

# Hospitalizations for vaccine preventable pneumonias in patients with inflammatory bowel disease: a 6-year analysis of the Nationwide Inpatient Sample

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**Background:** Pneumonias are among the most common causes of hospitalization among inflammatory bowel disease (IBD) patients. Guidelines published in 2004 advocate vaccination against *Streptococcus pneumoniae* and influenza virus. We sought to examine trends in hospitalizations for vaccine preventable pneumonias among IBD patients since the availability of published guidelines, and to identify whether *Haemophilus influenzae* is a causative organism for pneumonia hospitalizations among IBD patients.

**Methods:** This cross-sectional study on the Nationwide Inpatient Sample was used to identify admissions for pneumonias in patients with IBD between 2004 and 2009. A multivariate logistic regression analysis was performed comparing IBD patients to controls, accounting for potential confounders.

**Results:** There were more admissions for *S. pneumoniae* pneumonia than influenza virus or *H. influenzae* (787, 393, and 183 respectively). Crohn's disease (CD) as well as ulcerative colitis (UC) patients did not demonstrate increased adjusted odds of hospitalization for *S. pneumoniae* pneumonia (1.08; confidence interval [CI] 0.99–1.17 compared to 0.93; CI 0.82–1.06 respectively). Increased adjusted odds for hospitalization for pneumonias due to influenza virus were seen among UC patients in the bottom quartile of income (1.86; CI 1.46–2.37). Adjusted odds for *H. influenzae* pneumonia admission in patients with UC and CD patients were increased compared to controls (1.42; CI 1.13–1.79 and 1.28; CI 1.06–1.54, respectively).

**Conclusion:** The study identified lowest income UC patients as having higher adjusted odds, and these patients should be targeted for influenza virus vaccination. Additionally, *H. influenzae* may be another vaccine preventable cause for pneumonia among IBD patients.

**Keywords:** infection, Crohn's disease, colitis, ulcerative, vaccination, pneumonia

## Introduction

For over 30 years it has been known that those with inflammatory bowel disease (IBD) have a greater risk of developing pulmonary problems.<sup>1</sup> Bronchitis has been shown to be associated with IBD,<sup>2</sup> along with different types of pneumonia, pneumonitis, mycobacterium tuberculosis, as well as many other lung conditions.<sup>3</sup> Meta-analyses have shown increased mortality from chronic obstructive pulmonary disease in Crohn's disease (CD),<sup>4</sup> and in ulcerative colitis patients (UC);<sup>5</sup> IBD patients have also been shown to have decreased diffusion capacity of the lung for carbon monoxide and chronic inflammation of the lungs.<sup>6</sup> These related pulmonary diseases increase susceptibility to lung infections among IBD patients.

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Bacterial pneumonias have been shown to be more common in IBD patients.<sup>7</sup> Furthermore, bacterial pneumonias have been identified in several cohort studies as one of the commonest infections resulting in hospitalization in IBD patients on immunomodulators and/or TNF- $\alpha$  inhibitors.<sup>8,9</sup> *Streptococcus pneumoniae* (*S. pneumoniae*) as well as influenza virus have been identified as vaccine preventable causes of pneumonia among IBD patients and vaccinations against these have been advocated since 2004.<sup>10,11</sup> Population studies in other immunosuppressed states such as infection with human immunodeficiency virus (HIV) have also identified *Haemophilus influenzae* (*H. influenzae*) pneumonias to be more common than in the general population.<sup>12</sup> However, vaccine preventable invasive infections, and in particular pneumonias with *H. influenzae*, have not been well characterized in IBD patients.

Underutilization of vaccines among IBD patients including against *S. pneumoniae* as well as influenza virus has been demonstrated in the outpatient setting.<sup>13</sup> We sought to analyze hospitalizations for vaccine preventable pneumonias after publication of guidelines advocating vaccination for IBD patients, by examining primary inpatient admissions for pneumonias caused by *S. pneumoniae* as well as influenza virus. We also sought to identify whether *H. influenzae* is also a causative organism for hospitalizations with pneumonia among patients with a diagnosed history of IBD.

## Materials and methods

### Database

Admissions for pneumonias caused by *S. pneumoniae*, influenza virus as well as *H. influenzae* were studied in IBD patients using the Nationwide Inpatient Sample (NIS) database. The database has been created as part of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality.<sup>14</sup>

### Setting

The NIS dataset is a stratified sample containing 20% of all hospital inpatient discharges, using hospital strata characteristics based on geographic region (Northeast, Midwest, South and West), ownership/control (government non-Federal, private not-for-profit, and private investor-owned), location (urban or rural), teaching status (teaching or non-teaching), and hospital size for a given area (small, medium, and large). Included are 48,087,002 inpatient discharge visits between 2004 and 2009 which range from 37 to 44 different states, with 1004 to 1056 hospitals represented (with appropriate weight adjustments made to account for these differences).

The hospitals include all non-Federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions and short-term rehabilitation hospitals. To maximize the representative nature of the NIS databases, discharge weights are provided by HCUP to accurately estimate the total number of patients for the entire United States. The NIS data set is estimated to accurately represent 235,571,947 inpatient discharges between 2004 and 2009 and provides details on sex, age, race, primary (diagnosis [DX] 1) and secondary diagnoses (up to 14 additional diagnoses, DX 2–15).

### Participants

This is a cross-sectional study with the study group consisting of all patients, over the age of 20, discharged without a primary diagnosis of IBD and with a secondary diagnosis of IBD (DX 2–15) based on International Classification of Diseases, 9th Revision, Clinical Modification code (ICD-9-CM 555.x and 556.x).<sup>15</sup> The control group was composed of a 30% random sample of all discharges without a primary or secondary diagnosis of IBD.

### Predictor and outcome variables

The outcome variable of interest was a primary diagnosis code (DX 1) of pneumonia caused by *S. pneumoniae* (ICD-9-CM 481), influenza virus (ICD-9-CM 487.0), or *H. influenzae* (ICD-9-CM 482.2). Case-mix adjustment was performed using the updated Elixhauser Agency for Healthcare Research and Quality-Web ICD-9-CM comorbidity algorithms (Agency for Healthcare Research and Quality, Rockville, MD, USA), which include acquired immune deficiency syndrome, alcohol abuse, deficiency anemia, rheumatoid arthritis and other collagen vascular diseases, chronic blood loss anemia, congestive heart failure, chronic pulmonary disease, coagulopathy, diabetes without complications, diabetes with chronic complications, drug abuse (not including alcohol or tobacco usage), hypertension (both complicated and uncomplicated), hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, obesity, paralysis, peripheral vascular disorders, pulmonary circulation disorders, renal failure, solid tumor without metastasis, peptic ulcer disease excluding bleeding, valvular disease, weight loss, depression, psychoses, and other neurological disorders.<sup>16,17</sup> Additionally, we controlled for other well described risk factors for pneumonia, ascertained by ICD-9-CM codes including: tobacco usage (305.1), post-inflammatory pulmonary fibrosis (515), and respiratory conditions due to other and unspecified external agents

(507.x, 508.x), previous diagnosis of pneumococcal pneumonia, influenza pneumonia, and *H. influenzae* pneumonia (481, 487.0, or 482.2 respectively, anywhere within DX 2–15, not a DX 1) as well as the following patient and hospital characteristics: hospital region, teaching status of the hospital, hospital size, hospital control and ownership, median household quartile, and patient location (urban-rural).

## Statistical analysis

Data were analyzed using the SPSS 20.0 software package (IBM Corporation, Armonk, NY, USA). A Markov Chain Monte Carlo multiple imputation procedure was performed to provide estimates for missing data. Racial makeup was missing for 23.5% of the data, sex for 0.2%, patient location for 1.9%, income percentile for 2.5%, insurance for 0.2%, and hospital teaching status, size, and ownership for 0.4%. Five imputations were utilized to maximize predictive ability.<sup>18</sup> Chi-square tests with Yates' correction factor were used to identify significant differences between subsets of IBD patients with a pneumonia admission and the IBD population who did not have a pneumonia admission or the non-IBD population with the IBD population. In addition, multivariate regression analyses were performed to determine the adjusted odds ratios (aOR) for the adjusted odds of hospitalizations for pneumonias caused by *S. pneumoniae*, influenza virus as well as *H. influenzae*, in patients with a diagnosis of IBD, while controlling for the aforementioned risk factors (all comorbidities and characteristics in Tables 1 and 2, ie, Elixhauser index, additional list of comorbidities, patient demographic characteristics, and hospital characteristics). In a post hoc analysis, we also sought to identify target groups which may be at higher adjusted odds.

## Ethical considerations

The Institutional Review Board of NorthShore University Health System deemed the research protocol exempt from IRB review.

## Results

### Patient and hospital characteristics

There were an estimated 918,557 patient discharges of patients over the age of 20, with a secondary diagnosis of IBD (anywhere with the DX 2–15). Table 1 shows the various characteristic differences between those with IBD and those in the control group. Main significant differences are seen with IBD patients more likely to be white, lower income, on private insurance, and in a small metropolitan area than controls. IBD patients were also more likely to be discharged

**Table 1** Description of patient characteristics

Patient characteristics	IBD patients	Non-IBD patients	P-value
<b>Over 70</b>	25.1%	33.0%	<0.001
<b>Sex</b>			
Male	41.0%	39.8%	<0.001
White	83.8%	69.6%	<0.001
Black	8.1%	13.5%	<0.001
Hispanic	4.5%	10.4%	<0.001
<b>Race</b>			
Asian or Pacific Islander	1.0%	2.5%	<0.001
Native American	0.7%	1.0%	<0.001
Other	2.0%	3.0%	<0.001
<b>Income</b>			
First patient income quartile	21.7%	28.8%	<0.001
Second patient income quartile	25.0%	26.1%	<0.001
Third patient income quartile	25.9%	23.3%	<0.001
Fourth patient income quartile	27.4%	21.8%	<0.001
<b>Insurance</b>			
Medicare	43.4%	45.8%	<0.001
Medicaid	8.7%	13.3%	<0.001
Private insurance (including HMO)	41.3%	32.0%	<0.001
Self-pay	3.4%	5.1%	<0.001
No charge	0.4%	0.5%	<0.001
Other	2.8%	3.3%	<0.001
<b>Patient location</b>			
Patient in a large metropolitan	53.8%	53.6%	<0.001
Patient in a small metropolitan	28.3%	27.1%	<0.001
Patient in a micropolitan	11.2%	11.5%	<0.001
Patient in a non-metropolitan or micropolitan	6.7%	7.9%	<0.001
<b>Major co-morbidities</b>			
Diabetes mellitus	14.8%	20.5%	<0.001
Cardiovascular disorders	41.9%	48.8%	<0.001
Pulmonary disorders	18.7%	18.3%	<0.001
Renal disorders	6.2%	7.7%	<0.001

**Abbreviations:** HMO, health maintenance organization; IBD, inflammatory bowel disease.

from a teaching hospital, large in size, and located in the Midwest compared to controls (Table 2).

### Adjusted odds of *S. pneumoniae* pneumonia in IBD

There were 787 admissions for *S. pneumoniae* pneumonia in those with IBD between 2004 and 2009. The prevalence of *S. pneumoniae* pneumonia in IBD patients was 82.6 per 100,000 while only 69.2 per 100,000 for the control population. When adjusting for the various comorbidities in the Elixhauser index as well as secondary diagnoses (anywhere with the DX 2–15) for tobacco usage, post-inflammatory pulmonary fibrosis, and extrinsic allergic alveolitis as well as the aforementioned patient and hospital characteristics, CD as well as UC patients did not demonstrate

**Table 2** Description of hospital characteristics

Hospital characteristics	IBD patients	Non-IBD patients	P-value
<b>Teaching hospital</b>	48.2%	44.5%	<0.001
<b>Ownership</b>			
Government or private other category hospital	68.8%	63.8%	<0.001
Government, nonfederal hospital	5.2%	6.5%	<0.001
Private, non-profit hospital	18.1%	19.4%	<0.001
Private, investor-owned hospital	7.9%	10.3%	<0.001
<b>Size</b>			
Small hospital	11.9%	12.5%	<0.001
Medium hospital	23.4%	24.4%	<0.001
Large hospital	64.7%	63.1%	<0.001
<b>Location</b>			
Hospital in the Northeast	22.9%	20.1%	<0.001
Hospital in the Midwest	26.6%	23.4%	<0.001
Hospital in the South	33.9%	38.3%	<0.001
Hospital in the West	16.6%	18.2%	<0.001

**Abbreviation:** IBD, inflammatory bowel disease.

an increased adjusted odds of hospitalization for pneumonia due to *S. pneumoniae* (aOR 1.08; CI 0.99–1.17 compared to 0.93; CI 0.82–1.06 respectively).

## Adjusted odds of influenza virus pneumonia in IBD

Between 2004 and 2009, 393 admissions occurred for influenza virus pneumonia in those with IBD. The prevalence of influenza virus pneumonia was 41.2 per 100,000 discharges in the IBD population, with a prevalence in the control population of 39.5 per 100,000 discharges. After adjustments, in a logistic regression, for the various comorbidities in the Elixhauser index as well as secondary diagnoses (anywhere with the DX 2–15) for tobacco usage, post-inflammatory pulmonary fibrosis, and extrinsic allergic alveolitis as well as the aforementioned patient and hospital characteristics, those with CD and UC did not demonstrate an increased adjusted odds of hospitalization for pneumonia due to influenza virus (aOR 1.08; CI 0.95–1.23 compared to 1.05; CI 0.89–1.25 respectively). However, low income UC patients (those in the bottom quartile), had an increased adjusted odds of hospitalization for pneumonia due to influenza virus (aOR 1.86; CI 1.46–2.37).

## Adjusted odds of *H. influenzae* pneumonia admission in IBD

A total of 183 admissions for *H. influenzae* pneumonia in patients with IBD were seen over the 6-year period from 2004 to 2009. The prevalence of *H. influenzae* pneumonia

cases among IBD patients was 19.2 per 100,000 discharges with a secondary diagnosis of IBD (anywhere with the DX 2–15) compared to 14.0 per 100,000 discharges in the control population. After adjusting for the various comorbidities in the Elixhauser index as well as secondary diagnoses (anywhere with the DX 2–15) for tobacco usage, post-inflammatory pulmonary fibrosis, and extrinsic allergic alveolitis as well as various patient and hospital characteristics, IBD patients had increased adjusted odds of being admitted for *H. influenzae* pneumonia (aOR 1.34; CI 1.16–1.55) when compared to the non-IBD control group. Further differentiating by the type of IBD, patients with a history of UC had equal adjusted odds compared to those with a history of CD (aOR 1.42; CI 1.13–1.79 and aOR 1.28; CI 1.06–1.54, respectively).

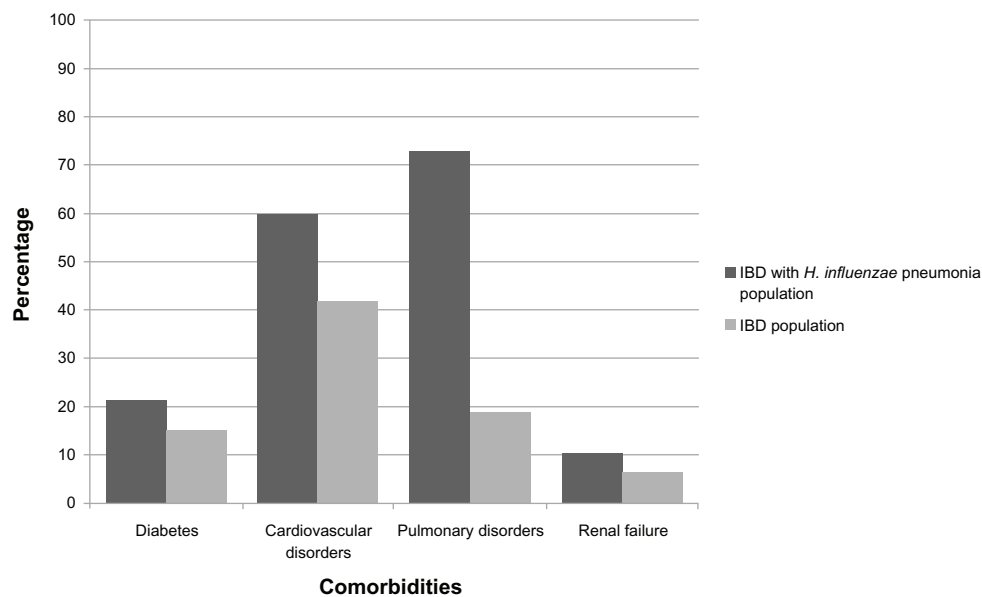
For the purpose of comparison of the distribution of the Elixhauser Agency for Healthcare Research and Quality-Web ICD-9-CM comorbidities, we combined diabetes mellitus with and without chronic complications into a single category of diabetes mellitus; congestive heart failure, hypertension, peripheral vascular disorders, and valvular disease into a single category of cardiovascular disorders; and chronic pulmonary disease, pulmonary circulation disorders, respiratory conditions due to other and unspecified external agents, and post-inflammatory pulmonary fibrosis into pulmonary disorders. IBD patients admitted with *H. influenzae* pneumonia compared to the IBD patients without these admissions had greater odds for the presence of certain comorbidities including diabetes (OR 1.56; CI 1.09–2.22), cardiovascular disorders (OR 2.09; CI 1.56–2.81), pulmonary disorders (OR 11.88; CI 8.56–16.48), and renal failure (OR 1.76, CI 1.10–2.83) (Figure 1).

## Mortality

During the 6-year period, 2004–2009, a total of 13 deaths occurred among IBD patients hospitalized due to *S. pneumoniae*, 16 among influenza virus pneumonia, and five deaths during hospitalizations for *H. influenzae* pneumonia. Based on Chi-square tests with Yates' correction, mortality during these admissions among IBD patients was not significantly higher than the control population.

## Discussion

Our study demonstrates that IBD patients are at higher adjusted odds for hospitalizations with *H. influenzae* pneumonias. The adjusted odds were not increased for IBD patients admitted for *S. pneumoniae* or influenza virus pneumonias. Considering *S. pneumoniae* was the largest group and considering most influenza virus patients did



**Figure 1** Comparison of comorbidities among IBD patients with a primary admission for *Haemophilus influenzae* pneumonia, and those without such an admission.  
**Abbreviation:** IBD, inflammatory bowel disease.

not have increased odds of pneumonia, gastroenterologists caring for IBD patients should feel reassured that the absolute incidence of pneumonia is not higher compared to the general population. This may be the result of widespread implementation of published guidelines to vaccinate IBD patients for these diseases.<sup>12</sup> However, the adjusted odds of hospitalization with pneumonias due to influenza virus were significantly higher for lower income UC patients (aOR 1.86; CI 1.46–2.37). Low income patients are known to be less likely to be immunized against influenza virus for a variety of reasons.<sup>19</sup> Hence, gastroenterologists caring for lower income UC patients need to be vigilant about being up to date with influenza virus vaccination especially prior to initiating immunosuppressive therapies in this population.

The mechanism for the increased odds for *H. influenzae* pneumonias in IBD patients is unclear. We theorized that the prevalence of pulmonary disorders in these patients predisposes them to the pneumonias, however the higher odds of *H. influenzae* pneumonia persisted even after controlling for a variety of chronic pulmonary disorders.<sup>1–6</sup> Long et al<sup>7</sup> were able to show a higher prevalence of bacterial pneumonias in IBD patients compared to controls, and an even higher prevalence in those using biologic medications, corticosteroids, thiopurines, proton-pump inhibitors, or narcotics.<sup>7</sup> Unfortunately, this study did not differentiate vaccine preventable pneumonias from others, so it is difficult to ascertain the impact of vaccination. Furthermore, this study did not look at pneumonias due to the influenza virus. Nonetheless, it provides a viable possibility for the higher

prevalence of *H. influenzae* pneumonia which was seen in this study.<sup>7</sup> Another possible mechanism is treatment-related exposure to immunomodulators and/or tumor necrosis factor (TNF)- $\alpha$  inhibitors, as they have been shown to increase the risk of infections in IBD patients.<sup>20,21</sup> Exposure to TNF- $\alpha$  inhibitors has also been reported to cause invasive infections with other encapsulated organisms such as *S. pneumoniae*.<sup>22</sup> Animal studies in mice have also shown impaired clearance of *S. pneumoniae* with the use of a TNF- $\alpha$  blocking agent.<sup>23</sup> However, the database used in our study lacked information on the drug treatment received by the IBD patients, and this can only be taken as speculation.

Our study demonstrates that among IBD patients, those with chronic cardiovascular, pulmonary, and renal disease as well as those with diabetes are at the highest odds for *H. influenzae* pneumonia. Additionally, those aged 65 years and older are at higher odds of developing *H. influenzae* pneumonia. In a study by Vila-Corcoles et al, *H. influenzae* was the fourth leading cause of community acquired pneumonia in those 65 and older.<sup>24</sup> Immunization against influenza virus and *S. pneumoniae* is recommended for these groups.<sup>12</sup> The higher odds in those aged 65 and older may also be due to the lack of availability of the *H. influenzae* serotype B (Hib) conjugate vaccine in the United States until 1989.<sup>25</sup> Furthermore, the Centers for Disease Control and Prevention does not recommend that adults (19 years of age and older) receive the Hib vaccine.<sup>26</sup> Therefore, most individuals aged 25 and older may not be vaccinated for Hib in the United States.



Current vaccine strategies in IBD patients recommend screening for vaccination history and risk at the time of the initial IBD consultation, and offering influenza and pneumococcal vaccine to all patients, regardless of immunosuppression status.<sup>27</sup> Based on the present study, IBD patients may also benefit from vaccination for Hib. This study does not include vaccination status, however, which means that determining, from the current data whether these patients are unvaccinated or if vaccinations are ineffective in these patients (or if there is a time dependency for vaccination relative to drug therapy) may be impossible. Nonetheless, if IBD individuals are considering therapy with an immunomodulator and/or a TNF- $\alpha$  inhibitor, it may be better to be immunized with the Hib vaccine before receiving immunosuppressive therapy, if vaccination is warranted. Considering that systemic lupus erythematosus patients on immunosuppressive drugs tended to have a lower response to Hib vaccination, IBD patients on similar immunosuppressants may also have a similar reduced response to the Hib vaccine.<sup>28</sup> Furthermore, Fiorino et al found that IBD patients had an impaired response to the 23-valent polysaccharide pneumococcal vaccine due to current use of anti-TNF therapy alone or in combination with azathioprine, which may also occur with the Hib vaccine.<sup>29</sup>

There are potential limitations to this study. As with most databases, causality cannot be determined. The use of the HCUP database did not allow a determination of the effect of therapy-related immunosuppression on the adjusted odds of *S. pneumoniae*, influenza virus, or *H. influenzae* pneumonia. Furthermore, patient vaccination histories are also unavailable in this dataset. The data in this study are reliant on administrative discharge diagnosis and may be subject to errors of miscoding and the codes used have not been previously validated. The study has utilized ICD-9 codes for identifying microbiological classes of the pneumonias. Hence, misclassification of cases is possible as the diagnostic accuracy of these codes in relation to the sputum or blood culture results has not been ascertained. However, we have attempted to minimize this misclassification by selecting only cases with a primary diagnosis of *S. pneumoniae*, influenza virus, or *H. influenzae* pneumonia as our index cases. Linkage data are not available for the NIS database; therefore, recurrent visits may result in duplicate patient records. Here again, this effect is minimized, although still exists, by selecting only primary admission diagnosis as our index case. Furthermore, we controlled for a history of those with *S. pneumoniae*, influenza virus, or *H. influenzae* pneumonia to minimize the effect of readmission in determining the strength of association.

Finally, the ICD 9-CM codes were primarily designed for billing rather than research. Therefore administrative databases created using these codes may have a residual element of up-coding in the diagnostic codes to increase reimbursement termed as “diagnosis related groups creep.”<sup>30</sup> We have attempted to minimize this through case-mix adjustment using standardized algorithms<sup>16,17</sup> as well as additional patient and hospital characteristics. Finally, *S. pneumoniae*, influenza virus, or *H. influenzae* pneumonia patients are also treated as outpatients, which our study does not capture. Hence the presence of certain comorbidities more significantly among IBD patients with *S. pneumoniae*, influenza virus, or *H. influenzae* may be reflective of the hospitalized patients rather than all IBD patients with this type of pneumonia.

In conclusion, this study highlights an association of higher odds of admissions for *H. influenzae* pneumonia in IBD patients and for pneumonias due to influenza virus among lowest income UC patients. Among IBD patients, those with chronic medical comorbidities such as cardiovascular, lung, and renal disease as well as those with diabetes as well as older individuals especially males, appear to be at a higher adjusted odds for *H. influenzae* pneumonias. The decision to vaccinate against *H. influenzae* in the high adjusted odds groups of IBD patients described in the study should be individualized in consultation with a health care provider, until these results are confirmed in larger, prospective studies.

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## Disclosure

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