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Definition of Immunocompromised Relevant to Implementation of NIAC Guidance on Extended Primary Vaccination Issued 30 August 2021 taking account of September 2021 update to Table 5a.2 of Chapter 5a of Immunisation Guidelines for Ireland

Updated 08 October 2021 [Changes in bold font]

Notes on how to operationalise this

The most easily identifiable immunocompromised patients are in general also those at highest risk and they are likely to be on regular follow up with hospital specialists (organ transplant, rheumatology, renal, cancer, primary immunedeficiency and some people living with HIV). The most effective way to identify many of these patients may be through the hospital system. If hospitals have their group 4 and 7 lists from early 2021 that may help but a lot of group 4 and 7 people are not immunocompromised. For this purpose it is important to consider if the patient **was immunocompromised at the time when the initial vaccination dose(s) were administered.**

The hardest group to identify may well be those on high dose systemic corticosteroids in the period before or during the earlier vaccination programme. Some of these patients may not be readily identifiable through the hospital system and may need to be identified through other pathways.

Clinical Definitions of Immunocompromise

The key point is Recommendation 2 as follows

> "*An additional mRNA vaccine dose should be given to those aged 12 and older with immunocompromise associated with a suboptimal response to vaccines who have completed their primary course, regardless of whether the primary course was of an mRNA or an adenoviral vector vaccine. This is an extended primary vaccination course. The additional vaccine should be given after a minimum interval of two months following the last dose of an authorised COVID-19 vaccine*."

This specific NIAC document does not **define** immunocompromise.

In the Background to the recommendations this document includes the following text

> "*Those aged 16 years and older with immunocompromise associated with a suboptimal response to vaccines (as listed in Chapter 5a, Table 5.2)"*

Thus this points to the use of Table 5a.2 of Chapter 5a as guide to interpretation of immunocompromised. Table 5a.2 was updated by NIAC in September 2021. The updated table is attached to this document as Appendix 2.

Table 5a.2 is "Medical conditions and medications associated with very high risk or high risk of severe COVID-19 disease."

It includes two groups (a) those shaded and (b) those not shaded. Those shaded are those groups that may be associated with a suboptimal response to vaccines. On that basis it was specified at the start of the vaccination campaign that these groups should preferentially be given an mRNA vaccine. For this purpose it is reasonable to consider those categories identified as "associated with a suboptimal response to vaccine" as intended to receive an extended primary vaccination course. The condition immunocompromise is not defined in the level of detail required for operational purposes in Table 5a.2 therefore the following is supplemented with material from Chapter 3 of Immunisation Guidelines (Immunisation of Immunocompromised Persons). People with hyosplenia and asplenia are included in Chapter 3 but are not included in this definition because there is no reason to expect that their response to COVID-19 vaccines differs from that of the general population.

Experience in hospitals with use of the earlier version of this document was that its application, in particular with respect to cancer patients, was extremely challenging. There was a significant concern that identification of some patients who would benefit from the additional dose would be delayed or that the patients may be missed because of these implementation challenges. In that context the operational guidelines for cancer patients have been modified to ease application while following the NIAC recommendations as closely as is practical.

The section on immunocompromise due to treatment is addressed in detail in Appendix 1.

Medical Condition (NIAC)	NIAC Detail	Comment
Cancer	All cancer patients receiving or within 6 weeks of receiving systemic therapy with cytotoxic chemotherapy, targeted therapy, monoclonal antibodies or immunotherapies	**For practical purposes included all patients who received cytotoxic chemotherapy, targeted therapy, monoclonal antibodies or immunotherapies in the past 12 months**
Cancer	All patients receiving treatment or pending treatment for a haematological cancer	**For practical purposes include anyone under your care who is being actively treated for a haematological malignancy, including those on 'watch & wait'**
Cancer	All patients undergoing or within 6 weeks of surgery or radical	**For practical purposes include all patients who were treated with**

Medical Condition (NIAC)	NIAC Detail	Comment
	radiotherapy for lung or head and neck cancer	**radiotherapy since March 2021 (including those currently on or booked for treatment)**
Cancer	All patients with advanced /metastatic cancer	
Cancer	Haematological-within 5 years of treatment	Table 5a.2 specifies "*Includes leukaemia, lymphomas, blood dyscrasias or other malignant neoplasms affecting the bone marrow or lymphatic systems*"
Cancer		**Any other patient not included above where there is a reasonable clinical basis for considering that they were likely to be profoundly immunosuppressed due to disease or treatment at or around the time when they are likely to have received vaccine. Clinical judgement should be exercised in identifying this cohort, including those who have received certain treatments (e.g. B-cell depleting agents) where the effects are expected to persist for more than 12 months post cessation.**
Chronic kidney disease	eGFR <30ml/min	
Immunocompromise due to treatment	Details as per appendix	Note this will include anyone who has had prednisolone (or equivalent dose of another corticosteroid) above a certain threshold as per Appendix 1 and 2. **Where there is practical difficulty correlating the timing of administration of treatment likely to lead to immunocompromise with the timing of administration of vaccine it may be necessary to include patients who have received treatment associated with immunocompromise anytime in the past 12 months.**
Immunocompromise due to disease	<u>Transplantation</u> Listed for solid organ or haematopoietic stem cell transplant (HSCT) Post solid organ transplant at any time Post HSCT within 12 months	**Note that patients on immunosuppressant therapy for the treatment of Graft-versus-Host disease should be included, regardless of time since transplant.**
Immunocompromise	Genetic disease	

Medical Condition (NIAC)	NIAC Detail	Comment
due to disease	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) Inborn errors in the interferon pathway	
Immunocompromise due to disease **(other)**	Persons living with HIV who are not on treatment or who have CD4 counts of less than $200x10^6L$	
Others based on clinical judgement and needs assessment	This is in a foreword to the table and is not further defined	For purpose of the following this is taken to mean anyone considered as immunocompromised by a consultant immunologist even if they do not fit into one of the categories below.
Below this line are categories of "other" not specifically referenced in Table 5a.2 of Chapter 5a but referenced as immunocompromised in Chapter 3 of Immunisation guidelines for Ireland. Note as mRNA is a non-live vaccine there is no contraindication to administration to anyone in these categories because of their condition.		
Primary immunedeficiency including ataxia telangiectasia, Brutun agammaglobulinaemia, chronic /cyclic neutropaenia, chronic granulomatous disease, complement deficiency, common variable immunedeficiency, other immunoglobulin deficiencies including isolated IgAand IgG subclass deficiency, Di George syndrome, Fanconi's anaemia, severe combined immunedeficiency, Wiskott Aldrich Syndrome		
Other immunedeficiency		This is taken to mean anyone considered as immunocompromised by a consultant immunologist even if they do not fit into one of the categories specified in this document.

Appendix 1

Medications and immunocompromise

1. Steroids and immune compromise

The following doses of prednisolone (or equivalent dose of other glucocorticoid) are likely to be immunosuppressive in adults or children weighing 10kg or greater and is grounds for administration of an extended primary vaccination schedule

Prednisolone more than 40 mg/day for more than 1 week in the 3 months prior to the first dose of vaccine
Prednisolone 20mg/day or greater for 2 weeks or longer in the 3 months prior to the first dose of vaccine
Other corticosteroids taken in the 3 months prior to first or second dose of vaccine should be assessed in terms of equivalent prednisolone dose.

Equivalent doses of the following glucocorticoids are likely to be immunosuppressive:

- Betamethasone
- Dexamethasone
- Hydrocortisone
- Methylprednisolone
- Triamcinolone

For dose equivalence see use widely available charts or calculators such as https://clincalc.com/corticosteroids/

The following steroid treatment is not considered immunosuppressive and is not considered sufficient to significantly impact on vaccine effectiveness

- Short term (less than 7 days) irrespective of dose
- Long term (2 weeks or greater) less than 5mg/day of prednisolone or equivalent
- Maintenance physiologic doses (replacement therapy)
- Topical (skin or eyes) or by inhalation
- Intra-articular, bursal, or tendon injection
- Fludrocortisone less than 300 micrograms/day
- Oral budesonide (gastro-resistant capsule)

In practical terms if significant uncertainty regarding the dose and time frame of exposure to corticosteroids remains after all practical efforts have been made to clarify this it is pragmatic to err on the side of assuming that the person was immunocompromised at the time of vaccination.

2. Other systemic medications potentially associated with immunocompromise

(note data is limited in relation to many of the agents a precautionary approach has been taken, in some cases the risk of poor vaccine response may be largely limited to a subset of patients on these medications, for example those on the medication and with lymphopaenia but for this purpose if all patients on the medication are considered at risk)

Immunomodulatory Treatments
Predominantly Antiproliferative agents
Azathioprine (Imuran®, Imuger®) (1-2 mgs/kg)
6-Mercaptopurine (Puri-Nethol®, Xaluprine®) (<1mg/kg)
Mycophenolic acid (Cellcept®, Myclausen®, Mycolat®, Myfenax®
Cyclophosphamide (Endoxana®)
Leflunomide (Arava®, Repso®)
Teriflunomide
Calcineurin / T cell signalling inhibitors
Tacrolimus (Advagraf®, Dailiport®, Envarsus® Modigraf®, Tacforius®
Ciclosporin (Neoral®, Sandimmun®, Deximune®)
Sirolimus (Rapamune®)
Everolimus (Afinitor®, Certican®, Votubia®)
Predominantly anti-inflammatory agents
Methotrexate (Methofill®, Jylamvo®, Metoject®, Nordimet®)
Apremilast (Otezia®)
Dimethyl Fumarate (Skilarence®, Tecfidera®)
JAK inhibitors
Tofacitinib (Xeljanz®)
Baricitinib (Olumiant®)
Ruxolitinib (Jakavi®)
Agents for multiple sclerosis
Fingolimod (Gilenya®)
Dimethyl Fumarate (Skilarence®, Tecfidera®)
Cladribine (Mavenclad®)
Ocrelizumab (Ocrevus®)
Natalizumab (Tysabri®)
Alemtuzumab (Lemtrada®)
Other Biological agents
TNF alpha inhibitors
Adalimumab (Amgevita®, Amsparity®,Halimatoz®, Hefiya®, Hulio®, Humira®, Hyrimoz®, Idacio®, Imraldi®)
Etanercept (Benepali®,Enbrel®, Erelzi®, Lifmior®)
Infliximab (Flixabi®, Inflectra®, Remicade®, Remsima®, Zessly®)
Golimumab (Simponi®)
Certolizumab (Cimzia®)
Interleukin inhibitors
IL1
Anakinra (Kineret®)

Canakinumab (Ilaris®)
Il-6
Tocilizumab (RoActemra®)
IL17/23
Ustekinumab (Stelara®)
Guselkumab (Termfya®)
Tildrakizumab (Ilumetri®)
Brodalumab (Kyntheum®)
Ixekizumab (Taltz®)
Secukinumab (Cosentyx®)
Other mechanisms
Abatacept (Orencia®)
Rituximab (Blitzima®, Mabthera®, Ritemvia®, Rixathon®, Riximyo®, Truxima®
Eculizumab (Soliris®)

Approved Generic drug name given first *(Proprietary/ Brand name(s)® in brackets*

The following treatment is not considered immunosuppressive and is not considered sufficient to significantly impact on vaccine effectiveness

Topical Agents: Use of topical Calcineurin inhibitors (TCIs, e.g., Tacrolimus and Pimecrolimus) for atopic dermatitis in otherwise healthy adults.

And the following systemic agents

Immunomodulatory Treatments
Agents for Multiple Sclerosis
Interferon
Monoclonal Antibodies for type 2 inflammation
Reslizumab (Cinqaero®)
Benralizumab (Fasenra®)
Mepolizumab (Nucala®)
Omalizumab (Xolair®)
Dupilumab (Dupixent®)
Other mechanisms
Vedolizumab (Entyvio®)

Approved Generic drug name given first *(Proprietary/ Brand name(s)® in brackets*

3. The following are not considered immunocompromised

Patients who have an autoimmune disease, with no clinical or laboratory evidence of cellular or humoral immunodeficiency, and who have no additional risks identified above. This group includes those taking the following medication hydroxychloroquine, sulfasalazine, mesalazine, gold products and penicillamine.

Appendix 2

Medical condition	Very high risk	High risk
Cancer	Receiving or within 6 weeks of receiving systemic cytotoxic chemotherapy, targeted therapy, monoclonal antibodies or immunotherapies Receiving treatment or pending treatment for a haematological cancer Undergoing or within 6 weeks of surgery or radical radiotherapy for lung or head and neck cancer Advanced/ metastatic cancer	Haematological[1] - within 5 years of treatment Non haematological cancer within 1 year following immunomodulating treatment All other cancers being treated (excluding hormonal treatment)
Chronic heart and vascular disease		e.g. heart failure, hypertensive cardiac disease
Chronic kidney disease	On dialysis, or eGFR <15 ml/min	eGFR <30ml/min
Chronic liver disease		e.g. cirrhosis or fibrosis
Chronic neurological disease or condition	With evolving ventilatory failure (requiring non-invasive ventilation) e.g. motor neurone disease, spinal muscular atrophy	Significantly compromising respiratory function and/or the ability to clear secretions e.g. Parkinson's disease, cerebral palsy
Chronic respiratory disease	Severe e.g. severe cystic fibrosis, severe COPD, severe pulmonary fibrosis	Other e.g. stable cystic fibrosis, severe asthma (continuous or repeated use of systemic corticosteroids), moderate COPD
Diabetes	HbA1C ≥58mmol/mol	All other diabetes (Type 1 and 2)

Immunocompromise due to disease or treatment	Severe e.g. Transplantation: - Listed for solid organ or haematopoietic stem cell transplant (HSCT) - Post solid organ transplant at any time - Post HSCT within 12 months Genetic diseases: - APECED[2] - Inborn errors in the interferon pathway Treatment: - included but not limited to Cyclophosphamide, Rituximab, Alemtuzumab, Cladribine or Ocrelizumab in the last 6 months	Other e.g. High dose systemic steroids[3] HIV, not on treatment or CD4 count <200 $x10^{-6}$L for adults
Inherited metabolic diseases	Disorders of intermediary metabolism/at risk of acute decompensation e.g. Maple Syrup Urine Disease	Disorders of intermediary metabolism not fulfilling criteria for very high risk
Intellectual disability	Down Syndrome	Intellectual disability excluding Down Syndrome
Obesity	BMI >40 Kg/m^2	BMI >35 Kg/m^2
Severe mental illness		e.g. schizophrenia, bipolar disorder, severe depression
Sickle cell disease	Sickle cell disease	

[1]Includes e.g., leukaemia, lymphomas, blood dyscrasias or other malignant neoplasms affecting the bone marrow or lymphatic systems

[2]APECED - autoimmune polyendocrinopathy candidiasis ecto-dermal dystrophy

[3] The following doses of prednisolone (or equivalent dose of other glucocorticoid) are likely to be immunosuppressive:

- Adults and children 10kg: ≥40mg/day for more than 1 week, or ≥20mg/day for 2 weeks or longer
- Children <10 kg: 2mg/kg/day for 2 weeks or longer

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