for pneumonia episodes cannot calculated for this cohort as HES linked data are required to establish pneumonia episodes

Post-Text Table 9 Patient Co-morbidities and Medications used in the Baseline Period (year before cohort entry)/Patient History of the New Users Free of Pneumonia at Index Date Excluded from Final Analysis due to Lack of HES Linkage

Variable	Cohort				p-value
	ICS Containing Drugs		LABD Containing Drugs		
	n=11,756	%	n=7,189	%	
Influenza Vaccination in baseline period	7,462	63.5	4,732	65.8	<0.01
Pneumococcal Vaccination in (up to) 5 years prior to cohort entry date	4,235	36.0	2,756	38.3	<0.01
BMI status					
No recording	1,403	11.9	569	7.9	<0.01
Underweight (0< - <18.5)	562	4.8	428	6.0	.
Low Normal (18.5 - <21)	1,056	9.0	736	10.2	.
High Normal (21 - <25)	2,951	25.1	1,843	25.6	.
Overweight (25 - <30)	3,442	29.3	2,129	29.6	.
Obese (≥30)	2,342	19.9	1,484	20.6	.
MI diagnosis	1,002	8.5	609	8.5	0.90
CHF diagnosis	1,002	8.5	480	6.7	<0.01
CVD diagnosis	916	7.8	561	7.8	0.98
Dementia diagnosis	126	1.1	68	<1	0.40
GERD diagnosis or GERD prescription	5,558	47.3	3,554	49.4	<0.01
Peptic Ulcer diagnosis	1,001	8.5	655	9.1	0.16
Peripheral Vascular Disease diagnosis	1,007	8.6	696	9.7	<0.01
Mild Liver Disease diagnosis	67	<1	44	<1	0.71
Moderate Liver Disease diagnosis	17	<1	13	<1	0.54
Connective Tissue Disorder diagnosis	518	4.4	316	4.4	0.97
Hemiplagia/Paraplegia diagnosis	42	<1	28	<1	0.72
Diabetes diagnosis	1,187	10.1	706	9.8	0.54
Diabetes (with complications) diagnosis	221	1.9	165	2.3	0.05
Anxiety diagnosis or Anxiety prescription	3,364	28.6	2,180	30.3	0.01
Depression diagnosis or Depression prescription	4,868	41.4	3,133	43.6	<0.01
Cancer (non-metastatic solid tumours) diagnosis	898	7.6	610	8.5	0.04
Cancer (Metastatic solid tumours diagnosis) diagnosis	35	<1	17	<1	0.43
Renal Diseases diagnosis	813	6.9	684	9.5	<0.01

1. This cohort meets all inclusion/exclusion criteria to be classified as New Users except that they either do not have HES Linkage or they do have HES Linkage but it does not cover the baseline period
2. Variables recorded in patient history “prior to cohort entry date” unless otherwise specified

Post-Text Table 10 Patient Medications used and Healthcare Utilization in the Baseline Period (year before cohort entry) of the New Users Free of Pneumonia at Index Date Excluded from Final Analysis due to Lack of HES Linkage

Variable	Cohort				p-value
	ICS Containing Drugs		LABD Containing Drugs		
	n=11,756	%	n=7,189	%	
Oral Corticosteroids (>4 Rx)	367	3.1	184	2.6	0.03
Oxygen	234	2.0	106	1.5	<0.01
Nebulized therapy	481	4.1	236	3.3	<0.01
SABD	8,187	69.6	5,082	70.7	0.13
Theophylline	308	2.6	151	2.1	0.02
ACE-inhibitors	2,754	23.4	1,826	25.4	<0.01
Statins	3,428	29.2	2,510	34.9	<0.01
Immunosuppresants	128	1.1	84	1.2	0.61
Count of GP visits					
0	270	2.3	124	1.7	<0.01
1-5	2,765	23.5	1,686	23.5	.
6-10	3,562	30.3	2,338	32.5	.
11-15	2,210	18.8	1,422	19.8	.
15-20	1,304	11.1	730	10.2	.
≥21	1,645	14.0	889	12.4	.
Count of Moderate COPD exacerbations					
0	7,502	63.8	4,926	68.5	<0.01
1	2,905	24.7	1,598	22.2	.
≥2	1,349	11.5	665	9.3	.
Count of COPD hospitalizations					
0	10,979	93.4	6,747	93.9	0.43
1	706	6.0	404	5.6	.
≥2	71	<1	38	<1	.

1. This cohort meets all inclusion/exclusion criteria to be classified as New Users except that they either do not have HES Linkage or they do have HES Linkage but it does not cover the baseline period
2. Variables recorded in baseline period unless otherwise specified

8.1.4. Censoring among the New User Cohort

Post-Text Table 11 First Pneumonia Events and Censoring Information among the New User Cohort Free of Pneumonia at Index Date

Event or Censoring	Cohort				Total Number of New Users
	ICS-Containing Drugs		LABD Drugs		
	n	%	n	%	N
Reason for censoring					
Pneumonia event	560	4.7	158	2.4	718
Death	598	5.0	208	3.2	806
Discontinuation of new use of therapy	8,877	74.9	3,052	46.4	11,929
Initiation of ICS or ICSLABA	.	.	1,944	29.5	1,944
End of follow up in GPRD	325	2.7	126	1.9	451
End of follow up in HES	1,493	12.6	1,094	16.6	2,587
All	11,853	100.0	6,582	100.0	18,435

Post-Text Table 12 Summary Statistics for Time Until Event or Censoring among the New User Cohort Free of Pneumonia at Index Date

Cohort	Variable	Statistic	Number of days	Number of years
ICS Containing Drugs	Time at risk	Mean	352.58	0.97
		Std Deviation	473.98	1.30
		Median	154.00	0.42
		Min	1.00	0.00
		Max	3,229.00	8.84
LABD Containing Drugs	Time at risk	Mean	286.28	0.78
		Std Deviation	354.44	0.97
		Median	144.00	0.39
		Min	1.00	0.00
		Max	3,116.00	8.53

8.2. Final Analysis Cohort before Propensity Score Balancing

8.2.1. Final Analysis Cohort Feasibility

Post-Text Table 13 New User Feasibility (Final Analysis Cohort): Estimates of New Users by Year Meeting Inclusion/Exclusion before PS Balancing

		Year of Cohort Entry									Total Number of New Users
		2002	2003	2004	2005	2006	2007	2008	2009	2010	
New Use Drug	Subcategory										
ICS Containing Drugs	ICSmonotherapy	1,479	1,086	955	738	651	525	537	477	363	6,811
	ICS-Containing fixed dose combination	180	307	601	582	619	663	683	604	495	4,734
	ICS-SABA	7	3	.	.	.	.	.	.	.	10
	Total	1,666	1,396	1,556	1,320	1,270	1,188	1,220	1,081	858	11,555
LABD Containing Drugs	Subcategory										
	LABA	312	271	327	289	243	201	206	170	146	2,165
	LAMA	15	206	361	456	458	510	743	749	829	4,327
	Total	327	477	688	745	701	711	949	919	975	6,492
Total Number of New Users		1,993	1,873	2,244	2,065	1,971	1,899	2,169	2,000	1,833	18,047

Post-Text Table 14 New User Feasibility (Final Analysis Cohort): First Pneumonia Events by Type before PS Balancing

Pneumonia Events	Year of Cohort Entry									Total Number of New Users
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode										
HAP	29	29	29	27	25	21	9	8	2	179
Severe CAP	379	352	365	312	252	184	155	89	36	2,124
Non-severe CAP	40	38	23	25	11	14	16	7	2	176
All Pneumonia	448	419	417	364	288	219	180	104	40	2,479

1. All First Pneumonia Events Occurring After or Equal Cohort Entry Date
2. Pneumonia event may occur after the patient is censored

Post-Text Table 15 New User Feasibility (Final Analysis Cohort): First Pneumonia Events by Type before PS Balancing that Cause the Patient to be Censored

Pneumonia Events	Year of Cohort Entry									Total Number of New Users
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode										
HAP	5	4	7	7	5	7	2	2	1	40
Severe CAP	77	75	73	82	92	63	68	56	29	615
Non-severe CAP	8	7	6	5	5	4	6	5	1	47
All Pneumonia	90	86	86	94	102	74	76	63	31	702

1. All first Pneumonia Events Occurring After or Equal Cohort Entry Date

8.2.2. Incidence among Final Analysis Cohort before Propensity Score Balancing

Post-Text Table 16 Incidence Density and Rates per 1,000 person-years of First Pneumonia Episodes (severe or non-severe pneumonia) in Final Analysis Population before PS Balancing

	Cohort					
	ICS Containing Drugs			LABD Containing Drugs		
	N	Person Years	Rate per 1000 PY	N	Person Years	Rate per 1000 PY
Overall	545	11,180.1	48.7	157	5,079.7	30.9
Age at cohort entry date						
45-64 yrs	76	3,811.2	19.9	20	1,452.6	13.8
65-79 yrs	276	5,556.4	49.7	85	2,719.1	31.3
>=80 yrs	193	1,812.5	106.5	52	908.0	57.3
Gender						
Female	199	5,117.7	38.9	71	2,207.5	32.2
Male	346	6,062.3	57.1	86	2,872.2	29.9
Smoking status prior to cohort entry date						
No	53	655.8	80.8	15	211.3	71.0
Ex	278	5,426.3	51.2	85	2,658.9	32.0
Yes	214	5,098.0	42.0	57	2,209.5	25.8
Asthma diagnosis prior to cohort entry date						
No	437	9,217.1	47.4	144	4,481.4	32.1
Yes	108	1,963.0	55.0	13	598.4	21.7
Pneumonia episode in baseline period						
No	507	11,014.2	46.0	151	5,013.9	30.1
Yes	38	165.9	229.1	6	65.9	91.1
COPD severity						
COPD Dx but spirometry conflicts	5	244.3	20.5	2	117.8	17.0
Restrictive COPD	25	750.8	33.3	10	383.3	26.1
GOLD I	7	282.3	24.8	1	162.2	6.2
GOLD II	49	1,773.7	27.6	26	1,232.8	21.1
GOLD III	59	1,496.7	39.4	19	770.4	24.7
GOLD IV	18	338.2	53.2	4	155.7	25.7
Unknown	382	6,294.0	60.7	95	2,257.6	42.1
Clinically significant dyspnea diagnosis						
No	505	10,395.5	48.6	135	4,390.7	30.7
Yes	40	784.6	51.0	22	689.0	31.9

1. This cohort meets all inclusion/exclusion criteria to be classified as New Users and in addition these patients do not have ongoing pneumonia at cohort entry or unacceptable Propensity Scores

8.3. Propensity Score Generation

Post-Text Table 17 Analysis of Effects of Covariates on Treatment for Propensity Score Generation

Type 3 Analysis of Effects			
Effect	DF	Wald Chi-Square	Pr > ChiSq
Age at Cohort Entry Date	1	18.2324	<.0001
Asthma diagnosis[1]	1	47.9706	<.0001
Pneumonia episode[2]	1	0.1088	0.7415
Influenza Vaccination[2]	1	4.3615	0.0368
Pneumococcal Vaccination in (up to) 5 years prior to cohort entry date	1	1.0292	0.3103
MI diagnosis[1]	1	0.1330	0.7153
CHF diagnosis[1]	1	9.7359	0.0018
CVD diagnosis[1]	1	0.3376	0.5612
Dementia diagnosis[1]	1	2.3226	0.1275
Peptic Ulcer diagnosis[1]	1	1.5783	0.2090
Peripheral Vascular Disease diagnosis[1]	1	0.1034	0.7478
Mild Liver Disease diagnosis[1]	1	0.0001	0.9921
Moderate Liver Disease diagnosis[1]	1	0.5418	0.4617
Connective Tissue Disorder diagnosis[1]	1	0.1802	0.6712
Hemiplagia/Paraplegia diagnosis[1]	1	2.0671	0.1505
Diabetes diagnosis[1]	1	0.8358	0.3606
Diabetes (with complications) diagnosis[1]	1	0.1100	0.7402
Cancer (non-metastatic solid tumours) diagnosis[1]	1	0.0363	0.8490
Cancer (Metastatic solid tumours diagnosis) diagnosis[1]	1	1.8245	0.1768
Renal Diseases diagnosis[1]	1	0.0907	0.7633
Anxiety diagnosis or Anxiety prescription[1]	1	1.2094	0.2714
Depression diagnosis or Depression prescription[1]	1	0.1991	0.6555
GERD diagnosis or GERD prescription[1]	1	0.4633	0.4961
Oxygen[2]	1	3.5134	0.0609
Nebulized therapy[2]	1	0.0729	0.7871
SABD[2]	1	31.5026	<.0001
Theophylline[2]	1	0.8628	0.3530
ACE-inhibitors[2]	1	0.0296	0.8634
Statins[2]	1	9.0025	0.0027
Immunosuppresants[2]	1	0.0714	0.7893
Dyspnea			
Grade1	1	0.0682	0.7939
Grade2	1	11.9526	0.0005
Grade3	1	3.4444	0.0635
Grade4	1	3.4859	0.0619
Grade5	1	0.0159	0.8996
Clinically significant dyspnea diagnosis	1	0.0903	0.7638
Gender	1	7.6307	0.0057
Cohort Entry Year	8	314.0614	<.0001
Smoking status[1]	2	27.3117	<.0001
COPD Severity (Gold Stage)	5	56.3478	<.0001
BMI	4	13.5418	0.0089
Townsend Deprivation quintile (Year 2001)	4	12.3095	0.0152
IMD Deprivation quintile closest to cohort entry date	4	4.5911	0.3319
Benzodiazepine[2]	1	0.7667	0.3812
Non-benzodiazepine[2]	1	3.1922	0.0740
GERD Diagnosis or GERD prescription[2]	1	1.2658	0.2606

Type 3 Analysis of Effects			
Effect	DF	Wald Chi-Square	Pr > ChiSq
Number of severe CAP episodes[2]	1	0.0516	0.8204
Count of GP visits[2]	4	2.1444	0.7092
Count of emergency hospital admissions[2]	2	40.6385	<.0001
Count of non-emergency hospital admissions[2]	2	6.5097	0.0386
Count of moderate COPD exacerbations[2]	2	0.9524	0.6211
Count of COPD hospitalizations[2]	1	0.9561	0.3282
Oral Corticosteroid Use (Rx[2])	1	38.9403	<.0001
Oral Corticosteroid Use (>4 Rx[2])	1	26.2661	<.0001

1. Prior to Cohort entry
2. In baseline period (year before cohort entry)

Post-Text Table 18 Maximum Likelihood Estimates of Covariates on Treatment for Propensity Score Generation

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	2.3876	0.1851	166.3644	<.0001
Age at Cohort Entry Date	1	-0.00817	0.00191	18.2324	<.0001
Asthma diagnosis[1]	1	0.3321	0.0479	47.9706	<.0001
Pneumonia episode[2]	1	-0.0833	0.2526	0.1088	0.7415
Influenza Vaccination[2]	1	-0.0830	0.0398	4.3615	0.0368
Pneumococcal Vaccination in (up to) 5 years prior to cohort entry date	1	-0.0361	0.0356	1.0292	0.3103
MI diagnosis[1]	1	-0.0225	0.0618	0.1330	0.7153
CHF diagnosis[1]	1	-0.1959	0.0628	9.7359	0.0018
CVD diagnosis[1]	1	0.0367	0.0632	0.3376	0.5612
Dementia diagnosis[1]	1	0.3140	0.2060	2.3226	0.1275
Peptic Ulcer diagnosis[1]	1	-0.0765	0.0609	1.5783	0.2090
Peripheral Vascular Disease diagnosis[1]	1	-0.0186	0.0577	0.1034	0.7478
Mild Liver Disease diagnosis[1]	1	-0.00205	0.2055	0.0001	0.9921
Moderate Liver Disease diagnosis[1]	1	-0.3818	0.5187	0.5418	0.4617
Connective Tissue Disorder diagnosis[1]	1	-0.0344	0.0811	0.1802	0.6712
Hemiplagia/Paraplegia diagnosis[1]	1	0.4521	0.3144	2.0671	0.1505
Diabetes diagnosis[1]	1	0.0565	0.0618	0.8358	0.3606
Diabetes (with complications) diagnosis[1]	1	-0.0413	0.1246	0.1100	0.7402
Cancer (non-metastatic solid tumours) diagnosis[1]	1	0.0113	0.0592	0.0363	0.8490
Cancer (Metastatic solid tumours diagnosis) diagnosis[1]	1	-0.4237	0.3137	1.8245	0.1768
Renal Diseases diagnosis[1]	1	0.0180	0.0597	0.0907	0.7633
Anxiety diagnosis or Anxiety prescription[1]	1	0.0452	0.0411	1.2094	0.2714
Depression diagnosis or Depression prescription[1]	1	0.0166	0.0372	0.1991	0.6555
GERD diagnosis or GERD prescription[1]	1	-0.0299	0.0439	0.4633	0.4961
Oxygen[2]	1	-0.2716	0.1449	3.5134	0.0609
Nebulized therapy[2]	1	-0.0290	0.1075	0.0729	0.7871
SABD[2]	1	-0.2096	0.0373	31.5026	<.0001
Theophylline[2]	1	-0.1084	0.1167	0.8628	0.3530
ACE-inhibitors [2]	1	-0.00714	0.0415	0.0296	0.8634
Statins[2]	1	-0.1230	0.0410	9.0025	0.0027
Immunosuppresants[2]	1	-0.0396	0.1480	0.0714	0.7893
Dyspnea					
Grade1	1	0.0203	0.0776	0.0682	0.7939
Grade2	1	-0.1893	0.0548	11.9526	0.0005
Grade3	1	-0.4626	0.2492	3.4444	0.0635

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Grade4	1	-0.4510	0.2416	3.4859	0.0619
Grade5	1	0.0378	0.2999	0.0159	0.8996
Clinically significant dyspnea diagnosis	1	0.0768	0.2557	0.0903	0.7638
Male	1	-0.0958	0.0347	7.6307	0.0057
Cohort Entry Year					
2003	1	-0.5110	0.0815	39.3168	<.0001
2004	1	-0.6905	0.0778	78.7580	<.0001
2005	1	-0.8740	0.0785	123.9710	<.0001
2006	1	-0.8297	0.0801	107.2896	<.0001
2007	1	-0.8817	0.0815	117.1049	<.0001
2008	1	-1.1388	0.0797	204.2475	<.0001
2009	1	-1.1576	0.0838	190.7743	<.0001
2010	1	-1.3945	0.0882	250.0003	<.0001
Smoking status[1]					
Ex	1	-0.3699	0.0769	23.1095	<.0001
Yes	1	-0.4137	0.0793	27.1963	<.0001
COPD Severity					
GOLD Stage Restrictive	1	0.1495	0.0701	4.5485	0.0329
GOLD Stage I	1	0.1579	0.0955	2.7362	0.0981
GOLD Stage III	1	0.1070	0.0575	3.4683	0.0626
GOLD Stage IV	1	0.0910	0.1094	0.6916	0.4056
GOLD Stage Unknown	1	0.3129	0.0440	50.4985	<.0001
BMI status[1]					
<18.5	1	-0.1023	0.0758	1.8224	0.1770
≥25-30	1	0.1248	0.0410	9.2676	0.0023
≥30	1	0.0595	0.0468	1.6165	0.2036
No recording	1	0.0521	0.0637	0.6687	0.4135
Townsend Deprivation quintile (Year 2001)					
Quintile 2	1	0.0776	0.0610	1.6223	0.2028
Quintile 3	1	0.0932	0.0695	1.8000	0.1797
Quintile 4	1	-0.0882	0.0818	1.1615	0.2811
Quintile 5	1	-0.0861	0.1003	0.7368	0.3907
IMD Deprivation quintile closest to cohort entry date					
Quintile 2	1	-0.0279	0.0609	0.2105	0.6464
Quintile 3	1	-0.1063	0.0699	2.3153	0.1281
Quintile 4	1	-0.00857	0.0813	0.0111	0.9161
Quintile 5	1	-0.00601	0.0982	0.0037	0.9512
Benzodiazepine[2]	1	-0.0513	0.0585	0.7667	0.3812
Non-benzodiazepine[2]	1	-0.1386	0.0776	3.1922	0.0740
GERD diagnosis or GERD prescription[2]	1	0.0537	0.0478	1.2658	0.2606
Number of severe CAP episodes[2]	1	-0.0647	0.2850	0.0516	0.8204
Count of GP visits[2]					
1	1	0.00205	0.0446	0.0021	0.9634
2	1	0.0439	0.0513	0.7333	0.3918
3	1	-0.0392	0.0626	0.3914	0.5316
4	1	0.0235	0.0648	0.1311	0.7173
Count of emergency hospital admissions[2]					
1-2 vs 0	1	0.2781	0.0472	34.7790	<.0001
>2 vs 0	1	0.4563	0.1316	12.0175	0.0005
Count of non-emergency hospital admissions[2]					
1-2	1	-0.1131	0.0443	6.5090	0.0107
>2	1	-0.0355	0.1116	0.1015	0.7500
Count of moderate COPD exacerbations[2]					

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
1	1	0.0338	0.0392	0.7430	0.3887
≥2	1	0.0652	0.1012	0.4149	0.5195
Count of COPD hospitalizations[2] ≥1	1	0.0723	0.0740	0.9561	0.3282
Oral Corticosteroid Use (Rx[2]) ≥1	1	0.2810	0.0450	38.9403	<.0001
Oral Corticosteroid Use (>4 Rx[2])	1	-0.5465	0.1066	26.2661	<.0001

3. Prior to Cohort entry
4. In baseline period (year before cohort entry)

Post-Text Table 19 Association of Predicted Probabilities and Observed Responses

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	66.3	Somers' D	0.330
Percent Discordant	33.3	Gamma	0.331
Percent Tied	0.4	Tau-a	0.152
Pairs	75015060	c	0.665

Post-Text Table 20 Hazard Ratios: All Pneumonia by Quintiles for PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.4430	1,951	1,909	42	0.0215	0.4565	1,658	1,592	66	0.0398	1.57	1.06	2.32
21-40	0.5699	1,606	1,570	36	0.0224	0.5730	2,004	1,912	92	0.0459	1.76	1.19	2.58
41-60	0.6424	1,301	1,266	35	0.0269	0.6457	2,308	2,191	117	0.0507	1.59	1.09	2.32
61-80	0.7138	992	968	24	0.0242	0.7160	2,618	2,493	125	0.0477	1.74	1.12	2.70
81-100	0.8109	642	622	20	0.0312	0.8228	2,967	2,822	145	0.0489	1.31	0.82	2.09
Overall	0.5921	6,492	6,335	157	0.0242	0.6673	11,555	11,010	545	0.0472	1.61	1.34	1.92

Post-Text Table 21 Hazard Ratios: Hospitalized Pneumonia by Quintiles for PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.4430	1,951	1,930	21	0.0108	0.4565	1,658	1,616	42	0.0253	1.95	1.14	3.33
21-40	0.5699	1,606	1,584	22	0.0137	0.5730	2,004	1,944	60	0.0299	1.85	1.14	3.02
41-60	0.6424	1,301	1,280	21	0.0161	0.6457	2,308	2,244	64	0.0277	1.42	0.87	2.33
61-80	0.7138	992	977	15	0.0151	0.7160	2,618	2,546	72	0.0275	1.61	0.92	2.81
81-100	0.8109	642	631	11	0.0171	0.8228	2,967	2,886	81	0.0273	1.30	0.69	2.44
Overall	0.5921	6,492	6,402	90	0.0139	0.6673	11,555	11,236	319	0.0276	1.62	1.28	2.05

Post-Text Table 22 Hazard Ratios: Severe Pneumonia (not censoring for non-severe pneumonia before severe) by Quintiles for PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.4430	1,951	1,910	41	0.0210	0.4565	1,658	1,595	63	0.0380	1.53	1.03	2.27
21-40	0.5699	1,606	1,572	34	0.0212	0.5730	2,004	1,919	85	0.0424	1.72	1.16	2.56
41-60	0.6424	1,301	1,267	34	0.0261	0.6457	2,308	2,197	111	0.0481	1.55	1.06	2.28
61-80	0.7138	992	970	22	0.0222	0.7160	2,618	2,501	117	0.0447	1.76	1.12	2.78
81-100	0.8109	642	626	16	0.0249	0.8228	2,967	2,830	137	0.0462	1.55	0.93	2.60
Overall	0.5921	6,492	6,345	147	0.0226	0.6673	11,555	11,042	513	0.0444	1.61	1.34	1.94

Post-Text Table 23 Propensity Score Distribution and Weight

	Propensity Score Distribution		Propensity Score Weight
	Exposed =0	Exposed=1	Combined
Minimum	0.1748932	0.2129630	0.4359768
1st Percentile	0.3045448	0.3540403	0.5494823
5th Percentile	0.3799557	0.4455866	0.6540187
25th Percentile	0.5065718	0.5843944	0.8071703
50th Percentile	0.5947917	0.6733728	0.9356890
75th Percentile	0.6789730	0.7600395	1.1025685
90th Percentile	0.7566535	0.8338542	1.3406013
95th Percentile	0.7998925	0.8627201	1.5548986
99th Percentile	0.8725841	0.9032310	2.2167058
Maximum	0.9409288	0.9550341	6.0897253

8.4. Matched Analysis Cohort after Propensity Score Balancing

8.4.1. Matched Final Analysis Cohort Feasibility

Post-Text Table 24 New User Feasibility (Matched Final Analysis Cohort): Estimates of New Users by Year Meeting Inclusion/Exclusion after PS Balancing

		Year of Cohort Entry									Total Number of New Users
		2002	2003	2004	2005	2006	2007	2008	2009	2010	
New Use Drug	Subcategory										
ICS Containing Drugs	ICSmonotherapy	312	349	412	417	354	298	397	368	333	3,240
	ICS-Containing fixed dose combination	28	104	267	322	333	427	524	494	460	2,959
	ICS-SABA	2	.	.	.	.	.	.	.	.	2
	Total	342	453	679	739	687	725	921	862	793	6,201
LABD Containing Drugs	Subcategory										
	LABA	312	271	324	287	239	200	195	157	114	2,099
	LAMA	15	206	360	453	456	505	701	698	708	4,102
	Total	327	477	684	740	695	705	896	855	822	6,201
Total Number of New Users		669	930	1,363	1,479	1,382	1,430	1,817	1,717	1,615	12,402

Post-Text Table 25 New User Feasibility (Matched Final Analysis Cohort): First Pneumonia Events by Type after PS Balancing

Pneumonia Events	Year of Cohort Entry									Total Number of New Users
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode										
HAP	5	11	26	20	15	15	8	8	2	110
Severe CAP	125	188	234	224	189	140	129	74	28	1,331
Non-severe CAP	16	15	8	16	7	7	15	5	2	91
All Pneumonia	146	214	268	260	211	162	152	87	32	1,532

1. All First Pneumonia Events Occurring After or Equal Cohort Entry Date
2. Pneumonia event may occur after the patient is censored

Post-Text Table 26 New User Feasibility (Matched Final Analysis Cohort): First Pneumonia Events by Type after PS Balancing that Cause the Patient to be Censored after PS Balancing

Pneumonia Events	Year of Cohort Entry									Total Number of New Users
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode										
HAP	1	3	4	5	3	4	1	2	1	24
Severe CAP	23	36	41	56	62	46	55	46	23	388
Non-severe CAP	4	2	2	2	4	1	5	3	1	24
All Pneumonia	28	41	47	63	69	51	61	51	25	436

1. All first Pneumonia Events Occurring After or Equal Cohort Entry Date

8.4.2. Incidence among Matched Final Analysis Cohort after PS Balancing

Post-Text Table 27 Incidence Density and Rates per 1,000 person-years of First Pneumonia Episodes (severe or non-severe pneumonia) in Matched Cohort after PS Balancing

	Cohort					
	ICS Containing Drugs			LABD Containing Drugs		
	N	Person Years	Rate per 1000 PY	N	Person Years	Rate per 1000 PY
Overall	286	5,690.5	50.3	150	4,901.4	30.6
Age at cohort entry date						
45-64 yrs	40	1,802.1	22.2	19	1,428.5	13.3
65-79 yrs	148	2,891.9	51.2	84	2,623.6	32.0
>=80 yrs	98	996.6	98.3	47	849.3	55.3
Gender						
Female	93	2,322.6	40.0	67	2,142.7	31.3
Male	193	3,367.9	57.3	83	2,758.7	30.1
Smoking status prior to cohort entry date						
No	13	220.1	59.1	15	211.3	71.0
Ex	166	2,859.5	58.1	81	2,561.8	31.6
Yes	107	2,611.0	41.0	54	2,128.4	25.4
Asthma diagnosis prior to cohort entry date						
No	258	5,035.7	51.2	138	4,308.0	32.0
Yes	28	654.8	42.8	12	593.5	20.2
Pneumonia episode in baseline period						
No	264	5,609.7	47.1	144	4,838.8	29.8
Yes	22	80.8	272.3	6	62.7	95.7
COPD severity						
COPD Dx but spirometry conflicts	4	138.4	28.9	2	117.5	17.0
Restrictive COPD	18	449.8	40.0	9	370.3	24.3
GOLD I	6	175.4	34.2	1	153.8	6.5
GOLD II	35	1,264.4	27.7	22	1,131.5	19.4
GOLD III	44	989.1	44.5	17	741.2	22.9
GOLD IV	16	209.8	76.3	4	154.8	25.8
Unknown	163	2,463.6	66.2	95	2,232.4	42.6
Clinically significant dyspnea diagnosis						
No	249	4,995.9	49.8	133	4,328.3	30.7
Yes	37	694.6	53.3	17	573.2	29.7

1. This cohort meets all inclusion/exclusion criteria to be classified as New Users and in addition these patients do not have ongoing pneumonia at cohort entry or unacceptable Propensity Scores

8.4.3. Censoring among the Matched Final Analysis Cohort

Post-Text Table 28 Summary Statistics for Time Until Event or Censoring among the Matched Final Analysis Cohort after PS Balancing

Cohort	Variable	Statistic	Number of days	Number of years
ICS Containing Drugs	Time at risk	Mean	335.18	0.92
		Std Deviation	418.79	1.15
		Median	161.00	0.44
		Min	1.00	0.00
		Max	3,198.00	8.76
LABD Containing Drugs	Time at risk	Mean	288.70	0.79
		Std Deviation	357.09	0.98
		Median	145.00	0.40
		Min	1.00	0.00
		Max	3,116.00	8.53

8.5. Final Analysis Cohort of Persistent Users

8.5.1. Final Analysis Cohort of Persistent Users Feasibility before Propensity Score Balancing

Post-Text Table 29 New User Feasibility (Final Analysis Cohort of Persistent Users): Estimates of New Users by Year Meeting Inclusion/Exclusion before PS Balancing

		Year of Cohort Entry									Total Number of New Users
		2002	2003	2004	2005	2006	2007	2008	2009	2010	
New Use Drug	Subcategory										
ICS Containing Drugs	ICS monotherapy	518	392	422	327	291	224	211	196	167	2,748
	ICS-Containing fixed dose combination	86	166	357	353	371	413	402	344	306	2,798
	ICS-SABA	2	1	.	.	.	.	.	.	.	3
	Total	606	559	779	680	662	637	613	540	473	5,549
LABD Containing Drugs	Subcategory										
	LABA	159	133	168	156	120	105	119	91	74	1,125
	LAMA	8	133	241	274	281	295	494	460	536	2,722
	Total	167	266	409	430	401	400	613	551	610	3,847
Total Number of New Users		773	825	1,188	1,110	1,063	1,037	1,226	1,091	1,083	9,396

Post-Text Table 30 New User Feasibility (Final Analysis Cohort of Persistent Users): First Pneumonia Events by Type before PS Balancing

Pneumonia Events	**Year of Cohort Entry**									**Total Number of New Users**
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode										
HAP	11	8	18	16	14	13	4	4	.	88
Severe CAP	165	169	192	171	141	98	86	51	11	1,084
Non-severe CAP	12	18	16	9	8	8	6	4	1	82
All Pneumonia	188	195	226	196	163	119	96	59	12	1,254

1. All First Pneumonia Events Occurring After or Equal Cohort Entry Date
2. Pneumonia event may occur after the patient is censored

Post-Text Table 31 New User Feasibility (Final Analysis Cohort of Persistent Users): First Pneumonia Events by Type before PS Balancing that Cause the Patient to be Censored

Pneumonia Events	Year of Cohort Entry									Total Number of New Users
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode										
HAP	2	2	6	7	4	6	2	1	.	30
Severe CAP	55	54	57	56	70	47	52	38	11	440
Non-severe CAP	5	5	6	5	5	4	3	4	.	37
All Pneumonia	62	61	69	68	79	57	57	43	11	507

1. All first Pneumonia Events Occurring After or Equal Cohort Entry Date

8.5.2. Persistent User Cohort: Propensity Score Generation

Post-Text Table 32 Hazard Ratios: All Pneumonia by Quintiles for Persistent Users PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.3617	1,179	1,147	32	0.0271	0.3810	700	686	14	0.0200	0.61	0.33	1.13
21-40	0.5078	958	939	19	0.0198	0.5084	921	864	57	0.0619	2.32	1.38	3.90
41-60	0.5932	767	735	32	0.0417	0.5967	1,113	1,039	74	0.0665	1.04	0.69	1.58
61-80	0.6721	567	550	17	0.0300	0.6778	1,312	1,212	100	0.0762	1.90	1.14	3.19
81-100	0.7885	376	355	21	0.0559	0.8086	1,503	1,362	141	0.0938	1.03	0.65	1.64
Overall	0.5317	3,847	3,726	121	0.0315	0.6314	5,549	5,163	386	0.0696	1.46	1.18	1.79

Post-Text Table 33 Hazard Ratios: Hospitalized Pneumonia by Quintiles for Persistent Users PS Model

Percentile	Exposed											
	No					Yes						
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.3617	1,179	1,162	17	0.0144	0.3810	700	693	7	0.0100	0.56	0.24	1.32
21-40	0.5078	958	948	10	0.0104	0.5084	921	883	38	0.0413	2.86	1.41	5.78
41-60	0.5932	767	746	21	0.0274	0.5967	1,113	1,064	49	0.0440	1.06	0.64	1.78
61-80	0.6721	567	555	12	0.0212	0.6778	1,312	1,254	58	0.0442	1.59	0.85	2.95
81-100	0.7885	376	362	14	0.0372	0.8086	1,503	1,418	85	0.0566	0.93	0.52	1.64
Overall	0.5317	3,847	3,773	74	0.0192	0.6314	5,549	5,312	237	0.0427	1.45	1.12	1.89

Post-Text Table 34 Hazard Ratios: Severe Pneumonia (not censoring for non-severe pneumonia before severe) by Quintiles for Persistent Users PS Model

Percentile	Exposed											
	No					Yes						
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.3617	1,179	1,148	31	0.0263	0.3810	700	688	12	0.0171	0.54	0.28	1.04
21-40	0.5078	958	940	18	0.0188	0.5084	921	871	50	0.0543	2.14	1.25	3.68
41-60	0.5932	767	737	30	0.0391	0.5967	1,113	1,040	73	0.0656	1.09	0.71	1.67
61-80	0.6721	567	551	16	0.0282	0.6778	1,312	1,219	93	0.0709	1.86	1.09	3.17
81-100	0.7885	376	356	20	0.0532	0.8086	1,503	1,371	132	0.0878	1.01	0.63	1.63
Overall	0.5317	3,847	3,732	115	0.0299	0.6314	5,549	5,189	360	0.0649	1.42	1.15	1.75

8.5.3. Final Analysis Cohort of Persistent Users Feasibility after Propensity Score Balancing

8.5.3.1. Matched Final Analysis Cohort of Persistent Users Feasibility

Post-Text Table 35 New User Feasibility (Matched Final Analysis Cohort of Persistent Users): Estimates of New Users by Year Meeting Inclusion/Exclusion after PS Balancing

		Year of Cohort Entry									Total Number of New Users
		2002	2003	2004	2005	2006	2007	2008	2009	2010	
New Use Drug	Subcategory										
ICS Containing Drugs	ICSmonotherapy	131	170	197	187	157	123	161	154	144	1,424
	ICS-Containing fixed dose combination	26	90	205	229	215	252	328	284	282	1,911
	ICS-SABA	1	1	.	.	.	.	.	.	.	2
	Total	158	261	402	416	372	375	489	438	426	3,337
LABD Containing Drugs	Subcategory										
	LABA	159	130	165	148	115	95	105	72	52	1,041
	LAMA	8	132	231	263	263	277	393	358	371	2,296
	Total	167	262	396	411	378	372	498	430	423	3,337
Total Number of New Users		325	523	798	827	750	747	987	868	849	6,674

Post-Text Table 36 New User Feasibility (Matched Final Analysis Cohort of Persistent Users): First Pneumonia Events by Type after PS Balancing

Pneumonia Events	**Year of Cohort Entry**									**Total Number of New Users**
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode										
HAP	3	4	14	10	11	9	4	3	.	58
Severe CAP	70	111	132	125	86	68	72	37	9	710
Non-severe CAP	7	9	8	7	8	4	5	3	.	51
All Pneumonia	80	124	154	142	105	81	81	43	9	819

1. All First Pneumonia Events Occurring After or Equal Cohort Entry Date
2. Pneumonia event may occur after the patient is censored

Post-Text Table 37 New User Feasibility (Matched Final Analysis Cohort of Persistent Users): First Pneumonia Events by Type after PS Balancing that Cause the Patient to be Censored

Pneumonia Events	Year of Cohort Entry									Total Number of New Users
	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Type of Pneumonia episode										
HAP	1	1	3	4	4	4	2	1	.	20
Severe CAP	27	34	32	36	40	30	41	27	9	276
Non-severe CAP	3	1	4	3	5	1	3	3	.	23
All Pneumonia	31	36	39	43	49	35	46	31	9	319

1. All first Pneumonia Events Occurring After or Equal Cohort Entry Date

8.5.3.2. Matched Final Analysis Cohort of Persistent Users Demographics

Post-Text Table 38 Descriptive Characteristics from the Baseline Period (year before cohort entry)/Patient History for the Matched Persistent User Cohort after PS Balancing

Variable	Cohort				p-value
	ICS-Containing Drugs		LABD Drugs		
	n=3,337	%	n=3,337	%	
Male	1,900	56.9	1,914	57.4	0.73
Age at cohort entry date					
45-64 yrs	1,035	31.0	990	29.7	0.36
65-79 yrs	1,690	50.6	1,747	52.4	.
>=80 yrs	612	18.3	600	18.0	.
Smoking status prior to cohort entry date					
No	139	4.2	136	4.1	0.77
Yes	1,468	44.0	1,497	44.9	.
Ex	1,730	51.8	1,704	51.1	.
COPD severity					
COPD Dx but spirometry conflicts	74	2.2	83	2.5	0.99
Restrictive COPD	233	7.0	231	6.9	.
GOLD I	108	3.2	104	3.1	.
GOLD II	729	21.8	715	21.4	.
GOLD III	527	15.8	532	15.9	.
GOLD IV	103	3.1	108	3.2	.
Unknown	1,563	46.8	1,564	46.9	.
Clinically significant dyspnea diagnosis	490	14.7	504	15.1	0.63
Asthma diagnosis prior to cohort entry date	401	12.0	405	12.1	0.88
Pneumonia episode in baseline period	58	1.7	57	1.7	0.93
Number of non-severe CAP episodes in baseline period					
0	3,321	99.5	3,324	99.6	0.58
1	16	<1	13	<1	.
Number of severe CAP episodes in baseline period					
0	3,295	98.7	3,293	98.7	0.98
1	41	1.2	43	1.3	.
2	1	<1	1	<1	.
Number of HAP episodes in baseline period	3,336	100.0	3,336	100.0	1.00
0	1	<1	1	<1	.
1					
Townsend Deprivation quintile (Year 2001)					
Quintile 1(Least deprived)	519	15.6	508	15.2	0.94
Quintile 2	648	19.4	653	19.6	.
Quintile 3	710	21.3	689	20.6	.
Quintile 4	820	24.6	827	24.8	.
Quintile 5 (Most deprived)	640	19.2	660	19.8	.
IMD Deprivation quintile closest to cohort entry date					
Quintile 1(Least deprived)	445	13.3	448	13.4	0.99
Quintile 2	655	19.6	640	19.2	.
Quintile 3	691	20.7	688	20.6	.
Quintile 4	769	23.0	771	23.1	.
Quintile 5 (Most deprived)	777	23.3	790	23.7	.

Post-Text Table 39 Patient Co-morbidities in the Baseline Period (year before cohort entry)/Patient History for the Matched Persistent User Cohort after PS Balancing

Variable	Cohort				
	ICS-Containing Drugs		LABD Drugs		
	n=3,337	%	n=3,337	%	p-value
Influenza Vaccination in baseline period	2,323	69.6	2,333	69.9	0.79
Pneumococcal Vaccination in (up to) 5 years prior to cohort entry date	1,377	41.3	1,386	41.5	0.82
BMI status					
No recording	263	7.9	247	7.4	0.98
Underweight (0< - <18.5)	173	5.2	178	5.3	.
Low Normal (18.5 - <21)	335	10.0	328	9.8	.
High Normal (21 - <25)	876	26.3	883	26.5	.
Overweight (25 - <30)	982	29.4	990	29.7	.
Obese (≥30)	708	21.2	711	21.3	.
MI diagnosis	255	7.6	286	8.6	0.16
CHF diagnosis	257	7.7	272	8.2	0.50
CVD diagnosis	231	6.9	250	7.5	0.37
Dementia diagnosis	14	<1	17	<1	0.59
GERD diagnosis or GERD prescription	1,601	48.0	1,623	48.6	0.59
Peptic Ulcer diagnosis	262	7.9	273	8.2	0.62
Peripheral Vascular Disease diagnosis	307	9.2	314	9.4	0.77
Mild Liver Disease diagnosis	22	<1	20	<1	0.76
Moderate Liver Disease diagnosis	2	<1	1	<1	0.56
Connective Tissue Disorder diagnosis	175	5.2	173	5.2	0.91
Hemiplagia/Paraplegia diagnosis	10	<1	10	<1	1.00
Diabetes diagnosis	361	10.8	351	10.5	0.69
Diabetes (with complications) diagnosis	72	2.2	68	2.0	0.73
Anxiety diagnosis or Anxiety prescription	917	27.5	923	27.7	0.87
Depression diagnosis or Depression prescription	1,451	43.5	1,465	43.9	0.73
Cancer (non-metastatic solid tumours) diagnosis	255	7.6	267	8.0	0.58
Cancer (Metastatic solid tumours diagnosis) diagnosis	6	<1	7	<1	0.78
Renal Diseases diagnosis	332	9.9	346	10.4	0.57

1. Variables recorded in patient history “prior to cohort entry date” unless otherwise specified

Post-Text Table 40 Patient Medications Used and Healthcare Utilization in the Baseline Period (year before cohort entry) for the Matched Persistent User Cohort after PS Balancing

Variable	Cohort				p-value
	ICS-Containing Drugs		LABD Drugs		
	n=3,337	%	n=3,337	%	
Oral Corticosteroids (>4 Rx)	104	3.1	104	3.1	1.00
Oxygen	47	1.4	45	1.3	0.83
Nebulized therapy	86	2.6	88	2.6	0.88
SABD	2,524	75.6	2,484	74.4	0.26
Theophylline	83	2.5	74	2.2	0.47
ACE-inhibitors	897	26.9	927	27.8	0.41
Statins	1,190	35.7	1,212	36.3	0.57
Immunosuppresants	40	1.2	46	1.4	0.51
Count of GP visits					
0	31	<1	24	<1	0.86
1-5	791	23.7	783	23.5	.
6-10	1,128	33.8	1,110	33.3	.
11-15	684	20.5	701	21.0	.
15-20	347	10.4	368	11.0	.
≥21	356	10.7	351	10.5	.
Count of emergency hospital admissions					
0	2,756	82.6	2,740	82.1	0.69
1-2	534	16.0	555	16.6	.
≥3	47	1.4	42	1.3	.
Count of non-emergency hospital admissions					
0	2,708	81.2	2,698	80.9	0.60
1-2	574	17.2	573	17.2	.
≥3	55	1.6	66	2.0	.
Count of moderate COPD exacerbations					
0	2,159	64.7	2,156	64.6	0.55
1	828	24.8	854	25.6	.
≥2	350	10.5	327	9.8	.
Count of COPD hospitalizations					
0	3,144	94.2	3,147	94.3	0.30
1	177	5.3	165	4.9	.
≥2	16	<1	25	<1	.

1. Variables recorded in baseline period unless otherwise specified

8.5.3.3. Censoring among the Matched Persistent User Cohort

Post-Text Table 41 First Pneumonia Events and Censoring Information among the Matched Final Analysis Persistent User Cohort after PS Balancing

Event or Censoring	Cohort				Total Number of New Users
	ICS Containing Drugs		LABD Containing Drugs		
	n	%	n	%	n
Reason for censoring					
Pneumonia event	206	6.2	113	3.4	319
Death	207	6.2	119	3.6	326
Discontinuation of new use of therapy	1,762	52.8	987	29.6	2,749
Initiation of ICS or ICS/LABA	.	.	1,341	40.2	1,341
End of follow up in GPRD	124	3.7	74	2.2	198
End of follow up in HES	1,038	31.1	703	21.1	1,741
All	3,337	100.0	3,337	100.0	6,674

Post-Text Table 42 Summary Statistics for Time until Event or Censoring among the Matched Final Analysis Persistent User Cohort after PS Balancing

Cohort	Variable	Statistic	Number of days	Number of years
ICS Containing Drugs	Time at risk	Mean	581.01	1.59
		Std Deviation	518.61	1.42
		Median	386.00	1.06
		Min	1.00	0.00
		Max	3,203.00	8.77
LABD Containing Drugs	Time at risk	Mean	430.34	1.18
		Std Deviation	419.44	1.15
		Median	301.00	0.82
		Min	1.00	0.00
		Max	3,116.00	8.53

8.6. New Users Cohort by Dose: Propensity Score Generation

Post-Text Table 43 Hazard Ratios: All Pneumonia by Quintiles for High Dose Users PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.1444	1,472	1,441	31	0.0211	0.1472	261	251	10	0.0383	1.46	0.73	2.91
21-40	0.1945	1,403	1,371	32	0.0228	0.1953	331	310	21	0.0634	1.91	1.08	3.40
41-60	0.2355	1,356	1,331	25	0.0184	0.2356	378	352	26	0.0688	3.16	1.83	5.46
61-80	0.2846	1,230	1,193	37	0.0301	0.2850	504	475	29	0.0575	1.28	0.78	2.10
81-100	0.3888	1,031	999	32	0.0310	0.4055	702	635	67	0.0954	2.03	1.32	3.12
Overall	0.2396	6,492	6,335	157	0.0242	0.2851	2,176	2,023	153	0.0703	2.11	1.68	2.65

Post-Text Table 44 Hazard Ratios: All Pneumonia by Quintiles for Not High Dose Users PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.3612	1,996	1,948	48	0.0240	0.3761	1,178	1,136	42	0.0357	1.27	0.84	1.92
21-40	0.5038	1,611	1,579	32	0.0199	0.5060	1,563	1,498	65	0.0416	1.80	1.18	2.75
41-60	0.5925	1,285	1,254	31	0.0241	0.5960	1,890	1,788	102	0.0540	1.96	1.31	2.93
61-80	0.6793	986	959	27	0.0274	0.6834	2,188	2,105	83	0.0379	1.27	0.82	1.97
81-100	0.7943	614	595	19	0.0309	0.8093	2,560	2,460	100	0.0391	1.13	0.69	1.85
Overall	0.5317	6,492	6,335	157	0.0242	0.6320	9,379	8,987	392	0.0418	1.46	1.21	1.76

Post-Text Table 45 Hazard Ratios: All Pneumonia by Quintiles for Medium Dose Users PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.2485	1,650	1,608	42	0.0255	0.2560	557	535	22	0.0395	1.24	0.73	2.10
21-40	0.3331	1,493	1,458	35	0.0234	0.3342	715	682	33	0.0462	1.68	1.04	2.71
41-60	0.3939	1,333	1,300	33	0.0248	0.3955	874	827	47	0.0538	1.71	1.10	2.67
61-80	0.4670	1,170	1,148	22	0.0188	0.4700	1,038	985	53	0.0511	2.32	1.41	3.82
81-100	0.6009	846	821	25	0.0296	0.6192	1,361	1,311	50	0.0367	0.98	0.60	1.60
Overall	0.3831	6,492	6,335	157	0.0242	0.4528	4,545	4,340	205	0.0451	1.49	1.21	1.84

Post-Text Table 46 Hazard Ratios: All Pneumonia by Quintiles for Low Dose Users PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.1628	1,885	1,846	39	0.0207	0.1736	380	367	13	0.0342	1.63	0.88	3.02
21-40	0.2990	1,594	1,556	38	0.0238	0.3041	671	652	19	0.0283	1.03	0.59	1.80
41-60	0.4209	1,320	1,290	30	0.0227	0.4258	946	898	48	0.0507	2.01	1.28	3.16
61-80	0.5346	1,043	1,014	29	0.0278	0.5422	1,222	1,186	36	0.0295	1.07	0.66	1.75
81-100	0.6904	650	629	21	0.0323	0.7140	1,615	1,544	71	0.0440	1.37	0.84	2.23
Overall	0.3613	6,492	6,335	157	0.0242	0.5148	4,834	4,647	187	0.0387	1.43	1.15	1.77

8.7. Persistent Users Cohort by Dose: Propensity Score Generation

Post-Text Table 47 Hazard Ratios: All Pneumonia by Quintiles for High Dose Persistent Users PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.1123	909	882	27	0.0297	0.1192	115	107	8	0.0696	1.81	0.85	3.84
21-40	0.1748	849	837	12	0.0141	0.1772	175	165	10	0.0571	2.82	1.26	6.31
41-60	0.2268	785	757	28	0.0357	0.2276	240	224	16	0.0667	1.16	0.61	2.21
61-80	0.2904	732	707	25	0.0342	0.2911	292	274	18	0.0616	1.11	0.61	2.03
81-100	0.4237	572	543	29	0.0507	0.4562	452	387	65	0.1438	1.76	1.13	2.74
Overall	0.2297	3,847	3,726	121	0.0315	0.3065	1,274	1,157	117	0.0918	1.95	1.51	2.53

Post-Text Table 48 Hazard Ratios: All Pneumonia by Quintiles for Not High Dose Persistent Users PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.2715	1,168	1,136	32	0.0274	0.2924	456	441	15	0.0329	0.95	0.52	1.73
21-40	0.4234	962	934	28	0.0291	0.4269	663	634	29	0.0437	1.08	0.64	1.81
41-60	0.5250	776	754	22	0.0284	0.5303	848	799	49	0.0578	1.36	0.82	2.26
61-80	0.6238	579	559	20	0.0345	0.6251	1,046	971	75	0.0717	1.60	0.97	2.62
81-100	0.7580	362	343	19	0.0525	0.7827	1,262	1,161	101	0.0800	1.00	0.61	1.64
Overall	0.4594	3,847	3,726	121	0.0315	0.5866	4,275	4,006	269	0.0629	1.30	1.05	1.62

Post-Text Table 49 Hazard Ratios: All Pneumonia by Quintiles for Medium Dose Persistent Users PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.1868	993	965	28	0.0282	0.1977	226	216	10	0.0442	1.14	0.56	2.29
21-40	0.2806	894	867	27	0.0302	0.2815	326	313	13	0.0399	0.94	0.49	1.79
41-60	0.3493	781	761	20	0.0256	0.3522	439	420	19	0.0433	1.09	0.58	2.06
61-80	0.4283	699	676	23	0.0329	0.4303	521	479	42	0.0806	1.64	0.98	2.74
81-100	0.5783	480	457	23	0.0479	0.6089	740	675	65	0.0878	1.30	0.81	2.10
Overall	0.3343	3,847	3,726	121	0.0315	0.4289	2,252	2,103	149	0.0662	1.37	1.07	1.75

Post-Text Table 50 Hazard Ratios: All Pneumonia by Quintiles for Low Dose Persistent Users PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.0951	1,057	1,025	32	0.0303	0.1062	117	113	4	0.0342	0.90	0.31	2.56
21-40	0.2047	951	930	21	0.0221	0.2073	223	217	6	0.0269	0.92	0.39	2.17
41-60	0.3220	810	786	24	0.0296	0.3253	364	344	20	0.0549	1.42	0.78	2.59
61-80	0.4474	627	604	23	0.0367	0.4485	547	513	34	0.0622	1.28	0.75	2.17
81-100	0.6234	402	381	21	0.0522	0.6652	772	716	56	0.0725	0.95	0.57	1.57
Overall	0.2826	3,847	3,726	121	0.0315	0.4627	2,023	1,903	120	0.0593	1.22	0.94	1.58

8.8. New User Final Analysis Cohort 2005-2010: Propensity Score Generation

Post-Text Table 51 Hazard Ratios: All Pneumonia by Quintiles for 2005-2010 New Users PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.4111	1,381	1,352	29	0.0210	0.4219	1,006	970	36	0.0358	1.58	0.97	2.57
21-40	0.5228	1,148	1,127	21	0.0183	0.5249	1,240	1,196	44	0.0355	1.67	0.99	2.80
41-60	0.5876	1,019	986	33	0.0324	0.5887	1,368	1,302	66	0.0482	1.31	0.86	1.99
61-80	0.6445	826	807	19	0.0230	0.6480	1,562	1,485	77	0.0493	1.71	1.03	2.82
81-100	0.7272	626	614	12	0.0192	0.7324	1,761	1,658	103	0.0585	2.32	1.28	4.23
Overall	0.5509	5,000	4,886	114	0.0228	0.6030	6,937	6,611	326	0.0470	1.66	1.34	2.06

8.9. New Users Cohort by Device: Propensity Score Generation

Post-Text Table 52 Hazard Ratios: All Pneumonia by Quintiles for New Users by Device (Mono Therapy) PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.2409	1,995	1,950	45	0.0226	0.2566	665	640	25	0.0376	1.69	1.04	2.75
21-40	0.3837	1,697	1,655	42	0.0247	0.3851	964	929	35	0.0363	1.37	0.88	2.14
41-60	0.4948	1,304	1,276	28	0.0215	0.4995	1,357	1,305	52	0.0383	1.75	1.11	2.77
61-80	0.6225	1,001	975	26	0.0260	0.6304	1,660	1,601	59	0.0355	1.37	0.86	2.17
81-100	0.7942	495	479	16	0.0323	0.8090	2,165	2,069	96	0.0443	1.36	0.80	2.31
Overall	0.4303	6,492	6,335	157	0.0242	0.5899	6,811	6,544	267	0.0392	1.49	1.22	1.81

Post-Text Table 53 Hazard Ratios: All Pneumonia by Quintiles for New Users by Device (Combination Therapy) PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.2825	1,580	1,548	32	0.0203	0.2901	667	649	18	0.0270	0.94	0.53	1.68
21-40	0.3656	1,463	1,429	34	0.0232	0.3665	784	740	44	0.0561	1.81	1.15	2.85
41-60	0.4193	1,296	1,266	30	0.0231	0.4206	952	900	52	0.0546	1.78	1.13	2.81
61-80	0.4730	1,198	1,165	33	0.0275	0.4750	1,049	986	63	0.0601	1.71	1.12	2.62
81-100	0.5616	955	927	28	0.0293	0.5703	1,292	1,191	101	0.0782	1.67	1.09	2.54
Overall	0.4047	6,492	6,335	157	0.0242	0.4461	4,744	4,466	278	0.0586	1.73	1.41	2.11

8.10. New Use of at least 30 Days: Propensity Score Generation

Post-Text Table 54 Hazard Ratios: All Pneumonia by Quintiles for New Use of at least 30 days PS Model

Percentile	Exposed												
	No					Yes							
	PS Score		Pneumonia Event		Event Proportion	PS Score		Pneumonia Event		Event Proportion	Hazard Ratio	95% Lower Limit	95% Upper Limit
			No	Yes				No	Yes				
0-20	0.4595	1,804	1,763	41	0.0227	0.4750	1,653	1,594	59	0.0357	1.44	0.96	2.15
21-40	0.5871	1,508	1,474	34	0.0225	0.5888	1,950	1,869	81	0.0415	1.65	1.11	2.46
41-60	0.6588	1,166	1,135	31	0.0266	0.6614	2,291	2,187	104	0.0454	1.45	0.97	2.17
61-80	0.7293	895	876	19	0.0212	0.7312	2,563	2,456	107	0.0417	1.83	1.12	2.98
81-100	0.8227	581	564	17	0.0293	0.8335	2,876	2,755	121	0.0421	1.22	0.73	2.04
Overall	0.6068	5,954	5,812	142	0.0238	0.6812	11,333	10,861	472	0.0416	1.50	1.24	1.81

APPENDIX 1: PNEUMONIA DATABASE CODES

Appendix Table 1 ICD-10 Pneumonia Code Recorded on the Censoring Date of the 751 Patients Censored due to Pneumonia

ICD-10 diagnosis code	Description	N
J18.1	Lobar pneumonia, unspecified	288
J18.9	Pneumonia, unspecified	221
J18.0	Bronchopneumonia, unspecified	85
J69.0	Pneumonitis due to food and vomit	44
J13	Pneumonia due to Streptococcus pneumoniae	7
J14	Pneumonia due to Haemophilus influenzae	7
J15.4	Pneumonia due to other streptococci	4
J15.2	Pneumonia due to staphylococcus	3
A16.9	Resp TB unspec without mention of bact or hist confirm	2
J15.1	Pneumonia due to Pseudomonas	2
J15.0	Pneumonia due to Klebsiella pneumoniae	2
J85.2	Abscess of lung without pneumonia	2
J15.9	Bacterial pneumonia, unspecified	1
J15.6	Pneumonia due to other aerobic Gram-negative bacteria	1
J11.0	Influenza with pneumonia, virus not identified	1
J15.5	Pneumonia due to Escherichia coli	1
B37.1	Pulmonary candidiasis	1
J85.1	Abscess of lung with pneumonia	1
A15.0	TB lung confirm sputum microscopy with or without culture	1
A16.2	TB lung without mention of bact or histological confirm	1
B01.2	Varicella pneumonia	1
J17.2	Pneumonia in mycoses	1
J16.8	Pneumonia due to other specified infectious organisms	1

1. Patients may have multiple recordings of pneumonia codes on the censoring date
2. HES ICD-10 codes recorded on the censoring date

Appendix Table 2 GPRD Medcodes Recorded on the Censoring Date Of the 751 Patients Censored due to Pneumonia

GPRD Medical Code (Events)	Description	N
572	Pneumonia due to unspecified organism	63
886	Bronchopneumonia due to unspecified organism	35
6094	Pneumonia or influenza NOS	21
1849	Lobar (pneumococcal) pneumonia	12
3683	Basal pneumonia due to unspecified organism	5
10086	Pneumonia and influenza	5
16287	Chest infection - unspecified bronchopneumonia	4
5202	Viral pneumonia	4
9639	Lobar pneumonia due to unspecified organism	4
14976	Viral pneumonia NOS	2
22795	Chest infection - other bacterial pneumonia	1
19400	Chest infection - pnemonia due to unspecified organism	1
13563	Other aspiration pneumonia as a complication of care	1
635	Pulmonary tuberculosis	1
38110	Pulmonary tuberculosis NOS	1
7133	Respiratory TB not confirmed bact or histologically	1
25694	Pneumonia due to other specified organisms	1

1. Note that patients may have multiple recordings of pneumonia codes on the censoring date
2. GPRD Medcodes recorded on the censoring date

Appendix Table 3 ICD-10 Pneumonia Code Used to Identify Pneumonia Events

ICD-10 diagnosis code	Description
J69	Pneumonitis due to solids and liquids
J690	Pneumonitis due to food and vomit
J691	Pneumonitis due to oils and essences
J698	Pneumonitis due to other solids and liquids
O740	Asp pneumonitis due to anaesthesia during labour and deliv
B671	Echinococcus granulosus infection of lung
J173	Pneumonia in parasitic diseases
J16	Pneumonia due to other infectious organisms NEC
J168	Pneumonia due to other specified infectious organisms
J17	Pneumonia in diseases classified elsewhere
J178	Pneumonia in other diseases classified elsewhere
J18	Pneumoniaorganism unspecified
J180	Bronchopneumonia, unspecified
J181	Lobar pneumonia, unspecified
J188	Other pneumonia, organism unspecified
J189	Pneumonia, unspecified
A065	Amoebic lung abscess
J85	Abscess of lung and mediastinum
J850	Gangrene and necrosis of lung
J851	Abscess of lung with pneumonia
J852	Abscess of lung without pneumonia
B206	HIV disease resulting in Pneumocystis carinii pneumonia
B371	Pulmonary candidiasis
B380	Acute pulmonary coccidioidomycosis
B381	Chronic pulmonary coccidioidomycosis
B382	Pulmonary coccidioidomycosis, unspecified
B390	Acute pulmonary histoplasmosis capsulati

ICD-10 diagnosis code	Description
B392	Pulmonary histoplasmosis capsulati, unspecified
B400	Acute pulmonary blastomycosis
B402	Pulmonary blastomycosis, unspecified
B410	Pulmonary paracoccidioidomycosis
B420	Pulmonary sporotrichosis
B450	Pulmonary cryptococcosis
B460	Pulmonary mucormycosis
B583	Pulmonary toxoplasmosis
B59	Pneumocystosis
B590	Pneumocystosis
B59X	Pneumocystosis
J172	Pneumonia in mycoses
A15	Respiratory TB bacteriologically and histologically confirmed
A150	TB lung confirm sputum microscopy with or without culture
A151	Tuberculosis of lung, confirmed by culture only
A152	Tuberculosis of lung, confirmed histologically
A153	Tuberculosis of lung, confirmed by unspecified means
A154	TB intrathoracic lymph nodes confirm bact histologically
A155	Tuberculosis of larynx, trachea & bronchus conf bact/hist'y
A156	Tuberculous pleurisy, conf bacteriologically/his'y
A157	Primary respiratory TB confirm bact and histologically
A158	Other respiratory TB confirm bact and histologically
A159	Respiratory TB unspec confirm bact and histologically
A16	Respiratory TB not confirmed bacteriologically or histologically
A160	Tuberculosis of lung, bacteriologically & histolog'y neg
A161	Tuberculosis lung bact and histological examin not done
A162	TB lung without mention of bact or histological confirm
A163	TB intrathoracic lymph node without bact or hist confirm
A164	TB larynx trachea and bronchus without bact or hist confirm
A165	TB pleurisy without mention of bact or histological confirm
A167	Prim respiratory TB without mention of bact or hist confirm
A168	Oth respiratory TB without mention of bact or hist confirm
A169	Resp TB unspec without mention of bact or hist confirm
A19	Miliary tuberculosis
A190	Acute miliary tuberculosis of a single specified site
A191	Acute miliary tuberculosis of multiple sites
A192	Acute miliary tuberculosis, unspecified
A198	Other miliary tuberculosis
A199	Miliary tuberculosis, unspecified
A310	Pulmonary mycobacterial infection
J65	Pneumoconiosis associated with tuberculosis
J650	Pneumoconiosis associated with tuberculosis
J65X	Pneumoconiosis associated with tuberculosis
B012	Varicella pneumonia
B052	Measles complicated by pneumonia
J100	Influenza with pneumonia, influenza virus identified
J110	Influenza with pneumonia, virus not identified
J12	Viral pneumonia, not elsewhere classified
J120	Adenoviral pneumonia
J121	Respiratory syncytial virus pneumonia
J122	Parainfluenza virus pneumonia
J128	Other viral pneumonia
J129	Viral pneumonia, unspecified
J171	Pneumonia in viral diseases classified elsewhere

ICD-10 diagnosis code	Description
A202	Pneumonic plague
A212	Pulmonary tularaemia
A221	Pulmonary anthrax
A420	Pulmonary actinomycosis
A430	Pulmonary nocardiosis
A481	Legionnaires' disease
J13	Pneumonia due to Streptococcus pneumoniae
J130	Pneumonia due to Streptococcus pneumoniae
J13X	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J140	Pneumonia due to Haemophilus influenzae
J14X	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonianot elsewhere classified
J150	Pneumonia due to Klebsiella pneumoniae
J151	Pneumonia due to Pseudomonas
J152	Pneumonia due to staphylococcus
J153	Pneumonia due to streptococcus, group B
J154	Pneumonia due to other streptococci
J155	Pneumonia due to Escherichia coli
J156	Pneumonia due to other aerobic Gram-negative bacteria
J157	Pneumonia due to Mycoplasma pneumoniae
J158	Other bacterial pneumonia
J159	Bacterial pneumonia, unspecified
J160	Chlamydial pneumonia
J170	Pneumonia in bacterial diseases classified elsewhere

Appendix Table 4 GPRD Medcodes Used to Identify Pneumonia

GPRD Medical Code	Description
9711	Pneumonitis due to inhalation of solids or liquids
10992	Aspiration pneumonitis
3847	Pneumonitis due to inhalation of food or vomitus
101204	Aspiration pneumonia
41781	Pneumonitis due to inhalation of regurgitated food
59083	Pneumonitis due to inhalation of gastric secretions
66104	Pneumonitis due to inhalation of milk
30996	Milk inhalation pneumonitis
45948	Pneumonitis due to inhalation of vomitus
56385	Vomit inhalation pneumonitis
25054	Aspiration pneumonia due to vomit
33837	Pneumonitis due to inhalation of food or vomitus NOS
56647	Pneumonitis due to inhalation of oil or essence
41015	Lipoid pneumonia (exogenous)
66773	Pneumonitis due to inhalation of oil or essence NOS
50876	Asp pneumonitis due to anaesthesia during labour and deliv
47504	Pneumonitis due to inhalation of other solid or liquid
54252	Pneumonitis due to inhalation of solid or liquid NOS
46066	Pneumonitis due to inhalation of solid or liquid NOS
99232	[X]Pneumonitis due to inhalation of other solids and liquids
13563	Other aspiration pneumonia as a complication of care
50408	Ornithosis with pneumonia
62408	Lung fluke disease
19992	Lung echinococcus granulosus
62623	Pneumonia with ornithosis

GPRD Medical Code	Description
98782	Pneumonia with toxoplasmosis
10086	Pneumonia and influenza
25694	Pneumonia due to other specified organisms
30653	Chest infection - pneumonia organism OS
34251	Pneumonia due to specified organism NOS
40498	Pneumonia with infectious diseases EC
69782	Pneumonia with other infectious diseases EC
70559	Pneumonia with other infectious diseases EC NOS
66362	Pneumonia with infectious diseases EC NOS
886	Bronchopneumonia due to unspecified organism
16287	Chest infection - unspecified bronchopneumonia
572	Pneumonia due to unspecified organism
19400	Chest infection - pnemonia due to unspecified organism
9639	Lobar pneumonia due to unspecified organism
3683	Basal pneumonia due to unspecified organism
5324	Atypical pneumonia
11849	Other specified pneumonia or influenza
6094	Pneumonia or influenza NOS
98381	[X]Pneumonia due to other specified infectious organisms
53753	[X]Other pneumonia, organism unspecified
34732	Amoebic lung abscess
21185	Abscess of lung and mediastinum
29005	Abscess of lung
33730	Single lung abscess
37711	Multiple lung abscess
57667	Gangrenous pneumonia
35189	Abscess of lung with pneumonia
11202	Abscess of lung NOS
34659	Abscess of lung and mediastinum NOS
27641	HIV disease resulting in Pneumocystis carinii pneumonia
48481	Candidiasis of lung
40299	Pneumonia - candidal
54540	Primary pulmonary coccidioidomycosis
101507	Histoplasma capsulatum with pneumonia
91481	Acute pulmonary histoplasmosis capsulati
54551	Chronic pulmonary histoplasmosis capsulati
101292	Histoplasma duboisii with pneumonia
59951	Pulmonary histoplasmosis
41404	Primary pulmonary blastomycosis
100742	Allergic bronchopulmonary aspergillosis
54906	Pulmonary cryptococcosis
35220	Pneumocystosis
96332	[X]Other pulmonary aspergillosis
34274	Pneumonia with aspergillosis
52071	Pneumonia with candidiasis
103404	Pneumonia with coccidioidomycosis
53969	Pneumonia with systemic mycosis NOS
27519	Pneumonia with pneumocystis carinii
22011	Primary tuberculous infection
16265	Primary tuberculous complex
46272	Tuberculous pleurisy in primary progressive tuberculosis
42630	Other primary progressive tuberculosis
37694	Primary tuberculous infection NOS
635	Pulmonary tuberculosis

GPRD Medical Code	Description
47336	Lung tuberculosis
53701	Infiltrative lung tuberculosis
48580	Nodular lung tuberculosis
16331	Tuberculosis of lung with cavitation
62468	Tuberculosis of bronchus
16741	Tuberculous fibrosis of lung
15693	Tuberculous bronchiectasis
9953	Tuberculous pneumonia
66441	Tuberculous pneumothorax
18950	Other specified pulmonary tuberculosis
38110	Pulmonary tuberculosis NOS
63959	Other respiratory tuberculosis
23472	Tuberculous pleurisy
37834	Tuberculosis of pleura
39512	Tuberculous empyema
14913	Tuberculous hydrothorax
56890	Tuberculous pleurisy NOS
58827	Tuberculosis of intrathoracic lymph nodes
5145	Tuberculosis of hilar lymph nodes
44129	Tuberculosis of mediastinal lymph nodes
49503	Tuberculosis of tracheobronchial lymph nodes
46926	Tuberculosis of intrathoracic lymph nodes NOS
69260	Isolated tracheal or bronchial tuberculosis
93015	Isolated tracheal tuberculosis
93948	Isolated bronchial tuberculosis
53473	Isolated tracheal or bronchial tuberculosis NOS
20333	Tuberculous laryngitis
31670	Resp TB bacteriologically and histologically confirmed
24413	TB lung confirm sputum microscopy with or without culture
93071	Tuberculosis of lung, confirmed by culture only
62530	Tuberculosis of lung, confirmed histologically
58588	Tuberculosis of lung, confirmed by unspecified means
44655	TB intrathoracic lymph nodes confirm bact histologically
44039	Tuberculosis of larynx, trachea & bronchus conf bact/hist'y
35443	Tuberculous pleurisy, conf bacteriologically/histologically
24517	Primary respiratory TB confirm bact and histologically
7133	Respiratory TB not confirmed bact or histologically
47832	Tuberculosis of lung, bacteriologically & histolog'y neg
41051	Tuberculosis lung bact and histological examin not done
40605	Prim respiratory TB without mention of bact or hist confirm
69471	Resp TB unspcf,w'out mention/bacterial or histol confrmtn
50902	Other specified respiratory tuberculosis
37598	Tuberculosis of mediastinum
72402	Tuberculosis of nasopharynx
97658	Tuberculosis of nasal septum
45861	Tuberculosis of nasal sinus
50147	Other specified respiratory tuberculosis NOS
16414	Miliary tuberculosis
72008	Acute miliary tuberculosis
31844	Acute miliary tuberculosis of a single specified site
42479	Acute miliary tuberculosis of multiple sites
32459	Other specified miliary tuberculosis
53331	Miliary tuberculosis NOS
32223	Pulmonary mycobacterial infection

GPRD Medical Code	Description
24425	Pulmonary mycobacterium avium-intracellulare infection
73185	[X]Other resp tubercul,confirmd bacteriologicly+histologicly
73225	[X]Resp tuberculos unspcfd,confirmd bacteriolog+histologicly
55298	[X]Resp TB unspcf,w'out mention/bacterial or histol confrmtn
97922	[X]Miliary tuberculosis, unspecified
63172	Pneumoconiosis associated with tuberculosis
47973	Herpes simplex pneumonia
32172	Postmeasles pneumonia
5202	Viral pneumonia
9389	Chest infection - viral pneumonia
67836	Pneumonia due to adenovirus
31269	Pneumonia due to respiratory syncytial virus
36675	Pneumonia due to parainfluenza virus
33478	Viral pneumonia NEC
14976	Viral pneumonia NOS
41034	Pneumonia with measles
43286	Pneumonia with cytomegalic inclusion disease
23726	Pneumonia with varicella
15912	Influenza with pneumonia
29457	Chest infection - influenza with pneumonia
13573	Influenza with bronchopneumonia
62632	Influenza with pneumonia, influenza virus identified
35745	Influenza with pneumonia NOS
52520	[X]Other viral pneumonia
53947	[X]Pneumonia in viral diseases classified elsewhere
58896	Salmonella pneumonia
70710	Primary pneumonic plague
47295	Pneumonic plague, unspecified
45161	Pulmonary anthrax
41084	Wool-sorters' disease
64306	Pulmonary actinomycosis
73340	Pulmonary nocardiosis
15308	Legionella
1849	Lobar (pneumococcal) pneumonia
29166	Chest infection - pneumococcal pneumonia
28634	Other bacterial pneumonia
22795	Chest infection - other bacterial pneumonia
23546	Pneumonia due to klebsiella pneumoniae
30591	Pneumonia due to pseudomonas
37881	Pneumonia due to haemophilus influenzae
48804	Pneumonia due to haemophilus influenzae
12423	Pneumonia due to streptococcus
63858	Pneumonia due to streptococcus, group B
5612	Pneumonia due to staphylococcus
50867	Pneumonia due to other specified bacteria
65419	Pneumonia due to escherichia coli
60299	E.coli pneumonia
45425	Pneumonia due to proteus
12061	Pneumonia - Legionella
52384	Pneumonia due to other aerobic gram-negative bacteria
43884	Pneumonia due to bacteria NOS
23095	Bacterial pneumonia NOS
60119	Pneumonia due to Eaton's agent
1576	Pneumonia due to mycoplasma pneumoniae

GPRD Medical Code	Description
73735	Pneumonia due to pleuropneumonia like organisms
17025	Chlamydial pneumonia
30437	Pneumonia with whooping cough
35082	Pneumonia with pertussis
61623	Pneumonia with actinomycosis
67901	Pneumonia with nocardiasis
60482	Pneumonia with Q-fever
72182	Pneumonia with salmonellosis
49398	Pneumonia with typhoid fever
63763	[X]Other bacterial pneumonia