Trust Guideline for adults (patients and close family members/carers) for the use of live vaccines following immunosuppressive therapy including lymphocyte depletion and anti-cytokine therapy

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A Clinical Guideline recommended

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For:	Adult
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This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

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Version and Document Control:

Date	Updated version number	Previous version number	Details
October 2013	V2	V1	HIV removed from guidance Guidance generally updated in line with DH Green Book revised version 2013 "*patients and close family members/carers*" added to title Shingles vaccine added Influenza removed (live only sued in children) Drug list updated
December 2015	V3	V2	Section on shingles updated in line with Green Book October 2015 update
February 2019	V4	V3	No changes.
November 2022	V5	V4	Section on shingles and immunosuppression updated in line with Green Book August 2021

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1. Abbreviations

BCG	Bacille Calmette-Guérin
CLL	Chronic Lymphocytic Leukaemia
DMARD	Disease modifying anti- rheumatic drugs
GVHD	Graft versus Host Disease
HIV	Human Immune deficiency Virus
MMR	Measles Mumps and Rubella
NHL	Non-Hodgkins Lymphoma
OD	Once daily
PCP	Pneumocystis carinii pneumoniae
TNF	Tumour necrosis Factor
VZV	Varicella Zoster Virus

2. Based on DH Green Book 2022 update and vaccine SPCs

The purpose of this guideline is as a reference for the use of **live** vaccines in adult patients who become immunosuppressed as a result of treatment.

Vaccines containing live organisms can cause severe acute or fatal infections in immunocompromised patients, due to extensive replication of the vaccine strain.

3. Live vaccines should NOT be given to severely immunocompromised individuals

Immunisation with any live vaccine should be given preferably 4 weeks but at least 14 days before starting immunosuppressive therapy.

Responses to non-live vaccines may be reduced in patients on immunosuppressive drugs and therefore where possible vaccination should be given at least 4 wks before commencing of immunosuppressive therapy but can be given at any time.

4. The following are live vaccines used in adults:

- BCG vaccine
- Measles, Mumps and Rubella vaccine (Priorix, MMRVaxPro)
- Rotavirus vaccine (Rotarix)
- Shingles vaccine (Zostavax)
- Oral typhoid vaccine (Ty21a)
- Varicella vaccine (Varilrix and Varilvax)
- Yellow fever vaccine

Most live vaccines should not be administered to individuals with primary or acquired immunodeficiency.

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Guideline does not cover patients with permanent or long-term immunosuppression from the underlying disease i.e. :

- chronic haematological disorders or haematological disorders not in remission such as leukaemia (acute and chronic) lymphoma (including Hodgkin lymphoma), myeloma and other plasma cell dyscrasia, bone marrow failure conditions and other disease of the reticuloendotelial system

WHO SHOULD NOT BE GIVEN ANY LIVE VACCINES

- **inherited disorders**. for this group current DoH guidelines in the "Immunisation against Infectious Diseases" book, and also several American guidelines state that patients with evidence of **severe** primary immunodeficiency, i.e. those with defective T cells, CD40 ligand deficiency, X-linked agammaglobulinemia, ataxia telangiectasia, severe combined immune deficiency (SCID), and Wiskott Aldrich Syndrome **should not receive** live viral or bacterial vaccine. However, those with defects in other parts of the immune system, e.g. Chronic Granulomatous Disease or complement deficiencies or hyposplenism, can be immunized
- having received an allogenic (cells from a donor) stem cell transplant in the past 24 months and only then if they are demonstrated not to have on-going immunosuppression or graft versus host disease (GVHD);
- having received an autologous (using their own stem cells) haematopoietic stem cell
- transplant in the past 24 months and only then if they are in remission
- **HIV** – seek advice from Sexual Health Department

This guidance also applies to **close family members or caregivers of such patients** apart from the **Varicella vaccine and Measles, Mumps and Rubella vaccine (MMR)** which, although contraindicated in immunosuppressed individuals, should be given to healthy susceptible contacts of immunocompromised patients where continuing close contact is unavoidable e.g siblings of a leukaemic child or a child whose parent is undergoing chemotherapy.

Eligible close contacts of immunosuppressed individuals should be fully immunised against shingles according to the national schedule. Susceptible household contacts of immunosuppressed individuals should also be offered vaccination against varicella to reduce the risk of exposure to chickenpox.

Similarly, despite extensive international experience, there is no evidence of harm from the transmission of measles, mumps and rubella viruses from recent vaccinees. Therefore, close contacts of immunosuppressed individuals should be fully immunised, against measles, mumps and rubella according to their national schedule.

5. Table 1

If in doubt whether a drug could be immunosuppressive - check with pharmacy or the SPC

Treatment	Vaccine advice
High dose systemic glucocorticosteroids - defined as a dose equivalent to prednisolone at ≥40mg/day for more than a week **long term lower dose glucocorticosteroids** (≥20mg per day for more than 14 days) **excludes** non-systemic glucocorticosteroids such as aerosols or topical or intra-articular preparations **NB** occasionally individuals on lower doses of steroids may be immunosuppressed as a result of concurrent therapies, previous treatments or the underlying disease and are therefore at increased risk from infection – caution should be applied to such cases and vaccines not given	Delay live vaccines for ≥3 months after treatment has stopped.
Chemotherapy	Delay live vaccines for ≥ 6 months after treatment has stopped
Other systemic anti cancer/immunosuppressive drugs list below e.g. autoimmune diseases, solid organ transplant recipients	Delay live vaccines for ≥ 6 months after treatment has stopped *except* **for shingles vaccine** see special cases section page 5
Lymphocyte depleting antibodies e.g. Alemtuzumab (MabCampath) Rituximab (MabThera) Ofatumumab (Arzerra)	Delay live vaccines for ≥ 12 months after treatment has stopped; *except* BCG (indefinite) and yellow fever see page 4
Cytokine modulators e.g. Abatacept (Orencia) ; Adalimumab (Humira); Anakinra (Kineret); Etanercept (Enbrel) Golimumab (Simponi) Infliximab (Remicade), Tocilizumab (Roactemra)	Delay live vaccines for ≥ 6 months after treatment has stopped
Post haematopoietic stem cell transplant no GvHD	Delay live vaccines ≥ 24 months after treatment has stopped
Post haematopoietic stem cell transplant with GvHD or ongoing immune suppression	Live vaccine contraindicated

Includes - This list is not comprehensive always check with pharmacy or the SPC if in doubt

Azathioprine *
Chloroquine
Ciclosporin
Cyclophosphamide
Everolinus
Hydroxychloroquine
Leflunomide
Mercaptopurine *
Methotrexate *
Mycophenalate
Sulfasalazine
Tacrolimus
Temsirolimus
Thioguanine

* see section on Shingles vaccine page 4

Adults with chronic inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease, psoriasis, glomerulonephritis) will be on stable long term low dose glucocorticosteroid therapy (defined as up to 20 mg prednisolone per day for more than 14 days in adult) either alone or in combination with other immunosuppressive drugs. Long term stable low dose glucocorticosteroid therapy,either alone or in combination with low dose non-biological oral immune modulating drugs (e.g.methotrexate 20 mg per week in adults, azathioprine 3.0mg/ kg/day or 6-mercaptopurine 1.5mg/kg/day), are not considered sufficiently immunosuppressive and these patients can receive live vaccines.

Non-systemic glucocorticosteroids, such as inhalers or topical or intra-articular preparations, do not cause substantial systemic immunosuppression and are therefore not contraindications to administration of live vaccines. Similarly, replacement glucocorticosteroids for people with adrenal insufficiency do not cause immunosuppression and are not, therefore, contraindications for administration of live vaccines.

6. Special cases

6.1 Yellow fever (YF)

Lymphocyte depleting antibodies – YF vaccine should not be given
If a yellow fever certificate is required for travel but there is no endemic infection risk then usually a doctor's letter will suffice in lieu of vaccine. If the patient is travelling to a yellow fever endemic area then immunisation will need to be considered on a case by case basis.

6.2 BCG

Lymphocyte depleting antibodies BCG should remain contraindicated indefinitely patients as the risk of infection seems to remain significant for long periods of time.

6.3 Shingles

There are two licensed shingles vaccines available in the UK:

1) Zostavax contains live, attenuated virus;
2) Shingrix is a recombinant, sub-unit vaccine (non-live).

From 2021, adults aged 70-79 years who are eligible to receive shingles vaccine, but who are contra-indicated to the receipt of the live vaccine due to **severe immunosuppression** (please see the table with clarification on the page 6) should be offered Shingrix instead.

The Green book states that live shingles vaccine (Zostavax) may be given to patients on lower level immunosuppression defined as:

- Azathioprine ≤ 3mg/kg/day
- 6-Mercaptopurine ≤1.5mg/kg/day
- Methotrexate ≤ 20 mg per week
- Long term moderate dose Prednisolone ≤10mg per day for <4 weeks in the previous 3 months
- Moderate to high dose corticosteroids (equivalent ≤20mg Prednisolone per day) for less than 10 days in the previous month

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N.B Avoid if any patient is taking any other concurrent immunosuppressive therapy even low dose glucocorticosteroids (please refer to table below)

Definition of severe immunosuppression
{UK HSA, The Gren Book, Chapter 28a: Shingles (herpes zoster)}

7. Individuals with primary or acquired immunodeficiency states due to conditions including:

- acute and chronic leukaemias, and clinically aggressive lymphomas (including Hodgkin's lymphoma) who are less than 12 months since achieving cure
- individuals under follow up for a chronic lymphoproliferative disorders including
- haematological malignancies such as indolent lymphoma, chronic lymphoid leukaemia,
- myeloma, Waldenstrom's macroglobulinemia and other plasma cell dyscrasias
- immunosuppression due to HIV/AIDS with a current CD4 count of below 200 cells/µl.
- primary or acquired cellular and combined immune deficiencies – those with lymphopaenia
- (<1,000 lymphocytes/ul) or with a functional lymphocyte disorder
- those who have received an allogeneic (cells from a donor) or an autologous (using their own cells) stem cell transplant in the previous 24 months
- those who have received a stem cell transplant more than 24 months ago but have
- ongoing immunosuppression or graft versus host disease (GVHD)

8. Individuals on immunosuppressive or immunomodulating therapy including:

- those who are receiving or have received in the past 6 months immunosuppressive
- chemotherapy or radiotherapy for any indication
- those who are receiving or have received in the previous 6 months immunosuppressive therapy for a solid organ transplant
- those who are receiving or have received in the previous 3 months targeted therapy for autoimmune disease, such as JAK inhibitors or biologic immune modulators including B-cell targeted therapies (including rituximab but for which a 6-month period should be considered immunosuppressive), monoclonal tumor necrosis factor inhibitors (TNFi), T-cell co-stimulation modulators, soluble TNF receptors, interleukin (IL)-6 receptor inhibitors.,IL-17 inhibitors, IL 12/23 inhibitors, IL 23 inhibitors

9. Individuals with chronic immune mediated inflammatory disease who are receiving or have received immunosuppressive therapy:

- moderate to high dose corticosteroids (equivalent ≥20mg prednisolone per day) for more than 10 days in the previous month

- long term moderate dose corticosteroids (equivalent to ≥10mg prednisolone per day for more than 4 weeks) in the previous 3 months
- any non-biological oral immune modulating drugs e.g. methotrexate >20mg per week
- (oral and subcutaneous), azathioprine >3.0mg/kg/day; 6-mercaptopurine >1.5mg/kg/day,
- mycophenolate >1g/day) in the previous 3 months
- certain combination therapies at individual doses lower than stated above, including those on ≥7.5mg prednisolone per day in combination with other immunosuppressants (other than hydroxychloroquine or sulfasalazine) and those receiving methotrexate (any dose) with leflunomide in the previous 3 months

Individuals who have received a short course of high dose steroids (equivalent >40mg prednisolone per day for more than a week) for any reason in the previous month.

10. Clinical audit standards

Adherence to the suggested timing schedule for administration of live vaccines.

11. Summary of development and consultation process undertaken before registration and dissemination

The first draft was written by Dr Grant Hill-Cawthorne (SpR in Micriobiology) and subsequently updated by Dr Samir Dervisevic and authors listed above on behalf of the NNUH. During its development and update it was has been circulated for comment to: Consultant Virologists and Microbiologists, Consultant Haematologists, Rheumatologists, Respiratory Physicians, Renal Physicians comments received have been incorporated into the final version.

This version has been endorsed by the Clinical Guidelines Assessment Panel.

12. Distribution list / dissemination method

Trust intranet

13. References / source documents

https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

http://www.cdc.gov/vaccines/

http://www.cdc.gov/vaccines/pubs/hemato-cell-transplts.htm

http://www.medicines.org.uk/emc/

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Appendix 1 Biologicals - Antibodies and Cytokine modulators

1. Lymphocyte depleting Monoclonal antibodies

Anti-B cell (CD52)-Alemtuzumab (MabCampath)

- Profound lymphocyte depletion occurs and will be prolonged.. There can be evidence of long lasting B cell immune suppression for over 11 years following treatment and CD4 count recovery may take even longer than this.
- The greatest risk of opportunistic infections is thought to be in the first 2 months following treatment. The recovery of CD4 counts to ≥200 cells/μL usually occurs by 6 months.
- There are no studies for live vaccination following alemtuzumab treatment but the manufacturer (Genzyme) recommends a 12 month gap before live viral vaccines are administered.

Anti-B cell (CD20)-Rituximab (MabThera)

- The safety of immunisation with live viral vaccines following treatment with Rituximab has not been studied for NHL and CLL patients. For this reason immunisation with live virus vaccines is not recommended by the manufacturer (Roche) whilst the patient is on Rituxumab or if they are peripherally B cell depleted.
- Immunisation should be completed at least 4 weeks prior to the first administration of rituximab.
- Rituximab induces B cell depletion in about 70-80% patient, but was associated with decreased serum immunoglobulins in only a minority of patients. Its target antigen, CD20, is only present on pre-B and mature B lymphocytes therefore treatment leaves haematopoietic stem cells, pro-B cells and normal plasma cells intact.
- For patients treated for haematological malignancies B cell repletion begins within 6 months of treatment returning to normal levels between 9 and 12 months after completion of therapy. In rheumatoid arthritis patients peripheral B cell counts began to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, regardless of co-administration with other DMARDs.
- Based on this data, immunisation with live vaccines following treatment with Rituximab is probably safe 12 months after the last dose assuming that the patient does not have a chronic malignancy and that B cell counts have reconstituted.

2. Cytokine modulators in common use

Anti-TNF-α-Infliximab (Remicade)

- Elimination of Infliximab may take up to 6 months after treatment.
- No data are available on response to immunisation with live vaccines by patients receiving anti-TNF-α therapy. Manufacturer (Schering-Plough) just recommends that live vaccines are not given concurrently.
- Live vaccines likely to be safe 6 months post-treatment.

Anti-TNF-α-Adalimumab (Humira)

- Manufacturer (Abbott) advises that patients on Adalimumab may receive concurrent immunisation, except for live vaccines.
- Half-life is approximately 2 weeks. Pregnancy and breast-feeding thought to be safe after 5 months so levels of immunoglobulin must be insignificant by this time.
- 6 month gap is likely to be safe.

Fusion Protein-Etanercept (Enbrel)

- Mean elimination half-life is 70 hours (range 7 to 300 hours)
- According to the manufacturer (Wyeth) live vaccine should not be given concurrently with Etanercept.
- No other data are available for length of TNF blockade with Etanercept. It is reasonable, therefore, to assume that a 6 month gap prior administration of live vaccines would be appropriate.