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CLINICAL PRACTICE GUIDELINES

Recommendations of the Spanish Group on Crohn's Disease and Ulcerative Colitis on the importance, screening and vaccination in inflammatory bowel disease patients

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Abstract Patients with inflammatory bowel disease (IBD) may require different immunosuppressive treatments throughout their illness. It is essential to assess the immunization status of patients at diagnosis or, if this is not possible, at least before the beginning of immunosuppressive therapy and, subsequently, administering the appropriate vaccines.

Therefore, the aim of this work is to establish clear and concise recommendations on vaccination in patients with IBD in the different settings of our clinical practice including vaccination in children, during pregnancy, breastfeeding or on trips. This consensus document emphasizes the differences between inactivated and attenuated vaccines and the different degrees of immunosuppression and correlates them with the administration of both mandatory and optional vaccines recommended to our patients with IBD. Finally, as a summary, 17 recommendations are established based on the available scientific evidence and expert opinion.

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A multidisciplinary team with extensive experience in IBD and vaccination, made up of specialists in gastroenterology, paediatrics, nursing and pharmacy, has participated in the preparation of these recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU).

PALABRAS CLAVE
Vacuna;
Enfermedad inflamatoria intestinal;
Cribado;
Prevención;
Infección

Recomendaciones del Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa sobre la importancia, el cribado y la vacunación en pacientes con enfermedad inflamatoria intestinal

Resumen Los pacientes con enfermedad inflamatoria intestinal (EII) pueden requerir diferentes tratamientos inmunosupresores a lo largo del curso de su enfermedad. Por ello, es fundamental evaluar el estado de inmunización en el momento del diagnóstico o, si no es posible, siempre antes de iniciar un tratamiento inmunosupresor y administrar las vacunas apropiadas.

El objetivo del presente documento es establecer unas recomendaciones claras y concisas sobre la vacunación en pacientes con EII en diferentes escenarios de práctica clínica, incluyendo situaciones especiales como la vacunación en la edad pediátrica, el embarazo, la lactancia o en viajes al extranjero. Se presentan las diferencias entre vacunas inactivadas y atenuadas, los diferentes grados de inmunosupresión y su relación con las pautas de administración de las diferentes vacunas (tanto obligatorias como opcionales) recomendadas a los pacientes con EII. En el documento, se establecen 17 recomendaciones basadas en la evidencia científica disponible y opinión de expertos. En la elaboración de estas recomendaciones del Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU) ha participado un equipo multidisciplinar con amplia experiencia en EII y vacunación formado por especialistas de gastroenterología, pediatría, enfermería y farmacia.

Introduction

Patients with inflammatory bowel disease (IBD) have a higher predisposition to infections than the general population,[1] some of which can be prevented with vaccinations.[2] Despite the existence of specific recommendations,[3,4] IBD patients have low immunisation rates.[5–7] In addition, vaccination schedules can vary by country and in the different clinical settings, hence recommendations should be adapted taking all these characteristics into account. For all these reasons, this consensus document endorsed by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) has been produced and which establishes clear vaccination guidelines applied to our setting.

Epidemiology: the risk of infection and immunisation rates in IBD patients

Treatment for Crohn's disease (CD) and ulcerative colitis has progressed significantly over the last 20 years. Many of the available drugs work by suppressing the immune system to a greater or lesser degree. These drugs include biological agents (infliximab, adalimumab, golimumab, vedolizumab and ustekinumab), corticosteroids, immunosuppressants (azathioprine, mercaptopurine, methotrexate, cyclosporine, tacrolimus) and Janus kinase (JAK) inhibitors (tofacitinib). In addition, the risk of developing infections increases when different immunosuppressive treatments that act on different targets are combined.[1]

Patients with IBD have an increased risk of any infection, especially opportunistic infections.[1,8] In the TREAT (Crohn's Therapy, Resource, Evaluation, and Assessment Tool) registry, after a follow-up of more than five years, an increased risk of infection was observed in patients with moderate-severe disease, those who were treated with infliximab, narcotic analgesics, or corticosteroids.[9] In addition, the risk of serious infections is higher in patients receiving combination treatment with thiopurines and TNF inhibitors compared to TNF inhibitor monotherapy.[10]

Many infections, which can be serious or even fatal, are immunopreventable with vaccinations. However, some studies have shown low seroprotection and adherence to vaccination programmes in patients with immunosuppressed IBD versus the general population. Some of the main reasons for these low immunisation rates are poor adherence to vaccination protocols, concerns about possible adverse effects and vaccine safety in immunocompromised patients, or high costs of some unfunded vaccines.[7,11,12] Thus, a recent survey of GETECCU partners reported that 3.5% of gastroenterologists specialising in IBD would currently recommend live attenuated vaccines in immunosuppressed patients, and 4.5% would not recommend inactivated vaccines during the first year of life of children born of mothers treated with biologics during pregnancy.[13]

Degree of immunosuppression and risk factors. Vaccine safety

Degree of immunosuppression and infection risk factors

The risk factors associated with the appearance of opportunistic infections include the use of immunosuppressive agents, particularly in combination with TNF inhibitors, advanced age, comorbidities, malnutrition, parenteral nutrition, intestinal surgery, IBD severity, and treatment with narcotics.

The main causes of immunosuppression in IBD are immunosuppressive and/or biological drugs used to control the disease, and malnutrition. Thus, the treatments used in IBD patients can be classified, according to the degree of immunosuppression, into:

1 Non-immunosuppressants: aminosalicylates.
2 Selective immunosuppressants: vedolizumab.
3 Low degree of immunosuppression: azathioprine at doses under 3 mg/kg/day, mercaptopurine at doses under 1.5 mg/kg/day, systemic corticosteroids at doses under 20 mg/kg/day for under two weeks and methotrexate at doses under 20 mg/week (<0.4 mg/kg/week). Maintenance treatment with budesonide up to a dose of 6 mg/day has no increased risk of infection compared with placebo.
4 High degree of immunosuppression: cyclosporine, tacrolimus, TNF inhibitors, tofacitinib, ustekinumab.[3] Azathioprine, mercaptopurine, systemic corticosteroids and methotrexate produce a high degree of immunosuppression at doses higher than those discussed in the previous section.

This classification makes it possible to establish the potential risk of opportunistic infections and the possibility or not of administration of live attenuated vaccines.

Are vaccines safe during immunosuppression?

The risk of adverse effects from vaccines depends on the degree of immunosuppression and the type of vaccine.[14–17] With the exception of live attenuated vaccines, vaccines have the same safety profile in the immunocompromised population as in the immunocompetent population, so immunosuppressive treatment should not be altered because of vaccination. There are five types of vaccines (the main two are summarised in Table 1).

- Inactivated vaccines. They contain particles of viruses, bacteria or toxins that have lost the ability to produce diseases as a result of chemical agents or physical processes.
- Live attenuated vaccines (live attenuated viruses or bacteria). Although these vaccines are based on attenuated microorganisms, they are still alive and are contraindicated in people receiving treatments that involve high immunosuppression. In this situation, there are two premises:
  - If immunosuppressive treatment is essential to control the underlying disease, it should not be delayed for vaccination. In this situation, treatment, and not vaccination, of the underlying disease is indicated.
  - If immunosuppressive treatment is not essential to control the underlying disease, vaccination can be carried out with a safety period prior to and after vaccination.

Patients treated with selective or low-dose immunosuppressive therapy should be assessed on an individual basis, taking into account the risks and benefits, and vaccination without the application of interruption intervals should be considered.[3,18]

- Antigenic subunit vaccines consist only of specific fragments of the virus or bacteria that are essential for the immune system to recognise.
- Viral vector-based vaccines introduce small fragments of RNA or DNA containing instructions for the body to directly produce a pathogen-specific protein. The innocuous virus serves as a platform for introducing the protein into the body.
- DNA or RNA vaccines consist of plasmids or liposomes containing a fragment of RNA or DNA of the infectious agent with genetic information for making a specific protein.

Screening and protocol prior to vaccination in patients on immunosuppressive and/or biologic treatment. When and how to vaccinate?

It is recommended that the immunisation status of patients with IBD be assessed at the time of diagnosis and the appropriate vaccines be administered to avoid infections.[3] A fact sheet on vaccines that can be administered to patients with IBD is provided in Annex 1.

The best time to vaccinate patients is at diagnosis or before the initiation of immunosuppressive therapy, since the response to vaccines may decrease with immunosuppression. In clinical practice this is not always possible and vaccination does not justify delaying the start of treatment. The response rate without immunosuppressive treatment is similar to the response rate in the general population. Table 2 summarises the recommended time intervals for withdrawal and the introduction of immunosuppression prior to and after vaccination, respectively.

Going through the following *checklist* is recommended for all patients, although it is mandatory before the start of any biologic or immunosuppressive treatment.[19,20]

- Screening for viral infections at IBD diagnosis: hepatitis A virus, hepatitis B virus (HBV), hepatitis c virus (HCV), human immunodeficiency virus (HIV), Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella zoster virus (VZV), mumps, rubella and measles (Annex 2).

At diagnosis, it is important to be aware of the serological situation regarding different infections such as HBV, HCV, HIV, mumps, rubella, measles,[21] Epstein-Barr virus, VZV (a history of varicella does not necessarily mean there is no need for serological determination) and cytomegalovirus

Table 1 Classification of vaccines according to the technology used in their manufacture.

Types of vaccine	Live attenuated	Inactivated
Mandatory in IBD	MMR (measles, mumps and rubella)	Pneumococcus
	Varicella	Influenza
		Hepatitis B
Optional in IBD	Rotavirus	Hepatitis A
	Oral polio	Meningococcal group B (Bexsero®)[c]
	Yellow fever	Meningococcal groups A, C, W, Y[c]
	Diphtheria, tetanus, whooping cough	Menveo® or Nimenrix®
	Bacillus Calmette–Guérin[a]	*Haemophilus influenzae* type B
	Herpes zoster[b] (Zostavax®)	Human papilloma virus
		Herpes zoster (Shingrix®)

[a] Currently, the vaccine against TB (Bacillus Calmette-Guérin) is not indicated in Spain. It is only indicated in people who will reside in high-prevalence countries for more than three months (especially children).
[b] Zostavax® is less effective than Shingrix®.
[c] Meningococcal B, Menveo® or Nimenrix® (A, C, W, Y) in the case of a risk group (splenic dysfunction).

Table 2 Immunosuppressive treatment interruption intervals for administration of live attenuated vaccines based on the half-life of each treatment.

	From treatment interruption to vaccination (weeks)	From vaccination to restart of treatment (weeks)
Corticosteroids: ≥20 mg/day prednisone or equivalent > 2 weeks in adults and >1 mg/kg >2 weeks in the paediatric age group	4	4
Bolus corticosteroids	12	4
Azathioprine/6-mercaptopurine	12	4
Methotrexate	4	4
TNF inhibitors	12	4
Ustekinumab	12	4
Vedolizumab	12—16	4
Tofacitinib	4	4
Cyclosporine	4	4
Tacrolimus	4	4

Source: Kucharzik et al.[3]

(not essential, it indicates whether or not infection has passed in view of the risk of cytomegalovirus reactivation in immunosuppressed patients).[22,23]

The study and vaccination of hepatitis A virus is not always mandatory and will depend on the patient's individual risk factors (profession, underlying liver disease, coagulation disorder, administration of hepatotoxic drugs or indication for solid organ transplantation, community where the patient lives and if they travel to endemic areas).

HBV serology should be performed because of the risk of reactivation with immunosuppressive therapy. More importantly, when positive serology is present, the possibility of occult HBV infection should be considered. It is also important to determine HCV serology, as patients with HCV infection on immunosuppressive therapy may present worsened liver disease.[24] Administration of immunosuppressants may also increase the risk of serious infections in patients with poorly controlled HIV infection.[25]

- Human papillomavirus (HPV) screening.

HPV cytology is recommended at the time of IBD diagnosis.[3] Immunosuppressed patients should have an annual cytology.[3]

- SARS-CoV-2 screening.

Current studies show that IBD patients (including immunosuppressed patients) are not at greater risk of infection or more serious infection than the general population.[26–29]

- Immune response to vaccines

The immune response to different vaccines may vary depending on the type of vaccine administered and the treatment the patient is receiving. The recommended vaccine dosage is listed in Table 3.

Table 3 Dosage of mandatory and optional vaccinations in patients with IBD.

Vaccinations	Patients who are *not* on IMS treatment (like the general population)	Dose	Patients who *are on* IMS treatment	Dose
Pneumococcus	Unvaccinated	One dose of conjugate vaccine (Prevenar® 13), followed at 2 months by a dose of PPSV23. After 5 years, 2nd and last dose of PPSV23. If the patient has already received a dose of PPSV23, they must wait a year for PCV13	Unvaccinated	One dose of conjugate vaccine (Prevenar® 13), followed at 2 months by a dose of PPSV23. After 5 years, 2nd and last dose of PPSV23. If the patient has already received a dose of PPSV23, they must wait a year for PCV13
Hepatitis B	Not immunised	3 doses 0-1-6 months Re-vaccination if anti-HBs < 100 IU	If anti-HBs < 100 IU	3 double doses (0-1-2 months) with *booster* between 6−12 m. Re-vaccination if anti-HBs < 100
Influenza	Unvaccinated in the current year	One annual dose	Unvaccinated in the current year	One annual dose
Measles, mumps, rubella	Not immunised	One or 2 doses (interval > 28 days)	Contraindicated	
Varicella	Not immunised	2 doses (0, 1−2 months)	Contraindicated	
Tetanus-diphtheria	Unvaccinated	3 initial doses (0, 1 and 7 months) + one dose/10 years until completion of 5 doses	Unvaccinated	3 initial doses (0, 1 and 7 months) + one dose/10 years until completion of 5 doses
DTaP (Diphtheria, tetanus, whooping cough)	Pregnancy (week 28−36, preferably 32)	One dose in each pregnancy	Pregnancy (week 28−36, preferably 32)	One dose in each pregnancy
Human papilloma virus	Females (males[a]) 11−14 years old (up to age 26 or having sexual intercourse) Women > 26 years with a history of CIN II-III or conisation	3 doses (0, 2, 6 months)	Females (males[a]) 11−14 years old (up to age 26 or having sexual intercourse) Women > 26 years with a history of CIN II-III or conisation	3 doses (0, 2, 6 months)
Poliomyelitis	Unvaccinated	3 doses (0, 1−2, 6−12 months)	Unvaccinated	3 doses (0, 1−2, 6−12 months)
Meningococcal group C	–	–	Unvaccinated	Single dose
Meningococcal group B	–	–	Unvaccinated	2 doses (0, 2 months)
Meningococcal ACWY	–	–	Unvaccinated	Single dose
Haemophilus influenzae type B	–	–	Unvaccinated	Single dose
Herpes zoster	Patients ≥ 50 years old	Single dose (Zostavax®) Two doses (Shingrix®)[a]	Patients ≥ 18 years on JAK inhibitors (funded)	Two doses (0, 2−6 months) (Shingrix®)

[a] Not funded in non-immunosuppressed patients.

Live attenuated vaccines

Herpes zoster virus

The infection may occur in the form of VZV or herpes zoster. There is an approximately 50% higher risk of herpes zoster in IBD patients compared to the general population. The risk is higher in patients receiving combined TNF inhibitors and thiopurines.[30] Tofacitinib may be associated with a higher risk of herpes zoster infection than TNF inhibitors, with the risk being greater with higher doses of tofacitinib.[31] Vedolizumab and ustekinumab have not been associated with an increased risk of herpes infection.

Zostavax® is a live attenuated virus vaccine, administered subcutaneously, with an efficacy of 50%–60%. It is indicated in patients older than 50 years and contraindicated in immunosuppressed patients, except those on low doses of immunosuppressants. In this case, it could be administered by assessing the risk on an individual basis. Short- and long-term studies have found that vaccine efficacy tends to decline over time (up to 21% at 11 years post-administration).[32]

Recently, the Shingrix vaccine has become available in Spain®. This is an inactivated recombinant vaccine, administered intramuscularly, with an effectiveness of more than 95%, sustained over the first four years.[33,34] Two doses are administered two months apart, if possible, before starting immunosuppressive therapy. It is currently only approved for patients $\geq$ 18 years of age who are starting JAK inhibitors or are on active therapy.[35]

MMR vaccine

Although most patients have already received the MMR vaccination (and some children have received the VZV vaccination), the absence of antibodies against these infections or against vaccination in a screening analysis renders its administration advisable before the start of immunosuppressive treatment, ideally at the diagnosis of IBD.[3]

In Spain, since 1995, two doses separated by at least four weeks have been recommended. Available data from 2018 indicate that 97% of Spanish children are vaccinated with the first dose, which guarantees good immunity, although only 94% of Spanish children are vaccinated with the second dose. In September 2018, in view of the increase in the number of measles cases, mainly outside Spain, the Ministerio de Sanidad, Consumo y Bienestar [Ministry of Health, Consumption and Welfare] recommended MMR vaccination (against mumps, measles and rubella, since there is no exclusive vaccine for measles) for all those born in 1970 or later who had not received both doses of the vaccine or had not had the disease. It is accepted that those born before 1970 had measles or were in contact with the wild virus and are therefore excluded from these general recommendations.

Inactivated vaccines

Routine vaccination against influenza, pneumococcus, and HBV (regardless of age and immunosuppression status) is recommended for IBD patients.

Flu (influenza) and pneumococcus (Streptococcus pneumoniae)

A retrospective cohort study compared the risk of influenza infection among 140,480 patients with IBD and controls without IBD. The IBD patients had a higher risk of infection and hospitalisation than the controls.[36,37] Seroconversion after vaccination against influenza and pneumococcus has been seen to be lower in patients on immunosuppressive treatment, especially in those with combined treatment (TNF inhibitors and immunosuppressive drugs). For this reason, the withdrawal of methotrexate for two weeks after vaccination and the administration of high doses of influenza vaccine in patients receiving TNF inhibitors are recommended to optimise vaccination outcomes.[38,39]

Among the risk groups likely to receive influenza and pneumococcal vaccinations, subjects on immunosuppressant therapy and patients with IBD (regardless of whether or not they are immunosuppressed) have been considered. With regard to the new biologic treatments, a recent study reports adequate immunogenicity following influenza vaccination in CD patients treated with ustekinumab.[40] In addition, ustekinumab does not appear to influence the response to the HBV or pneumococcal vaccine (although published studies do not include IBD patients). Similarly, treatment with vedolizumab does not appear to decrease the effectiveness of the influenza and pneumococcal vaccines.[41] In patients treated with tofacitinib, it has been observed that the effectiveness of the pneumococcal vaccine PPSV23 may be diminished, but not the influenza vaccine.

Sequential vaccination with both vaccines, conjugate (PCV13 or Prevenar® or 13-valent conjugate) and polysaccharide (PPSV23 or 23-valent polysaccharide), is recommended, respecting the minimum intervals between doses and type of vaccine. The vaccination schedule depends on the person's age and on whether they have been vaccinated before. After age six years, the sequential regimen (PCV13 + PPSV23) is administered with a recommended interval of at least eight weeks. In all situations, a dose of PPSV23 is administered and should be repeated every five years.

Human papilloma virus

The HPV vaccine is recommended for women under 26 years.[3] In addition, national guidelines are considering including boys of school age.

The HPV vaccine is inactivated and highly effective in preventing HPV infection, precursor lesions of cervical, vaginal, and vulvar cancer, and genital warts caused by serotypes 6, 11, 16 or 18 in women who have not been infected with these serotypes. It is administered in three doses (at zero, two and six months). In 2017 Gardasil9®, a novel vaccine that includes nine serotypes: 6, 11, 16, 18, 31, 33, 45, 52 and 58, was marketed. It is funded by the Spanish National Health System (according to the systematic schedule) for school-age girls, for HIV-infected men and women <26 years, and for women diagnosed with advanced-grade cervical intraepithelial neoplasia (CIN II or III) or endocervical adenocarcinoma *in situ*. For other patients this should be consulted, since, although recommended, the vaccine is not funded in most autonomous communities in immunosuppressed patients.

There are exceptions, such as in the Autonomous Community of the Canary Islands, where funding for 18–65-year-old women with a history of IBD is approved. For the screening and diagnosis of HPV infection, an annual cytology is recommended in women with IBD, especially if they are on immunosuppressive therapy. A history of old infection or an active HPV infection does not contraindicate immunosuppressive treatment, since most infections are transient and disappear within two years.[3,42,43]

Hepatitis B virus

Patients with IBD are not at increased risk of HBV infection. Conversely, HBV reactivation has been observed in 7.5% of patients with a history of HBV infection treated with infliximab.[24] All reactivations in IBD patients have occurred in those who were on immunosuppressive or biologic treatment, with the use of two or more immunosuppressants entailing a higher risk. HBV vaccine efficacy is 95% in the general population. However, immunosuppressed IBD patients may have a low response rate (about 50%).[44]

Vaccination is recommended due to the potentially fatal consequences of infection. In patients on immunosuppressive treatment, the rapid, double-dose regimen results in increased immunisation and seroconversion. When there are anti-HBs antibody (Ab) levels > 100 IU, higher response percentages are also obtained.[45,46] However, although the recommendation is to achieve anti-HBs levels > 100 IU in IBD patients, in some autonomous communities it is not funded if anti-HBs levels are higher than 10 IU. In patients who are already vaccinated, anti-HBs Ab levels should be determined every one to two years to assess whether they have <100 IU/l. In such a case, a *booster* dose could be considered and new anti-HBs Ab level determinations at two to three months to check efficacy. If the titres are low, a new vaccination regimen will be necessary.

Attention should be paid to the recommended guidelines for each vaccine available (antigen quantity or number of doses). For example, vaccine overdose errors have been reported with the Engerix® 20 μg vaccine due to it being presumed equal to Fendrix® 20 μg. The Fendrix® vaccine contains 20 μg but it is adjuvanted, so it is considered an immunity-enhanced vaccine and the antigenic response is much greater. A study was recently published that randomised 173 IBD patients to receive a double dose of Engerix®-B (53%) or a single dose of Fendrix® at months zero, one, two and six (46%). Forty-five percent of patients responded (anti-HBs ≥ 100 IU/l) after three doses and 71% after the fourth dose. The response rate after the fourth dose, was 75% with Fendrix® compared to 68% with Engerix®-B. Advanced age and treatment with steroids, immunosuppressants or TNF inhibitors were associated with a lower likelihood of response. However, Fendrix® was not superior to Engerix®, so either one may be recommended. This study highlights the importance of the fourth dose (more effective than the three-dose regimen) and the importance of taking into account the >100 IU/l anti-HBs Ab threshold, because the rate of antibody loss during the first year is very rapid (20%/patient-year).[47] In contrast, a recent study in patients treated with vedolizumab obtained a response similar to that observed in the vaccination of non-immunosuppressed patients.[41]

The following scenarios are considered:

- Immunocompetent patient: standard dose and normal regimen: HBVaxPro® 10 μg or Engerix® 20 μg 0-1-6 months.
- Patient with immunosuppression or not responding to a first vaccination regimen: double dose intensified with fourth dose: HBVaxPro® 40 μ or Fendrix® 20 μg 0-1-2-6/12 months. Subsequent annual or six-monthly anti-HBs Abs monitoring. In the case of low Abs (in previously responsive patients), administer a *booster* dose (Fendrix® 20 μg or HBVaxPro® 40 μg) and serological control 1–3 months. If there is no response, start a re-vaccination regimen (maximum two rounds of re-vaccination).

Recommendations for vaccination against SARS-CoV-2 infection

The approval and availability of Pfizer-BioNTech and Moderna vaccines, messenger RNA (mRNA) vaccines, and AstraZeneca and Janssen (modified adenovirus) vaccines, with information provided by the Agencia Española de Medicamentos y Productos Sanitarios [Spanish Agency for Medicines and Medical Devices] confirms that the vaccines are safe and effective.[48,49]

Recent articles recommend vaccination against SARS-CoV-2 in IBD patients with any available vaccine, regardless of the underlying immunosuppressive treatment.[50,51] Vaccination against SARS-CoV-2 should not be delayed if the patient is on immunosuppressive treatment, although it may decrease the immune response to the vaccine.[52] In the vaccine trials, no patient had a worsening of a pre-existing autoimmune disease. As in the general population, vaccinated IBD patients may present the infection, although it is less likely and with a milder course. Patients who have had the infection should also be vaccinated.

Serological responses following SARS-CoV-2 vaccination may be weaker in immunosuppressed individuals. Recently, a study of 6935 IBD patients with symptomatic SARS-CoV-2 infection was published showing that patients treated with infliximab have a lower seroprevalence, seroconversion, and anti-SARS-CoV-2 antibody reactivity magnitude compared to patients treated with vedolizumab. In addition, only one third of patients receiving concomitant immunosuppressive treatment (thiopurines or methotrexate) with infliximab had post-infection anti-SARS-CoV-2 antibodies.[53] Another recent systematic review of 46 studies evaluating seroconversion rates after full vaccination against SARS-CoV-2 in patients with IBD found that with the mRNA vaccines seroconversion rates are similar in patients with IBD and controls (healthy population). Although seroconversion rates are lower in patients treated with corticosteroids and the combination of TNF inhibitors and immunosuppressants, seroconversion >90% is observed after full vaccination. Treatment with TNF inhibitors, vedolizumab, ustekinumab, and JAK inhibitors were all associated with good seroconversion rates with the complete vaccination regimen. The lifespan of antibody response after full vaccination against SARS-CoV-2 is a matter of ongoing evaluation. Many studies point to a decrease in antibody titres from the fourth week post-vaccination, it being greater in patients who are on treatment with TNF inhibitors alone or in combination with

Table 4 Vaccination recommendations abroad.

Vaccinations in travellers				
	Non-immunosuppressed patients		Immunosuppressed patients	
Yellow fever	Endemic areas in South America and Africa	Single dose	Contraindicated	–
Typhoid fever	Endemic areas in India and South Africa	3 oral doses (0, 2, 4 days)	Endemic areas in India and South Africa	Single intramuscular dose
Hepatitis A	Not immunised	2 doses (0, 6–12 months)	Not immunised	2 doses (0, 6–12 months)
Cholera	Endemic areas with insufficient access to clean water sources	2 doses (0, 1 week)	Endemic areas with insufficient access to clean water sources	2 doses (0, 1 week)
Japanese encephalitis	Endemic areas of Asia	2 doses (0, 1 month)	Endemic areas of Asia	2 doses (0, 1 month)
Central European encephalitis	Endemic areas of central and north-eastern Europe	3 doses (0, 1–3, 9–18 months)	Endemic areas of central and north-eastern Europe	3 doses (0, 1–3, 9–18 months)
Rabies	Endemic areas	3 doses (0, 7, 21–28 days)	Endemic areas	3 doses (0, 7, 21–28 days)

immunosuppressants. This systematic review shows that there is a decrease in antibody responses after vaccination against SARS-CoV-2 in patients with IBD, more rapid in patients treated with TNF inhibitors, immunosuppressants or a combination thereof, meaning that additional doses could be considered in these patients.[54]

Interactions with other inactivated vaccines have not been demonstrated. It is therefore recommended that patients with IBD follow the same vaccination regimen established by the competent bodies as the general population.[55]

Are there vaccines specifically recommended for IBD patients? For cohabitants as well?

Routine mandatory vaccinations are part of the Spanish Public Health programme, whether or not a person has an IBD. Specific mandatory vaccines are those that are not given to the general population on a regular basis, but are mandatory in patients with IBD. Optional vaccines are indicated according to the individual patient's risk (comorbidities, risky contacts, etc.). Recommendations for routine and IBD-specific mandatory vaccines are defined in Table 3.

Cohabitants of patients with diseases who are at risk of infection should have received all the vaccines recommended for their age, including live attenuated vaccines. Vaccination will prevent the disease in contacts and prevent potential transmission to the immunocompromised patient. No vaccine marketed in Spain is contraindicated in cohabitants of at-risk patients.[56] Annual influenza vaccination is recommended for cohabitants. The MMR vaccine should be administered according to the usual recommendations and without requiring any special precautions, since the transmission of any of the viruses contained in the vaccine has not been described. Although precautions should be taken, the administration of VZV, MMR, Zostavax® and rotavirus vaccinations to cohabitants of immunosuppressed people has been shown to be safe and effective.[57]

The patient should be informed of the risk of live attenuated vaccines (oral typhoid, VZV, yellow fever, rotavirus, BCG).

Vaccines abroad

Before going on a trip, an individualised vaccination schedule assessment is recommended, taking into account personal characteristics and the destination, at least four to eight weeks before departure, as there are vaccines that cannot be administered together, or multiple doses or a latency time are required until they are effective.[58] Travellers with IBD should go to their referral centre and consult their IBD specialist and travel prevention specialist.[3] Travellers with IBD are advised to be aware of the guidelines to follow in the event of an outbreak and to request a medical report specifying their disease, treatment (generic name of drug) and dose. They can submit queries or enquiries to the IBDPassport[59] website, which has a Spanish version, or the World Health Organization and the U.S. Centers for Disease Control and Prevention prevention guidelines,[60] which provide country-specific risk information. If patients are not immunosuppressed, the recommendations are the same as those for the general population. If they are immunosuppressed, live attenuated viral vaccines should be avoided.

Three types of vaccinations can be administered (Table 4):

- Mandatory vaccinations: vaccinations that are not part of the Spanish vaccination schedule but may be required by the health authorities of the destination country. This type of vaccination may vary depending on the country visited, the type of trip and the age of the traveller. Yellow fever, meningococcal disease and poliomyelitis vaccinations are included.
- Recommended vaccinations: vaccinations that are not mandatory or part of the Spanish public health programme, but are recommended in case of an

individual or environmental risk of contracting the disease. These include typhoid, hepatitis, cholera, rabies, Japanese encephalitis, central European borne encephalitis, influenza and rabies, but also poliomyelitis and meningococcal meningitis (already discussed).
- Routine or universal vaccination: vaccinations recommended for the entire population to protect susceptible people from the disease but also the general population. This type of vaccination includes tetanus, diphtheria, hepatitis B, measles, mumps, rubella and VZV.

The simultaneous administration of vaccines is safe and effective, with certain exceptions[58]:

- Different vaccine formulations against the same disease should not be administered simultaneously, such as meningococcal or pneumococcal conjugate vaccines.
- If the oral cholera vaccine is administered and others are to be administered, an least an interval of one hour should be allowed to elapse between them.
- The oral poliomyelitis vaccine may reduce the response to the rotavirus vaccine, so it is advisable to administer them separately.
- The simultaneous administration of the MMR and yellow fever vaccines conditions a reduction in humoral response to yellow fever, rubella and mumps and it is therefore advisable to separate them by a minimum of four weeks.

Vaccinations in IBD patients during pregnancy and breast-feeding. Which vaccinations, and when can they be given to children of mothers who have received biologic treatment during pregnancy?

Pregnancy and breast-feeding in IBD patients

The indications for vaccination in pregnancy are summarised in Table 5.

Vaccination during breast-feeding has two main objectives: to protect the mother from vaccine-preventable diseases and to protect the infant by protecting the mother (cocooning) and transferring antibodies through breast milk (>90% IgA secretory). Breastfeeding does not adversely affect vaccination the success or safety.[61,62]

Vaccination of the newborn of a mother with IBD

The vaccination of a newborn of a mother with IBD should follow the same recommendations as for other newborns and should be performed according to the schedule established in the common vaccination schedule (see the peculiarities of each autonomous community). However, if the mother is exposed to biologic therapy, it is recommended that live attenuated vaccines be avoided for the first 12 months of life (or newborn drug levels for mothers treated with TNF inhibitors be obtained).[63,64] Biologics are actively transported through the placenta, especially in the second half of pregnancy. Drug levels are detected in the newborn and, in the case of TNF inhibitors, can remain detectable for up to six to 12 months. The detection of these immunosuppressive drugs in the plasma of the newborn with a possible involvement of the immune system prompts the recommendation not to administer live attenuated vaccines during the first year of life.

Live attenuated vaccines should be avoided during the first 6–12 months of life in children who have been exposed to biologic treatment in the uterus during the third trimester, including: MMR, VZV, BCG, intranasal influenza, oral polio (not used in Spain, replaced by intramuscular inactivated), yellow fever and typhoid fever.[65]

The Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) is a US data registry of children of mothers with IBD from 2007 to 2016 that compares the response to vaccination of children exposed during pregnancy to treatment with: 5-aminosalicylates, steroids, azathioprine, mercaptopurine, infliximab, adalimumab, golimumab, certolizumab, natalizumab, vedolizumab, or ustekinumab, and it concludes that there are no differences in immune response to the vaccinations received and that neither is there a greater number of adverse reactions. However, overall response was slightly lower than the figure reported in the general population. Data from this registry showed that rotavirus vaccine administration is safe, albeit with a sample of only 43 newborns from mothers on biologic treatment (19 infliximab, 12 certolizumab, 7 adalimumab, 1 infliximab and certolizumab, 1 ustekinumab), with the appearance of mild adverse effects: 26% fever and 5% diarrhoea (vs. 42% and 19%, respectively, in the general population).[66]

Orally-administered rotavirus vaccine is the only live attenuated vaccine administered before six months of age. The rotavirus vaccine Summaries of Product Characteristics warn of the need to assess the potential benefits and risks of vaccine administration in children who have been exposed to immunosuppressive and/or biologic treatment in the uterus. A French retrospective abstract study evaluated the administration of live attenuated vaccines < 12 months (BCG, rotavirus, and MMR) in 143 mothers with IBD who received TNF inhibitors treatment during pregnancy, without observing any complications.[67]

Vaccines in paediatric IBD

Increased diagnosis of paediatric IBD[68,69] is accompanied by an increased use of drugs with immunomodulatory capacity in these patients. Specific guidelines for the treatment of paediatric CD and ulcerative colitis recommend the early use of immunosuppressive drugs and biologic treatments.[70–72]

The Vaccines Committee of the Asociación Española de Pediatría [Spanish Association of Paediatrics] defines and periodically reviews the vaccination schedule, regarded as being of universal compliance for children to stay healthy in the initial years of life. This vaccination schedule undergoes modifications in the different autonomous communities. Immunisation with live attenuated virus vaccines should be completed by the age of four years. Diagnosing the classical forms of IBD at this stage of life is quite rare. Therefore, most patients diagnosed with IBD in paediatric age should have already received all the live attenuated virus vaccines listed in the vaccine schedule. For cases in which vaccination has not been carried out at the established ages,

Table 5 Type of vaccine and indication in pregnant patients with IBD.

Vaccine	Indication
DTaP (diphtheria, tetanus, whooping cough)	Pregnant (week 28–36, preferably 32[a])
Influenza	Any trimester
Other inactivated vaccines: HAV, HBV, meningococcal, pneumococcal	Selective vaccination if there are associated risk factors[b]
Measles, mumps and rubella (MMR)	Contraindicated because it is a live attenuated virus vaccine
Varicella	Contraindicated because it is a live attenuated virus vaccine
Herpes zoster	Zostavax® contraindicated because it is a live attenuated virus vaccine
SARS-CoV-2	Recommended

[a] The body takes two weeks to synthesise protective antibodies against whooping cough that are transferred to the foetus via the placenta. Vaccination must be performed sufficiently in advance of labour to meet this criterion.
[b] Risk factors: HAV: occupational risk, chronic liver disease; meningococcus: occupational exposure, asplenia, complement deficiencies, HIV up to 26 years or in post-exposure prophylaxis; HBV: occupational risk, advanced chronic kidney disease, liver disease, HIV; pneumococcus: HIV, asplenia, advanced chronic kidney disease.

the Asociación Española de Pediatría also establishes recommendations through the so-called rescue or accelerated guidelines. Two models have been established for these recommendations: one for children up to 6 years of age and one for children and adolescents between 7 and 18 years of age.[73]

In this regard, and as reflected in a document from the IBD Working Group of the *European Society for Paediatric Gastroenterology Hepatology and Nutrition* –ESPGHAN–, published in 2012, children with IBD should have live attenuated virus vaccinations at least three to four weeks before starting treatment with immunosuppressants or TNF inhibitors.[74] The nutritional treatment phase at the onset of paediatric CD or initial salicylate treatment in mild-to-moderate ulcerative colitis are the most appropriate periods for initiating these rescue strategies in incorrectly vaccinated patients or those with inadequate immunisation. If, due to the specific needs of these patients, such a plan cannot be carried out, the administration of these vaccines should be postponed at least until three months after cessation, which will not always be feasible.[75]

As in the adult population, it is recommended that the vaccination history of patients be assessed at the time of diagnosis and the most appropriate strategy for correct immunisation be established. However, the data currently available indicate that follow-up to these recommendations in the paediatric community is frankly suboptimal. A retrospective survey published in 2020 by the ESPGHAN analysed immunisation rates in paediatric patients with IBD, showing vaccination rates of 89% for MMR, 82% for *Haemophilus influenzae* Type B, 23% for meningococcal C, 18% for VZV, 19% for pneumococcus, 5.9% for HPV and 1.9% for rotavirus. The rate of patients with full immunisation was only 8.8%.[76] With regard to vaccine safety, the rate of adverse effects in IBD patients did not differ from that of healthy controls, regardless of the base treatment.[77]

How can adherence to vaccination programmes by patients and healthcare workers be improved?

Adherence is defined by the World Health Organization ''the degree to which the person's behaviour corresponds with the agreed recommendations from a health care provider''.[78] Lack of adherence to vaccination is common in patients with IBD, mainly due to fear of side effects and as it is not seen as necessary despite medical recommendations.[79] It is important to individualise the intervention so that the IBD patient feels heard, welcomed and understood with a view to building a trust-based relationship.[80] Health education about vaccines, demystifying and explaining their side effects, and informing about the importance of having the vaccine schedule up to date, especially in immunosuppressed patients, is an important task of the IBD unit team. Harmonising criteria in vaccination guidelines is important in providing the same coverage to patients. This also reduces administration errors in different vaccination regimens.

GETECCU recommendations on the importance of screening and vaccination in IBD patients

Based on the review in this document, the following GETECCU recommendations on the importance, screening and vaccination of IBD patients (adult and paediatric populations) are summarised below:

1 Patients with IBD are at higher risk of infection than the general population.
2 A vaccination programme is part of the initial standardised *checklist* to be performed with IBD patients. Possible risk factors for infection, demographic and epidemiological variables, disease history and comorbidities should be considered before initiating immunosuppressive therapy.
3 The best time to vaccinate patients, both adult and paediatric, is *before the start of immunosuppressive therapy, if possible when IBD is diagnosed*. Otherwise, the risk-benefit ratio of vaccination during treatment should be assessed.
4 At the time of diagnosis of IBD, hepatitis B, influenza, pneumococcus, VZV, HPV, diphtheria-tetanus-pertussis, poliomyelitis and MMR vaccinations are recommended.
5 Live attenuated vaccines in both the paediatric and adult populations should be administered at least four weeks before starting treatment with immunosuppressants,

JAK (tofacitinib) inhibitors or biologics. If this is not possible, it is recommended that the administration of these vaccines be postponed at least until three months after cessation of immunosuppressive therapy and one month after termination of steroids.

6 In patients on low-dose immunosuppression or selective immunosuppressants, live attenuated vaccines can be considered on an individual basis by assessing the risk-benefit ratio.

7 The live attenuated vaccines that are contraindicated in immunosuppressed patients are: yellow fever, VZV, BCG, MMR, rotavirus, oral polio, nasal influenza and oral typhoid fever.

8 Influenza vaccination is recommended annually and pneumococcal vaccination is recommended sequentially with a PPSV23 booster at five years.

9 The baseline serological study and vaccination against the hepatitis A virus is not always mandatory and depends on the risk factors and the community in which the patient resides.

10 All HBV seronegative patients should be vaccinated. In immunocompetent patients, the standard hepatitis B vaccination regimen may be used. In immunosuppressed patients with titres <100 IU/mL, a double, rapid-dose regimen should be recommended. Four-dose regimens are more effective than 3-dose regimens.

11 In patients vaccinated against hepatitis B, anti-HBs Ab levels should be determined every one to two years. If the anti-HBs Ab levels are <100 IU/l a *booster* dose should be considered and new level determinations performed at two to three months to check efficacy. If the titres are low, a new vaccination regimen will be necessary.

12 HPV vaccination does not exclude cytology and gynaecological screening for cervical cancer. Vaccination is always recommended in patients who have had a history of HPV infection, CIN II-III, or cervical cancer. Having been infected with one HPV type does not protect against infection with another serotype, and vaccination would continue to be recommended. Administration in men is recommended, although it is not funded in Spain.

13 The vaccine (Zostavax®) against herpes zoster is recombinant with live attenuated viruses and should be recommended in patients >50 years. It is contraindicated in immunosuppressed patients, except those on low-dose immunosuppressants. The inactivated virus vaccine (Shingrix®) is now authorised in Spain for patients $\geq$ 18 years who are going to start or are already on treatment with JAK inhibitors.

14 There is no evidence of an increased risk of SARS-CoV-2 vaccine in IBD patients, so it is recommended that all IBD patients be vaccinated against SARS-CoV-2 regardless of their baseline treatment. Full vaccination against SARS-CoV-2 is associated with seroconversion in most IBD patients. The decrease in antibody titres over time requires the consideration of additional doses, particularly in patients on certain therapies (TNF inhibitors, immunosuppressants or a combination thereof). As understanding of the management of this pandemic is increasing rapidly, recommendations could change.

15 The patient should be informed if they are to travel to areas of endemic diseases, especially those on immunosuppressive treatment. IBD patients going on a trip should consult one to two months before the trip.

16 As a rule, live attenuated virus vaccines in the children of mothers who have received biologic treatment during pregnancy should be avoided within the first 6–12 months or be assessed, according to drug levels in the blood, prior to vaccination.

17 Low immunisation rates in IBD could be explained by scant awareness in the medical profession, lack of protocolisation of vaccination circuits and concern about possible adverse effects and vaccine safety in immunocompromised patients.

Conflicts of interest

Rocío Ferreiro-Iglesias has been a speaker for or received research funding from Takeda, MSD, AbbVie, Janssen, Pfizer, Palex, Shire Pharmaceuticals, Tillotts Pharma and Casen Recordati.

Marta Piqueras has been a speaker for or received research funding from Takeda, AbbVie and Janssen.

Elena Ricart has been a speaker for or has received research funding from MSD, AbbVie, Janssen, Takeda, Ferring, Pfizer, Amgen and Fresenius Kabi.

Laura Sampere has been a speaker for or received research funding from Pfizer and Janssen.

Mariona Roca has been a speaker for or received research funding from Pfizer, MSD, GSK, Fresenius Kabi, Braun, Nutricia, Abbott and Nestlé.

Javier Martín de Carpi has been a speaker for or received research funding from MSD, AbbVie, Janssen, Fresenius Kabi, Adacyte, Nestlé, Abbott, Lactalis, Ferrer, Kern and Celltrion.

Olga Benítez has been a speaker for or received research funding from Janssen, Biogen and MSD.

Yamile Zabana has been a speaker for or has received research funding from AbbVie, MSD, Ferring, Amgen, Janssen, Pfizer, Dr. Falk, Tillotts, Galapagos and Takeda.

Miriam Mañosa has been a speaker for or has received research funding from AbbVie, MSD, Takeda, Ferring, Janssen, Pfizer, Tillotts, Faes Farma, Gilead, Fresenius, Dr. Falk, Kern and Adacyte.

Francisco Rodríguez-Moranta has been a speaker for or has received research funding from AbbVie, MSD, Takeda, Ferring, Janssen, Pfizer and Dr. Falk.

Manuel Barreiro-de Acosta has been a speaker for or has received research funding from Pfizer, MSD, Takeda, AbbVie, Kern, Janssen, Fresenius Kabi, Biogen, Sandoz, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk, Chiesi, Gebro Pharma, Adacyte and Tillotts.

None of these activities by the authors were related to this study.

Appendix A. Supplementary data[81]

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.gastre.2022.03.004.

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