IBD & Vaccination

A practical guideline for adults & children with IBD

RATIONALE

IBD patients treated with immunomodulators have an increased risk of opportunistic infections and complications.

Vaccination is an effective measure to prevent vaccine-preventable infections and severe complications.

This guideline document aims to clarify the optimal vaccination strategy in the different stages of the disease and in the case of travel.

This guideline is developed based on the most recent ECCO-guidelines: Kucharzik T, et al., ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease, Journal of Crohn's and Colitis (2021), https://doi.org/10.1093/ecco-jcc/jjab052

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BIRD
BELGIAN INFLAMMATORY BOWEL DISEASE RESEARCH AND DEVELOPMENT

BeSPGHAN

This guidance document was developed in collaboration with BIRD & BeSPGHAN represented by Prof. Dr. T. Lobaton, Prof. Dr. J-F. Rahier, Prof. Dr. B. Verstockt, Prof. Dr. P. Bontems, Prof. Dr. G. Veereman & Dr. M-A. De Scheerder.

Background :

Vaccine-preventable diseases are a significant source of morbidity and mortality in patients with altered immune competence. IBD patients are considered to be significantly immunocompromised, mainly because of the immunomodulatory medications they take. Routine and specific immunizations are therefore important to consider in this population. Whenever possible, immunization should be considered prior to administering any immunomodulator in order to optimize the immunological response. Prior to foreign travel, IBD patients are best advised by travel medicine specialists familiar with this complex and vulnerable population.[1]

Definition of immunosuppressive therapy[1-3] :

Patients are considered immunosuppressed if treated with any of these drugs:

- Prednisone >20mg/day for >2 weeks
- Azathioprine, 6-mercaptopurine
- Methotrexate
- Anti-TNF therapies (infliximab, adalimumab, golimumab), IL-12/23 p40 inhibitors (ustekinumab), IL-23 p19 inhibitors (risankizumab, mirikizumab), pan-JAK inhibitors (tofacitinib), JAK1-preferential inhibitors (filgotinib, upadacitinib), S1P-receptor modulators (ozanimod)
- Vedolizumab (integrin antagonists): mainly working gut-selective[1]
- Ciclosporine, tacrolimus

Any treatment above, within the past 3 months, except for corticosteroids (within the past month)

Patients are not considered immunosuppressed if treated with:

- Prednisone <10mg/day or cumulative dose <700mg
- Beclomethasone dipropionate: systemic immunosuppression when used at high dose (10mg)
- Budesonide ≤ 6mg/day: systemic immunosuppression when used at high dose (>6mg/day for budesonide)

1. Kucharzik T, et al., ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease. J Crohns Colitis. 2021;15(6):879-913.
2. Belgian Superior Health Council Advisory report 9158 regarding the vaccination of immunocompromised children and adults (SHC no 9158, Sep 2019) (https://www.health.belgium.be/en/advisory-report-9158-ic-patients-and-vaccination), (accessed August 1st, 2023).
3. Agentschap Zorg & Gezondheid: www.zorg-en-gezondheid.be (accessed August 1st, 2023)

	Indication	Vaccine & adminstration schedule
Live attenuated vaccines ⚠		
Varicella zoster virus	Varicella-IgG negative	Varilrix®: 2 doses with 4 to 6 weeks in between Varivax®: 2 doses with 4 to 8 weeks in between
Measles, Mumps and Rubella (MMR)	Measles, mumps and/or rubella IgG negative	MMR VaxPro®: 2 doses, with at least 1 month in between Priorix®: if 2 doses, at least 1 month in between
MMR & Varicella combined	On individual basis	ProQuad®: 2 doses with 4 to 6 weeks in between
Rotavirus	On individual basis	Rotarix®: 2 doses; at least 4 weeks in between RotaTeq®: 3 doses; at least 4 weeks in between
Yellow fever ✈	To discuss. For future travel to high-risk areas.	Stamaril®: 1 dose Measure neutralizing antibodies for travel to high-risk areas, update if necessary
Available, but not used in Belgium: Poliomyelitis (oral), Typhoid fever (oral) ✈ & Tuberculosis (BCG)		
Non-living vaccines (inactivated, subunit, recombinant)		
Tetanus (T), diphtheria (da), pertussis (p) (Tdap)	All patients	Triaxis®: 1 dose, every 10 years If previous vaccination more than 20 years ago: 2nd dose after 6 months
Hepatitis A virus (HAV) ✈	All patients	Havrix®: 2 doses with 6 months interval Twinrix®: 3 doses day 0 – 1 month – 6 months
Hepatitis B virus (HBV)	All patients	Engerix-B® or Twinrix®: 3 doses day 0 – 1 month – 6 months (or accelerated schedules). HBV booster if HBs <10
Human papillomavirus (HPV)	All patients < 18y On individual base thereafter	Gardasil-9®: • 12-14 years: 2 doses; Day 0 – between 5 to 13 months • As of 15 years: 3 doses; Dag 0 – 2 months – 6 months Note: In case of immunosuppression always schedule with 3 doses
Pneumococcal diseases	All patients	First Apexxnar® (PCV20), Pneumovax23® (PPV23) after 5 years and every 5 years thereafter Note: if PCV 13 (Prevenar 13®) was given first, give Pneumovax23® (PPV23) after 8 weeks and every 5 years thereafter
Poliomyelitis (inactivated) (IPV)	On individual basis Legally required vaccination in Belgium for children.	IMOVAX®
Influenza Seasonal virus	All patients	Annual, 1 dose (only available during flu season)
Herpes Zoster	On individual basis Varicella-IgG positive	Shingrix®: 2 doses; Day 0 - 2 months Note: If flexibility in the vaccination schedule is necessary, the 2nd dose can be administered between 2 and 6 months after the 1st dose
Meningococcal meningitis type A, C, W135 and Y & Type B	All patients < 18y At-risk* patients thereafter	Menveo® (MenACWY): 1 dose, every 5 years Nimenrix® (MenACWY): 1 dose, every 10 years Bexsero® (MenB): 2 doses; at least 1 month in between Trumenba® (from 10 years old) (MenB): 2 doses, 6 months in between
Haemophilus influenza type b (Hib)	At-risk* patient previously unvaccinated	Act-Hib®: 1 dose
Rabies ✈	To discuss. For future travel to high-risk areas.	Rabipur®: 2 doses with 1 week in between Note: in case of immunosuppression always use a 3-dose schedule (day 0 - day 7 - day 21 or 28)
Japanese Encephalitis ✈	To discuss. For future travel to high-risk areas.	Ixiaro®: refer www.itg.be
Typhoid fever ✈	To discuss. For future travel to high-risk areas.	Typhim Vi®: refer www.itg.be
Tick-borne encephalitis (TBE) ✈	To discuss. For future travel to high-risk areas.	FSME-IMMUN®: refer www.itg.be
COVID-19 vaccine	Following governmental criteria & dosing : www.info-coronavirus.be/en/vaccination	

*At-risk patients: anatomical/functional asplenia, sickle cell disease, congenital/acquired complement deficiency (including Eculizumab).

✈ travel-related vaccine - ⚠ Live vaccines are contraindicated during immunosuppressive therapy

BCG: Bacillus Calmette-Guérin; IPV: inactivated poliomyelitis vaccine.

Sources: 1. Belgian Superior Health Council Advisory report 9158 regarding the vaccination of immunocompromised children and adults (SHC no 9158, Sep 2019); 2. Kucharzik T, et al. JCC. 2021;15(6):879; 3. www.zorg-en-gezondheid.be/basisvaccinatieschema (accessed August 1st, 2023); 4. www.itg.be (accessed August 1st, 2023)

Notes

Basic Vaccination Schedule for children[1-3]

The basic vaccination schedule is an overview of the recommended vaccinations that children should receive to be optimally protected against a dozen infectious diseases. The schedule determines the best age for vaccination. It includes the vaccines that vaccinators, general practitioners, pediatricians, Kind en Gezin, Services de Promotion de la Santé à l'Ecole (SPSE), ONE and CLBs can order free of charge.

Age	Vaccine 1 (brand name)	Vaccine 2 (brand name)	extra vaccine
8 weeks	IPV-DTPa-Hib-HBV (Hexyon®)	Pnc-13 (Prevenar 13®)	Rota‡, § MenB (Bexsero®) &,§
12 weeks	IPV-DTPa-Hib-HBV (Hexyon®)	Pnc-13 (Prevenar 13®)^	Rota‡, §
16 weeks	IPV-DTPa-Hib-HBV (Hexyon®)	Pnc-13 (Prevenar 13®)	(Rota‡, §)
12 months	MMR (MMR VAX Pro®)	Pnc-13 (Prevenar 13®)	
15 months^	IPV-DTPa-Hib-HBV (Hexyon®)	MenC (NeisVac-C®)# MenACWY (Nimenrix®)*	MenACWY (Menveo®) MenB (Bexsero®)
6 years	IPV-DTPa (Infanrix-IPV®)		
7-8#/9 years*	MRR (MMR VAX Pro®)		
12 years*/ 13-14 years#	HPV (Gardasil 9®)†		
14 years*/ 15-16 years#	dTpa (Boostrix®)		

COVID-19 vaccination for children[2]: Following governmental criteria & dosing

For more information & most recent updates please refer to:

- **www.one.be** (office de la naissance et de l'enfance)
- **www.kindengezin.be**
- **www.vaccinnet.be**

*: for the Flemish Community.[1] For the MenACWY, only catch-up vaccination possible for people who have not yet received meningococcal conjugate vaccine. For the MMR 2nd dose administration, in the 2023-2024 school year, 10-year-olds will also still be vaccinated as they have not yet received their second dose of the vaccine. #: for the Wallonia-Brussels Federation.[3] The MenC vaccination can be replaced by MenACWY, recommended by the Superior Health Counsil but this is not free for the Wallonia-Brussels Community. &: from 2 months old and is also supported by the Superior Health Council but on an individual basis, so not administered by Kind en Gezin. The number of administrations depends on the age at which the vaccination is started (for dosing schedule, refer to source 4). Trumenba® can only be administered from the age of 10 (2 doses, 6 months in between). †: 2 doses with an interval of 6 months between each dose. ‡: oral vaccine, number of doses: 2 or 3 depending on vaccine brand. §: recommended but not free. ^: At a gestational age of less than 37 weeks: • An additional dose of pneumococcal disease is administered at 12 weeks of age. • Vaccines will be brought forward from 15 months to 13 months.

CLB: Centrum voor Leerlingenbegeleiding; **D**: vaccine against diphtheria (d: reduced dose); **dTpa**: diphtheria, tetanus, pertussis; **HBV**: vaccine against hepatitis B; **Hib**: vaccine against Haemophilus influenzae type b; **HPV**: vaccine against human papillomavirus; **IPV**: inactivated injectable vaccine against polio; **MMR**: vaccine against measles, mumps and rubella; **Pa**: vaccine against pertussis (pa: reduced dose); **Pnc**: conjugate vaccine against pneumococci; **T**: vaccine against tetanus.

Sources: 1. Agentschap Zorg & Gezondheid: www.zorg-en-gezondheid.be/basisvaccinatieschema (accessed August 1st, 2023),
2. http://www.info-coronavirus.be (accessed August 1st, 2023) & 3. www.vaccination-info.be (accessed August 1st, 2023)
4. https://lci.rivm.nl/richtlijnen/meningokokken-b-vaccinatie (accessed August 1st, 2023)

SCENARIO 1 : What should be done **at diagnosis** or

1. Check with the general practitioners the routine vaccination scheme and immunization history.

Verify serology levels & update vaccinations accordingly:

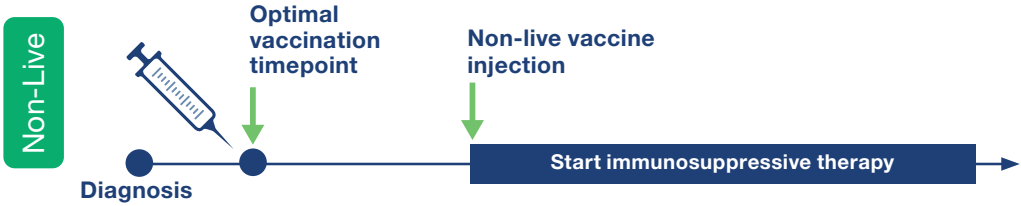
- ❍ **Measles-IgG, Mumps-IgG, Varicella-IgG, Rubella-IgG**
- ❍ **Anti-HAV (if previously vaccinated)**
- ❍ **HCV/HBV (HCV-Ab and HBs-Ag, HBs-Ab, HBc-Ab)**
- ❍ **Mantoux / IGRA**

Verify only serology for EBV IgG, CMV IgG, HIV (HIV-Ab)

SITUATION A: Non-live vaccine

There is no contraindication to perform vaccination with non-live vaccine while the patient is under immunosuppressive therapies.[1]

However, for optimal immunization -and if time allows- it is preferable to complete (or at least start) the vaccinations before the start of immunosuppressive therapies.[1]



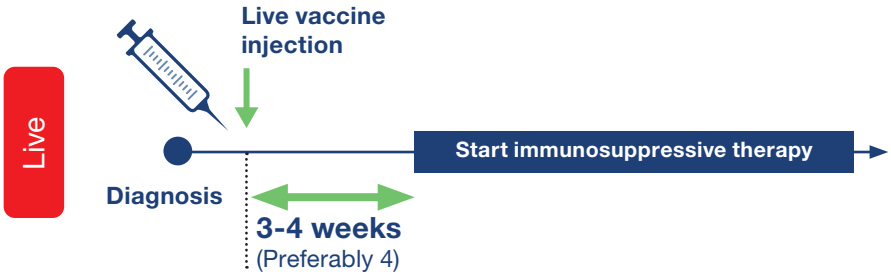
Update if necessary:

Non-live vaccinations

- ❍ **Diphtheria** (every 10 years)
- ❍ **Tetanus** (every 10 years)
- ❍ **Pertussis** (one boost in adulthood & pregnancy)
- ❍ **Human papilloma virus** (for patient 10-26 years)
- ❍ **Influenza** (with (seasonal) inactivated vaccine, every year)
- ❍ **Pneumococcal diseases**
- ❍ **Hepatitis B**
- ❍ **Herpes Zoster** (Shingrix®)
- ❍ **Hepatitis A**
- ❍ **Typhoid fevers** (Typhim Vi®)
- ❍ **COVID-19**

SITUATION B: Live vaccine

Live vaccine cannot be given when patients are treated with immunosuppressors. Therefore a minimum of 3 weeks delay after the last injection of the live vaccine is necessary before starting immunosuppressive therapies.[1]



For vaccination scheme of patients already under immunosuppressive therapy, refer to scenario 2.

Update if necessary:

Live Vaccinations

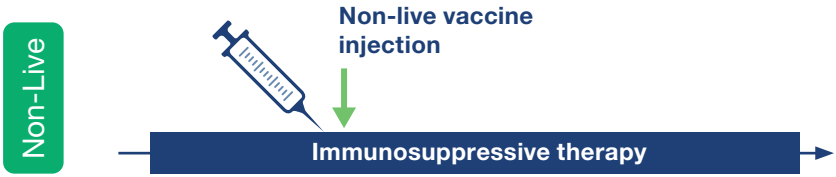
- ❍ **Varicella zoster virus**
- ❍ **Measles, Mumps and Rubella** (M.M.R.)
- ❍ **Yellow fever**
- ❍ **Rotavirus**

EBV: Epstein-Barr-virus; **HAV:** hepatitis A virus; **IgG:** Immunoglobuline G; **IGRA**: Interferon-Gamma Release Assay; **HIV-Ab**: human immunodeficiency virus antibody; **HCV-Ab**: hepatitis C virus antibody; **HBs-Ag**: hepatitis B surface antigen; **HBs-Ab**: hepatitis B surface antibody; **HBc-Ab**: hepatitis B core antibody; **IBD**: inflammatory bowel disease; **CMV**: cytomegalovirus; **IMM**: Immunomodulator Medications

SCENARIO 2 : What should be done **during immunosup**

SITUATION A: Non-live vaccine

Non-live vaccine can be given to patients on immunosuppressive therapy.
It is not necessary to interrupt the therapy, however efficacy of vaccine may be suboptimal and in some cases booster injections are needed.[1]



Update if necessary:

Non-live vaccinations

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- ❍ **Tetanus** (every 10 years)
- ❍ **Pertussis** (one boost in adulthood & pregnancy)
- ❍ **Human papilloma virus** (for patient 10-26 years)
- ❍ **Influenza** (with (seasonal) inactivated vaccine, every year)
- ❍ **Pneumococcal diseases**
- ❍ **Hepatitis B**
- ❍ **Herpes Zoster** (Shingrix®)
- ❍ **Hepatitis A**
- ❍ **Typhoid fevers** (Typhim Vi®)
- ❍ **COVID-19**

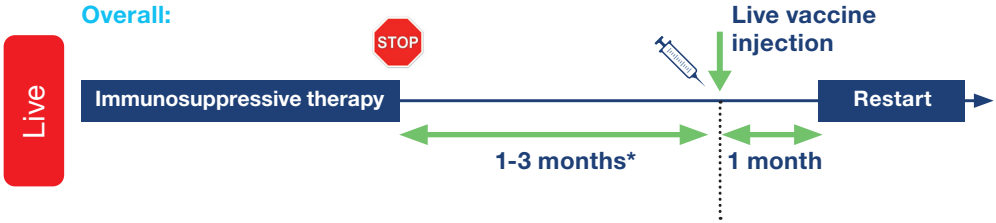
SITUATION B: Live vaccine

Live vaccines are contraindicated during immunosuppressive therapy.[1]
In Belgium available live vaccines are:

- **Varicella zoster virus**
- **Measles, Mumps and Rubella** (M.M.R)
- **Yellow fever**
- **Rotavirus**

If vaccination with live vaccine is required during immunosuppressive therapy, the therapy must be stopped 1-3 months before vaccination, and should be withheld for 1 month after live vaccine injection.[1]

Recommended timelines



* See ECCO reference table below.

1. Kucharzik T, et al., ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease. J Crohns Colitis. 2021;15(6):879-913.

Degree of Immunosuppression and suggested timeframe for live attenuated vaccination* for different IBD Therapeutics (modified from Ref. 1)

Drugs $	Degree of immuno-suppression	Half-life	Stopping before live vaccines*	Re-start after live vaccines	Comment
Aminosalicylates		Not Applicable			No systemic effects
Topical steroids		Not Applicable			Systemic immunosuppression with oral topical steroids (oral budesonide) in doses higher than 6 mg per day
Systemic steroids (prednisone) >1 mg/kg, >14 days (children) >20 mg/day, >14 days (adults)		2–3 hours	1 month	1 month	Moderate – severe Immunosup-pression with doses of ≥ 20 mg for >2 weeks
Vedolizumab		25 days	3-4 months	1 month	Gut-selective treatment. No systemic effects, but increased risk of intestinal infections
Methotrexate		3–10 hours	1 month	1 month	Moderate – severe Immunosuppression with >20 mg per week (>0.4 mg/kg/week). Lower doses can be considered as low immunosuppression.
Thiopurines (azathioprine and 6-MP. ~2h)		Several days (6-TGN)	3 months	1 month	Moderate – severe Immunosuppression with >3 mg/kg/d (AZA) or >1.5 mg/kg/d (6-MP). Lower doses can be considered as low immunosuppression.
Cyclosporine		8.4 hours (10–27)	1 month	1 month	Calcineurin inhibitors (cyclos-porine, tacrolimus), anti-TNF, JAK inhibitors and anti-IL12/23 are considered moderate to severe immunosuppression. Combination therapy (combination of any of these or combination with other immunosuppressive drugs such as AZA, MTX or steroids) results in an increased risk of opportunistic infections.
Tacrolimus		23–46 hours	1 month	1 month	
Anti-TNF	Infliximab	7–12 days	3 months	1 month	
	Adalimumab	~2 weeks			
	Golimumab	~2 weeks			
Tofacitinib		3 hours	1 month	1 month	
Ustekinumab		~19 days	3 months	1 month	

No Selective Low Moderate/Severe

$: No ECCO recommendation yet on filgotinib, upadacitinib, risankizumab, ozanimod and mirikizumab. To be discussed with your infectious specialist. *: elimination of half-life of the drugs x5.

6-MP: 6-mercaptopurine; **6-TGN**: 6-thioguanine nucleotides; **AZA**: azathioprine; **MTX**: methotrexate

1. Kucharzik T, et al., ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease. J Crohns Colitis. 2021;15(6):879-913.

During IMM

Travel

What should be done if patients want to travel to regions requiring specific vaccinations?

Recommended vaccinations for travel-specific countries can be found on the ITG website: www.itg.be

For an overview of ITG Travel clinics / yellow fever vaccination centres refer to: www.wanda.be/en/a-z-index/yellow-fever-vaccination-centres

Additional information & latest updates by the HGR/CSS (Hoge Gezondheidsraad/Conseil Supérieur de la Santé) can found at:

- **www.health.belgium.be/nl/vaccinatie**
- **www.health.belgium.be/fr/vaccination**

IMPORTANT NOTE:

A regular discussion between patient and gastro-enterologist on the patient's desire to travel is advised. Prior to foreign travel, IBD patients are best referred to a travel medicine expert, for example from the Institute of Tropical Medicine, to discuss possible vaccinations and other specific safety measures e.g. other preventive measures, antibiotics, etc.

Considerations for patients and cohabitants regarding vaccination

1. When **cohabitants are vaccinated with a live vaccine,** appropriate consideration should be made to ensure that an immunocompromised patient will not be contaminated.
   - **Measles, Mumps, Rubella and Varicella:**
     Avoid contact with immunosuppressed patient in case of rash induced by vaccination.
   - **Rotavirus:**
     Highly immunocompromised patients should avoid handling diapers of infants who have been vaccinated with rotavirus vaccine for 4 weeks after vaccination.
   - **Yellow fever and typhoid fever:**
     No risk or problem to vaccinate cohabitants.

2. When **live vaccination of the patient is not possible** due to ongoing immunosuppressive therapy, cohabitants should have their immunity checked. In cases where immunity is no longer effective the vaccination scheme should be updated to ensure that the patient is indirectly protected.
   - **Measles, Mumps and Rubella**
   - **Varicella**
   - **Rotavirus** (only in babies before the age of 6 months)

This guidance document was developed in collaboration with Prof. Dr. T. Lobaton, Prof. Dr. J-F. Rahier, Prof. Dr. B. Verstockt, Prof. Dr. P. Bontems, Prof. Dr. G. Veereman & Dr. M-A. De Scheerder.

The authors are open for any suggestions on this guide.

Sources:

1. Kucharzik T, et al. JCC. 2021;15(6):879.
2. Belgian Superior Health Council Advisory report 9158 regarding the vaccination of immunocompromised children and adults (SHC no 9158, Sep 2019).
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4. www.itg.be (accessed August 1st, 2023).

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