ADVISORY REPORT SUPERIOR HEALTH COUNCIL (n° 8561) regarding the vaccination of immunocompromised children and adults with a chronic illness

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List of abbreviations used

- BCG Bacille Calmette Guerin (TB vaccine)
- CDC Centers for Disease Control and Prevention, USA
- DTPa Vaccine against diphtheria, tetanus, and (acellular) pertussis, paediatric dosage
- dTpa Vaccine against diphtheria, tetanus, and (acellular) pertussis, adult dosage
- Hib *Haemophilus influenzae* b
- HIV Human Immunodeficiency Virus
- IgG Immunoglobulin G
- IgM Immunoglobulin M
- IPV Inactivated Polio Vaccine
- MMR Measles, Mumps and Rubella
- PCV Pneumococcal Conjugate Vaccine
- PCV7 7-valent Pneumococcal Conjugate Vaccine - later 10- or 13-valent

- PPS23V (Unconjugated) 23-valent Pneumococcal Polysaccharide Vaccine
- SHC Superior Health Council
- SOT Solid Organ Transplantation
- WHO World Health Organisation

This factsheet complements the SHC vaccination guide (www.health.belgium.be , click on: Nl / Fr; keyword: vaccin) and the additional SHC recommendations on specific vaccinations, amongst other things against seasonal influenza and pneumococcal infections (www.health.belgium.be; click on Nl / Fr; keyword: Vaccin). Therefore, also consult the vaccination guide and vaccination factsheets for the **standard recommendations** and contraindications for specific vaccines.
This text and the tables will be **reviewed** on a regular basis in order to keep them up to date with the latest findings, data and the consensus among international experts.

1. Introduction

A distinction is drawn between:

- **Primary** or **congenital** immune disorders;
  These are rare conditions (see footnote **2.2.6** for children under the age of 16).
- **Secondary** or **acquired** immune disorders;
  Appear during one's lifetime and are much more common.
  Can be triggered by an **immunosuppressive disorder** or by **taking immunosuppressive medications** (see "**4** List of potentially immunosuppressive medications").

As regards individuals with an **immunosuppressive disorder** or on **immunosuppressive medications:**

- These individuals are more prone to some of the infections against which there is a vaccine and are at a greater risk of a serious or more complicated course of disease.
  - In the case of **primary** (congenital) immune disorders, this increased risk of infection is inherent to the underlying disease itself;
  - In the case of **secondary** (acquired) immune disorders:
    - This increased risk of infection is sometimes partially due to the underlying condition. Untreated, chronic **inflammatory (auto-)immune disorders**, also known as *Immune Mediated Inflammatory Diseases or* **IMID** (such as rheumatic conditions and systemic diseases (vasculitis and connective tissue disease), inflammatory bowel disease and psoriasis) are usually not or not significantly immunosuppressive by themselves. An exception is active lupus;
    - In most cases, this increased risk of infection is mainly triggered by **immunosuppressive medication**. The type of medication or combination of medications, dosage and total duration of its administration play a crucial part in immunosuppression, which can be highly variable.

- There are no contraindications for vaccination with the inactivated and live vaccines that are recommended in the vaccination factsheets of the Superior Health Council in the event of **inflammatory (auto) immune disorders that are not treated by means of immunosuppressive medication**. (www.health.belgium.be click on: Nl / Fr; keyword: Vaccine); they are just as indicated as they are for the general population.
  NB: As regards the **live** vaccines under discussion: see tables **2.1** (children aged < 16) **& 3.**1 (adults and teenagers aged ≥ 16).

- The vaccinations themselves do not destabilise or exacerbate the **inflammatory (auto-)immune disorder**, nor are they responsible for causing it in the first place. Despite the existence of a few poorly documented case studies, in most cases, there is no evidence to support a causal link. If possible, it is advisable to wait until the disorder has reached a more stable or peaceful stage, but if necessary, the vaccination may also be administered in case of moderate or serious disease activity (after having consulted the treating specialist and on the basis of an individual assessment).

- It is safe to administer **inactivated vaccines**. However, the immune response is often suboptimal (the protection conferred by the vaccination is either less certain or of shorter duration – see below), but usually does offer sufficient protection to a large group of patients. It is therefore likely that the immune response after a first vaccination is not good in patients having taken immunosuppressive medications; conversely, the immune response after a booster with a vaccine that was administered before the onset of immunosuppression is probably curbed to a lesser extent by the immunosuppressive medication.

- Administering **live vaccines** results in a potential risk of a greater replication and/or invasive infections with the vaccine micro-organism. This can result in vaccine-related complications, persistence of the micro-organism in the patient and/or unwanted transmission. Examples include the oral polio vaccine (no longer used in Belgium), the measles vaccine and the yellow fever vaccine. Except in the case of HIV-infection, there are no precise markers available to show from which stage of immunosuppression live vaccines are liable to trigger such an infection. It is best to consult a specialist on this issue.

- Ideally, there should be a 4-week waiting period between administering **live vaccines** and (re-)initiating immunosuppressive medication. In principle, no such interval is required for **inactivated** vaccines if the vaccination is urgently needed (e.g. travel medicine). For the waiting periods between discontinuing immunosuppressive medication and administering live vaccines, see << **4** (list of immunosuppressive medications) >>

- The efficacy of vaccination has rarely been examined **directly** (measuring the number of cases of disease). In a few situations, the immunogenicity has been examined through the detection of **antibodies**. The number of antibodies is not always an optimal indicator for the protection conferred by the vaccination. Indeed, this parameter does not take into account the overall immune function (affinity/ avidity of the antibodies, duration of the humoral immune response, immunological memory, cellular immunity such as T-cell function, non-specific immune system). The immune response may therefore be suboptimal, both quantitatively and qualitatively, and the duration of protection is probably shorter. That makes it difficult to draw clear conclusions about the efficacy of vaccination in this patient group. The effect of higher doses or additional boosters on antibody synthesis and kinetics has only been examined in a limited number of situations, with highly inconsistent or even disappointing results.

- For these patients, it is not only necessary to take into account the **basic vaccination schedule** (see the SHC vaccination guide - (www.health.belgium.be click on Nl / Fr; keyword: vaccin), but often also **additional disease-specific vaccinations**, as they require a more extensive protection against infectious diseases. Examples are influenza and pneumococcal infections: patients with severe or moderately severe

immune disorders are at an increased risk from severe, invasive pneumococcal infections and complications after influenza. For further details on these specific vaccinations, see the discussions on the specific disorder types.
As regards individuals who

- **are to** undergo a solid organ **transplantation**;
- **are to** be treated with **immunosuppressive medication**;
- or **are to** undergo **elective splenectomy**,

it is necessary to

- verify the status of the *basic vaccinations*
- as well as that of the additional disease-–specific vaccinations

before providing any of these forms of treatment, and, if possible, offer the required vaccines first.
If appropriate, consider *vaccinating against yellow fever* PRIOR to transplantation or initiating immunosuppressive medication, depending on the likelihood of the patient travelling to a region in which yellow fever is endemic at a later stage.

There is no consensus over the use of serological titres in monitoring the immunological status of immunocompromised patients. Monitoring the antibody synthesis is currently recommended for a limited number of vaccinations only, i.e. systematically after vaccinating against hepatitis B, rabies (WIV-ISP – rabies department) and in some cases (international travelling) after vaccinating against hepatitis A and yellow fever.

- It is important to vaccinate those **close to immunocompromised patients** against **influenza** each year, including **healthcare professionals**, in order to improve the protection of the patients themselves.
- The following **live vaccines** may be administered to **those living under the same roof as the patients**:
  - Vaccinating those living under the same roof against **Measles-Mumps-Rubella** and **varicella** is highly advisable if they have not yet acquired immunity against these infections themselves. Temporarily avoid contact with an immunocompromised patient if a vaccinated individual develops a rash after having been vaccinated against the measles and varicella.
  - The **rotavirus** vaccine may be administered to infants under the age of 6 months who come into contact with individuals with an immune deficiency. It is advisable to take the appropriate hygiene measures (avoid contact with faeces of babies who have been vaccinated with the rotavirus vaccine).
  - The **yellow fever vaccine** and the **oral typhoid fever vaccine** may be administered to **those living under the same roof** if it is indicated for them.

- The various specialists are required to provide the treating physician with clear information on the precise vaccination programme (for the individuals with an immune problem and those close to them).

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2.1. Children < 16

DISORDERS (footnotes) / VACCINES (general observations, cf. 2.2.0)	HIV < 15% CD4 (2.2.1.)	HIV ≥ 15% CD4 (2.2.1.)	Solid organ transplantation (SOT): Heart, liver, kidney, pancreas, lung, intestine (2.2.2)	PRIOR TO bone marrow or stem cell transplantation (2.2.3.)	AFTER bone marrow or stem cell transplantation (2.2.3.)	Immune-mediated inflammatory diseases (IMID) treated with immune modulators (2.2.4.)	Haematological malignancies & influence of chemotherapy; oncological chemotherapy (2.2.5.)	Severe Primary immune disorders (2.2.6.)
INACTIVATED VACCINES								
DTPa, dTpa	S	S	S	S	A	S	S	S
IPV	S	S	S	S	A	S	S	S
***Haemophilus influenzae* b**	S	S	S	S	A	S	S	S
Hepatitis A (2.2.0.)	A	A	R	R	R	R	R	R
Hepatitis B (2.2.0.)	S	S	S	S	A	S	S	S
Influenza (annually) (2.2.0.)	A	A	A	A	A	A	A	A
Pneumococcal vaccine (2.2.0.)	S	S	S	S	A	S	S	S
Meningococcal C (conjugate) vaccine (2.2.0.)	S	S	S	S	A	S	S	S
HPV	S	S	S	S	S	S	S	S

KEY

A: Strongly **advised**, given the additional risk posed by increased susceptibility and/or increased severity, and/or increased risk from complications.
R: To consider in case of epidemiological or personal **risk.**
NA: **Not applicable.**
S: **Standard indication** for vaccination because this concerns routine vaccinations that are part of the basic vaccination schedule that holds for the general population.
X: **Inadvisable** due to contraindications.

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LIVE VACCINES								
Rotavirus (2.2.0.)	S	S	NA	X	NA	NA	NA	X
Measles, mumps and rubella (MMR) (2.2.0.)	X	A	X	X	A	X	X	X
Varicella (2.2.0.)	X	A	X	X	A	X	X	X
INACTIVATED VACCINES FOR TRAVEL-RELATED EXPOSURES								
– **Japanese encephalitis** – **European tick-borne encephalitis** – **Typhoid fever - inactivated** – **Rabies** – **Quadrivalent meningococcal vaccine-polysaccharide or conjugate**	R	R	R	R	R	R	R	R
LIVE VACCINES FOR TRAVEL-RELATED EXPOSURES								
Yellow fever	X	R	X	X	R	X	X	X
Typhoid fever:	X	R	X	X	X	X	X	X

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oral vaccine								
BCG	X	X (R)	X	X	R	X	X	X

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2.2. Footnotes children < 16

2.2.0. General observations / recommendations for children < 16 years	
Hepatitis A	• For the at-risk groups, see the recommendations of the SHC on vaccinating against hepatitis A in the SHC vaccination guide. (www.health.belgium.be click on : Nl / Fr; keyword: Vaccin). • Once-only antibody testing can be indicated if travelling abroad. • However, no recommendations have been examined for non-responders.
Hepatitis B	• For the at-risk groups, see the recommendations of the SHC on vaccinating against hepatitis B in the SHC vaccination guide. (www.health.belgium.be click on : Nl / Fr; keyword: Vaccine). Since 1999, all infants and teenagers have been systematically vaccinated. Hepatitis B vaccination is therefore a standard indication. • Antibody monitoring is required. (SHC: If, after full vaccination, the anti-HBs titre is < 10 IU/l and a hepatitis B infection has been ruled out, the vaccinated individual is considered a non-responder and thus unprotected against hepatitis B. A repeat vaccination schedule can then be offered, either by initiating an entirely new schedule (e.g. 0, 1, 6 months) or a schedule of 2 doses administered simultaneously (one in the left and one in the right M. deltoideus), followed 2 months later by 2 more doses (in the left and right M. deltoideus). Serologic testing for antibodies (anti-HBs) should be carried out again after having completed the repeat vaccination schedule. • In the event of persistent immunosuppression, the antibodies need to be monitored on an annual basis, the immune response being unpredictable and often far from sufficient. The antibody titre has to be kept ≥ 10 IU/l by means of additional boosters.
	• Vaccination schedule for children: see the recommendations of the SHC on the vaccination against seasonal influenza and the SHC vaccination guide. (www.health.belgium.be click on : Nl / Fr; keyword: Vaccin). • The vaccination should be repeated each year. • For most individuals with immune problems, there are no data available that show that there is a specific increase in mortality or an increased risk of complications as a result of influenza infections. However, according to the CDC, influenza does constitute a risk factor for secondary bacterial infections in immunocompromised individuals, which can result in severe disease. In some patients, the clearance of the influenza virus is disturbed, with sustained virus replication and possibly also longer disease duration as a consequence.
Pneumococcal vaccine	• See the recommendations of the SHC on pneumococcal vaccination and the SHC vaccination guide. (www.health.belgium.be click on : Nl / Fr; keyword: Vaccin). • Pneumococcal conjugate vaccine (PCV) until the age of 5 (for further details, see the recommendations of the SHC on pneumococcal vaccination in paediatric at-risk groups). • There are few data on conjugated vaccines in patients with an immune disorder: however, as they are inactivated, there are no risks involved in administering them.
Meningococcal C (conjugate) vaccine	• SHC factsheet catch-up vaccinations for individuals up to the age of 18 (www.health.belgium.be ; click on: Nl / Fr; keyword: Vaccin). If it should turn out that this vaccination was not yet carried out, 1 dose may be administered immediately. • The role of the quadrivalent meningococcal conjugate vaccine (ACWY) will be assessed when more scientific data are made available.

Rotavirus	• Is never administered after the age of 6 months. This is also true if the vaccine has never been administered.
MMR & varicella	• When necessary and when there are no contraindications, an accelerated schedule can be applied for MMR and varicella: o The MMR-vaccine may be administered from the age of 6 months in children; this early administration provides temporary immunisation and needs to be followed by the recommended schedule (2 doses > 12 months). o The varicella-vaccine can be administered from the age of 9 months; this early administration provides temporary immunisation and needs to be followed by the recommended schedule (2 doses > 12 months). o The booster vaccinations for varicella and MMR can already be administered after 4 to 6 weeks. o Both live vaccines can be administered simultaneously or within one month of each other.

2.2.1. HIV < 15% CD4 and HIV ≥ 15% CD4	
In this case, the HIV-infection occurs almost exclusively through vertical transmission: the infant should therefore be actively monitored from birth, and antiretroviral therapy should be initiated as soon as the diagnosis of an HIV-infection is made. The basic vaccination schedule should be implemented before the onset of any significant immunodeficiency. For children over the age of 6 months, the situation is less clear. When assessing the efficacy of the vaccines that have already been administered and those that still have to be, the following factors need to be taken into account: age, degree of immunodeficiency, antiretroviral treatment, duration of treatment and the quality of the immunological recovery in response to this treatment.	
Hepatitis A	• For the at-risk groups, see the recommendations of the SHC on vaccinating against hepatitis A in the SHC vaccination guide. (www.health.belgium.be , click on: Nl / Fr; keyword: Vaccin). Children of immigrants travelling to their country of origin form a substantial portion of these HIV-infected children and therefore qualify for vaccination. • Once-only antibody testing can be indicated if travelling abroad. Additional boosters have no proven use in non-responders in the case of HIV-infection.
Hepatitis B	• Antibody monitoring and non-responders: see footnote **2.2.0**
Rotavirus	• Vaccination is safe for HIV-positive infants under the age of 6 months: the immune response is efficient and there is no worsening of the HIV infection or immunosuppression.
Yellow fever	• T4 cells over 25% or 400/mm³: this does not pose a problem if the vaccination is really indicated. • T4 cells below 15% or 200/mm³ (**severe** immunosuppression): the vaccine should not be administered. Travelling to a region in which yellow fever is endemic should be advised against. • T4-cells between 200/mm³ (15%) and 400/mm³ (25%) (**moderate** immunosuppression): the specialised vaccination centre should balance the risk of infection with the yellow-fever virus against the risk of complications caused by the vaccine virus. If the patient is asymptomatic, the decision to administer the vaccine can still be fairly straightforward; in other cases, this decision will have to be made on a case-by-case basis (consider having an "informed consent" form signed if the patient decides to have the vaccine administered, or if he/she decides to travel without having received it). What matters is the CD4-count obtained through HAART therapy, not the nadir prior to treatment. In order to obtain the best possible immune response with a minimal risk of adverse effects, this should be postponed until 3 to 6 months after the immunity has started to recover.
Typhoid fever - oral	• The inactivated typhoid fever vaccine should also be preferred if **the CD4 percentage is over 15%.**

vaccine	

2.2.2. Solid organ transplantation (SOT): Heart, liver, kidney, pancreas, lung, intestine	
PRIOR TO TRANSPLANTATION • Remember to complete the **basic vaccination schedule** PRIOR to transplantation. The **hepatitis B** vaccination should always be carried out prior to organ transplantation (also determine the antibody titre). It is also advisable to vaccinate against **hepatitis A** before a liver transplantation. • Patients who have not yet contracted **varicella** should receive the varicella-vaccine, provided there is enough time (i.e. more than one month prior to transplantation). If necessary, an accelerated schedule for **varicella** (and, if need be, for **MMR**) may be used: See footnote : **2.2.0**. • If appropriate, consider vaccinating against **yellow fever** PRIOR to transplantation depending on the likelihood of the patient travelling to a region in which yellow fever is endemic at a later stage. • Consider vaccinating those close to the patient (see introductory). AFTER TRANSPLANTATION • Depending on the recovery of cellular immunity, it is advised to wait for **6 to 12 months** after the transplantation before administering **inactivated vaccines**. • **Live vaccines** (against MMR, varicella, yellow fever) cannot be administered because of the obligatory permanent immunosuppression; only in extremely rare cases where the immunosuppressive medication can be discontinued after all, can vaccination be considered **as from 12 to 24 months** after the transplantation, depending on the degree of cellular immunosuppression (to be determined by a specialist).Yet there are a few studies in which live vaccines against MMR and varicella were in fact administered to small numbers of paediatric patients on immunosuppressive medication.	
Hepatitis B	• Hepatitis B vaccination is always performed prior to organ transplantation. The antibody titre should be determined prior to transplantation as well as 3 months afterwards: it should be ≥ 10 IU/l (non-responders: see footnote **2.2.0**)
Yellow fever	• No vaccination as long as the state of immunosuppression persists after the transplantation (wait for at least three months after ending immunosuppressive therapy; yet it is usually impossible to discontinue the latter).

2.2.3. Bone marrow and stem cell transplantation
PRIOR TO TRANSPLANTATION • Remember to complete the **basic vaccination schedule** PRIOR to transplantation. **Vaccinating against hepatitis B** should always be done prior to organ transplantation (determine the antibody titre). • Consider vaccinating those close to the patient (see introductory). • The role of donor-vaccination will be assessed when more scientific data are made available. AFTER TRANSPLANTATION • The same rules apply to **autologous** stem cell transplantation as for **allogeneic** stem cell transplantation. • The full basic vaccination schedule has to be reinitiated with the **inactivated vaccines**, starting **6 to 12 months** after the transplantation,

	depending on the degree of cellular immunosuppression. For the actual vaccination schedules, also consult the SHC factsheet "catch-up vaccinations" (www.health.belgium.be , click on: Nl / Fr; keyword: Vaccin). • Yearly influenzavaccination • **Live vaccines** (against MMR, varicella, yellow fever) **cannot** be administered because of the obligatory permanent immunosuppression; only in extremely rare cases where the immunosuppressive medication can be discontinued after all, can vaccination be considered **as from 12 to 24 months** after the transplantation, depending on the degree of cellular immunosuppression (to be determined by a specialist).Yet there are a few studies in which live vaccines against MMR and varicella were in fact administered to small numbers of paediatric patients on immunosuppressive medication.
dTpa – IPV-Hib - Hep B	**The hexavalent paediatric vaccine** may be used, even though it contains a higher dosage of **DTPa components**, because the immune system is once again "naïve", as is the case in children.

2.2.4. Immune-mediated inflammatory diseases & immunosuppressive medications (see 4).	
BEFORE INITIATING MEDICATION • Determine the **vaccination status** of individuals who will require immunosuppressive medication BEFOREHAND, and ensure that the basic vaccination schedule has been completed. Determine the **hepatitis B** antibody titre. • Patients who have not yet contracted **varicella** should receive the varicella-vaccine, provided there is enough time (i.e. more than one month prior to transplantation). If necessary, an accelerated schedule for **varicella** (and, if need be, for **MMR**) may be used: See footnote: **2.2.0.** • If appropriate, consider vaccinating against **yellow fever** PRIOR to initiating the medication, depending on the likelihood of the patient travelling to a region in which yellow fever is endemic at a later stage. • Consider vaccinating those close to the patient (see introductory).	
MMR & varicella	• Administering this vaccine is contraindicated for patients taking immunosuppressive medication. • See **table 4** for a list with the medication for which there is an absolute contraindication, or no contraindication at all. When in doubt, consult a specialist. Also see **table 4** for the waiting periods that have to be observed (1) before administering the vaccine after having discontinued immunosuppressive medication and (2) before reinitiating immunosuppressive medication after having administered the vaccine.
Yellow fever	• Administering this vaccine is contraindicated for patients taking immunosuppressive medication. • See **table 4** for a list with the medication for which there is an absolute contraindication, or no contraindication at all. When in doubt, consult a specialised "travel clinic". Also see **table 4** for the waiting periods that have to be observed (1) before administering the vaccine after having discontinued immunosuppressive medication and (2) before reinitiating immunosuppressive medication after having administered the vaccine.
Typhoid fever Oral vaccine	• Not in patients with inflammatory bowel diseases. • Administering this vaccine is contraindicated for patients taking immunosuppressive medication. • To be replaced by the inactivated typhoid fever vaccine.

2.2.5. Haematological malignancies and oncological conditions & the influence of chemotherapy

- As regards children **who are receiving treatment for oncohaematological conditions, the basic vaccination schedules initiated prior to the disorder should not be continued during treatment, but should be fully reinitiated afterwards.**
- Children who had **already received the full basic schedule** before the onset of the disease should receive booster doses of the vaccines.
- **Inactivated vaccines** can be administered as from **3 months** after the end of treatment.
- **Live vaccines** can only be administered as from **6 months** after the end of treatment.
- After **extensive radiotherapy** (consult a specialist), there should be a **3-month waiting period** before administering **live vaccines**.

Rotavirus	There are no data available to date on the safety and efficacy of the vaccine in infants under the age of 6 months suffering from leukaemia, lymphoma or other oncological conditions.

2.2.6. Primary immune disorders

I. Primary **humoral** immune deficiencies (B-cell disorder)

1. Severe XLA (*X-linked agammaglobulinemia)* , CVID (*common variable immunodeficiency, late-onset hypogammaglobulinemia*): contraindication for **live** vaccines; the use of **inactivated** vaccines is recommended

   These conditions require monthly preventive replacement therapy by means of intravenous or subcutaneous immunoglobulins (IVIG/SCIG); for vaccination after IVIG: see **table 3.15**.

   They also require passive immunisation after exposure (IVIG preferably administered < 96 hrs after contact with varicella).

   After vaccination, there will be no or only a very weak antibody response. There will either be no vaccine-induced protection, or it will be uncertain, depending on the cellular response. Nonetheless, it is still important to vaccinate with inactivated vaccines, because the immune deficiency will rarely be so severe that the vaccination will remain completely ineffective.

2. Mild: IgG subclass deficiency with or without IgA deficiency, selective IgA-deficiency, *Specific antibody deficiency with normal immunoglobulin concentrations* (SAD) (e.g. pneumococcal antibody deficiency), Transient hypogammaglobulinemia of infancy (lower IgG and IgA): **all** vaccines are safe and recommended.

   NB: secondary immunoglobulin deficiencies may occur as a result of excessive protein loss (amongst other things in the case of nephrotic syndrome, *protein-losing gastroenteropathy)* or as a result of disturbed antibody synthesis (haematological malignancies, during the first twelve months after treatment with rituximab).

II. I. Primary **cellular** immune deficiencies (T-cell disorder)

1. Complete: SCID (*Severe Combined Immune Deficiency syndrome*) and other combined immune deficiencies (CID), hyper IgM syndrome, DiGeorge syndrome, and others.

Contraindication for **live** vaccines, **inactivated** vaccines are recommended. For further advice see severe primary **humoral** immune deficiencies.

2. Partial: Wiskott Aldrich syndrome; partial DiGeorge syndrome, ataxia-telangiectasia, hyper IgE (*Job's*) syndrome (HIES), and others.

Contraindication for **live** vaccines, **inactivated** vaccines are recommended.

III. Other immune disorders

1. Defective phagocytosis and chemotaxis: e.g. *chronic granulomatous disease* (CGD), Shwachman-Diamond syndrome (impaired chemotaxis):
   No **live bacterial** vaccines such as BCG-vaccine and oral typhoid fever vaccine. All the other vaccines are safe and recommended (including MMR and varicella).
2. **Complement cascade** factor deficiencies: all other vaccines are safe and recommended. See TABLE **3.14** under **Complement deficiencies** for (additional) recommended vaccines.

Observations:

1. The severity of several disorders may vary, especially as regards T-cell abnormalities. There is a broader range of phenotypes for these conditions than was previously thought. Functional T-cell tests can measure the T-cell function, which makes it possible to administer live vaccines to some extent after all, such as e.g. MMR, after having consulted an immunologist.
2. Improved molecular diagnostics have led to a shift in the range of immune disorders, which means that a simple classification such as the one above is not always possible, and the various disorder types may in fact overlap. As a result, the classification of the immune disorders may not be looked upon as a fixed entity.

2.3. Adults and teenagers ≥ 16

DISORDERS (footnotes) / VACCINES (general observations, cf. 2.4.0)	HIV CD4 < 200/mm³ (2.4.1.)	HIV CD4 200-500/mm³ (2.4.1.)	Solid organ transplantation (SOT): Heart, liver, kidney, pancreas, lung, intestine (2.4.2)	PRIOR TO bone marrow or stem cell transplantation (2.4.3.)	AFTER bone marrow or stem cell transplan-tation (2.4.3.)	Immune-mediated inflammatory diseases treated with immune modulators (2.4.4.)	Haematological malignancies & influence of chemotherapy: oncological chemotherapy (2.4.5.)
INACTIVATED VACCINES							
dTpa	S	S	S	S	A	S	S
IPV	R	R	R	S	A	R	R
Haemophilus influenzae b	NA	NA	NA	S	A	NA	NA
Hepatitis A (2.4.0.)	R	R	R	R	R	R	R
Hepatitis B (2.4.0.)	A	A	A	A	A	R	R
Influenza (annually) (2.4.0.)	A	A	A	A	A	A	A
Pneumococcal vaccine (2.4.0.)	A	A	A	A	A	A	A
Meningococcal C (conjugate) vaccine (2.4.0.)	S up to the age of 18	S up to the age of 18	S up to the age of 18	S up to the age of 18	A up to the age of 18	S up to the age of 18	S up to the age of 18
HPV (2.4.0.)	R	R	R	R	R	R	R

LEGENDE

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S: **Standard indication** for vaccination because this concerns routine vaccinations that are part of the basic vaccination schedule that holds for the general population.
X: **Inadvisable** due to contraindications.

DISORDERS (footnotes) / VACCINES (general observations, cf. 2.4.0)	HIV CD4 < 200/mm³ (2.4.1.)	HIV CD4 200-500/mm³ (2.4.1.)	Solid organ transplantation (SOT): Heart, liver, kidney, pancreas, lung, intestine (2.4.2)	PRIOR TO bone marrow or stem cell transplantation (2.4.3.)	AFTER bone marrow or stem cell transplan-tation (2.4.3.)	Immune-mediated inflammatory diseases treated with immune modulators (2.4.4.)	Haematological malignancies & influence of chemotherapy: oncological chemotherapy (2.4.5.)
LIVE VACCINES							
MMR (2.4.0.)	X	R	X	X	A	X	X
Varicella (2.4.0.)	X	R	X	X	A	X	X
Zoster (2.4.0.)	X	R	X	X	A	X	X
INACTIVATED VACCINES FOR TRAVEL-RELATED EXPOSURES							
• **Japanese encephalitis** • **European tick-borne encephalitis** • **Typhoid fever -inactivated** • **(Rabies)** • **(quadrivalent meningococcal vaccine - polysaccharide or conjugate)**	R	R	R	R	R	R	R
LIVE VACCINES FOR TRAVEL-RELATED EXPOSURES							
• **Yellow fever**	X	R	X	X	R	X	X

LEGENDE

A: Strongly **advised**, given the additional risk posed by increased susceptibility and/or increased severity, and/or increased risk from complications.
R: To consider in case of epidemiological or personal **risk**
NA: **Not applicable.**
S: **Standard indication** for vaccination because this concerns routine vaccinations that are part of the basic vaccination schedule that holds for the general population.
X: **Inadvisable** due to contraindications.

DISORDERS (footnotes) / VACCINES (general observations, cf. 2.4.0)	HIV CD4 < 200/mm³ (2.4.1.)	HIV CD4 200-500/mm³ (2.4.1.)	Solid organ transplantation (SOT): Heart, liver, kidney, pancreas, lung, intestine (2.4.2)	PRIOR TO bone marrow or stem cell transplantation (2.4.3.)	AFTER bone marrow or stem cell transplan-tation (2.4.3.)	Immune-mediated inflammatory diseases treated with immune modulators (2.4.4.)	Haematological malignancies & influence of chemotherapy: oncological chemotherapy (2.4.5.)
• **Typhoid fever: oral vaccine**	X	R	X	X	R	X	X

LEGENDE

A:	Strongly **advised**, given the additional risk posed by increased susceptibility and/or increased severity, and/or increased risk from complications.
R:	To consider in case of epidemiological or personal **risk**
NA:	**Not applicable.**
S:	**Standard indication** for vaccination because this concerns routine vaccinations that are part of the basic vaccination schedule that holds for the general population.
X:	**Inadvisable** due to contraindications.

2.4. Footnotes adults and teenagers ≥ 16

2.4.0. General recommendations	
Hepatitis A	• For the at-risk groups, see the recommendations of the SHC on vaccinating against hepatitis A in the SHC vaccination guide. (www.health.belgium.be click on : Nl / Fr; keyword: Vaccin). • Once-only antibody testing can be indicated if travelling abroad. • However, no recommendations have been examined for non-responders.
Hepatitis B	• For the at-risk groups, see the recommendations of the SHC on vaccinating against hepatitis B in the SHC vaccination guide. (www.health.belgium.be click on : Nl / Fr; keyword: Vaccine). Since 1999, all infants and teenagers have been systematically vaccinated. Vaccination against hepatitis B is therefore a standard indication for all teenagers and young adults. • Antibody monitoring is required. (SHC: If, after full vaccination, the anti-HBs titre is < 10 IU/l and a hepatitis B infection has been ruled out, the vaccinated individual is considered a non-responder and thus unprotected against hepatitis B. A repeat vaccination series can then be offered, either by initiating an entirely new schedule (e.g. 0, 1, 6 months) or a schedule of 2 doses administered simultaneously (one in the left and one in the right M. deltoideus), followed 2 months later by another 2 doses (in the left and right M. deltoideus). Serologic testing for antibodies (anti-HBs) should be carried out again 4 to 6 weeks after having completed the repeat vaccination series. • In the event of persistent immunosuppression, the antibodies need to be monitored on an annual basis, the immune response being unpredictable and often far from sufficient. The antibody titre has to be kept > 10 IU/l by means of additional boosters. However, part of the population remains non-respondent.
Influenza	• See the recommendations of the SHC on the vaccination against seasonal influenza and the SHC vaccination guide (www.health.belgium.be , click on: Nl / Fr; keyword: Vaccin). • It is advisable to repeat the vaccination each year. Two doses generate a better response. • As regards most individuals with immune problems, there are no data available that show that there is a specific increase in mortality or an increased risk of complications as a result of influenza infections. Conversely, according to the CDC, influenza does constitute a risk factor for secondary bacterial infections in immunocompromised individuals, which can result in severe disease. In some patients, the clearance of the influenza virus is disturbed, with sustained virus replication and possibly also longer-lasting disease as a consequence.
Pneumococcal vaccine PPS23V	• See the recommendations of the SHC on the vaccination against pneumococcal infections and the SHC vaccination guide (www.health.belgium.be , click on: Nl / Fr; keyword: Vaccin). • For teenagers up to the age of 18 (for further details, see the recommendations of the SHC on pneumococcal vaccination in paediatric at-risk groups). • Pneumococcal vaccine (PPS23V) every 3-5 years • Te re-assess as soon as more data on the conjugate vaccine are available.
Meningococcal C (conjugate) vaccine	• SHC factsheet “Catch-up vaccinations” (www.health.belgium.be click on : Nl / Fr; keyword: Vaccin) for individuals up to the age of 18. If it should turn out that this vaccination was not yet carried out, 1 dose may be administered immediately. • The role of the quadrivalent meningococcal conjugate vaccine (ACWY) will be assessed when more scientific data are

	made available.
HPV	• SHC factsheet/booklet: Indicated for teenage girls and young women (aged 14 to 26) who have not yet had sexual intercourse; the treating physician decides on an individual basis whether or not it is useful to vaccinate teenage girls and young women (aged 14 to 26) who have already had sexual intercourse.
MMR & varicella	• Individuals born before 1970 are considered immune against measles. • When necessary and when there are no contraindications, an accelerated schedule can be applied for MMR and varicella. The booster vaccinations for varicella and MMR can already be administered after 4 to 6 weeks. Both live vaccines can be administered simultaneously or within one month of each other.
Zoster	• For adults aged 60 and up. Recommendations will be issued when there are enough scientific data available for immunocompromised adults.

2.4.1. HIV < 200 CD4 / HIV 200-500 CD4	
For CD 4 counts • **Over 500/mm^3** : the immune disorder is **minor,** • Between **200 en 499/mm^3** : it is **moderate**. • Below **200 /mm^3 :** it is **severe.** There is still no certainty over the extent to which the immunity fully recovers when the CD-4 positive cell count rises as a result of antiretroviral therapy. For the time being, the immunity is assumed to have sufficiently recovered if the CD4 count has risen over 500/mm^3, unless the patient has been on antiretroviral therapy for less than 3 to 6 months.	
Haemophilus influenzae b	• CDC : consider use of Hib vaccine for persons with HIV infection who did not receive the vaccine during infancy or childhood. • UK : HIV-infected adults who have recovered from Hib disease and have risk factors for further disease, those with recurrent pulmonary infections or other risk factors for severe disease should be considered for vaccination with one Hib dose.
Hepatitis A	• For the at-risk groups, see the recommendations of the SHC on the vaccination against hepatitis A in the SHC vaccination guide. Amongst others, it is advisable to vaccinate travellers to endemic regions, homosexual and bisexual men against hepatitis A. • Once-only antibody testing may be useful if travelling abroad. Additional boosters have no proven use in non-responders in the case of HIV-infection.
Hepatitis B	• For the at-risk groups, see the recommendations of the SHC on the vaccination against hepatitis B in the SHC vaccination guide. Amongst others, it is advisable to vaccinate the following individuals against hepatitis B: male homosexuals, prostitutes, drug consumers, patients who have been diagnosed with a sexually transmittable infection and those with multiple sexual partners. • Antibody monitoring and non-responders: see footnote **2.4.0**
Pneumococcal vaccine	**PPS23V (pending further results on conjugate vaccines in adults)** • For HIV with CD4 counts < 200, intensive research is being carried out on alternative vaccination schedules, considering the diminished response to the 23-valent polysaccharide vaccine. It may be the case that, for this patient group, it is more indicated to use the conjugate vaccine or priming induced by a conjugate vaccine followed by the 23-valent polysaccharide

	vaccine.
Yellow fever	• CD4+ cells over 4-500/mm³: This does not pose a problem if the vaccination is really indicated. • CD4+ below 200/mm³ (**severe** immunosuppression): The vaccine should not be administered, which means that travelling to a region in which yellow fever is endemic should be advised against. • CD4+ between 200 and 4-500 /mm³ (**moderate** immunosuppression): The specialised vaccination centre should balance the risk of infection with the yellow-fever virus against the risk of complications caused by the vaccine virus. If the patient is asymptomatic, the decision to administer the vaccine can still be fairly straightforward; in other cases, this will be a decision that will have to be made on an individual basis. You may consider having an "informed consent" form signed if the patient decides to have the vaccine administered, or if he/she decides to travel without having received it. The CD4+ count has to be determined when the patient is receiving HAART therapy, not during the nadir prior to treatment. In order to obtain the best possible immune response with a minimal risk of adverse effects, administering this vaccine should be deferred until 3 to 6 months after the immunity has started to recover.
Typhoid fever - oral vaccine	• The inactivated typhoid fever vaccine should also be preferred if **the CD4 count is > 200.** • The (live, attenuated) oral vaccine is not formally contraindicated, but the preference goes to the inactivated typhoid fever vaccine.

2.4.2. Solid organ transplantation (SOT): Heart, liver, kidney, pancreas, lung, intestine

PRIOR TO TRANSPLANTATION

- Remember to complete the **basic vaccination schedule** PRIOR to transplantation. It is advisable to vaccinate liver transplant candidates against **hepatitis A**. **Vaccinating against hepatitis B** should always be performed prior to organ transplantation (determine the antibody titre).
- Patients who have not yet contracted **varicella** should receive the varicella-vaccine, provided there is enough time (i.e. more than one month prior to transplantation).If necessary, an accelerated schedule for **varicella** (and, if need be, for **MMR)** may be used: See footnote **2.2.0.**
- Also consider **vaccinating against yellow fever** PRIOR to transplantation depending on the likelihood of the patient travelling to a region in which yellow fever is endemic at a later stage.
- Consider vaccinating those close to the patient (see introductory).

AFTER TRANSPLANTATION

Hepatitis B	• The vaccination should always be performed prior to organ transplantation. The antibody titre should be determined prior to transplantation as well as 3 months afterwards: the latter should be ≥ 10 IU/l (non-responders: see footnote **2.4.0**)
Pneumococcal vaccine	• Patients who have received an organ transplantation should be vaccinated with the 23-valent pneumococcal polysaccharide vaccine for the indications mentioned the SHC recommendations on pneumococcal vaccination. (www.health.belgium.be click on : Nl / Fr; keyword: Vaccin). • If the patient is to receive Rituximab, it is best to carry out the vaccination prior to the transplantation. • This recommendation will be reassessed when the conjugate vaccine for adults has become available.
MMR	• As the immunosuppressive medication cannot normally be discontinued, the vaccination is contraindicated.
Varicella	• As the immunosuppressive medication cannot normally be discontinued, the vaccination is contraindicated.

Yellow fever	• As the immunosuppressive medication cannot normally be discontinued, the vaccination is contraindicated.

2.4.3. Bone marrow or stem cell transplantation

PRIOR TO TRANSPLANTATION

- Remember to complete the **basic vaccination schedule** PRIOR to transplantation. The **hepatitis B** vaccination should always be carried out prior to organ transplantation (determine the antibody titre).
- Consider vaccinating those close to the patient (see introductory).
- The role of donor-vaccination will be assessed when more scientific data are made available.

AFTER TRANSPLANTATION

- The same rules that apply to **allogeneic** stem cell transplantation also hold for **autologous** stem cell transplantation.
- The full basic vaccination schedule has to be reinitiated with the **inactivated vaccines**, starting **6 to 12 months** after the transplantation, depending on the degree of cellular immunosuppression. For the actual vaccination schedules, also consult the SHC factsheet "catch-up vaccinations" (www.health.belgium.be click on : Nl / Fr; keyword: Vaccin).
- **Live vaccines** can be administered as **from 24 months** after the transplantation, provided there is no "graft-versus-host" disease and the patient no longer receives any immunosuppressive medication (which can never or only very rarely be discontinued, however) (or depending on the degree of cellular immunosuppression, to be determined by the transplantation specialist, if need be in consultation with a vaccination specialist/infectiologist).

dTpa – IPV- Hib - Hep B	**It is preferable to use the hexavalent paediatric vaccine, with a higher dosage of diphtheria and tetanus toxoids and acellular pertussis components. Indeed, the immune system is once again "naïve", as is the case in unvaccinated children.**
Separate components:	
dTpa - IPV	Initiate the basic vaccination schedule **as from 6 months** after the transplantation (3 doses at a 1-month interval and a booster after 1 year).
Haemophilus influenzae b	Initiate the basic vaccination schedule **as from 6 months** after the transplantation (3 doses at a 1-month interval and a booster after 1 year). NB: patients with chronic GVHD are at a risk of developing functional hyposplenism.
Hepatitis B	Initiate the basic vaccination schedule or catch-up vaccination schedule **as from 6 months to 1 year** after stem cell transplantation. 2 doses at a 1-month interval and a booster after 4-12 months.
Influenza	Initiate vaccination **as from 6 months to 1 year** after the transplantation (**annually**).
Pneumococcal vaccine	• Initiate vaccination with the 23-valent pneumococcal **polysaccharide vaccine** (**PPS23V) as from 1 year** after the transplantation. **Pneumococcal vaccine (PPS23V**) (every 3-5 years). • This recommendation will be reassessed when the **conjugate vaccine** for adults has become available. • ***NEW:*** *Pneumococcal conjugate (PCV) at (3–)6 months – 3 doses in monthly doses. Following the primary series of three PCV doses, a dose of the 23-valent polysaccharide pneumococcal vaccine (PPSV23) to broaden the immune response*

	might be given. For patients with chronic GVHD who are likely to respond poorly to PPSV23, a fourth dose of the PCV should be considered instead of PPSV23 (Ljungman et al. **2009;** Hilgendorf et al. **2011**
Meningococcal C (conjugate) vaccine	• SHC factsheet "Catch-up vaccinations" (www.health.belgium.be click on : Nl / Fr; keyword: Vaccin) for individuals up to the age of 18. If it should turn out that this vaccination was not yet carried out, 1 dose may be administered immediately. • Provide an additional dose after the transplantation (Hilgendorf et al., **2011**). • The role of the quadrivalent meningococcal conjugate vaccine (ACWY) will be assessed when more scientific data are made available.
MMR	• can be administered as **from 24 months** after the transplantation, provided there is no "graft-versus-host" disease and the patient does not receive any immunosuppressive medication (or depending on the degree of cellular immunosuppression, to be determined by the specialist). However, the latter can never or only very rarely be discontinued.
Varicella	• can be administered as **from 24 months** after the transplantation, provided there is no "graft-versus-host" disease and the patient does not receive any immunosuppressive medication (or depending on the degree of cellular immunosuppression, to be determined by the specialist). However, the latter can never or only very rarely be discontinued.
Yellow fever	• If indicated, **as from 24 months** after stem cell transplantation, for patients with no "graft-versus-host-disease" and who are not on any immunosuppressive medication. However, the latter can never or only very rarely be discontinued.

2.4.4. Immune-mediated inflammatory diseases & immunosuppressive medication (see 4).

BEFORE INITIATING MEDICATION

- Determine the **vaccination status** of individuals who will require immunosuppressive medication BEFOREHAND, and ensure that the basic vaccination schedule has been completed. Determine **the hepatitis B** antibody titre.
- Patients who have not yet contracted **varicella** should receive the varicella-vaccine, provided there is enough time. If necessary, an accelerated schedule for **varicella** (and, if need be, for **MMR**) may be used: See footnote **4.2.0.**
- If appropriate, consider vaccinating against **yellow fever** PRIOR to initiating the medication, depending on the likelihood of the patient travelling to a region in which yellow fever is endemic at a later stage.
- Consider vaccinating those close to the patient (see introductory).

MMR & varicella	• Administering this vaccine is contraindicated for patients taking immunosuppressive medication. • See **table 4** for a list with the medication for which there is an absolute contraindication or no contraindication at all. When in doubt, consult a specialist. Also see **table 4** for the waiting periods that have to be observed (1) before administering the vaccine after having discontinued immunosuppressive medication and (2) before reinitiating immunosuppressive medication after having administered the vaccine.
Zoster	• For adults aged 60 and up. Definitive recommendations will be issued when there are enough scientific data available for immunocompromised adults. • Administering this vaccine is contraindicated for patients taking immunosuppressive medication. • See **table 4** for a list with the medication for which there is an absolute contraindication or no contraindication at all (e.g. low-dose corticosteroids). When in doubt, consult a specialist. Also see **table 4** for the waiting periods that have to be observed (1) before administering the vaccine after having discontinued immunosuppressive medication and (2) before reinitiating immunosuppressive medication after having administered the vaccine.

	• Exception: Treatment with low doses of immunosuppressive medication such as methotrexate (0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day) or 6-mercaptopurine (<1.5 mg/kg/day) to treat rheumatoid arthritis, polymyositis, sarcoidosis, IBD, etc. is not considered to be sufficiently immunosuppressive as regards the safety ***of this vaccine***, and does no constitute a contraindication for administering the zoster vaccine (which is not the case for other live vaccines) (*MMWR RR-5June 6, 2008 / Vol 57)*
Yellow fever	• Administering this vaccine is contraindicated for patients taking immunosuppressive medication. • See **table 4** for a list with the medication for which there is an absolute contraindication and no contraindication at all. When in doubt, consult a specialised "travel clinic". Also see **table 4** for the waiting periods that have to be observed (1) before administering the vaccine after having discontinued immunosuppressive medication and (2) before reinitiating immunosuppressive medication after having administered the vaccine.
Typhoid fever - oral vaccine	• Not in patients with inflammatory bowel diseases. • Administering this vaccine is contraindicated for patients taking immunosuppressive medication. • To be replaced by the inactivated typhoid fever vaccine.

2.4.5. Haematological malignancies and oncological conditions & the influence of chemotherapy	
• As regards patients receiving **immunosuppressive chemotherapy**, **inactivated vaccines** should be postponed until at least **3 months** after the end of treatment, depending on the recovery of the immune system. **Live vaccines** can only be administered as from **3-6 months** after the end of treatment. • After **extensive radiotherapy** (consult a specialist), there should be **a 3-month waiting period** before administering **live vaccines**.	
Influenza	• Vaccination prevents influenza-induced interruptions in the chemotherapy.
MMR	• Live vaccine. Administering this vaccine is contraindicated for patients taking immunosuppressive medication. Wait for 6 months after having discontinued this medication.
Varicella	• Live vaccine. Administering this vaccine is contraindicated for patients taking immunosuppressive medication. Wait for 6 months after having discontinued this medication.
Yellow fever	• Can be administered as from **3 months** after the last chemotherapy session.
Typhoid fever: oral vaccine	• Can be administered as from **3 months** after the last chemotherapy session.

3. Vaccinating individuals with a chronic condition that may be associated with moderate immunosuppression

Recommended vaccinations for a few chronic conditions that may be associated with moderate immunosuppression

- There are absolutely no contraindications against proceeding with the **routine basic vaccinations** (see individual SHC factsheets and "catch up vaccinations" (www.health.belgium.be click on: Nl / Fr; keyword: Vaccin).
- There are absolutely no contraindications against proceeding with the **vaccinations for travel-related exposures**, including the **live vaccines**. Exception:
  (1) Individuals with functional or anatomical thymectomy: The **live** vaccines (special comment on the yellow fever vaccine) should not be administered, see **3.13**.
  (2) As regards individuals with advanced renal insufficiency, cirrhosis of the liver or severe diabetes, the specialised vaccination centre should balance the risk of infection with the yellow-fever virus against the risk of complications caused by the vaccine virus itself (taking into account a more or less moderate state of immunosuppression caused by the severity of the pathological condition, its duration and stability, the presence of complications or comorbidities)

KEY: "advisable" As a result of the additional risk posed by increased susceptibility and/or increased severity, and/or increased risk from complications.

	3.A. Children < 16		**3.B. Adults and teenagers ≥ 16**
3.1 Diabetes mellitus	Recommended: • **Influenza** (annually)		Recommended: • **Influenza** (annually)
3.2 Metabolic disorders, including morbid obesity with BMI > 35	Recommended: • **Influenza** (annually)		Recommended: • **Influenza** (annually)
3.3 Kidney failure (including nephrotic syndrome and renal dialysis)	Recommended: • **Influenza** (annually); • **hepatitis** B; • **Pneumococcal vaccine** (for further details: see SHC factsheet – "*pneumokokkenvaccinatie bij pediatrische risicogroepen" (i.e.: "pneumococcal vaccination for paediatric at-risk groups").* Remember to administer the live vaccine in time in the event of a possible evolution towards transplantation		Recommended: • **Influenza** (annually); • **hepatitis B** (in adults double dosage or adjuvant hepatitis B vaccine (from the age of 15)); • **Pneumococcal vaccine PPS23V** (*to re-assess when more data on the conjugate vaccine are available*). Remember to administer the live vaccines in time in the event of a possible evolution towards transplantation

	3.A. Children < 16		**3.B. Adults and teenagers ≥ 16**
3.4 Chronic liver disease and liver failure	Recommended: • **Influenza** (annually); • **hepatitis A & B;** Remember to administer the live vaccines in time in the event of a possible evolution towards transplantation		Recommended: • **Influenza** (annually); • **hepatitis A & B**; • **Pneumococcal vaccine PPS23V** from the age of 50 or in the event of alcohol abuse (with or without cirrhosis) (see SHC factsheet *pneumokokken risicogroepen* "pneumococcal vaccination: at-risk groups" – to be reassessed when more data are available on the conjugate vaccine). Remember to administer the live vaccines in time in the event of a possible evolution towards transplantation
3.5 Chronic cardiopulmonary conditions (including heart failure, severe COPD, asthma, bronchiectasis)	Recommended: • **Influenza** (annually); • **Pneumococcal vaccine** (for further details: see SHC factsheet – "*pneumokokkenvaccinatie bij pediatrische risicogroepen" (i.e.: "pneumococcal vaccination for paediatric at-risk groups").*		Recommended: • **Influenza** (annually); • **Pneumococcal vaccine PPS23V** from the age of 50 (see SHC factsheet *pneumokokken risicogroepen* – "pneumococcal vaccination: at-risk groups" – to be reassessed when more data are available on the conjugate vaccine).
3.6 Cystic fibrosis	Recommended: • **Influenza** (annually); • **hepatitis A & B;** Remember to administer the live vaccines in time in the event of a possible evolution towards transplantation		Recommended: • **Influenza** (annually); • **hepatitis A & B;** Remember to administer the live vaccines in time in the event of a possible evolution towards transplantation
3.7 Chronic aspirin treatment	Recommended: • **Influenza** (annually)		Not applicable
3.8 Sickle-cell anaemia	Recommended: • **Influenza** (annually); • **Pneumococcal vaccine** (for further details: see SHC factsheet – "*pneumokokkenvaccinatie bij pediatrische risicogroepen" (i.e.: "pneumococcal vaccination for paediatric at-risk groups").*		Recommended: • **Influenza** (annually); • **Pneumococcal vaccine PPS23V** (see SHC factsheet *pneumokokken risicogroepen* "pneumococcal vaccination: at-risk groups" – to be reassessed when more data are available on the conjugate vaccine).
3.9. Haemophilia	Recommended: **hepatitis A & B;**		Recommended: hepatitis A & B;
3.10 Anatomical or	Recommended:		Recommended:

	3.A. Children < 16		**3.B. Adults and teenagers ≥ 16**
functional hyposplenia/asplenia	• **Influenza** (annually); *There are no data that show that there is a specific increase in mortality or risk of complications - "however, influenza is a risk factor for secondary bacterial infections that can cause severe disease among persons with asplenia - Risk of severe bacterial sepsis is higher in children having splenectomy for hematological reasons and in those who have received immunosuppressive treatment* • **Meningococcal C** (conjugate) vaccine; the quadrivalent conjugate vaccine Menveo ® can be used from the age of 12 (no data available yet on its use in younger children, booster frequency, but booster inoculations are probably necessary). • **Pneumococcal vaccine** (for further details: see SHC factsheet – "*pneumokokkenvaccinatie bij pediatrische risicogroepen" (i.e.: "'pneumococcal vaccination for paediatric at-risk groups');* • **Haemophilus influenzae b** (2 doses UK)		• **Influenza** (annually); There are no data that show that there is a specific increase in mortality or risk of complications - "*however, influenza is a risk factor for secondary bacterial infections that can cause severe disease among persons with asplenia - Risk of severe bacterial sepsis is higher in patients having splenectomy for hematological reasons and in those who have received immunosuppressive treatment* • **Meningococcal vaccine quadrivalent** (from 2011 preferably the conjugate vaccine, Menveo - there are no data available to date regarding booster frequency, but booster inoculations are probably necessary). The unconjugated quadrivalent meningococcal vaccine should be repeated every 3 years. • **Pneumococcal vaccine PPS23V** every 3-5 years (to be reassessed when more data are available on the conjugate vaccine). • **Haemophilus influenzae b** 1x
3.11 . Cerebrospinal fluid leak, Cochlear implant	Recommended: • **Pneumococcal vaccine** (for further details: see SHC factsheet – "*pneumokokkenvaccinatie bij pediatrische risicogroepen" (i.e.: "pneumococcal vaccination for paediatric at-risk groups").*		Recommended: • **Pneumococcal vaccine PPS23V** (see SHC factsheet *pneumokokken risicogroepen* – "pneumococcal vaccination: at-risk groups" – to be reassessed as soon as more data are available on the conjugate vaccine).
3.12 Extensive radiotherapy	Recommended: • **Influenza** (annually) Vaccination with **live vaccines**: if indicated, this is only possible as from 3 months after the end of radiotherapy (to discuss with the specialist).		Recommended: • **Influenza** (annually) Vaccination with **live vaccines**: if indicated, this is only possible as from 3 months after the end of radiotherapy (to discuss with the specialist).

	3.A. Children < 16		3.B. Adults and teenagers ≥ 16
3.13 Functional or anatomical thymectomy for thymoma or in case of mantle field radiation therapy	• Absolute contraindication for vaccination against yellow fever, measles-mumps-rubella and varicella. • If indicated, the measles-mumps-rubella vaccination can be offered after assessment and after informed consent regarding the theoretical risks (e.g. no previous vaccination & travel plans to exotic regions) • The CDC (MMWR 2010) mentions that this contraindication becomes "relative" if the thymectomy was not the outcome of a thymic pathology (i.e. only incidental resection) or if the radiation therapy was administered in the remote past and the thymus happened to be located in the radiation field, in which case the CDC states that upon assessment of the theoretical risks and after having obtained the patient's informed consent, the yellow fever vaccine may be given after all if there is a specific indication for this (e.g. no previous vaccination at all & travel plans to exotic regions). (specialist advice is indicated)		• If indicated, the measles-mumps-rubella vaccination can be offered after assessment and with the informed consent of the patient regarding the theoretical risks (e.g. no previous vaccination & travel plans to exotic regions) • Absolute contraindication for vaccination against yellow fever. The CDC (MMWR 2010) mentions that this contraindication becomes "relative" if the thymectomy was not the outcome of a thymic pathology (i.e. only incidental resection) or if the radiation therapy was administered in the remote past and the thymus happened to be located in the radiation field, in which case the CDC states that upon assessment of the theoretical risks and after having obtained the patient's informed consent, the yellow fever vaccine may be given after all if there is a specific indication for this (e.g. no previous vaccination at all & travel plans to exotic regions). (specialist advice is indicated)
3.14 Complement deficiencies	Recommended: • **Influenza** (annually) • all the other vaccinations in the SHC basic vaccination schedule. Distinction between <u>early</u> [C1-4] and <u>late</u> complement factor defects [C5-9], properdin, factor B. In the event of late complement factor or properdin defects. • **Meningococcal vaccine (quadrivalent conjugate meningococcal vaccine).** There are no data available yet on the use of the quadrivalent meningococcal vaccine in children aged < 12; it is likely that boosters will also be required. • (NB early complement factor defects mainly generate inflammatory conditions)		Recommended: • **Influenza** (annually) In the event of deficiencies of the terminal complement factors or properdin. • **Quadrivalent meningococcal vaccines** (PS vaccine) Are indicated every 3 years (there are no data available to date regarding the quadrivalent meningococcal vaccine Menveo, it is likely that boosters will also be required) • Pneumococcal and HiB vaccinations are not specifically indicated for this population group.

	3.A. Children < 16		**3.B. Adults and teenagers ≥ 16**
3.15 Patients on intravenous / subcutaneous immunoglobulin replacement therapy (IVIG/SCIG)	IVIG/SCIG have an adverse effect on the immune response after vaccination against varicella, measles and rubella. When administering IVIG/SCIG, there should, if possible, be a 6-8 month waiting period (after ending IVIG/SCIG treatment) before offering these live, vaccines in order to obtain a proper immune response (*Red Book 2009(1): 37; MMWR-RR 28 jan 2011*). If persistent replacement is required for the patient, there can be no 6-month waiting period. In addition, these patients will always develop but a weak antibody response themselves. In such cases, a waiting period of 3-4 weeks may be applied. Administering inactivated vaccines and the yellow fever vaccine does not pose a problem during IVIG/SCIG - replacement, there is no interference with the immune response (*MMWR-RR 28 jan 2011).*		IVIG have an adverse effect on the immune response after vaccination against varicella, measles and rubella. When administering IVIG, there should, if possible, be a 6-8 month waiting period (after ending IVIG treatment) before offering these live, attenuated vaccines in order to obtain a proper immune response (*Red Book 2009(1): 37; MMWR-RR 28 jan 2011*). If persistent replacement is required for the patient, there can be no 6-month waiting period. In addition, these patients will always develop but a weak antibody response themselves. In such cases, a waiting period of 3-4 weeks may be applied. Administering inactivated vaccines and the yellow fever vaccine does not pose a problem during IVIG-replacement, there is no interference with the immune response (*MMWR-RR 28 jan 2011).*

4. List of (potentially) immunosuppressive medications

In order to find the brand names of the various medications, see:
Gecommentarieerd Geneesmiddelen Repertorium (Belgisch Centrum voor Farmacotherapeutische informatie; www.bcfi.be)
Répertoire Commenté des Médicaments (Centre Belge d'Information Pharmaco thérapeutique; www.cbip.be)
(the following table mentions the different groups as they are listed by the BCFI-CBPI):

- **5.3.2. SELECTIVE OESTROGEN RECEPTOR MODULATORS**
- **5.3.3. AROMATASE INHIBITORS**
- **5.4. GLUCOCORTICOIDS**
- **9.2. MEDICATION FOR RHEUMATIC DISEASES**
- **12.3.1. IMMUNE MODULATORS: IMMUNOSUPPRESSION IN THE EVENT OF TRANSPLANTATION**
- **12.3.2. IMMUNE MODULATORS: MEDICATION FOR CHRONIC IMMUNE-MEDIATED DISEASES**
- **13. ANTICANCER MEDICATIONS**
- **13.1. Alkylating agents**
- **13.2. Antimetabolites**
- **13.3. Antitumor antibiotics**
- **13.4. Topoisomerase inhibitors**
- **13.5. Microtubular inhibitors**
- **13.6. Monoclonal antibodies**
- **13.7. Tyrosine kinase inhibitors**
- **13.8. Various anticancer medications**

4.1. Definitely immunosuppressive

(Mainly based on "Immunocompromised travellers". Chapter 8. CDC Yellow Book : Health Information for International Travel 2012. Oxford University Press & http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-8-advising-travelers-with-specific-needs/immunocompromised-travelers.htm)

- High-dose corticosteroids: Children (up to 10 kg) who have been taking 2 mg/kg prednisone or more a day for over two weeks; children > 10kg and adult patients who have been taking 20 mg prednisone or more a day for over 2 weeks. As regards the vaccination against yellow fever: less than 10 mg/ day is safe, between 10 en 20 mg requires consulting a specialised vaccination centre.
- Methotrexate
- Leflunomide
- Azathioprine & 6-mercaptopurine
- Cyclosporine A
- Cyclophosphamide
- Tacrolimus, Everolimus, Sirolimus, Temsirolimus
- Mycophenolate mofetil
- Antilymphocyte immunoglobulins
- Tumor Necrosis Factor (TNF)-blockers: Adalimumab (Humira®), certolizumab (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®) and infliximab (Remicade®) **(**see **chapter 12** www.bcfi.be / www.cbip.be)

- Other monoclonal antibodies and biologicals : Rituximab (Mabthera®), Abatacept (Orencia®), Tocilizumab (Roactemra®), Basiliximab (Simulect®), Natalizumab (Tysabri®) (see **chapter 12** www.bcfi.be / www.cbip.be), and others under development : Muromonab-CD3, …
- Anticancer medications: Alkylating agents, antimetabolites, antitumor antibiotics, topoisomerase inhibitors, microtubular inhibitors and various anticancer medications (see **chapter 13** www.bcfi.be / www.cbip.be).

It is only possible to vaccinate with a live vaccine as from 1 month after discontinuing high-dose prednisone (≥ 20 mg /day) and 3 months after discontinuing immunosuppressive medication and chemotherapy.
It is necessary to wait for 12 months after Rituximab and 2 years after Leflunomide (unless washout with Questran; to consider with the rheumatologist).

In most situations, it will therefore be necessary to discontinue the medication for at least 4 months (exception: prednisone) (exclusively in consultation with the treating physician) in order to be able to vaccinate against **yellow fever**; indeed, it is preferable to wait for another 3-4 weeks after the yellow fever vaccination (risk of viraemia) before reinitiating the immunosuppressive medication.

4.2. Not immunosuppressive
***(Mainly based on "Immunocompromised travellers". Chapter 8. CDC Yellow Book : Health Information for International Travel 2012. Oxford University Press** & http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-8-advising-travelers-with-specific-needs/immunocompromised-travelers.htm)*

- Paracetamol, NSAID, Sulphasalazine, (hydroxy)chloroquine
- Corticosteroids
  - Short- or long-term daily or alternate-day therapy with <10 mg of prednisone or equivalent
  - Maintenance physiologic doses (replacement therapy)
  - Steroid inhalers
  - Topical steroids (skin, ears, or eyes)
  - Intra-articular, bursal, or tendon injection of steroids
  - Budesonide enteric coated (Entocort ®, etc)
- Glatiramer acetate *Copaxone ® (Sanofi-Aventis)* (MS) (www.bcfi.be / www.cbip.be**)**
- **Selective oestrogen receptor modulators** (treatment of hormone- dependent breast cancer) : clomifen, tamoxifen, toremifen, raloxifene, fulvestrant (www.bcfi.be / www.cbip.be)
- **Aromatase inhibitors** (oestrogen synthesis inhibitors; treatment of hormone- dependent breast cancer): Anastrozole, letrozole, exemestan (www.bcfi.be / www.cbip.be)
- Inosine-pranobex Isoprinosine® *(Sanofi-Aventis)* (MS) (www.bcfi.be / www.cbip.be**)**
- **Growth factors:** haematopoietic growth factors (Granulocyte colony- stimulating factors, G-CSF)
- **Ribavirin** – as is the case for none of the antiviral medications in general

4 c Probably not immunosuppressive

4 c 1 "very probably not" immunosuppressive

- Hydrea
- Monoclonal antibodies against
    - VEGF (vascular endothelial growth factor),
    - EGFR (epidermal growth factor),
    - growth factor HER-2

      (see chapter 10.2 www.bcfi.be / www.cbip.be)
        - *Bevacizumab* (*Avastin®)*
        - *Cetuximab* (*Erbitux®)*
        - *Panitumumab* (*Vectibix®)*
        - *Trastuzumab* (*Herceptin®)*

4 c 2 "probably not" immunosuppressive

- interferon (a, b and g) (www.bcfi.be / www.cbip.be)
    - **A.** Intron® A - Pegasys® - Pegintron® - Rebif®- Roferon®-pen - Roferon® A
    - **B.** Avonex® Bio-set - Betaferon® - Extavia®
    - **C.** Immukine®
        - Risk for neutropenia, but no clinically apparent increase in opportunistic infections.
        - No information is available on
        - possible decreased vaccine efficacy (physiopathologically plausible)
        - increased adverse events with live viral antigens (physiopathologically not plausible; on the contrary it will inhibit intracellular viral multiplication)

          but definitive data are lacking.
        - In general not considered to compromise immunity
        - No formal contraindication for YF vaccination
        - Quid Pegylated-interferon ? probably immunodepressive ?

4 d Probably immunosuppressive – for new biologicals, consult a specialist

- Lenalidomide Revlimid®
- Tasonermin: Beromun®
- Aldesleukine Proleukin® (Chiron) gemodifieerd interleukine-2
- Tyrosine kinase inhibitor (Glivec ®)
- Omalizumab Xolair®
- Eculizumab Soliris®

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