Insufficient vaccination and inadequate immunization rates among Korean patients with inflammatory bowel diseases

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Abstract
This study aimed to evaluate self-reported vaccination rates, immunity, knowledge of and attitudes toward vaccination among Korean patients with inflammatory bowel disease (IBD) as well as to identify factors associated with proper vaccination.

Between November 2013 and February 2015, consecutive patients with IBD were invited to complete a standardized questionnaire on vaccination. Moreover, immune status for common vaccine-preventable diseases was evaluated via serologic tests.

A total of 310 patients with IBD were invited to the questionnaire survey and 287 patients (92.6\%) who completed the questionnaires were finally enrolled (men, 188 [65.5\%]; median age at survey, 29.9 years [interquartile range, 22.3–39.2\, years], ulcerative colitis: Crohn disease = 165:122). Self-reported vaccine uptake rates were as follows: hepatitis A virus (HAV; 13.2\%), hepatitis B virus (HBV; 35.2\%), seasonal influenza (43.2\%), pneumococcus (4.9\%). Most of the patients (67.1\%) did not know that proper vaccination has been recommended for patients with IBD. Up to 64.8\% and 32.8\% of patients were negative for IgG antibody to HAV and HBV, respectively. In a multivariable analysis, newspaper subscription (aOR [adjusted odds ratio] 2.185, 95\% confidence interval [CI] 1.136–4.203, \( P = .019\)), ever recommendation of vaccination by a physician (aOR 2.456, 95\% CI 1.240–4.862, \( P = .010\)), and use of anti-tumor necrosis factor agents (aOR 4.966, 95\% CI 1.088–22.484, \( P = .037\)) showed a significant association with uptake of adult vaccines recommended for patients with IBD.

Vaccine uptake rates, positivity of antibody to HAV and HBV, and knowledge of patients with IBD regarding vaccination were not sufficient. Proper educational information and recommendation from physicians could enhance awareness among patients with IBD about the need for vaccination and thereby improve vaccination rates.

Trial registration number: NCT01984879.

Abbreviations: BCG = Bacillus Calmette-Guérin, CD = Crohn disease, DTaP = diphtheria-tetanus-acellular pertussis, HAV = hepatitis A virus, HBV = hepatitis B virus, HPV = human papillomavirus, HZV = Herpes zoster virus, IBD = inflammatory bowel disease, MMR = measles-mumps-rubella, Td = tetanus-diphtheria, Tdap = tetanus toxoid, reduced diphtheria toxoid and acellular pertussis, TFN = tumor necrosis factor, UC = ulcerative colitis, VZV = Varicella-zoster virus.

Keywords: inflammatory bowel disease, knowledge, vaccine

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1. Introduction

Although the pathophysiologic mechanisms of inflammatory bowel disease (IBD) remain unclear, it is believed to develop from a complex interplay between the intestinal microbiome, environmental components, and immunologic factors in genetically susceptible individuals.[1] The mainstays of treatments for IBD are immunosuppressive agents including corticosteroids, thio- purines, and anti-tumor necrosis factor (TNF) agents.

Generally, IBD patients are considered to be vulnerable to various infections owing to multiple reasons such as IBD activity itself, malnutrition, surgery, and most importantly, immunosuppressive therapy.[2,3] Because many of these opportunistic infections can be prevented through proper vaccination,[4–7] immunization guidelines for immunosuppressed IBD patients have been suggested by several experts.[8–11] Most of these guidelines suggest that all IBD patients should be administered with routine vaccines recommended to the general population; additionally, pneumococcal and annual influenza vaccines as well as hepatitis A virus (HAV) and hepatitis B virus (HBV) vaccines should be administered in all patients, regardless of age; human papillomavirus (HPV) vaccines should be given to patients between 9 and 26 years; and meningococcal vaccines should be given to at-risk patients.[9–13] However, certain live-attenuated vaccines such as the herpes zoster vaccine are not recommended for patients on high-level immunosuppressive therapy because there have been concerns about disease dissemination after administration of live-attenuated vaccines.[14–17]

Despite such clear practical recommendations regarding vaccination for patients with IBD, a substantial proportion of patients with IBD are unaware of the need for immunization; consequently, a significant number of these patients do not take the recommended vaccines.[13–17] A recent Canadian study on 300 patients reported that the vaccination uptake rate was 61.3% for influenza, 10.3% for pneumococcus, 61.0% for HBV, 52.0% for HAV, 26.0% for varicella, 20.7% for meningococcus, 5.3% for herpes zoster, and 11.0% for HPV (women).[17] Furthermore, in a recent Belgian study, only 32% of 505 patients were completely vaccinated according to the guidelines.[18]

Although suboptimal vaccination rates among IBD patients in Western countries are documented, this subject has not been sufficiently explored in the context of Asian patients with IBD, whose disease characteristics and prognosis may be different from those of Caucasian patients.[19–22] Moreover, the immune status of patients with common vaccine-preventable diseases, knowledge of vaccination recommendations, and attitude towards vaccination have rarely been explored even in the context of Western IBD patients.[17] Therefore, this study aimed to evaluate the current vaccination rates, immune status, knowledge of and attitudes towards vaccination among Korean patients with IBD as well as identify factors associated with proper vaccine uptake.

2. Materials and methods

2.1. Study population

Between November 2013 and February 2015, consecutive patients with IBD managed at the Inflammatory Bowel Disease Center of Asan Medical Center, a tertiary-care teaching hospital, Seoul, Korea, were invited to complete a standardized questionnaire on vaccination. We included all patients with either Crohn disease (CD) or ulcerative colitis (UC) who had provided informed consent on study participation.

2.2. Questionnaire

The questionnaire comprised 3 general categories. In the first category, patients were asked 18 questions on general information, medical history, and activities, including their vaccination records, education level, history of communal dwelling such as dormitories or military barracks, past history of vaccine-preventable diseases (measles, mumps, rubella, chicken pox, tuberculosis, seasonal influenza [during the last 3 years], hepatitis A, hepatitis B, and herpes zoster), other comorbidities, working as a member of IBD patients community (on-line and/or off-line), subscription to a newspaper, and use of internet for searching information. For the second category that consisted of vaccination history, participants were asked if they ever received vaccines against measles-mumps-rubella (MMR), diphtheria-tetanus-pertussis (DTaP), tuberculosis (Bacillus Calmette-Guérin, BCG), poliomyelitis, additional Tdap (Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis) or Td (Tetanus-Diphtheria), seasonal influenza (at least once during the last 3 years), pneumococcus, HAV, HBV, HPV for women aged <26 years, herpes zoster virus (HZV) for patients aged >60 years, and meningococcus for communal dwellers. In the last category, questions were asked pertaining to the participants’ knowledge of and attitude toward vaccination; whether they knew that vaccination has been recommended for IBD patients, whether they knew that vaccines are largely consisted of live-attenuated vaccines and inactivated vaccines, which vaccines constitute the category of live-attenuated vaccines, and whether the patients and their household members were eligible to receive live-attenuated vaccines while receiving immunosuppressive therapy. They were also asked the route by which they obtained information on IBD and vaccination and whether they have ever been recommended any vaccine uptake from their treating physicians. Finally, they were asked for their opinions on the need for vaccination-related education.

2.3. Data acquisition

We also collected patients’ clinical information, including age at survey, disease duration, location of residence (urban vs rural), disease extent, and medication use, from the previously described IBD registry of the Asan Medical Center.[20,21] Urban area was defined as a city having a population of >500,000 people. Blood tests were performed to measure levels of antibodies specific for measles, mumps, rubella, varicella-zoster virus (VZV), HAV, and HBV. While the antibody levels specific for measles, mumps, rubella, and VZV were measured using enzyme-linked fluorescent assay (ELFA) (VIDAS, bioMérieux, Marcy l’Etoile, France), those of IgG anti-HAV antibody and IgG anti-HBV surface antigen were measured via chemiluminescent immunoassay (CLIA) (Architect I4000SR, Abbott Laboratories, Abbott Park, IL).

2.4. Definition of childhood and adult vaccines

We defined childhood vaccines as the vaccines recommended by the Korea Centers for Disease Control and Prevention and provided free of cost to all children under the age of 12 years. Currently, they include MMR, DTaP, polioymelitis, chicken pox, haemophilus influenza B, BCG, Japanese encephalitis, HAV, and HBV vaccines. However, because HAV had not been included...
under childhood vaccines category until 2015, we considered it as an adult vaccine in this study. Adult vaccines were defined as all other vaccines recommended to adults depending on age and risk. They include seasonal influenza vaccines, Tdap or Td for all adults aged >19 years, pneumococcal vaccine for all healthy adults aged >60 years or for those who are at risk, regardless of age, HZV vaccine for all adults aged >60 years, HPV vaccine for all women aged ≤26 years, and meningococcal vaccines for all communal dwellers.

2.5. Study endpoints
The primary endpoint was self-reported vaccine uptake rate. The secondary endpoints were seroprevalence of vaccine-preventable diseases, factors associated with adult vaccine uptake and patients’ knowledge of and attitudes towards vaccination.

2.6. Statistical analysis
Categorical variables are expressed as numbers and percentages, and continuous variables are expressed as median and interquartile range (IQR). For comparisons among the groups, the chi-squared test was used for categorical variables and the Mann–Whitney U test was used for continuous variables. Univariable and multivariable logistic regression analyses were used to identify factors affecting vaccination in IBD patients. A backward elimination process was used for multivariable analysis of variables that achieved a statistical significance at a P value of <.2 in univariable analysis. All data were analyzed using IBM SPSS Statistics for Windows (IBM Corp., released in 2016. Version 24.0. Armonk, NY) and a P value of <.05 was considered to be statistically significant for all tests.

2.7. Ethical considerations
The study was approved by the institutional review board of the Asan Medical Center (IRB No. 2013–0592), and written informed consent was obtained from all study participants. This study was also registered at www.clinicaltrials.gov (NCT01984879).

3. Results
3.1. Patient characteristics
A total of 310 patients with IBD were invited to participate in the study and 287 patients (92.6%) who provided informed consent and completed the questionnaires and blood tests were finally included in this study. The demographic and clinical characteristics of these patients are listed in Table 1. Among 287 patients, 188 patients (65.5%) were men and 165 patients (57.5%) had UC. The

| Table 1 | Demographic and clinical characteristics of patients. |
|---------|-----------------------------------------------------|
|         | Total patients (N = 287) | Crohn disease (n = 122) | Ulcerative colitis (n = 165) |
| Male    | 188 (65.5%) | 92 (75.4%) | 96 (58.2%) |
| Median age at diagnosis (IQR), yrs | 27.2 (20.2–36.1) | 21.8 (18.8–29.6) | 32.3 (23.3–43.2) |
| Median age at survey (IQR), yrs | 29.9 (22.3–39.2) | 24.2 (20.2–32.5) | 34.3 (25.4–45.5) |
| Median disease duration at survey (IQR), mo | 7.9 (1.6–35.3) | 5.1 (1.3–40.1) | 9.9 (1.8–33.9) |
| Residence |
| Rural area | 151 (52.6%) | 63 (51.6%) | 88 (53.3%) |
| Urban area∗ | 136 (47.4%) | 59 (48.4%) | 77 (46.7%) |
| Education level at survey |
| Not educated | 1 (0.3%) | 0 (0%) | 1 (0.6%) |
| Elementary school graduate | 4 (1.4%) | 1 (0.8%) | 3 (1.8%) |
| Middle school graduate | 32 (11.1%) | 14 (11.5%) | 18 (10.9%) |
| High school graduate | 101 (35.2%) | 52 (42.6%) | 49 (29.7%) |
| University graduate | 134 (46.7%) | 50 (41.0%) | 84 (50.9%) |
| Graduate school | 15 (5.2%) | 5 (4.1%) | 10 (6.1%) |
| Communal living at survey |
| Military | 4 (1.4%) | 3 (2.5%) | 1 (0.6%) |
| Dormitory | 14 (4.9%) | 8 (6.6%) | 6 (3.6%) |
| Location of CD at diagnosis by Montreal classification |
| Ileum | 28 (22.9%) |
| Colon | 3 (2.5%) |
| Ileocolon | 91 (74.6%) |
| Behavior of CD at diagnosis by Montreal classification |
| B1 (non-stricturing, non-penetrating) | 79 (64.8%) |
| B2 (stricturing) | 18 (14.8%) |
| B3 (penetrating) | 25 (20.5%) |
| Disease extent of UC at diagnosis |
| Proctitis | 68 (41.2%) |
| Left-sided colitis | 53 (32.1%) |
| Extensive colitis | 44 (26.7%) |
| Ever use of medication |
| Corticosteroids | 127 (44.3%) |
| Thiopurines | 112 (39.0%) |
| Anti-TNF agents | 18 (6.3%) |

CD = Crohn disease, IQR = interquartile range, TNF = tumor necrosis factor, UC = ulcerative colitis.

∗ An urban area was defined as a city having a population of >500,000 people.
median age at diagnosis of IBD was 27.2 years (IQR, 20.2–36.1), and the median age at survey was 29.9 years (IQR, 22.3–39.2). A total of 136 patients (47.4%) lived in an urban area. Among 165 patients with UC, 68 (41.2%) patients had psoriasis. Although corticosteroids and thiopurines had previously been used in 127 (44.3%) and 112 patients (39.0%), respectively, anti-TNF agents had been used in only 18 patients (6.3%).

3.2. Self-reported vaccination history and infectious disease history

Table 2 shows the self-reported uptake history of each vaccine. Among the childhood vaccines, highest vaccination rates were observed for BCG (60.3%) followed by HBV (35.2%), DTaP (22.6%), MMR (18.1%), and poliomyelitis (16%) vaccines. However, up to 69.7% of patients answered that they did not remember their detailed vaccination history. On the other hand, patients could remember receiving some of the adult vaccines, such as influenza, pneumococcus, and hepatitis, better than they could remember receiving childhood vaccines. All patients aged >60 years knew their vaccination history for HZV, all female patients aged ≤26 years remembered their history of HPV vaccination, and 82.4% of the communal dwellers knew their vaccination history for meningococcosis. Of 287 patients, 272 (94.8%) remembered their vaccination history of seasonal influenza. Despite such good recollection rates for adult vaccination history, insufficient rates of vaccination (43.2% for seasonal influenza [at least once during the last 3 years], 35% for HPV, 20% for VZV, 13.6% for additional Tdap or Td, 13.2% for HAV, and 4.9% for pneumococcus) were reported. Self-reported infectious disease history is shown in Table S1, Supplemental Digital Content, http://links.lww.com/MD/G474, and responders who reported that they had ever had each disease were generally low except chicken pox (30.3%) and influenza (15.0%).

3.3. Seropositivity rates of measles, mumps, rubella, varicella-zoster, and hepatitis A and B viruses

Seropositivity rates are listed in Table 3. Although the rates of self-reported vaccination history and previous history of measles, mumps, and rubella were low, the seropositivity rates against these viruses were relatively high (74.2% in anti-mumps IgG, 82.2% in anti-mumps IgG, and 73.2% in anti-rubella IgG). Seropositivity rate of IgG anti-hepatitis B surface antigen was lower than that of other antibodies (67.2%); the seropositivity rate of anti-hepatitis A IgG was even lower (35.2%).

### Table 2

| Vaccine          | Yes (n) | No (n) | Unknown (n) |
|------------------|---------|--------|-------------|
| MMR              | 52 (18.1%) | 41 (14.3%) | 194 (67.6%)  |
| DTaP             | 65 (22.6%) | 37 (12.9%) | 185 (64.5%)  |
| BCG              | 173 (60.3%) | 15 (5.2%) | 99 (34.5%)  |
| Poliomyelitis    | 46 (16%) | 41 (14.3%) | 200 (69.7%)  |
| Additional Tdap or Td | 39 (13.6%) | 40 (13.9%) | 207 (72.1%)  |
| Influenza (at least once during the last 3 yrs) | 124 (43.2%) | 148 (51.6%) | 15 (5.2%) |

### Table 3

| Antibody                                | Seropositive | Seronegative |
|-----------------------------------------|--------------|--------------|
| Anti-mumps IgG                          | 213 (74.2%)  | 74 (25.8%)   |
| Anti-rubella IgG                        | 236 (82.2%)  | 51 (17.8%)   |
| Anti-hepatitis B virus                  | 210 (73.2%)  | 77 (26.8%)   |
| Anti-varicella zoster IgG               | 244 (85.0%)  | 43 (15.0%)   |
| Anti-hepatitis A IgG                    | 101 (35.2%)  | 186 (64.8%)  |
| Anti-hepatitis B surface IgM            | 193 (67.2%)  | 94 (32.8%)   |

We defined the seropositivity levels for anti-mumps as IgG ≥ 15 IU/mL, anti-rubella as IgG ≥ 20 IU/mL, anti-varicella zoster as IgG ≥ 20 IU/mL, anti-hepatitis A as IgG ≥ 1.0 IU/mL, and anti-hepatitis B as surface IgG ≥ 10 IU/mL.

3.4. Factors affecting adult vaccine uptake in patients with IBD

To assess which factors could affect vaccine uptake in patients with IBD, we divided 287 patients into 2 groups, namely those who had not received any of the recommended adult vaccines (n = 112) and those who had received at least one such vaccine (n = 175). Table 4 shows differences in various characteristics between the 2 groups. In the univariable logistic regression analysis, age at IBD diagnosis, smoking, IBD type (CD or UC), exposure to thiopurines, exposure to anti-TNF agents, subscription to a newspaper, having a knowledge that vaccines have been recommended for patients with IBD, and ever recommendation of vaccine uptake by a physician showed an association (P value < .2) with adult vaccine uptake and were included in the multivariable logistic regression analysis. In the multivariable logistic regression analysis, subscription to a newspaper (aOR [adjusted odds ratio] 2.185, 95% confidence interval [CI] 1.136–4.203, P = .019), ever recommendation of vaccination by a physician (aOR 2.456, 95% CI 1.240–4.862, P = .010), and exposure to anti-TNF agents (aOR 4.966, 95% CI 1.098–22.464, P = .037) were significantly associated with an uptake of adult vaccines (Table 5).

3.5. Knowledge about and attitudes towards vaccination in patients with IBD

Most of the patients (87.1%) did not know that proper vaccination has been recommended for patients with IBD (Fig. 1A). Moreover, only 54 patients (18.8%) knew that vaccines were largely consisted of live-attenuated vaccines and inactivated vaccines (Fig. 1B), and 44 (81.5%) of those 54 patients responded that live-attenuated vaccine were derived from cultured virus itself (Fig. 1C). However, among the 54 patients, most did not have an accurate knowledge of the details of live-attenuated vaccines. For example, only 10 of the 54 patients (18.5%) knew that MMR, VZV, and HZV vaccines were largely consisted of live-attenuated vaccines (Fig. 1D). Additionally, only 15 (27.8%) of the 54 patients knew that patients under immuno-
modulators or anti-TNFs should avoid uptake of live-attenuated vaccines (Fig. 1E). Finally, only 2 (3.7%) of the 54 patients knew that household members of patients receiving immunomodulators or anti-TNFs should avoid uptake of live-attenuated vaccines (Fig. 1E). Patients obtained information on IBD and vaccinations most commonly through doctors (n = 99, 34.5%), followed by internet websites (n = 75, 26.1%), and family members (n = 68, 23.7%) (Table S2, Supplemental Digital Content, http://links.lww.com/MD/G474). However, only 59 patients (20.6%) replied that they had ever been recommended any vaccine uptake by their treating physicians at least once in the past; furthermore, most of the patients (243, 84.7%) agreed on the need of education regarding vaccination for patients with IBD.

### Table 4
Factors affecting adult vaccine uptake by IBD patients.

|                                | No uptake of any of the adult vaccines (n = 112) | Uptake of at least one of the adult vaccines (n = 175) | \( \chi^2 \) \( P \) |
|--------------------------------|-----------------------------------------------|--------------------------------------------------|------------------|
| Male                           | 76 (67.9%)                                    | 112 (64.0%)                                     | .527             |
| Median age at survey (IQR), years | 32.1 (22.8–42.4)                             | 28.2 (21.8–37.7)                                | .086             |
| Median age at diagnosis (IQR), years | 29.6 (21.3–40.9)                            | 26.1 (19.5–33.8)                                | .028             |
| Median disease duration at survey (IQR), months | 6.8 (1.6–27.8) | 8.6 (1.7–39.9) | .306 |
| IBD type                       |                                               |                                                 | .038             |
| CD                             | 39 (34.8%)                                    | 83 (47.4%)                                     | .397             |
| UC                             | 73 (65.2%)                                    | 92 (52.6%)                                     | .063             |
| Family history of IBD at diagnosis | 3 (2.7%)                                         | 10 (5.7%)                                      | .262             |
| Ever use of medication         |                                               |                                                 | .385             |
| Corticosteroids                | 46 (41.1%)                                    | 81 (46.3%)                                     | .397             |
| Thiopurines                    | 36 (32.1%)                                    | 76 (43.4%)                                     | .063             |
| Anti-TNF agents                | 2 (1.8%)                                      | 16 (9.1%)                                      | .012             |
| Comorbidities\(^{\ddagger}\)  | 10 (8.9%)                                     | 17 (9.7%)                                      | .840             |
| Smoking status at diagnosis    |                                               |                                                 | .385             |
| Never smoker                   | 67 (59.8%)                                    | 119 (68.0%)                                    | .999             |
| Former smoker                  | 16 (14.3%)                                    | 20 (11.4%)                                     | .717             |
| Current smoker                 | 29 (25.9%)                                    | 36 (20.6%)                                     | .717             |
| Residence                      |                                               |                                                 | .278             |
| Rural area                     | 59 (52.7%)                                    | 92 (52.6%)                                     | .717             |
| Urban area                     | 53 (47.3%)                                    | 83 (47.4%)                                     | .999             |
| Education level at survey      |                                               |                                                 | .024             |
| University and graduate school | 60 (53.6%)                                    | 89 (50.9%)                                     | .024             |
| Graduates below university level | 52 (46.4%)                                         | 86 (49.1%)                                     | .024             |
| Member of IBD community        | 17 (15.2%)                                    | 36 (20.6%)                                     | .029             |
| Type of accessible media       |                                               |                                                 | .029             |
| Internet user                  | 105 (93.8%)                                   | 164 (93.7%)                                    | .999             |
| Newspaper subscriber           | 15 (13.4%)                                    | 43 (24.6%)                                     | .003             |
| Proportion of responder knowing that proper vaccination is recommended for patients with IBD | 8 (7.1%) | 29 (16.6%) | .003 |
| Ever recommended vaccination by a physician | 13 (11.6%) | 46 (26.3%) | .003 |

\( aOR \) = adjusted odds ratio. \( TNF \) = tumor necrosis factor.

\( ^{\ddagger} \) Adult vaccines include seasonal influenza vaccine, additional Tdap or Td, pneumococcal vaccine, meningococcal vaccine, hepatitis A virus vaccine, and human papilloma virus vaccine.

\( ^{\ddagger\ddagger} \) Hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease and pulmonary disease.

\( ^{\ddagger\ddagger\ddagger} \) An urban area was defined as a city having a population of > 500,000 people.

### Table 5
Factors affecting adult vaccine uptake by patients with inflammatory bowel diseases in the final multivariable logistic regression model.

|                                | \( \text{aOR (95\% CI)} \) | \( P \) |
|--------------------------------|----------------------------|-------|
| Newspaper subscription        | 2.185 (1.136–4.203)       | .019  |
| Ever recommendation of vaccination by a physician | 2.456 (1.240–4.862) | .010  |
| Use of anti-TNF agent          | 4.966 (1.098–22.464)      | .037  |

\( aOR \) = adjusted odds ratio. \( TNF \) = tumor necrosis factor.

Adult vaccines include seasonal influenza vaccine, additional Tdap or Td, pneumococcal vaccine, meningococcal vaccine, hepatitis A virus vaccine, and human papilloma virus vaccine.

4. Discussion

Our study revealed that Korean patients with IBD were not undergoing proper vaccination, and most of the IBD patients had insufficient knowledge regarding the need for vaccination. Regarding seropositivity of protective antibodies, approximately two-thirds and one-third of the patients were negative for anti-hepatitis A IgG and anti-hepatitis B surface IgG, respectively. Subscription to a newspaper, vaccine recommendation by a physician, and exposure to anti-TNF agents were significantly associated with adult vaccine uptake.

A recent study reported that patients with IBD were more likely to have pneumonia, especially when they used corticosteroids and narcotics.\(^{[23]}\) Other studies have also reported increased risk of varicella and herpes zoster infection in patients with IBD who used corticosteroids, thiopurines, or anti-TNF agents.\(^{[24,25]}\)
Therefore, guidelines have emphasized the importance of proper immunization to reduce the risk of these vaccine-preventable infectious diseases in patients with IBD. However, most studies that investigated self-reported vaccination rates in patients with IBD revealed that vaccination rates were still inadequate. The inadequate vaccination rates were not considerably different in our study compared with those reported in previous studies. In our study, the self-reported vaccination rates for all vaccines, except BCG, were <50%, and vaccination rate was relatively higher for seasonal influenza vaccine (43.2%) than that for the other vaccines. Seasonal influenza vaccination rate was usually the highest and even exceeded 80% in one of the studies. This is probably because seasonal influenza vaccine is the most well-known vaccine, and this result showed that cognition of vaccine itself is an important motivation to uptake it.

According to several studies, suboptimal vaccination rates among patients with IBD were generally caused by the lack of knowledge about vaccines and patients’ concerns regarding the safety of vaccines. Physicians’ indifference to recommend vaccination was also known to result in low vaccination rates among IBD patients. In our study, most of the patients (87.1%) were not aware that vaccines have been recommended for patients with IBD, and a majority of the patients (79.4%) replied that they had never been recommended any vaccine uptake from their treating doctors, although doctors were found to be the most common source for procuring information regarding vaccines (34.5%). Multivariable analysis conducted in our study revealed that vaccination recommendation by a doctor was a significant predictor of vaccine uptake, and this reflects the importance of doctors’ attention to and recommendation for vaccine uptake; moreover, use of anti-TNF agents was also a significant predictor of vaccine uptake. This is probably because doctors and IBD patients pay more attention to the patients’ immune status before starting a more immunosuppressive agent. Other factor proven to be significant was subscription to a newspaper. This factor could be related to knowledge about vaccination because newspaper could also be a route through which information on diseases is procured. One unexpected result in our study is that internet use was not a significant predictor of vaccine uptake although internet websites were the second most frequently used source of information on diseases and vaccines in our survey. However, this could be explained by the fact that internet use is already widespread in Korea and internet use alone did not represent active searching for information on diseases and vaccines.

One strong point of our study is that we checked various antibody levels to evaluate immune status of all patients based on recommendations from USA and Europe. Seropositivity rates of MMR, VZV, and HBV were relatively high, ranging from 67.2% to 85%; meanwhile, seropositivity rates of HAV were low (35.2%). This is because the former 3 vaccines were included in the National Immunization Program of Korea, whereas HAV
was recommended as the only optional vaccine until 2014 in Korea. One point to focus in our results is the discrepancy between patients’ recall of vaccination history and seropositivity of disease for each vaccine. The discrepancy could be explained by the following reasons. The first is recall bias. Because our study was performed based on a questionnaire, recall bias was inevitable. The second reason is our strict and conservative way of definition for patients’ recall; in cases where patients replied that they had certainly received a specific vaccine, we regarded such patients as vaccinated. The third reason is previous infection by viruses. Previous infection by viruses can induce the production of protective antibodies, thereby resulting in a state of seropositivity. This discrepancy is the reason why we should perform serological tests to confirm immune status of patients to vaccine-preventable diseases instead of relying on their ability to recall their vaccination history. Moreover, most of the patients in our study did not remember their vaccination history and infection history. Once high-level immunosuppressive therapy is given, live-attenuated vaccines such as MMR and HZV are recommended to be avoided; doctors should check for antibodies to viruses included in live-attenuated vaccines at the time of IBD diagnosis and should recommend these vaccines to patients before starting immunosuppressive therapy.[10,12,26,36]

Ultimately, our study revealed the need for education regarding vaccination and preventive care for patients with IBD. Even among the 54 patients who responded that they knew about live-attenuated vaccines, less than 30% of patients actually had correct knowledge about the types of live-attenuated vaccines and risk associated with these vaccines during immunosuppressive therapy. This shows the importance of doctors’ interest in and attention to preventive care for patients with IBD.

There are some limitations to our study. First, our study was performed based on a questionnaire, owing to which responder bias could be the main limitation followed by recall bias. The documents listing vaccines previously administered to each patient could not be acquired; hence, all vaccination rates were evaluated solely based on patients’ recall. However, a recent study demonstrated a high accuracy of self-reported vaccination status among IBD patients in the United States, which is needed to be replicated in other patient groups.[37] Second, since influenza vaccine is a seasonal vaccine that should be given every year, it is proper to investigate influenza vaccination history year by year. However, assuming a low uptake rate for seasonal influenza vaccine, influenza vaccination history for the last 3 years was asked. If stricter criteria were applied, a vaccination rate for seasonal influenza would have been lower than the current result. For HPV vaccination, women aged 26 years or less were surveyed according to the domestic guidelines at the time of study design, but HPV vaccine is now recommended for both women and men aged 11 to 26 years.[12] Similarly, vaccination history for HZV was asked for patients aged 60 or older according to the domestic guidelines at the time of study design, whereas HZV vaccination is currently recommended for patients aged 50 or older.[12] Third, because of an outpatient-based study design, there is a possibility of selection bias toward clinically more stable patients. Generally, ambulatory patients are relatively well-controlled IBD patients; thus, their interest in information regarding diseases and recommended vaccinations could be lower than that of patients with worse IBD. Finally, our study has limitations in terms of generalizability because of its single-center-based design.

In conclusion, our study mainly revealed that many patients with IBD are not aware of the recommended vaccinations and do not possess exact knowledge about vaccines. They also showed inappropriate vaccine uptake rates and low seroprotection rates for HAV and HBV. Therefore, recommendation and education of vaccination by physicians can motivate IBD patients to uptake proper vaccines.

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