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Influenza Vaccination Coverage in Pediatric Patients with Inflammatory Bowel Disease

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**INFLUENZA VACCINATION COVERAGE IN PEDIATRIC PATIENTS WITH
INFLAMMATORY BOWEL DISEASE**

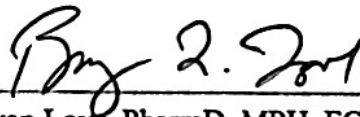
By

Kelly Brown

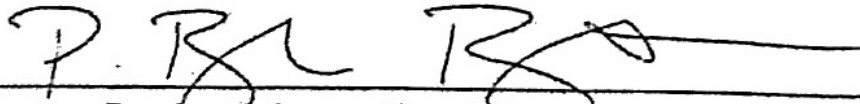
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THESIS SUMMARY

Influenza is a viral respiratory illness with higher activity in the colder months. It is estimated that across the United States, 9,000,000 to 45,000,000 people become ill with influenza and 12,000 to 60,000 die due to influenza each year. There is a yearly vaccine for influenza available beginning at the start of each influenza season.

Children are at especially higher risk of becoming infected and transmitting influenza due to their under-developed immune systems and their general lack of good hand hygiene practices. Children with chronic diseases, like inflammatory bowel disease (IBD), are especially vulnerable to dangerous complications from influenza due to their disease and treatment. Therefore, children with chronic diseases are a target group for influenza vaccine efforts. Childhood immunization coverage has been examined in many countries and groups of children for many vaccines. However, influenza vaccination coverage and predictors of vaccination have not been analyzed in children with IBD.

To examine influenza vaccine coverage in children with IBD, data from South Carolina Medicaid was analyzed to identify vaccination patterns over time and predictors and barriers of vaccination in children with and without IBD in South Carolina. 1,184 children with IBD and 4,736 children without IBD were included.

This project provides more information about the universal topic of vaccine coverage among children. The project analyzes vaccination coverage for an important illness among a vulnerable group of children. This project demonstrates that influenza vaccination coverage in all children is increasing over time in children in South Carolina and that disparities in influenza vaccination coverage exist among certain groups of children.

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ABSTRACT

Introduction: Children with chronic health conditions, including IBD, are at especially high risk for influenza infection and resulting complications. The Crohn's & Colitis Foundation's Top 10 Quality Process Indicators for IBD and American College of Gastroenterology's clinical guidelines for preventative health maintenance recommend that IBD patients should receive annual influenza vaccination. The aims of this study were to evaluate influenza vaccination coverage over time and identify predictors of influenza vaccination in pediatric IBD and non-IBD patients.

Methods: We utilized longitudinal data (2001 to 2016) from South Carolina Medicaid to conduct a matched cohort study. The primary exposure of interest was diagnosis of IBD based upon ICD-9/10 diagnosis codes. The included subjects were eligible for SC Medicaid at least 9 months out of 12 each year and had no months of ineligibility occurring between October and May. Children with IBD were matched 1:4 to children without IBD on age and sex. Influenza vaccination coverage for IBD and non-IBD groups for each season were calculated as $[\# \text{ receiving vaccine}] / [\# \text{ eligible}]$. We calculated 95% confidence intervals for these estimates using 10,000 nonparametric bootstrap replications adjusted for clustering. A multivariable random effects logistic regression model was used to identify predictors of influenza vaccination.

Results: Overall, 1,184 IBD subjects and 4,736 matched non-IBD subjects were identified during the study period. Among the IBD patients, 698 were diagnosed with ulcerative colitis, 348 were diagnosed with Crohn's disease, and 138 patients had diagnosis codes for both. The average age was 9.5 years and the majority of patients were male (52.7%). Among pediatric IBD patients, influenza vaccination coverage increased from 2% in 2001 to 40% in 2016. Children

with IBD, children residing in urban zip codes, white females, and children receiving corticosteroids had higher odds of obtaining an influenza vaccination.

Conclusion: Influenza vaccination coverage for both pediatric IBD and non-IBD patients significantly increased from 2001 to 2016. Disparities in influenza vaccination coverage were identified among black patients and patients living in rural zip codes. IBD patients were more likely to get vaccinated compared to non-IBD patients, although vaccination coverage in SC remains below target levels. Overall, efforts to increase influenza vaccination in pediatric IBD patients are needed.

INTRODUCTION

Most adults who become infected with influenza recover within two weeks. Children, however, particularly children younger than five years old and especially children under two years old, have an increased risk for developing complications from influenza infection. Children with chronic health conditions, including inflammatory bowel disease (IBD), are at especially high risk for influenza infection and resulting complications.¹ Serious complications of influenza include pneumonia, myocarditis, rhabdomyolysis, encephalitis, and multiple-organ failure.² Pediatric patients are both at higher risk of contracting influenza and of spreading it. Therefore, influenza vaccination is especially important in pediatric patients because of their high susceptibility. A study from July 2010 through June 2014 found that influenza vaccination reduces the risk of influenza-associated death in pediatric patients.³

IBD includes Crohn's disease and ulcerative colitis. The specific pathologies of these two conditions share some characteristics; both diseases involve chronic inflammation of the gastrointestinal tract in varying areas and degrees of severity.⁴ Studies suggest that IBD is at least partially caused by an impaired immune response to environmental and/or infectious factors.⁵ Research has been focused on finding specific genetic markers of IBD that are linked with activity of the immune system.⁶ Through the genome-wide association study, specific genetic loci associated with IBD and the immune system have been found. There are immune deficiency genes associated with both Crohn's disease and ulcerative colitis.⁷ Therefore, IBD patients are known to have an impaired immune system by nature of the disease which may make them more susceptible to viral infections, including influenza.

The Crohn's Colitis Foundation has published the Top 10 Quality Process Indicators for IBD which recommends annual influenza vaccination to IBD patients on immunosuppressive medications.⁸ The American College of Gastroenterology also has a list of clinical guidelines for preventative health maintenance which states that IBD patients should receive annual influenza vaccination.⁹ Despite those recommendations, limited evidence suggests that influenza vaccination in IBD patients may be suboptimal. A study from Canada indicated that 10% of pediatric IBD patients had incomplete childhood immunizations. IBD-related reasons for incomplete vaccination included use of immunosuppressant medications and disease flare up at the time of immunization.¹⁰ However, this was only a snapshot, and the change in vaccination patterns over time was not assessed. Similarly, a Polish study found that children with IBD were two times less likely to receive the annual influenza vaccine than controls.¹¹ Additionally, a French survey study found that only 22% of IBD pediatric patients had received annual influenza vaccination in 2011.¹² Therefore, it is likely that children with IBD have poor influenza vaccination coverage.

This research was completed with support from the Crohn's & Colitis Foundation Student Research Award Grant. The aims of this study were to evaluate influenza vaccination coverage over time and identify predictors of influenza vaccination in pediatric IBD and non-IBD patients.

METHODS

We utilized longitudinal data (2001 to 2016) from South Carolina Medicaid to conduct a matched cohort study. The primary exposure of interest was diagnosis of IBD based upon International Statistical Classification of Diseases and Related Health Problems (ICD-9/10) diagnosis codes. The diagnosis codes used are listed in the Appendix. The included subjects were eligible for SC Medicaid at least 9 months out of 12 each year and had no months of ineligibility occurring between October and May. Children with IBD were matched 1:4 to children without IBD on age and sex.

We analyzed differences in characteristics between IBD and non-IBD patients as well as between patients with Crohn's disease, ulcerative colitis, and indeterminate IBD (patients who had ICD-9/10 codes for both diseases). We also analyzed medication use by patient-years in patients with Crohn's disease, ulcerative colitis, and indeterminate IBD. The medications identified by class are listed in the Appendix. Influenza vaccination coverage for IBD and non-IBD groups for each season were calculated as [# receiving vaccine] / [# eligible]. The billing codes used to identify influenza vaccination are listed in the Appendix. We calculated 95% confidence intervals for these estimates using 10,000 nonparametric bootstrap replications adjusted for clustering. A multivariable random effects logistic regression model was used to identify predictors of influenza vaccination. All analyses were calculated using Stata/MP, version 15.1 (StataCorp).

RESULTS

Overall, 1,184 IBD subjects and 4,736 matched non-IBD subjects were identified during the study period. The average age was 9.5 years and the majority of patients were male (52.7%). The characteristics of the IBD and matched non-IBD patients are listed in Table 1.

Table 1: Characteristics of IBD and Non-IBD Patients

	IBD (n=1,184)	Non-IBD (n=4,736)	p-value
Age, years	6.85	6.38	<0.01
Male, %	52.7	52.7	>0.05
Race, %			
White	47.13	37.01	>0.001
Black	34.84	50.12	>0.001
Other	18.02	21.88	>0.001
Zip Code, %			
Rural	31.93	35.56	0.019
Urban	68.07	64.44	0.019

Among the IBD patients, 698 were diagnosed with ulcerative colitis, 348 were diagnosed with Crohn's disease, and 138 patients had diagnosis codes for both. The characteristics of the IBD patients by disease are listed in Table 2.

Table 2: Characteristics of IBD Patients by Disease

	Ulcerative Colitis (n=698)	Crohn's Disease (n=348)	Indeterminate[†] (n=138)
Age, years	9.30	9.45	10.90
Male, %	54.09	50.29	51.45
Race, %			
White	46.25	50.64	42.52
Black	36.09	29.62	41.73
Other	17.66	19.75	15.75
Zip Code, %			
Rural	36.50	25.64	34.41
Urban	63.50	74.36	65.59

[†] Patients had ICD-9/10 codes for both diseases.

In patients with ulcerative colitis and Crohn's disease, corticosteroids were used most frequently. In patients with indeterminate IBD, aminosalicylates (5-ASA's) were used most frequently. The medication use among IBD patients is listed in Table 3.

Table 3: Medication Usage Among IBD Patients by Person-Years of Observation

	Ulcerative Colitis	Crohn's Disease	Indeterminate[†]
Total P-Y	5,035	2,410	1,087
IBD Drugs, P-Y of use (%)			
5-ASAs	403 (8)	196 (8.13)	396 (36.43)
Immuno-suppressants	255 (5.06)	76 (3.15)	192 (17.66)
Biologics	35 (0.7)	3 (0.12)	50 (4.6)
Corticosteroids	576 (11.44)	310 (12.86)	251 (23.09)
Influenza Vaccine, P-Y (%)	1,071 (21.27)	560 (23.24)	223 (20.52)

[†] Patients had ICD-9/10 codes for both diseases.

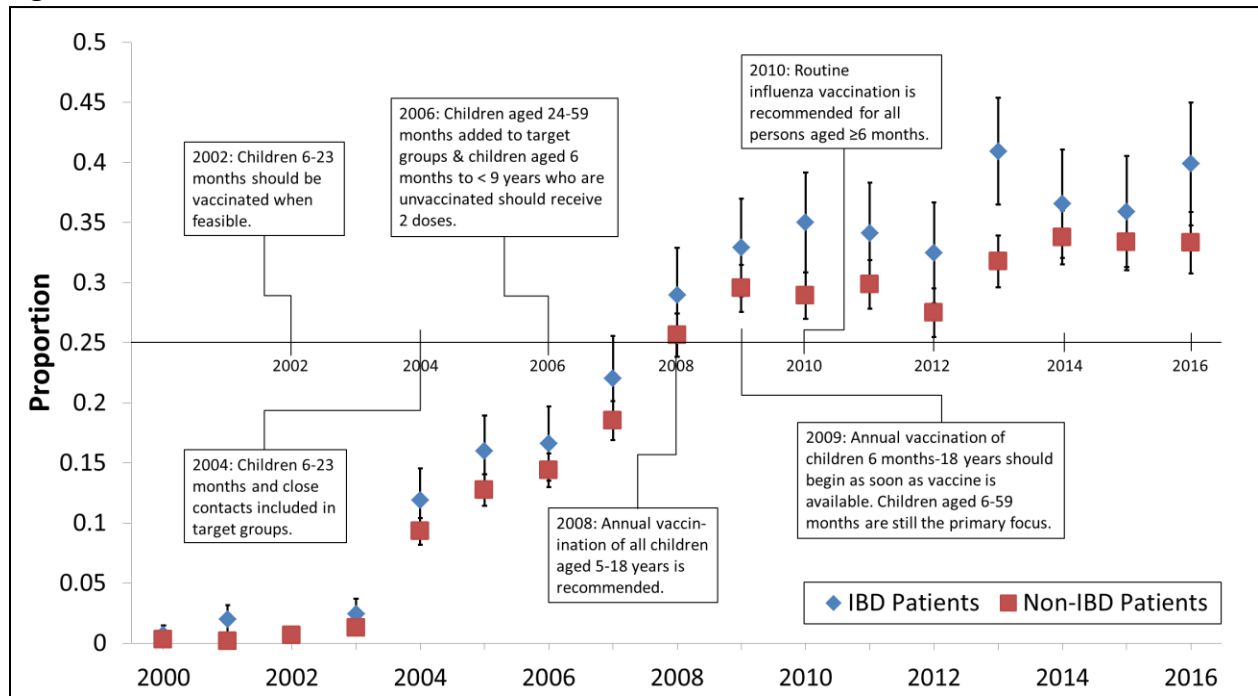
Compared to non-IBD subjects, children with IBD had higher odds of obtaining an influenza vaccination (OR=1.22, $p<0.001$). Children residing in urban locations had higher odds of obtaining an influenza vaccination (OR=1.56, $p=0.001$) compared to children from rural locations. Compared to white females, black females (OR=0.85, $p=0.017$) and black males (OR=0.84, $p=0.012$) had significantly lower odds of obtaining an influenza vaccination. Children receiving corticosteroids had higher odds of obtaining an influenza vaccination (OR=1.21, $p<0.001$) compared to children not receiving corticosteroids. The identified predictors of influenza vaccination are listed in Table 4.

Table 4: Predictors of Influenza Vaccination

	Odds Ratio	95% CI	p-value
Birth Year	1.24	1.23-1.25	<0.001
IBD Diagnosis	1.22	1.10-1.36	<0.001
Age	0.90	0.89-0.91	<0.001
Race & Sex			
White Female	1.0	-	-
Black Female	0.85	0.74-0.97	0.017
Other Female	1.26	1.03-1.53	0.023
White Male	0.94	0.82-1.08	>0.05
Black Male	0.84	0.74-0.96	0.012
Other Male	1.20	1.03-1.41	0.023
Zip Code			
Rural	1.0	-	-
Urban	1.56	1.42-1.71	<0.001
Corticosteroid Use	1.21	1.08-1.36	<0.01

Among pediatric IBD patients, influenza vaccination coverage increased from 2% in 2001 to 40% in 2016. For each year into the study, children had higher odds of obtaining an influenza vaccination (OR=1.24, $p<0.01$). Influenza vaccination over time is shown in Figure 1.

Figure 1: Influenza Vaccination Over Time



[†] Advisory Committee on Immunization Practices (ACIP) recommendations are shown in boxes.

^{††} 95% confidence intervals are shown for each data point.

DISCUSSION

Predictors of influenza vaccination included IBD diagnosis, later birth year, an urban zip code, corticosteroid use, and patients of other (non-white and non-black) races of both sexes. This project identified potential target groups for increased vaccination efforts; disparities in influenza vaccination coverage were identified among black patients and patients living in rural zip codes.

Influenza vaccination coverage for both pediatric IBD and non-IBD patients significantly increased from 2001 to 2016. However, even the latest data from 2016 showed that less than 50% of patients are getting vaccinated. IBD patients were more likely to get vaccinated compared to non-IBD patients, although influenza vaccination coverage in South Carolina remains below target levels. SC ranks lower than the national average in other childhood vaccines such as measles, mumps, rubella; *Haemophilus influenzae* type b; birth dose of hepatitis B; and both hepatitis A doses.¹⁸ This project has shown that efforts to increase influenza vaccination in both pediatric IBD and non-IBD patients are needed.

The strengths of this study include the use of data from the entire state of South Carolina and the use of a control group. Some limitations of this study include the small sample size and the lack of information about severity of disease. Also, some patients may have lost Medicaid coverage and re-enrolled in Medicaid later, so some years of data may have been lost for some patients. Also, some patients may have received vaccination through the Centers for Disease Control (CDC) Vaccines for Children program or other programs for which we did not have the data.

Further studies could be completed to find interventions to increase vaccination coverage in target populations, including IBD pediatric patients. Also, further research to identify and analyze health outcomes associated with influenza vaccination in IBD pediatric patients is needed.

In conclusion, the data from this study demonstrate that vaccination rates remain below target levels among all pediatric patients in South Carolina. Overall, efforts to increase influenza vaccination in pediatric IBD patients are needed.

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APPENDIX

IBD Drugs

Salicylates – AHFS code 28:08.04.24

- Sulfasalazine (Azulfidine®, Azulfidine EN®) – 28:08.04.24
- Mesalamine suppository (Rowasa®) – 28:08.04.24, 56:36
- Mesalamine enema (Canasa®) – 28:08.04.24, 56:36
- Mesalamine oral (Asacol HD®, Apriso®, Lialda®, Pentasa®, Delzicol®) – 28:08.04.24, 56:36
- Olsalazine (Dipentum®) – 28:08.04.24
- Balsalazide (Colazal®) – 28:08.04.24

Immunosuppressants (antimetabolites) – AHFS code 92:44

- Azathioprine (Imuran®, Azasan®) – 92:44
- Cyclosporine (Gengraf®, Neoral®, Sandimmune®) – 92:44
- Mercaptopurine (Purinethol®) – 92:44, 10:00
- Methotrexate (no branded IM injection) – 92:36, 10:00

Monoclonal Antibodies – AHFS code 8:18.24

- Adalimumab (Humira®) – 8:18.24, 56:92, 92:20, 92:36
- Cetolizumab (Cimzia®) – 8:18.24, 56:92, 92:36, 92:36
- Infliximab (Remicade®, Inflectra®, Renflexis®, Ixifi®) – 8:18.24, 56:92, 92:20, 92:36
- Natalizumab (Tysabri®) – 8:18.24, 56:92, 92:20, 92:36
- Vedolizumab (Entyvio®) – 8:18.24, 56:92, 92:20, 92:36
- Golimumab (Simponi®) – 8:18.24, 56:92, 92:20, 92:36

Corticosteroids (adrenals) – AHFS code 84:06.08

- Budesonide (Enterocort EC®, Uceris®) – 84:06.08, 68:04
- Prednisone (Deltasone®, Rayos®, Sterapred®) – 84:06.08, 68:04
- Methylprednisolone (Medrol®) – 84:06.08, 68:04
- Hydrocortisone (Cortef®) – 84:06.08, 68:04
- Dexamethasone (Decadron®) – 84:06.08, 68:04

HCPCS Codes for Influenza Vaccination

- Q2034-Q2039
- Administration Code: G0008

CPT Codes for Influenza Vaccination

- 90460-90461
- 90471-90474
- 90630
- 90653-90664
- 90666
- 90668
- 90672-90674
- 90682
- 90685-90688
- 90724
- 90749
- 90756

ICD-9 Codes

- Ulcerative Colitis – 555.xx
- Crohn's Disease – 556.xx
- Influenza – 487.xx, 488.xx
- Influenza vaccine – V04.81, V06.6, 99.52

ICD-10 Codes

- Ulcerative Colitis – K51.xx
- Crohn's Disease – K50.xx
- Influenza – J09.xx, J10.xx, J11.xx
- Influenza vaccine – Z23