Digestion

Brief Report

Digestion 2021;102:956–964
DOI: 10.1159/000516111

Received: November 18, 2020
Accepted: March 14, 2021
Published online: May 10, 2021

Risk of Vaccine-Preventable Infections in Swiss Adults with Inflammatory Bowel Disease

Laure F. Pittet[a] Charlotte M. Verolet[a] Pierre Michetti[b, c] Elsa Gaillard[a] Marc Girardin[d] Pascal Juillerat[e] Christian Mottet[f] Michel H. Maillard[b, c] Claire-Anne Siegrist[g] Klara M. Posfay-Barbe[a] The Swiss Inflammatory Bowel Disease Cohort Study Group

[a]Department of Pediatrics, Pediatric Infectious Disease Unit, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland; [b]Crohn's and Colitis Center, Gastroenterology Beaulieu SA, Lausanne, Switzerland; [c]Department of Medicine, Service of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [d]Department of Medical Specialities, Gastroenterology Service, Geneva University Hospitals, Geneva, Switzerland; [e]Service of Gastroenterology, Clinic of Visceral Surgery and Medicine, Bern University Hospital, Bern, Switzerland; [f]Service of Gastroenterology, Hôpital Cantonal, Sion, Switzerland; [g]Departments of Pathology-Immunology and Pediatrics, Centre for Vaccinology, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Keywords
Crohn's disease · Ulcerative colitis · Vaccine-preventable infection · Immunization

Abstract
Background: Patients with inflammatory bowel disease (IBD) have a higher risk of infection and are frequently not up to date with their immunizations. ***Objectives:*** This study aims to review vaccination status and evaluate whether age, disease type, or treatment regimen could predict the absence of seroprotection against selected vaccine-preventable infection in adults with IBD. ***Methods:*** Cross-sectional study using questionnaire, immunization records review, and assessment of tetanus-specific, varicella-specific, and measles-specific immunoglobulin G concentrations. ClinicalTrials.gov: NCT01908283. ***Results:*** Among the 306 adults assessed (median age 42.7 years old, 70% with Crohn's disease, 78% receiving immunosuppressive treatment), only 33% had an immunization record available. Absence of seroprotection against tetanus (6%) was associated with increasing age and absence of booster dose; absence of seroprotection against varicella (1%) or measles (3%) was exclusively observed in younger patients with Crohn's disease. There was no statistically significant difference in immunoglobulin concentrations among treatment groups. Although vaccinations are strongly recommended in IBD patients, the frequencies of participants with at least 1 dose of vaccine recorded were low for nearly all antigens: tetanus 94%, diphtheria 87%, pertussis 54%, poliovirus 22%, measles-mumps-rubella 47%, varicella-zoster 0%, *Streptococcus pneumoniae* 5%, *Neisseria meningitidis* 12%, hepatitis A 41%, hepatitis B 48%, human papillomavirus 5%, and tick-borne encephalitis 6%. ***Conclusions:*** Although many guidelines recommend the vaccination of IBD

karger@karger.com
www.karger.com/dig

Correspondence to:
Laure F. Pittet, laure.pittet@hcuge.ch
Klara M. Posfay-Barbe, klara.posfaybarbe@hcuge.ch

patients, disease prevention through immunization is still often overlooked, including in Switzerland, increasing their risk of vaccine-preventable diseases. Serological testing should be standardized to monitor patients' protection during follow-up as immunity may wane faster in this population.

Introduction

As the immune system of patients with inflammatory bowel disease (IBD) is altered, their vulnerability to infections is greater [1–3]. Several international groups of experts have hence issued structured recommendations on vaccination in immunocompromised hosts and IBD patients [4–9], recently reviewed in this journal [10]. Unfortunately, a number of studies have pointed out that the vaccination status of IBD patients is suboptimal [11–15], and that their immune responses to nearly all vaccinations can be impaired [16], in particular in those under immunosuppressive treatment [17]. Our aim was to document the vaccination status in Swiss adults with IBD and identify whether age, disease type, or treatment regimen could predict the absence of seroprotection against selected vaccine-preventable infections.

Materials and Methods

This cross-sectional study was nested in a phase IV multicenter study evaluating the safety and immunogenicity of the 13-valent pneumococcal conjugate vaccine in 306 adults with IBD [18]. Participants from 4 regions in Switzerland (Bern, Geneva, Neuchatel, and Vaud) were included as previously described and provided their written informed consent. Temporary exclusion criteria were pregnancy, current IBD flare pregnancy, pneumococcal immunization in the previous 5 years, and influenza immunization in the previous 4 weeks [18]. The protocol was approved by the Ethics Committee of all participating institutions (CER 12-211), and the study was conducted in compliance with the Declaration of Helsinki.

Two questionnaires were completed at inclusion collecting details on participants' disease and treatment (306 questionnaires completed) and querying previous history of vaccine-preventable infections and/or vaccinations (299 questionnaires completed), including review of immunization records (101 records available). Blood was collected from all 306 participants at inclusion; tetanus-specific, varicella-specific, and measles-specific immunoglobulin G (IgG) concentrations were measured using ELISA on the platform DSX® (Dynex® Technologies, Chantilly, VA, USA). The cutoffs for defining seroprotective concentration against tetanus, varicella, and measles were set as 100 IU/L, 50 IU/L, and 150 IU/L, respectively. These were experimentally defined as the lowest concentration associated with the presence of neutralizing antibodies in a series of independent sera from healthy subjects (unpublished data).

Mann-Whitney tests were used for comparison of IgG concentration among gender and diagnostic groups. Kruskal-Wallis tests were used for comparison among participants' age (18–35 years old, 35–50 years old, 50–65 years old, and above 65 years old), region (Bern, Geneva, Neuchatel, and Vaud), and treatment groups (no immunosuppression, immunosuppression without anti-TNF, and immunosuppression with anti-TNF), followed by Mann-Whitney tests for comparisons between subgroups. All analyses were 2-sided and performed using Stata 13® (StataCorp, College Station, TX, USA), and $p < 0.05$ was considered statistically significant. Bonferroni adjustment was used for multiple comparisons. ClinicalTrials.gov identifier: NCT01908283.

Table 1. Participant characteristics

	Participants (n = 306)
Sex	158 female (52%) 148 male (48%)
Age, years	Median 42.7, IQR, 29.4–52.5
Diagnostic	213 Crohn's disease (70%) 93 ulcerative colitis (30%)
Treatment regimen	
Treatment-free	28 (9%)
Nonimmunosuppressive treatment	93 (30%)
5-Aminosalicylic acid	67 (22%)
Sulfasalazine	2 (1%)
Topical corticosteroids	5 (2%)
Vedolizumab	26 (9%)
Immunosuppressive treatment	235 (77%)
Systemic corticosteroids	25 (8%)
Prednisone	18 (6%)
Budesonide	7 (2%)
Thiopurines	63 (21%)
6-Mercaptopurine	7 (2%)
Azathioprine	56 (18%)
Methotrexate	12 (4%)
Anti-TNF-alpha agents	155 (51%)[a]
Infliximab	114 (37%)
Adalimumab	26 (9%)
Certolizumab pegol	9 (3%)
Golimumab	7 (2%)
Serology results	
Anti-tetanus IgG, IU/L	Median 1,080, IQR, 516–2,098
Anti-varicella IgG, IU/L	Median 1,485, IQR, 1018–2,078
Anti-measles IgG, IU/L	Median 3,866, IQR, 943-11–407

Anti-TNF, antitumor necrosis factor; IQR, interquartile range; IgG, immunoglobulin G. [a] One patient was receiving both adalimumab and certolizumab pegol.

Table 2. Vaccination status of Swiss IBD patients

Vaccine	Patients with ≥1 dose documented, %	Details
Tetanus	94	Doses, *n*: median 5 (IQR: 3–6) Delay since last dose: median 11.5 yr (IQR: 5.3–23.5)
Diphtheria	87	Doses, *n*: median 5 (IQR: 3–6) Delay since last dose: median 10.5 yr (IQR: 5.2–23.1)
Pertussis	54	Doses, *n*: median 4 (IQR: 3–4) Delay since last dose: median 25.9 yr (IQR: 13.1–40)
Poliovirus	22	Doses, *n*: median 1 (IQR: 1–4) Delay since last dose: median 10.4 yr (IQR: 7.1–23.5)
Varicella-zoster	0	Comment: neither varicella nor zoster vaccine
Measles-mumps-rubella	47	Doses, *n*: 1 dose in 17/47 participants (36%) and 2 to 3 doses in 30/47 participants (64%)
Pneumococcus	5	Vaccine type: PPSV23 in 5/5 participants (100%), no PCV Doses, *n*: 1 dose in 4/5 participants (80%), 2 doses in 1/5 participants given 13 years apart (20%)
Meningococcus	12	Vaccine type: MCV-C in 10/12 participants (83%), MPV-ACWY in 1 participant (8%), MCV-ACWY in 1 participant (8%) Doses, *n*: 1 dose in 11/12 participants (92%), 2 doses (of MCV-C) in 1/12 participant (8%)
Hepatitis A	41	Doses, *n*: 1 dose in 13/41 participants (32%), 2 doses in 15/41 participants (37%), ≥3 doses in 13/41 (32%)
Hepatitis B	48	Doses, *n*: 1 dose in 2/48 participants (4%), 2–3 doses in 35/48 (73%), >3 doses in 11/48 (23%; 4 doses in 7/48, 5 doses in 2/48, 6 doses in 1/48, and 7 doses in 1)
Human papillomavirus	5	Doses, *n*: 3 doses in 5/5 participants (100%)
Tick-borne encephalitis	6	Doses, *n*: 3 doses in 5/6 participants (83%), 2 doses in 1/6 participants (17%)
Yellow fever	7	Doses, *n*: 1 dose in 5/7 participants (71%), 2 doses in 2/7 participants (29%)
Typhoid	9	Doses, *n*: 1 dose in 6/9 participants (67%), 2 doses in 1/9 participants (11%), 3 doses in 2/9 participants (22%)
Rabies	2	Doses, *n*: 2 doses in 1/2 participants (50%), 6 doses in 1/2 participants (50%)

Swiss recommendations for vaccination in IBD patients are summarized in Table 3. IBD, inflammatory bowel disease; IQR, interquartile range; MCV-ACWY, meningococcal conjugate vaccine against serogroups A, C, W, and Y; MCV-C, meningococcal conjugate vaccine against serogroup C; MPV-ACWY, meningococcal polysaccharide vaccine against serogroups A, C, W, and Y; PCV, pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Results

A total of 306 participants aged 18.0–92.5 years (median 42.7) were assessed (Table 1). The majority had Crohn's disease (70%) and was receiving an immunosuppressive treatment (78%), mostly anti-TNF agents (51%) [18]. Only 101 participants had an immunization record available (Table 2); their status was compared to the Swiss recommendation (summarized in Table 3). According to the questionnaire, approximately a third of the cohort (112/299) had been immunized against influenza during the preceding winter and 61% (186/299) had received the influenza vaccine at least once in their life. Among those, nearly half (86/186) were immunized yearly.

Seroprotection rates against tetanus, varicella, and measles were high (Fig. 1). Nearly all participants (288/306, 94%) were seroprotected against tetanus. Tetanus-specific IgG concentration was the highest in the 35-

Table 3. Summary of recommendations regarding vaccine-preventable diseases in Swiss IBD patients

Pathogens	Serological testing						Vaccination			Comments
	which	when		estimation of protection[#]			when			
		Dx	R	none	short term	long term	Dx	others	booster	
Tetanus diphtheria pertussis poliovirus	Anti-tetanus IgG, IU/L	C	C	<100	100–1,000	>1,000	C		10 y	C: if no vaccination record available, give 1 dose of tetanus-diphtheria-polio (±pertussis, see below) and check tetanus serology 1 month after to guide whether further doses are needed (see[1]) Diphtheria-tetanus booster every 10 y. Pertussis booster at 25 yo, each pregnancy, and every 10 y if in contact with infant <6 mo. Polio booster every 10 y if traveling to endemic countries
Varicella-zoster	Anti-varicella IgG, IU/L	X		<50	50–150	>150	C	≥50 yo (zoster)		Check serology at least once. Some experts advise monitoring serology regularly if immune suppression C: vaccination with 2 doses if not immune and low/no immune suppression[§] Zoster vaccination recommended if ≥50 yo and on low/no immune suppression. Nonlive zoster vaccine not yet authorized in Switzerland but could enable zoster vaccination of all patients in the future
Measles mumps rubella	Anti-measles IgG, IU/L	X		<50	50–150	>150	C			Check serology at least once. Some experts advise monitoring serology if immunosuppression C: vaccination with 1–2 doses if not immune and low/no immune suppression[§]
Influenza	No routine assay available								1 y	Vaccination every year before the flu season; use high-dose vaccine if ≥65 yo. Live-attenuated influenza vaccine (not available in Switzerland) contraindicated if immune suppression
Pneumococcus	Serotype-specific IgG, mg/L			<0.3	0.3–1	>1	X		C	One dose of PCV13 at least once. May not be reimbursed in IBD patients (92 CHF/dose). Swiss recommendation does not recommend PPSV23; if have received PPSV23 previously wait for 1 y[2] C: some experts recommend PCV13 booster every 5–10 years, or as guided by monitoring of serologies
Meningococcus	No routine assay available						C		C	C: higher risk not demonstrated in IBD patients (rare disease) but plausible (given functional hyposplenia) and seriously life threatening. Swiss recommendation in hyposplenic patients: 2 doses of MCV4, booster every 5 years. May not be reimbursed in IBD patients (64 CHF/dose)
Hepatitis A	Anti-HAV	X	C				C			Assess immunity, give 2 doses if not immune C: European guidelines recommend checking serological response vaccination in immune-compromised patient before travel to endemic area [7]
Hepatitis B	Anti-HBs IgG, IU/L	X	X	<10	10–100	>100	C			C: screen for infection (HBsAg, anti-HBs IgG, anti-HBc IgG), immunization with 3 doses, check serology 1 month after (~40% risk of nonresponse). If <100 IU/L, readminister the entire HBV series using twice the standard dose or the combined hepatitis A/B vaccine. Some experts advise monitoring serology every 1–2 y
HPV	Not recommended routinely							11–26 yo		Three doses if aged 11–26 yo (2-dose regimen not validated if immune compromised)

Table 3 (continued)

Pathogens	Serological testing					Vaccination			Comments
	which	when		estimation of protection#		when			
		Dx	R	none	short term	long term	Dx	others	booster	
Tick-borne encephalitis	Not recommended routinely					C		10 y	C: 3 doses if at risk of exposition (see[1]), booster every 10 y

This table summarizes all the published recommendations for IBD patients [4–9] applied to the Swiss population[1]. C: recommended in certain conditions, see comments; CHF, Swiss Franc; Dx, at diagnostic or at least once; HAV, hepatitis A virus; HBV, hepatitis B virus; HPV, human papillomavirus; IU/L, international unit per liter; IBD, inflammatory bowel disease; IgG, immunoglobulin G; MCV4, 4-valent meningococcal conjugate vaccine (serogroups A, C, W, and Y); mo, month old; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; R, after vaccination, confirm vaccine responses; X, recommended; y, year; yo, year old. # The serological cutoff is given as an indication (as published in the Swiss guidelines[1]), but can vary between laboratories. § Mild immunosuppression defined as prednisone ≤20 mg/day; methotrexate ≤0.4 mg/kg/week; azathioprine ≤3 mg/kg/day; or 6-mercaptopurine ≤1.5 mg/kg/day; no biologic agents such as tumor necrosis factor antagonists or rituximab. Anticipate at least 1 month between vaccine doses and start of immunosuppression. [1] Office fédéral de la santé publique, Commission fédérale pour les vaccinations. Plan de vaccination suisse 2019. Directives et recommandations. In: Unité de direction Santé publique: Division Maladie transmissible, editor. Berne, Switzerland: Office fédéral de la santé publique (OFSP); 2019, pp 1–49. [2] Federal Office of Public Health. Commission fédérale pour les vaccinations. Vaccination contre les pneumocoques: recommandations visant à prévenir les maladies invasives à pneumocoques chez les groupes à risque. Bull OFSP 2014;8:129–141.

to 50-year-old group ($p = 0.003$, compared with the rest) and the lowest in the >65-year-old group ($p < 0.001$, compared with the rest). Overall, tetanus-specific IgG concentrations were slightly lower in participants with Crohn's disease ($p = 0.09$, compared with participants with ulcerative colitis). There was no difference among treatment and region groups; 5 of the 18 nonseroprotected participants were not receiving any immunosuppressive treatment. Among the 18 nonseroprotected participants, only 3 had an immunization record available, and their last tetanus doses documented were nearly 30 years before inclusion.

A quarter of the participants either did not recall previous history of chickenpox disease (19%) or believed they never had it before (9%). Nevertheless, 99% of participants were seroprotected against varicella. There was no statistically significant difference in varicella-specific IgG concentration between the gender, treatment, age, region, and disease groups. The 2 nonseroprotected participants were in their 30s and had Crohn's disease.

Nearly all participants (97%) were seroprotected against measles. A third of the participants (32%) recalled having measles disease and had significantly higher IgG concentration. Higher measles-specific IgG concentration was associated with increasing age (Fig. 1); the level was the highest in the >65-year-old group ($p < 0.001$, compared with the rest). All the nonseroprotected participants were <30 years old and had Crohn's disease; most of them (7/10) were receiving immunosuppressive treatment. Only 2 of them had an immunization record available, with 1–2 doses of measles-mumps-rubella documented. There was no statistically significant difference in measles-specific IgG concentration between the region groups.

Discussion

Although numerous immunization guidelines exist [4–9], this cross-sectional study of over 300 adults with IBD suggests that there are many missed opportunities for disease prevention through vaccination, putting these patients at risk for infection. Only a third of the participants had an immunization record available, with low vaccination rates for nearly all pathogens, emphasizing the room for improvement. This is in line with previous reports in IBD patients from other regions, revealing that physicians' and patients' compliance with the published recommendations remains poor [19, 20]; vaccinations are indeed the least frequently followed quality of care

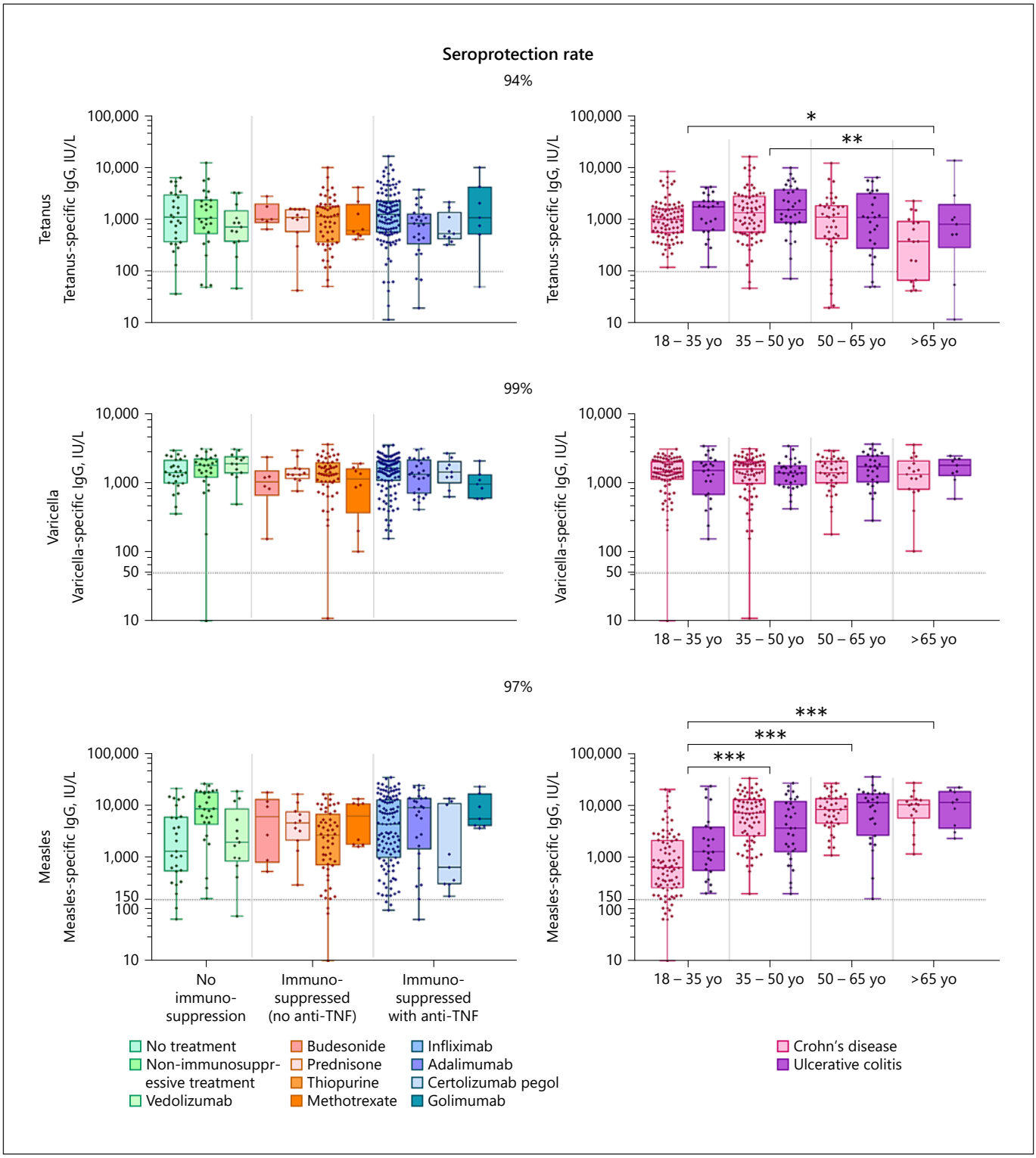

Fig. 1. Serologic status of adult IBD patients against tetanus, varicella, and measles, by age, disease, and treatment. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. IBD, inflammatory bowel disease; IgG, immunoglobulin G; IU/L, international unit per liter; TNF, tumor necrosis factor; yo, years old.

recommendations for this population [21]. This may be attributed to numerous factors [11–15], such as fear of vaccine-induced adverse events and/or of interference of treatment on vaccine responses [22, 23].

At least 1 dose of tetanus-containing vaccine was documented on nearly all vaccination records. However, most participants were not up to date, with insufficient number of doses, and long delays since the last vaccine dose recorded, whereas boosters are recommended every 10 years in immunocompromised patients [4]. Eighteen participants had undetectable tetanus serology, in whom a soiled wound would carry significant risk. Our data suggest that this was probably due to waning immunity with age, in the absence of booster dose. However, both the disease and treatment likely had an impact as well, given the overall lower seroprotection rate and antitetanus IgG concentration compared to those reported in the healthy population [24]. Interestingly, 5 nonseroprotected participants were not receiving any immunosuppressive treatment, highlighting the need for serological monitoring regardless of the treatment regimen.

An alarming low number of participants were vaccinated against hepatitis virus A and B; among them, a high proportion had received more vaccine doses than usually indicated, suggesting that they were probably "nonresponders." Additionally, only few participants were vaccinated against the human papillomavirus, whereas this vaccine is highly recommended in this population, given their higher risk of HPV-related malignancy [7, 25]. Only 5% of the participants with an available vaccination record had received a pneumococcal vaccine. IBD patients have an increased risk of pneumococcal infection [2, 26–28]; the safety and immunogenicity of the pneumococcal conjugate vaccine have now been established in adults with IBD, regardless of their underlying treatment [18, 29], and therefore the use of this vaccine should be strongly promoted in this population. Annual vaccination against influenza virus is also highly recommended to prevent hospitalization and secondary infection with pneumococcus; however, less than half of the participants surveyed were following this recommendation. All those facts strongly advocate for systematically updating the IBD patients' immunization status and emphasize the importance of monitoring vaccine responses in this population.

Varicella and measles infections have a higher risk of complications in immunocompromised patients [30], including those with IBD [31], with mortality rates up to 7% and 40–70%, respectively [32–34]; Janus kinase inhibitor in particular greatly increases the risk of herpes zoster [35, 36]. Guidelines recommend serological testing at IBD diagnosis, with immunization updating, and postexposure prophylaxis in case of contact [7]. Our study shows that nearly all participants were seroprotected against both infections. In Switzerland, varicella vaccination is recommended in all individuals aged ≥11 years who never had chickenpox. As a result, the virus circulates in the community, enabling seroprotected individuals to boost their immunity regularly. This may explain why we found such high varicella-specific antibody concentration across all age groups. Our results may not be generalizable to populations with lower circulation rate of the varicella virus. Nevertheless, 2 participants were not seroprotected and were unaware of their risk of severe infection if exposed to varicella. Our results also confirm prior assumption that questioning patients on previous history of disease is not reliable enough [37] since a quarter of the seroprotected participants could not recall having had chickenpox previously. As for measles, universal vaccination started in the 1960s, and therefore nearly all individuals aged ≥50 had presumably been in contact with the virus during childhood. This might explain why in our study the individuals aged >65 years old had the highest antimeasles antibody concentration. All the nonseroprotected participants were <30 years old. Previous vaccination was documented in the 2 participants with an available vaccination record. Measles infections could potentially be fatal in these 10 nonseroprotected patients, most of them having immunosuppressive treatment. Our data, in line with previous studies from other regions [38, 39], suggest that serological testing should be standardized in all IBD patients.

In conclusion, disease prevention in immunocompromised patients through immunization is often overlooked, but is indeed needed; serological testing should be standardized to monitor patients' protection during follow-up as immunity may wane faster in this population. Temporary withholding of immunomodulating treatment is recommended during an infectious illness, which could have an impact on disease activity. Therefore, by preventing infections, vaccines also indirectly spare IBD flaring [2, 7]. Awareness raising campaigns must be organized to promote the systematic monitoring of specific disease immunity status and subsequent vaccination strategies among the IBD population, regardless of the treatment regimen [19, 20]. Campaigns should convince physicians and patients that vaccines are safe even for patients with immune-mediated inflammatory diseases, in whom they do not trigger disease flare, and that protection is likely to be reached, especially when

vaccination is performed during periods of reduced immune suppression [6], even if vaccine immunogenicity might be slightly attenuated due to immunosuppression [40–46].

Acknowledgements

This study was partly nested in the existing cohort of patients recruited into the Swiss IBD Cohort Study (SIBDCS). We gratefully thank the Platform of Clinical Research in Pediatrics of the Department of Pediatrics, Geneva University Hospitals, a Swiss-PedNet hub, for the logistic support and tremendous work. We also thank all the study participants and the investigators, particularly Katja Barahona, José Bengoa, Gianna Cadau, Philippe De Saussure, Suzanne Duperret, Christian Felley, Barbara Lemaitre, Cassandra Oropesa, Sophie Restellini, Maria Isabel Rodriguez, Carole Salomon, Alain Schoepfer, Paolo Valenti, and Christina Wylie. Special thanks to Natacha Noël for her substantial contribution to the enrollment of participants and data collection. We also thank the contributions of the Clinical Research Center of the Geneva University Hospitals and the Faculty of Medicine.

Statement of Ethics

This research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Subjects have given their written informed consent, and the study protocol was approved by the institute's committee on human research of all participating sites (CER 12–211), by the Swiss Agency for Therapeutic Products (Swissmedic No. 2012DR2022), and by the SIBDCS scientific board (Project No. 2012-17).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

L.F.P. is supported by the Swiss National Science Foundation (Early Postdoc.Mobility Grant No. P2GEP3_178155). This work was supported by the Center for Vaccinology and Neonatal Immunology (University of Geneva), grants from The Swiss Inflammatory Bowel Disease Cohort Study, which is financially supported by the Swiss National Science Foundation since 2005 (Grant No. 33CS30-148422), grants from the Foundation for Liver and Gut Studies, and the Schweizerische Morbus Crohn/Colitis ulcerosa Vereinigung.

Author Contributions

Study concept and design: L.F.P., C.M.V., K.M.P.B., and C.A.S.; obtained funding: L.F.P., K.M.P.B., and C.A.S.; enrollment of participants, acquisition of data, and administrative, technical, or material support: L.F.P., C.M.V., P.M., E.G., M.G., P.J., C.M., and M.H.M.; statistical analysis and drafting of the manuscript: L.F.P.; critical revision of the manuscript for important intellectual content and approval of the final draft submitted: C.M.V., P.M., E.G., M.G., P.J., C.M., M.H.M., K.M.P.B., and C.A.S.

References

1 Murdaca G, Spano F, Contatore M, Guastalla A, Penza E, Magnani O, et al. Infection risk associated with anti-TNF-alpha agents: a review. Expert Opin Drug Saf. 2015;14:571–82.
2 Ananthakrishnan AN, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. J Crohns Colitis. 2012;7(2):107–12.
3 Zabana Y, Rodríguez L, Lobatón T, Gordillo J, Montserrat A, Mena R, et al. Relevant infections in inflammatory bowel disease, and their relationship with immunosuppressive therapy and their effects on disease mortality. J Crohns Colitis. 2019;13(7):828–37.
4 Coukos J, Farraye FA. Update on vaccinating the patient with inflammatory bowel disease. Curr Treat Options Gastroenterol. 2018;16(4):548–60.
5 Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG clinical guideline: preventive care in inflammatory bowel disease. Am J Gastroenterol. 2017;112(2):241–58.
6 Kotton CN. Vaccines and inflammatory bowel disease. Dig Dis. 2010;28(3):525–35.
7 Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis. 2014;8(6):443–68.
8 Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):309–18.
9 Sands BE, Cuffari C, Katz J, Kugathasan S, Onken J, Vitek C, et al. Guidelines for immunizations in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2004;10(5):677–92.
10 Manser CN, Maillard MH, Rogler G, Schreiner P, Rieder F, Bühler S, et al. Vaccination in patients with inflammatory bowel diseases. Digestion. 2020;101(Suppl 1):58–68.
11 Wilckens V, Kannengiesser K, Hoxhold K, Frenkel C, Kucharzik T, Maaser C. The immunization status of patients with IBD is alarmingly poor before the introduction of specific guidelines. Scand J Gastroenterol. 2011;46(7–8):855–61.
12 Case DJ, Copeland LA, Stock EM, Herrera HR, Pfanner TP. Pneumococcal vaccination rates in VHA patients with inflammatory bowel disease. Medicine. 2015;94(6):e417.
13 Melmed GY, Ippoliti AF, Papadakis KA, Tran TT, Birt JL, Lee SK, et al. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. Am J Gastroenterol. 2006;101(8):1834–40.
14 Pandey N, Herrera HH, Johnson CM, MacCarthy AA, Copeland LA. Preventative care for patients with inflammatory bowel disease in the Veterans health administration. Medicine. 2016;95(27):e4012.
15 Parker S, Chambers White L, Spangler C, Rosenblum J, Sweeney S, Homan E, et al. A quality improvement project significantly increased the vaccination rate for immunosuppressed patients with IBD. Inflamm Bowel Dis. 2013;19(9):1809–14.
16 Marin AC, Gisbert JP, Chaparro M. Immunogenicity and mechanisms impairing the response to vaccines in inflammatory bowel disease. World J Gastroenterol. 2015;21:11273–81.

17 Cao Y, Zhao D, Xu AT, Shen J, Ran ZH. Effects of immunosuppressants on immune response to vaccine in inflammatory bowel disease. Chin Med J. 2015;128(6):835–8.
18 Pittet LF, Verolet CM, Michetti P, Girardin M, Juillerat P, Mottet C, et al. High immunogenicity of the pneumococcal conjugated vaccine in immunocompromised adults with inflammatory bowel disease. Am J Gastroenterol. 2019;114(7):1130–41.
19 Wasan SK, Coukos JA, Farraye FA. Vaccinating the inflammatory bowel disease patient: deficiencies in gastroenterologists knowledge. Inflamm Bowel Dis. 2011;17(12):2536–40.
20 Gupta A, Macrae FA, Gibson PR. Vaccination and screening for infections in patients with inflammatory bowel disease: a survey of Australian gastroenterologists. Intern Med J. 2011;41(6):462–7.
21 Feuerstein JD, Castillo NE, Siddique SS, Lewandowski JJ, Geissler K, Martinez-Vazquez M, et al. Poor documentation of inflammatory bowel disease quality measures in academic, community, and private practice. Clin Gastroenterol Hepatol. 2016;14(3):421–e2.
22 Malhi G, Rumman A, Thanabalan R, Croitoru K, Silverberg MS, Hillary Steinhart A, et al. Vaccination in inflammatory bowel disease patients: attitudes, knowledge, and uptake. J Crohns Colitis. 2015;9(6):439–44.
23 Walsh AJ, Weltman M, Burger D, Vivekanandarajah S, Connor S, Howlett M, et al. Implementing guidelines on the prevention of opportunistic infections in inflammatory bowel disease. J Crohns Colitis. 2013;7(10):e449–56.
24 Hammarlund E, Thomas A, Poore EA, Amanna IJ, Rynko AE, Mori M, et al. Durability of vaccine-induced immunity against tetanus and diphtheria toxins: a cross-sectional analysis. Clin Infect Dis. 2016;62(9):1111–8.
25 Ruel J, Ko HM, Roda G, Patil N, Zhang D, Jharap B, et al. Anal neoplasia in inflammatory bowel disease is associated with HPV and perianal disease. Clin Transl Gastroenterol. 2016;7:e148.
26 Kantso B, Simonsen J, Hoffmann S, Valentiner-Branth P, Petersen AM, Jess T. Inflammatory bowel disease patients are at increased risk of invasive pneumococcal disease: a nationwide Danish cohort study 1977–2013. Am J Gastroenterol. 2015;110:1582–7.
27 Pelton SI, Shea KM, Weycker D, Farkouh RA, Strutton DR, Edelsberg J. Rethinking risk for pneumococcal disease in adults: the role of risk stacking. Open Forum Infect Dis. 2015;2(1):ofv020.
28 Shea KM, Edelsberg J, Weycker D, Farkouh RA, Strutton DR, Pelton SI. Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis. 2014;1(1):ofu024.
29 Kantso B, Halkjaer SI, Thomsen OO, Belard E, Gottschalck IB, Jorgensen CS, et al. Immunosuppressive drugs impairs antibody response of the polysaccharide and conjugated pneumococcal vaccines in patients with Crohn's disease. Vaccine. 2015;33:5464–9.
30 Heininger U, Seward JF. Varicella. Lancet. 2006;368(9544):1365–76.
31 Cullen G, Baden RP, Cheifetz AS. Varicella zoster virus infection in inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(12):2392–403.
32 Feldhoff CM, Balfour HH Jr., Simmons RL, Najarian JS, Mauer SM. Varicella in children with renal transplants. J Pediatr. 1981;98(1):25–31.
33 Lynfield R, Herrin JT, Rubin RH. Varicella in pediatric renal transplant recipients. Pediatrics. 1992;90(2 Pt 1):216–20.
34 Kaplan LJ, Daum RS, Smaron M, McCarthy CA. Severe measles in immunocompromised patients. JAMA. 1992;267(9):1237–41.
35 Winthrop KL, Melmed GY, Vermeire S, Long MD, Chan G, Pedersen RD, et al. Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. Inflamm Bowel Dis. 2018;24(10):2258–65.
36 Colombel JF. Herpes zoster in patients receiving JAK inhibitors for ulcerative colitis: mechanism, epidemiology, management, and prevention. Inflamm Bowel Dis. 2018;24(10):2173–82.
37 Kopylov U, Levin A, Mendelson E, Dovrat S, Book M, Eliakim R, et al. Prior varicella zoster virus exposure in IBD patients treated by anti-TNFs and other immunomodulators: implications for serological testing and vaccination guidelines. Aliment Pharmacol Ther. 2012;36(2):145–50.
38 Gómez-Outomuro A, Castaño-García A, Flórez-Díez P, de Francisco R, Rodriguez M, Huerta-González I, et al. P850 Measles virus immune status in a cohort of Spanish patients with inflammatory bowel disease. J Crohns Colitis. 2019;13(Suppl 1):S549.-S.
39 deBruyn JCC, Soon IS, Fonseca K, Feng S, Purtzki M, Goedhart C, et al. Serologic status of routine childhood vaccines, cytomegalovirus, and Epstein-Barr virus in children with inflammatory bowel disease. Inflamm Bowel Dis. 2019;25(7):1218–26.
40 Nguyen DL, Nguyen ET, Bechtold ML. Effect of immunosuppressive therapies for the treatment of inflammatory bowel disease on response to routine vaccinations: a meta-analysis. Dig Dis Sci. 2015;60(8):2446–53.
41 Melmed GY, Agarwal N, Frenck RW, Ippoliti AF, Ibanez P, Papadakis KA, et al. Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease. Am J Gastroenterol. 2010;105(1):148–54.
42 Fiorino G, Peyrin-Biroulet L, Naccarato P, Szabò H, Sociale OR, Vetrano S, et al. Effects of immunosuppression on immune response to pneumococcal vaccine in inflammatory bowel disease: a prospective study. Inflamm Bowel Dis. 2012;18(6):1042–7.
43 Cullen G, Bader C, Korzenik JR, Sands BE. Serological response to the 2009 H1N1 influenza vaccination in patients with inflammatory bowel disease. Gut. 2012;61(3):385–91.
44 Lu Y, Jacobson DL, Ashworth LA, Grand RJ, Meyer AL, McNeal MM, et al. Immune response to influenza vaccine in children with inflammatory bowel disease. Am J Gastroenterol. 2009;104(2):444–53.
45 Andrisani G, Frasca D, Romero M, Armuzzi A, Felice C, Marzo M, et al. Immune response to influenza A/H1N1 vaccine in inflammatory bowel disease patients treated with anti TNF-alpha agents: effects of combined therapy with immunosuppressants. J Crohns Colitis. 2013;7:301–7.
46 Lee CK, Kim HS, Ye BD, Lee KM, Kim YS, Rhee SY, et al. Patients with Crohn's disease on anti-tumor necrosis factor therapy are at significant risk of inadequate response to the 23-valent pneumococcal polysaccharide vaccine. J Crohns Colitis. 2014;8(5):384–91.