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Serologic protection to routine vaccinations in children with Inflammatory Bowel Disease

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Treatment for inflammatory bowel disease (IBD) frequently involves the aggressive use of immunosuppressants that increases susceptibility to and severity of other infections. There is limited knowledge of coverage and serologic protection of routine immunizations. The aim of this study was to evaluate serologic protection to and completeness of routine vaccinations in children with IBD. In this single-center cross-sectional study, children with IBD followed at the Alberta Children's Hospital were recruited from September 15, 2011 to August 15, 2012. IBD history, demographics, immunosuppressive medication use, vaccination records, and serum were evaluated. 155 children with IBD underwent serum collection; complete vaccine records were available for 152 of these children. At enrollment, 93 participants (60.0%) were using immunosuppressive medications; an additional 30 participants had a history of medical immunosuppression. Only 69.7% of the participants had up to date MMR (measles, mumps, and rubella), DTap-IPV-Hib, and HBV immunizations. Serologic protection was mounted by 20.6% (hepatitis A), 59.4% (mumps), 63.2% (hepatitis B), 64.5% (measles), 71.0% (varicella), 78.1% (rubella), 80.0%, (diphtheria), and 81.3% (tetanus) of the participants. Children with IBD are at risk for vaccine-preventable illnesses due to lack of receiving complete vaccine series and mounting an inadequate serologic response to vaccinations. Serologic response to vaccinations was independent of immunomodulator therapy, suggesting that the altered immunocompetence is a consequence of the IBD diagnosis. Therefore, clinicians caring for patients with IBD should be conscientious about adherence to recommended vaccination schedules, measurement of immune response to vaccines, and administering booster vaccinations where appropriate.

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing and remitting condition of inflammation in the gastrointestinal tract[1]. It is an immune-mediated disease resulting from an inappropriate inflammatory response to an environmental stimulus in a genetically susceptible host[2,3]. It can be divided into two subclasses; ulcerative colitis primarily affects the mucosa of the large colon, while Crohn's disease causes patchy transmural inflammation of the entire gut[1,3]. Though IBD affects individuals of all ages, some of the manifestations unique to children include severe malnutrition and impaired growth[1]. Per 100 000 children, IBD affects 70 with 4.7 new pediatric

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cases each year in North America and Western Europe, the regions of highest prevalence[1,4,5].

Treatment for IBD frequently involves the use of potent immunosuppressants to reduce intestinal inflammation, limit complications and induce and maintain remission[2]. Specifically, immunosuppressants, such as systemic corticosteroids (prednisone, methylprednisolone, and budesonide), immunomodulators (azathioprine, 6-mercaptopurine, methotrexate, and thalidomide), calcineurin inhibitors (tacrolimus and cyclosporin), and anti-tumor necrosis factor alpha (anti-TNFα) biologics (infliximab and adalimumab) effectively treat and prevent flare-ups[5]. The choice of therapy depends on the severity, behaviour, and location of the disease, as well as any side effects and adverse events from medical treatment[3]. Increasingly, medical management has moved towards earlier introduction of immunosuppressive therapies and concomitant treatments[6], however, this more aggressive top-down regime of general immunosuppression increases susceptibility to and severity of opportunistic infections[2,7].

The health care maintenance of immunocompromised individuals is unique due to the balance of protection against vaccine-preventable disease and the risk of vaccine adverse events in an immunosuppressed individual[2,8]. International guidelines encourage immunosuppressed individuals to adhere to the same vaccination schedules recommended for the general population with live agent vaccines as the only exception[2,7]. Attenuated live vaccines, such as the varicella vaccine, need to be administered a minimum of 3 weeks preceding the start of immunosuppressive therapy[6]. Canada's universal health care plan provides all legal residents free access to health services including routine childhood immunizations[9]. The 7th edition of the Canadian Immunization Guide provides specific immunization recommendations for individuals who are medically immunosuppressed[9]. The general principles include:

1. Assume all individuals are susceptible except if serologic tests prove otherwise.

2. Avoid immunizations during periods of altered immunity. If appropriate, vaccination and immunosuppression schedules should be modified to optimize vaccine response.

3. Boost aggressively as altered immunocompetence may decrease the magnitude and duration of vaccine-induced protection.

4. Unless data is available to support their use, postpone live attenuated vaccines until immune function has improved due to the risks of vaccine-associated infections.

However, in spite of these guidelines, many individuals continue to postpone or refuse immunizations due to lack of awareness, unstable disease activity, or fear of disease exacerbation[2]. The childhood immunization schedule varies between provinces in Canada; the schedule for the province of Alberta is outlined in Table 1[10].

In the last decade, additions to the Alberta schedule included varicella (chickenpox) vaccine (2001), pneumococcal conjugate vaccine (pneumococcal conjugate vaccine - 7-valent: 2002, pneumococcal conjugate vaccine - 13-valent: 2010), meningococcal-C conjugate vaccine (2002), meningococcal conjugate vaccine (Groups A, C, W-135, and Y: 2011), and human papilloma virus vaccine (2008)[9].

Newly diagnosed patients with IBD often inquire about the course of the disease and expectations related to quality of life, therefore, it is essential to understand the relationship between immunosuppressant medical therapy, immune health, and opportunistic infections[3,5,11]. In children with IBD, the completeness of routine childhood vaccinations along with the presence and duration of serologic protection to routine childhood vaccines are unknown. The relationship between immunosuppressive therapy at time of or after vaccination on serologic protection is also unknown. Knowledge of the presence and duration of serologic protection to immunizations in children with IBD may help guide potential future recommendations for routine and booster vaccinations to optimize protection against vaccine- preventable illnesses[7]. This information is especially important for children with IBD at risk for increased incidence and severity of infections due to medical immunosuppression. In addition, knowledge of the trends for incomplete vaccinations will be a valuable asset for health care providers seeking to optimize vaccination completeness in children with IBD. The objective of this study was to evaluate the serologic protection to and completeness of routine childhood vaccinations in children with IBD.

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Table 1: Alberta Childhood Vaccination Schedule

Age or Time of Vaccination	Vaccine
2 months	• DTaP-IPV-Hib[1] • PCV13[2] • Men C[3]
4 months	• DTaP-IPV-Hib • PCV13 • Men C
6 months	• DTaP-IPV-Hib • PCV13 (for high risk children only)
≥ 6 months	• Influenza (annually during influenza season)
12 months	• MMRV[4] • PCV13 • Men C
18 months	• DTaP-IPV-Hib
4–6 years	• DTaP-IPV[5] • MMR • PCV13 (catch up program: only for children up to 71 months)
Grade 5	• HBV[6] (3 doses) • HPV[7] (3 doses for females)
Grade 9	• dTap[8] • HPV (catch up program: only females for three years, from Sept. 2009 to June 2012) • MCV4[9]

Government of Alberta Health and Wellness, updated August 1, 2012[10]

1. Diphtheria, tetanus, acellular pertussis, polio, *haemophilus influenzae* type b
2. Pneumococcal conjugate
3. Meningococcal conjugate
4. Measles, mumps, rubella, and varicella
5. Diphtheria, tetanus, acellular pertussis, polio
6. Hepatitis B
7. Human papilloma virus
8. Diphtheria, tetanus, acellular pertussis
9. Meningococcal conjugate vaccine (Groups A, C, W-135 and Y)

Methods

Participants

Participants for this single-center cross-sectional study were recruited from September 15, 2011 to August 15, 2012 through the pediatric Gastroenterology clinic at the Alberta Children's Hospital. Potential participants were identified through nonprobability convenience sampling and enrollled by mail, telephone, or in person at the time of a visit. Individuals who had previously participated in the 2008 study "Immunogenicity and Safety of Influenza Vaccine in Children with

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Inflammatory Bowel disease" (Ethics ID 21876) were also recruited. The inclusion criteria for the cohort were a diagnosis of IBD established by accepted criteria for endoscopy, histology, clinical course, radiology, and surgery[12] and age between 2 to 18 years. The exclusion criterion was parent or legal guardian unwilling or unable to provide signed informed consent. Participants were not paid to participate.

Study Conduct

Demographic data and medical history were collected from participants using a standardized questionnaire. This included information about IBD history (IBD type, date of diagnosis, and start and end date of all IBD medications). The IBD medications considered to be immunosuppressive included: systemic corticosteroids (prednisone, methylprednisolone, and budesonide), immunomodulators (azathioprine, methotrexate, and thalidomide), calcineurin inhibitors (tacrolimus and cyclosporin), and anti-TNFα biologics (infliximab and adalimumab).

Data was also collected on infectious history for varicella infection (date of infection and parental recall versus physician diagnosis versus laboratory confirmation) and risk factors for hepatitis B infection (country of birth, ethnicity, history of jaundice or liver disease, international travel, household exposure to individuals with hepatitis B, blood transfusions, percutaneous risk factors [intravenous drug use, tattoos, and body piercings], and nosocomial risk factors [needle stick injury]).

A copy of immunization records was obtained from either the Public Health Clinic or from personal immunization cards. A vaccine dose was considered valid if the written record documented the type of vaccine and date of administration. Invalid records included parental recall without documentation of the type and date of vaccine administration. Written informed consent was attained to access immunization records and medical record shadow charts from the pediatric Gastroenterology clinic to confirm collected data.

Serum was collected (3-5 mL in a gold-top Vacutainer tube) from each participant to assess for serologic protection. In addition to collecting new serum from patients, consent was obtained from participants who had previously participated in the 2008 study"Immunogenicity and Safety of Influenza Vaccine in Children with Inflammatory Bowel disease" (Ethics ID 21876) to use the residual serum volume for testing.

Immunization Completeness

Patient immunization records were compared with the routine immunization schedule provided by the Government of Alberta Health and Wellness to determine completeness of immunizations. Criterion for up to date and age appropriate immunizations were:[10,12]

- MMR-2 doses (at 12 months and 4 to 6 years)
- DTaP-IPV-Hib- 5 doses (at 2 months, 4 months, 6 months, 18 months, 1-6 years [except Hib])
- HBV- 3 doses (at grade 5 or 9 to 11 years)
- HAV- 2 doses (6-12 months apart)
- VZV- 1 dose (if aged 12 months to 12 years old) or 2 doses (28 days apart if greater than 13 years of age)
- PCV13- 1 dose (if greater than 23 months of age) or 3 doses (if aged 2 to 23 months)
- Men C- 1 dose (if greater than 12 months of age) or 2 doses (if aged 2 to 12 months)
- HPV- 3 doses (females at grade 5 or 9 to 11 years starting in 2008 or at grade 9 or 13 to 15 years from 2009 to 2012)

In the last decade, the Albertan schedule added the varicella virus (VZV) vaccine, pneumococcal conjugate vaccine (PCV13), meningococcal-C conjugate vaccine (Men C), and human papilloma virus (HPV) vaccine, some of which were not part of the immunization schedule for all participants. The majority of these participants received vaccines under the previous recommended immunization schedule that only included the: 1) measles, mumps, and rubella vaccine (MMR), 2) diphtheria, tetanus, acellular pertussis, inactivated polio virus vaccine and *Haemophilus influenzae* type b conjugate vaccine (DTaP-IPV-Hib), and 3) hepatitis B vaccine (HBV). These three vaccines constituted the standard childhood immunizations for assessing completeness of vaccinations.

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Serologic Protection

The Provincial Laboratory for Public Health (Microbiology), Calgary, Alberta, stored the serum at −20 °C and conducted the serologic testing[13]. Antibodies to HBV surface antigen, hepatitis A virus (HAV), VZV, measles, mumps, rubella, *Corynebacterium diphtheria* toxin, and *Clostridium tetani* toxin were measured by microparticle enzyme immunoassays for the viruses. The assays for HAV, VZV, measles, mumps, *Corynebacterium diphtheria* toxin, and *Clostridium tetani* toxin were qualitatively reported as positive, indeterminate, or negative; a positive result indicated serologic protection. The assays for rubella IgG antibody and antibody to HBV surface antigen were quantitative and were reported in IU/ml and IU/L, respectively. Serological protection for rubella was indicated by a rubella IgG titer $\geq$ 15 IU/ml and an antibody titer $\geq$ 10 IU/L for hepatitis B surface antigen. The laboratory technicians and virologists performed the serologic testing without knowledge of the participants diagnosis, immune status, or medical treatment.

Statistical Analysis

Data was entered into a database with Excel XP (Microsoft Corp, Redman, WA). We described demographic characteristics, IBD history, and immunization completeness. For each vaccine, the proportion of children with IBD with serologic protection was calculated. For vaccine completeness, the proportion of children with IBD and complete routine childhood vaccinations was evaluated. Descriptive statistics were determined as medians (with first quartile [Q1] and third quartile [Q3]) or proportions where appropriate. Statistical tests were two-sided with significance assigned at $P<0.05$.

The Alberta Childrens Hospital pediatric Gastroenterology Clinic follows approximately 200 children with IBD. Attempts to contact all of these children over the enrollment period were made by mail, telephone, or clinic/hospital visit.

Results

Study Participants

There were 155 patients who enrollled in the study and provided serum: 93 Crohn's disease, 46 ulcerative colitis, and 16 IBD-unclassified. Complete vaccine records were available for 152 of these children. The median age at enrollment was 15.9 years (Table 2).

Immunosuppressive Medication Use

At enrollment, 93 participants (60.0%) were on immunosuppressive therapy: 20 participants (12.9%) on systemic corticosteroids (15 on prednisone, 2 on methylprednisolone, and 3 on budesonide); 70 participants (45%) on immunomodulators (41 on azathioprine, 28 on methotrexate, and 1 on thalidomide); and 48 participants (31%) on biologics therapy (45 on infliximab and 3 on adalimumab). Of these patients on immunosuppressive therapy, 41 participants (44.1%) were on combination therapy: 9 on corticosteroids and immunomodulators; 2 on corticosteroids and biologics; 26 on immunomodulators and biologics; and 4 on corticosteroids, immunomodulators, and biologics. Participants with Crohn's disease (74.2%) were more likely to be on immunosuppressants than either ulcerative colitis (34.8%) or IBD- unclassified (50.0%) ($p<0.001$).

A total of 123 participants (79.4%) reported having ever used immunosuppressants: 105 used systemic corticosteroids (104 used prednisone, 9 used methylprednisolone, and 10 used budesonide); 98 used immunomodulators (88 used azathioprine, 43 used methotrexate, and 1 used thalidomide); and 59 used biologics (58 used infliximab and 3 used adalimumab).

From review of the 152 vaccination records, the proportion with complete series for each vaccine according to the Alberta schedule (at age of vaccination) was evaluated. 106 participants (69.7%) had the standard immunizations up to date: 142 participants (93.4%) for MMR, 130 participants (85.5%) for DTap-IPV-Hib, and 127 participants (83.6%) for HBV (Table 3).

For the HPV vaccinations, 126 participants (82.9%) did not receive the vaccine: 25 female participants did not receive the vaccine, 20 female participants were outside of the appropriate age bracket, and 82 male participants were excluded from the numbers for HPV. Of note, 1 of the 82 male participants with valid immunization documentation received the HPV vaccine. For varicella, 60 participants received at least one dose of varicella vaccine (55 participants received 1 dose, 5 received 2 doses); 85 participants had a history of chickenpox infection (51 participants reported diagnoses by a physician and 10 cases were

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Table 2: Baseline Characteristics and Risk Factors

Characteristics	Total Cohort *n* =155	Immunizations Up to Date *n* =106	Immunizations Not Up to Date *n* =46
Inflammatory bowel disease type, *n* (%)			
Crohn's disease	93 (60.0%)	65 (61.3%)	26 (56.5%)
Ulcerative colitis	46 (29.7%)	31 (29.2%)	14 (30.4%)
Indeterminate colitis	16 (10.3%)	10 (9.4%)	6 (13.0%)
Sex, *n* (%)			
Male	83 (53.5%)	56 (52.8%)	26 (56.5%)
Female	72 (46.5%)	50 (47.2%)	20 (43.5%)
Median diagnosis age in years (Q1, Q3)	12.1 (9.0, 14.5)	12.6 (9.5, 14.6)	10.5 (7.2, 13.8)
Median current age in years (Q1, Q3)	15.9 (12.8, 17.6)	16.3 (13.7, 17.7)	14 (11.5, 16.9)
Medically Immunocompromised, *n* (%)			
Any immunosuppressant use	123 (79.4%)	81 (76.4%)	39 (84.8%)
Current immunosuppressant use	93 (60.0%)	61 (57.5%)	30 (65.2%)
Any corticosteroid use	105 (67.7%)	70 (66.0%)	32 (69.6%)
Current corticosteroid use	20 (12.9%)	13 (12.3%)	5 (10.9%)
Any immunomodulator use	98 (63.2%)	67 (63.2%)	31 (67.4%)
Current immunomodulator use	70 (45.2%)	47 (44.3%)	23 (50.0%)
Any biologics use	59 (38.1%)	37 (34.9%)	20 (43.5%)
Current biologics use	48 (31.0%)	30 (28.3%)	16 (34.8%)
Chicken pox risk factors, *n* (%)			
Previously infected	87 (56.1%)	62 (58.5%)	23 (50.0%)
Vaccinated	62 (40.0%)	42 (39.6%)	18 (39.1%)
No vaccinations/infection	10 (6.5%)	5 (4.7%)	5 (10.9%)
Hepatitis B risk factors, *n* (%)			
Caucasian	107 (69.0%)	74 (69.8%)	31 (67.4%)
Born in Canada	140 (90.3%)	100 (94.3%)	39 (84.8%)
Jaundice	30 (19.4%)	20 (18.9%)	10 (21.7%)
Liver disease	7 (4.5%)	6 (5.7%)	1 (2.2%)
Travel outside Canada	131 (84.5%)	90 (84.9%)	39 (84.8%)
Household exposure to Hep B	3 (1.9%)	3 (2.8%)	0
Blood transfusion	22 (14.2%)	11 (10.4%)	9 (19.6%)
Needle stick injury	1 (0.6%)	0	1 (2.2%)
Body piercings	49 (31.6%)	39 (36.8%)	10 (21.7%)
Tattoos	3 (1.9%)	3 (2.8%)	0

Up to date for all age appropriate standard immunizations (measles, mumps, and rubella vaccine, diphtheria, tetanus, acellular pertussis, inactivated polio virus vaccine, and *Haemophilus influenzae* type b conjugate vaccine); Q1, first quartile; Q3, third quartile; 3 participants did not have valid documentation of immunization records

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Table 3: Vaccination Coverage Status

	Up to date			Not up to date		
Vaccinations, *n* (%)	*n* =152	Complete (series)	Complete for age	*n* =152	No Doses	Partial (Series)
MMR	142 (93.4%)	139/142 (97.9%)	3/142 (2.1%)	10 (6.6%)	5/10 (50.0%)	5/10 (50.0%)
DTaP-IPV-Hib	130 (85.5%)	73/130 (56.2%)	57/130 (43.8%)	22 (14.5%)	1/22 (4.5%)	21/22 (95.5%)
HBV	127 (83.6%)	114/127 (89.8%)	13/127 (10.2%)	25 (16.4%)	14/25 (56.0%)	11/25 (44.0%)
HAV	13 (8.6%)	9/13 (69.2%)	4/13 (30.8%)	139 (91.4%)	137/139 (98.6%)	2/139 (1.4%)
VZV	142 (93.4%)	60/142 (42.3%)	*85/142 (60.0%)	10 (6.6%)	10/10 (100.0%)	0
PCV13	17 (11.2%)	16/17 (94.1%)	1/17 (5.9%)	135 (88.8%)	135/135 (100.0%)	0
Men C	111 (73.0%)	111/111 (100.0%)	0	41 (27.0%)	36/41 (87.8%)	5/41 (12.2%)
HPV[§]	41 (58.6%)	21/41 (51.2%)	20/41 (48.8%)	29 (41.4%)	25/29 (86.2%)	4/29 (13.8%)

Complete (series)- received all scheduled doses; Complete for age- received all doses appropriate for age; No doses- zero doses received; Partial (series)- received ≥1 dose, still missing ≥1 dose; * 85 participants had previous infection history with 3 also receiving vaccinations; § 70 female participants with valid immunization documentation

Table 4: Serologic Protection

	All children with IBD (*n*=155)	Children with IBD using immunosuppressants (*n*=93)	Children with IBD with complete vaccine series
Varicella, *n* (%)	110 (71.0%)	69 (74.2%)	103/145[a] (71.0%)
Measles, *n* (%)	100 (64.5%)	61 (65.6%)	94/139 (67.6%)
Mumps, *n* (%)	92 (59.4%)	58 (62.3%)	88/139 (63.3%)
Rubella, *n* (%)	121 (78.1%)	73 (78.4%)	114/140 (81.4%)
Hepatitis B, *n* (%)	98 (63.2%)	57 (61.3%)	82/114 (71.9%)
Hepatitis A, *n* (%)	32 (20.6%)	19 (20.4%)	9/9 (100.0%)
Diptheria, *n* (%)	124 (80.0%)	75 (80.6%)	63/73 (86.3%)
Tetanus, *n* (%)	126 (81.3%)	75 (80.6%)	67/73 (91.8%)

[a] n=146 with past history of vaccination or chickenpox infection

confirmed by a blood test). However 10 of 152 participants had neither been infected nor vaccinated, including 7 participants who were currently using immunosuppressive medications. Whether or not the participants received immunosuppressive therapy did not affect their serologic response (Table 4). The proportion of all IBD participants with serologic protection ranged from 61% to 79%, while the proportion of those on immunosuppressive medications ranged from 61% to 81%. Similarly, serologic protection was mounted in 61% to 100% of participants who had received age appropriate vaccines. Therefore, approximately two-fifths of children with IBD may not have had serologic protection in spite of completing their vaccination series.

Only 26 of the 140 participants with the completed MMR series lacked serologic protection to rubella, including 15 participants who were currently using immunosuppressive medications. Participants with serologic protection for tetanus were older at diagnosis (median age in years [Q1,Q3]: 14.4 [11.9, 15.6] versus 11.2 [11.7, 9.6], P=0.007). Similarly, 100.0% of the participants who received the complete tetanus vaccination before diagnosis mounted serologic protection compared to those which received the final dose following diagnosis (82.5%, P=0.01).

For hepatitis B, 150 participants (96.7%) had at least one known risk factor. Twenty-two (14.2%) reported a history of packed red blood cell transfusion with a total number of 29 transfused units (range 1 to 3). Though 114 participants completed the HBV series, 33 of these participants lacked serologic protection to HBV. Of the participants with complete 3-dose HBV vaccination series, serologic protection was mounted by participants with older diagnosis age (median age in years [Q1,Q3]: 13.7 [11.0, 15.1] versus 11.6 [8.8, 13.4], P=0.002). In total, 57 of 155 (36.8%) participants lacked serologic protection to HBV. Fourteen participants either did not receive or received incomplete HBV vaccine series (not accounted for by age less than recommended age of vaccination). In the non-immunized group, potential risk factors for infection included past history of travel

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outside of Canada (n=49), blood transfusion (n=8), and body piercing (n=15).

For hepatitis A, 9 participants completed the HAV series and all mounted serologic protection. Interestingly, 23 of 137 participants with no prior HAV vaccination mounted serologic protection to HAV; although 19 of these participants were born in Canada, all 23 participants had travelled outside of Canada.

Discussion

Sixty percent of participants were receiving immunosuppressive therapy and of these participants almost three-quarters were also using concomitant immunosuppressive medications. Immunosuppressive medications increase the risk of opportunistic infections; risk is increased by 2 fold with biologics alone[8], 2 to 3 times with corticosteroid monotherapy, and 15-fold with corticosteroid and immunomodulator use[11]. Double or triple immunosuppressive therapy drastically increases the risk of opportunistic infections. Clinicians caring for patients with IBD should ensure appropriate immunizations are administered and up to date at time of diagnosis and preceding start of medical therapy.

Only 69.7% of the participants had the standard immunizations (MMR, DTap-IPV-Hib, and HBV) up to date. Nearly a third of individuals in a high-risk group for more frequent and severe infections had not received protection against vaccine- preventable disease. Vaccination coverage ranged from 8.6% for HAV to 93.4% for MMR and VZV. In general, the individuals with better access to vaccinations, or those with less severe disease course had a greater proportion of the standard immunizations up to date[6]. For the individuals with the standard immunizations up to date, they were in general older at diagnosis (median age of 12.6 versus 10.5 years) and born within Canada (94.3%versus 84.8%). The older age of diagnosis suggests that fewer immunizations may have been deferred as a result of the onset of the disease. As well, in general, children born in Canada have greater accessibility to medical care, increased awareness of immunizations, and free routine child immunizations. In comparison, there were several trends suggesting a more severe disease course in the individuals who had not received the standard immunizations. A greater proportion had a history of medical immunosuppression (84.8% versus 76.4%) and had received blood transfusions (19.6% versus 10.4%), Medical immunosuppression may have acted as a deterrent to receiving immunizations, and blood transfusions often indicate a more severe and acute disease course.

Ten participants (6.5%) did not have either previous exposure to the varicella infection or immunizations. The number of children without any serologic protection to the varicella virus is very alarming as infection during immunosuppression tends to be more serious[6]. The low proportion of patients with IBD with up to date vaccinations in general demonstrates the necessity for medical staff and caregivers to address the risk of infections and benefits of immunizations[6,7]. Adherence to the recommended immunization schedule is especially important for those patients who are medically immunocompromised and at a higher risk of infection.

There was no difference between serologic protection in individuals who had or had not received immunosuppressive therapy. The proportion of all IBD participants with serologic protection ranged from 61% to 79%, while the proportion of those on immunosuppressive medications ranged from 61% to 81%. For each specific vaccine, there was at most a 3% difference in proportion of serologic protection, suggesting that medical immunosuppression does not affect vaccination efficacy. Another similar pediatric study determined that patients receiving immunosuppressive medication, including 2 individuals with IBD among the 25 participants, found a decreased but insignificant difference in influenza sero-conversion with the immunocompetent control group[14]. On the other hand, a systematic review that assessed the relationship between individuals receiving immunosuppressive therapy and influenza and pneumococcal vaccines identified a diminished response[15]. However, this conflict may be due to the difference in study population. The participants for both studies included any patients receiving immunosuppressive therapy; neither were specific to individuals with IBD like this study. Therefore, further large cohort studies are needed to elucidate the effect of immunosuppressive medications on vaccinations and immunogenic response in the pediatric IBD population.

A high proportion of individuals received the completed vaccine series but failed to mount an appropriate serologic response. Serologic response

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in participants with complete vaccine series ranged from 63.3% for mumps to 91.8% for tetanus. In comparison, healthy children aged 1 to 12 years of age retained varicella vaccine efficacy for up to 10 years (94.4% for one does and 98.3% for two doses, $P < 0.001$)[16]. This marked difference in serologic response combined with the apparent independence from immunosuppressive medication status, suggests that a diagnosis of IBD inherently causes general immune dysfunction[3].

The only vaccine to achieve a 100% immunogenic response was HAV, as well as an additional 19 individuals who did not receive the HAV vaccinations but demonstrated serologic immunity. The most likely explanation is that they were inadvertently exposed to the virus from traveling outside of Canada[2].

This study was limited by the small sample size and incomplete immunization data for several of the participants. Although the goal was to enroll 200 participants, 155 underwent serum collection and complete vaccination records were available for 152 participants. This study would have benefited from a healthy control group that included children of similar demographics to compare serologic response to vaccines. On the other hand, this study is representative of children elsewhere with similar disease type and treatment, as even though the data is from a single tertiary-care pediatric hospital, the participants were managed closely in a multidisciplinary IBD clinic.

As well, while enrollment was open to children aged 2 to 18 years old, the majority of participants were over 12 years old. The immunization schedule recommends that most children receive the majority of their vaccines before this age[10]. Therefore, because of a small sample size and immunization schedules for children less than 12 years of age, our findings should be generalized only to children with IBD over 12 years of age.

The pattern of immunogenicity requires further elucidation as the results in this study suggest that medical immunosuppression does not affect the magnitude and duration of vaccine-induced immunity. However, previous studies have identified an increased risk of opportunistic infections for patients with IBD, especially those on immunosuppressive medical therapy[2,7]. In addition, we do not know if differing vaccination timing relative to immunosuppressive treatment may alter immunological protection. Thus, ongoing assessment of the outcomes of aggressive vaccination in immunosuppressed children is essential, as is critical revisions to the recommended vaccination schedule to include booster shots[8]. Further studies on the relationship between vaccine-induced immunity and vaccine completeness in the pediatric inflammatory bowel disease population are warranted.

Conclusions

This study provides additional information to the currently available literature on the use of vaccinations in children with IBD. Specifically, this study reinforces the notion that all children with IBD, regardless of medical immunosuppression, should adhere to the recommended schedule (aside from live vaccines) as immunizations decrease the risk of vaccine-preventable illnesses. Interestingly, serologic protection was independent of immunosuppressive therapy, suggesting that a diagnosis of IBD inherently compromises response to vaccination. Data suggests that a history of childhood infection and previous complete immunization does not guarantee immunogenic protection. If there is any question as to whether vaccines were administered or were immunogenic, repeating immunizations is a recommended and acceptable option[11].

The low proportion of participants with complete up to date immunizations demonstrates the need to address the risk of infections from vaccine-preventable disease in patients with IBD, especially those using immunosuppressive medications. Therefore, clinicians caring for patients with IBD should be conscientious about adherence to recommended vaccination schedules, measurement of immune response and serologic protection to vaccines, and booster vaccinations where appropriate.

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