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REVIEW

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Vaccination strategies for patients under monoclonal antibody and other biological treatments: an updated comprehensive review based on EMA authorisations to January 2024

Mario Rivera-Izquierdo [a,b,c,d], Arturo Morales-Portillo[e,f], Inmaculada Guerrero-Fernández de Alba[a], Nicolás Francisco Fernández-Martínez [c,d,g], Joan Antoni Schoenenberger-Arnaiz[e,f], José Luis Barranco-Quintana [h,i,j] and Carmen Valero-Ubierna[a]

[a]Service of Preventive Medicine and Public Health, Hospital Universitario San Cecilio, Granada, Spain; [b]Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain; [c]Instituto de investigación biosanitaria de Granada (ibs.GRANADA), Granada, Spain; [d]CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain; [e]Service of Pharmacy, Hospital Universitari Arnau de Vilanova, Lleida, Spain; [f]Pharmacoepidemiology and Pharmacodynamics Group, Institut de Recerca Biomèdica de Lleida (IRBLleida), Lleida, Spain; [g]Andalusian School of Public Health (EASP), Granada, Spain; [h]Service of Preventive Medicine and Public Health, Hospital Universitario Reina Sofía, Córdoba, Spain; [i]Maimonides Biomedical Research Institute of Cordoba (IMIBIC) Córdoba, Spain; [j]Expert Committee on Andalusian Vaccine Plan, Consejería de Salud y Familias, Junta de Andalucía, Sevilla, Spain

ABSTRACT

Introduction: Monoclonal antibodies (mAbs) and other biological agents are being increasingly approved in the last years with very different indications. Their highly heterogeneous immunosuppressive effects, mechanisms of action and pharmacokinetics require comprehensive individualized vaccination schedules.
Areas covered: Vaccination for immunocompromised patients. Prevention and treatment with mAbs and other biological therapies.
Expert opinion: Current recommendations on vaccine schedules for patients under mAbs or other biological treatments are based on expert opinions and are not individualized according to each vaccine and treatment. No studies are focusing on the high heterogeneity of these agents, which are exponentially developed and used for many different indications. Recent paradigm changes in vaccine development (boosted by the COVID-19 pandemic) and in the mAbs use for prophylactic purposes (changing 'vaccination' by 'immunization' schedules) has been witnessed in the last years. We aimed at collecting all mAbs used for treatment or prevention, approved as of 1 January 2024, by the EMA. Based on available data on mAbs and vaccines, we propose a comprehensive guide for personalizing vaccination. Recent vaccine developments and current population strategies (e.g. zoster vaccination or prophylactic nirsevimab) are discussed. This review aims to be a practical guideline for professionals working in vaccine consultations for immunosuppressed patients.

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KEYWORDS
Biologic therapy; biologics; immunosuppression; mAbs; nirsevimab; vaccine; vaccine schedule

1. Introduction

Monoclonal antibodies (mAbs) have become an increasing source of therapeutic, diagnostic and, recently, preventive strategies. They are considered as biological agents and are characterized by an enormous target specificity [1]. MAbs, along with other biological drugs, have revolutionized the treatment of numerous diseases, mainly inflammatory and autoimmune diseases, and various types of cancer [2]. These molecules, normally γ-immunoglobulins (Ig G), include a hypervariable region that binds specifically to the target antigen [3]. They are all named with the suffix -mab, meaning *monoclonal antibody*, and various prefixes referring to the source and the target. Several development strategies have been developed in the industry, including chimerization, humanization and even complete human mAb generation [4].

Their rapid development and the explosive authorization and commercialization of these drugs [5], as well as their highly varied mechanisms of action, indications, and effects, make it necessary for clinicians who manage these agents to be constantly updated.

Several mAbs, given its indications for autoimmune diseases or cancer, have immunosuppressive effects, which makes it necessary to reinforce their immunological protection through specific vaccination schedules [6]. Nevertheless, insufficient attention has been given to specific vaccine recommendations according to each type of mAb, underlying disease or vaccine. Since the last and only review on this topic published in 2020 by our research group [6], an alarming lack of works regarding this research line has been noticed. During the COVID-19 pandemics, however, great efforts were put in conducting studies regarding the impact of mAbs (especially anti-CD20 therapies) in COVID-19 vaccine immunogenicity [7–9]. Also, prophylactic mAbs for preventing COVID-19 outcomes were also developed and studied [10,11]. The question is: why are these efforts not being

CONTACT Mario Rivera-Izquierdo mariorivera@ugr.es Department of Preventive Medicine and Public Health, University of Granada, Avenida de la Investigación 11, Granada 18016, Spain

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Article highlights

- A total of 144 monoclonal antibodies (mAbs), 63 of them immunosuppressive (imAbs) have been approved by the EMA as of January 1, 2024.
- ImAbs presents very different mechanisms of action, elimination half-life, hepatotoxic, and immunosuppressive properties, thus affecting different vaccine recommendations.
- Recent advances on vaccine development and indications (e.g. herpes zoster vaccine) and new uses of mAbs (e.g. nirsevimab as prophylaxis) must be considered when designing appropriate vaccine schedules for the immunocompromised patient.
- This review presents a comprehensive list of mAbs and imAbs, specific recommendations regarding each type of vaccine, optimal vaccination time schedules and insights regarding future research for protecting patients under imAb treatments.

conducted for other vaccines that prevent from even more severe diseases?

The objective of this review was to comprehensively collect all mAbs (and other biological treatments relevant for vaccination) authorized by the European Medicines Agency (EMA) to 1 January 2024 and to summarize all the available information regarding vaccination recommendations for patients under these treatments. Secondarily, this review also aimed at analyzing the current developments on mAbs use, and the future required research in immunization.

2. Current authorized mAbs

This review includes all mAbs authorized by the EMA [5,12]. To 1 January 2024, a total of 114 mAbs were identified. Furthermore, 16 additional biological treatments of interest for immunization were included in this review. The selected biological treatments included anakinra and fusion proteins (drugs that end with the suffix *-cept*) drugs (abatacept, aflibercept VA, aflibercept IV, belatacept, etanercept and luspatercept), given their high frequency of use and their immunosuppressive effects. Anti-JAK drugs were also included (abrocitinib, baricitinib, deucravacitinib, filgotinib, rictlecitinib, ruxolitinib, tofacitinib and upadacitinib) given the specific vaccine recommendations regarding herpes zoster reactivation.

Therefore, a total of 130 drugs were analyzed. Nevertheless, it is important to note that the uses and effects of mAbs are highly varied. Therefore, it would be relevant not to consider this group of drugs as a homogeneous one. Table 1 summarizes the main current uses and implications of mAbs, with representative examples.

According to the information provided by the EMA [12] and the Animal Cell Technology Industrial Platform (ACTIP) [13], and after a careful review of the technical data sheet of each drug, detailed information on each drug is provided in Table 2. Specifically, the international Anatomical Therapeutic Chemical (ATC) code, trade names, specific antigen target, main indications and immunosuppressive effects are detailed.

2.1. Current therapeutic immunosuppressive monoclonal antibodies (imAbs)

Of the total identified mAbs, 63 (55.3%) presented immunosuppressive properties (as well as all the other 16 selected biological treatments of interest). This means that around half of the authorized mAbs do not require specific vaccine recommendations by themselves. Regarding immunosuppressive mAbs (imAbs), studies conducted during the last 20 years reported the increased frequency of infectious diseases under these treatments, especially regarding anti-CD20 drugs [14–16].

Urinary and respiratory infections had been reported in clinical studies for patients under anti-CD20 mAbs [14], serious bacterial infections were reported in patients under necrosis factor alpha antagonists [15] or, more recently, higher frequency of reactivation of latent infections, neutropenia and superinfections were reported for COVID-19 patients under tocilizumab treatment [16]. Those are examples of an extended list of studies reporting infectious clinical outcomes caused by imAb treatments [17]. Despite this, the risk–benefit balance is still positive, given the great effectiveness of these therapies for certain severe diseases [18]. Therefore, consensus documents by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) propose prevention and control strategies for reducing infectious diseases in patients under biological treatments [19]. In a review published in 2020 by Davis et al. [20], a comprehensive list of infectious complications following imAb therapies can be consulted.

The data regarding safety in clinical trials and plans to minimize the risk of infection can be consulted in the European Public Assessment Reports (EPAR) of the EMA [12]. These potential adverse events require that patients initiating treatments with imAbs have a specific vaccination consultation to prevent future possible infections. Nevertheless, in many cases, clinicians may assume that all mAbs have

Table 1. Current uses, examples, and implications of monoclonal antibodies (mAbs).

Use	Examples	Implications
Therapeutic immunosuppressive mAbs (imAbs)	Adalimumab, eculizumab, infliximab, rituximab, etc.	They generate, by themselves, the need for vaccination indication for the immunocompromised patient
Therapeutic non-immunosuppressive mAbs	Alirocumab, bevacizumab, denosumab, omalizumab, etc.	By themselves, they do not generate an indication for vaccination. Concomitant treatments and underlying diseases should be evaluated to decide on vaccination
Prophylactic mAbs (for primary and tertiary prevention)	Cilgavimab-tixagevimab, palivizumab, nirsevimab, etc.	Used to generate passive pre-exposure immunity
Diagnostic mAbs (for imaging)	Besilesomab, sulesomab, etc.	Used, together with a radionuclide (usually radioactive technetium, 99mTc), for diagnostic imaging
Laboratory-research mAbs	Anti-myosin, anti-CA 19.9, anti-CEA, anti-granulocyte, etc.	They are not drugs, but pure compounds used for research (e.g. for immunohistochemistry or immunofluorescence as markers). They are not the subject of this review, as they have no therapeutic or preventive indications and do not generate vaccination indications.

Table 2. Main characteristics of therapeutic mAbs and other biological agents of interest authorized by the EMA as of January 1, 2024.

Agent (drug)	ATC code	Tradename	Target antigen	Main clinical indications[a]	IS[b]
Monoclonal antibodies (mAbs)					
Abciximab	B01AC13	Reopro®	Glycoprotein GpIIb/IIIa	Ischaemic heart disease, unstable angina	No
Adalimumab	L04AB04	Amgevita®, Hukyndra®, Hulio®, Humira®, Hyrimoz®, Idacio®, Imraldi®, Libmyris®, Yuflyma®	TNF-alpha	Rheumatoid arthritis, juvenile idiopathic arthritis, axial spondylarthrosis, psoriasis, pediatric psoriasis, hidradenitis suppurativa, Crohn's disease (adult and pediatric), ulcerative colitis, uveitis	Yes
Alemtuzumab	L04AA34	Lemtrada®	CD52	Active relapsing remitting multiple sclerosis	Yes
Alirocumab	C10AX14	Praluent®	PCSK9	Primary hypercholesterolemia, mixed dyslipidaemia, atherosclerotic disease	No
Amivantamab	L01FX181	Rybrevant®	EGFR (and MET)	Advanced non-microcytic lung cancer	No
Anifrolumab	L04AA51	Saphnelo®	Interferon receptor type 1 (IFNAR1)	Moderate-severe systemic lupus erythematosus	Yes
Atezolizumab	L01XC32	Tecentriq®	PD-1 (PD-L1)	Urothelial carcinoma, non-microcytic lung cancer, triple-negative breast cancer	No[c]
Avelumab	L01XC31	Bavencio®	PD-1 (PD-L1)	Merkel cell carcinoma, renal cell carcinoma	No
Basiliximab	L04AC02	Simulect®	IL-2 receptor (CD25).	Prophylaxis of acute rejection in *de novo* allogeneic kidney transplantation	Yes
Belimumab	L04AA26	Benlysta®	BLyS	Active systemic lupus erythematosus	Yes
Belantamab mafotodina	L01FX15	Blenrep®	BCMA	Multiple myeloma	Yes
Benralizumab	R03DX10	Fasenra®	Subunit alpha of the human IL-5 receptor (IL-5 Rα)	Eosinophilic asthma	No
Besilesomab	V09HA03	Scintimun®	Granulocytes (BW250/183)	Diagnosis of osteomyelitis of the extremities	No
Bevacizumab	L01XC07	Abevmy®, Alymsys®, Avastin®, Onbevzi®, Oyavas®	VEGF	Colon or rectum, breast, non-small cell lung cancer, renal cell, epithelial ovarian, fallopian tube, or primary peritoneal cervix carcinoma	No
Bezlotoxumab	J06BB21	Zinplava®	*Clostridium difficile* B toxin	Prevents recurrence of *C. difficile* infection	No
Blinatumomab	L01XC19	Blincyto®	CD19 and CD3	Acute lymphoblastic leukemia	Yes
Bimekizumab	L04AC21	Bimzelx®	IL-17RA	Plaque psoriasis	Yes
Brentuximab-vedotina	L01XC12	Adcetris®	CD30	CD30+ Hodgkin's lymphoma, systemic anaplastic large cell lymphoma, CD30+ cutaneous T-cell lymphoma	Yes
Brodalumab	L04AC12	Kyntheum®	IL-17RA	Moderate to severe plaque psoriasis	Yes
Brolucizumab	S01LA06	Beovu®	VEGF-A	Neovascular exudative age-related macular degeneration, diabetic macular edema	No
Burosumab	M05BX05	Crysvita®	FGF-23	X-linked hypophosphatemia	No
Canakinumab	L04AC08	Ilaris®	IL-1 beta	Periodic fever syndromes, arthritic gout, Still's disease	Yes
Caplacizumab	B01AX07	Cablivi®	von Willebrand factor A1	Acquired thrombotic purpura	No
Casirivimab – Imdevimab	NA	Ronapreve®	SARS-CoV-2 capsid spike protein	Pre-exposure prophylaxis for COVID-19. Treatment of COVID-19 at high risk of progression to severe	No
Catumaxomab	L01XC09	Removab®	EpCAM and CD3	Malignant ascites	No
Cemiplimab	L01FF06	Libtayo®	PD-1	Squamous cell carcinoma of the skin	No
Certolizumab-pegol	L04AB05	Cimzia®	TNF-alpha	Rheumatoid arthritis, axial spondyloarthropathy, psoriatic arthritis, plaque psoriasis	Yes
Cetuximab	L01XC06	Erbitux®	EGFR	Colorectal cancer, squamous cell head and neck cancer	No[c]
Crizanlizumab	B06AX01	Adakveo®	P-selectin	Prevention of occlusive crises in sickle cell disease	No
Daclizumab	L04AA08	Zenepax®, Zynbrita®	IL-2-alpha receptor (CD25)	Prophylaxis of acute rejection in allogeneic renal transplantation, multiple sclerosis	Yes
Daratumumab	L01XC24	Darzalex®	CD38	Multiple myeloma	Yes
Denosumab	M05BX04	Prolia®, Xgeva®	RANK-L	Preventing bone fractures in osteoporosis and bone metastases	No
Dinutuximab beta	L01XC	Qarziba®	GD2	Neuroblastoma	Yes
Dostarlimab	L01FF07	Jemperli®	PD-1 (PD-L1 y PD-L2)	Endometrial cancer	No
Dupilumab	D11AH05	Dupixent®	IL-4 and IL-13 receptors	Atopic dermatitis	No
Durvalumab	L01XC28	Imfinzi®	PD-1 (PD-L1)	Non-microcytic lung cancer	No
Eculizumab	L04AA25	Bekemv®, Epysqli®, Soliris®	C5 (complement)	Paroxysmal nocturnal hemoglobinuria, hemolytic uremic syndrome, myasthenia gravis, neuromyelitis optica in patients with antibodies against aquaporin 4	Yes
Efalizumab	L04AA21	Raptiva®	LFA-1 CD11a	Plaque psoriasis	Yes
Elotuzumab	L01XC23	Empliciti®	SLAMF7	Multiple myeloma	Yes
Emicizumab	B02BX06	Hemlibra®	Activated factor IX and factor X (coagulation)	Haemophilia A	No
Enfortumab vedotin	L01FX13	Padcev®	Nectin-4	Urothelial carcinoma	No[d]
Epcoritamab	L01FX27	Tepkinly®	CD20 (and CD-3)	Diffuse large B-cell lymphoma	Yes
Eptinezumab	N02CD05	Vyepti®	CGRP	Migraine prophylaxis	No
Erenumab	N02CX07	Aimovig®	CGRP	Migraine prophylaxis	No

(*Continued*)

Table 2. (Continued).

Agent (drug)	ATC code	Tradename	Target antigen	Main clinical indications[a]	IS[b]
Evinacumab	C10AX17	Evkeeza®	ANGPTL3	Homozygous familial hypercholesterolemia	No
Evolocumab	C10AX13	Repatha®	PCSK9	Hypercholesterolemia and mixed dyslipidaemia, homozygous familial hypercholesterolemia, established atherosclerotic cardiovascular disease	No
Faricimab	S01LA09	Vabysmo®	VEGF-A and Ang-2	Neovascular age-related macular degeneration, diabetic macular edema	No
Fremanezumab	N02CD03	Ajovy®	CGRP	Migraine prophylaxis	No
Galcanezumab	N02CX08	Emgality®	CGRP	Migraine prophylaxis	No
Gemtuzumab-ozogamicina	L01XC05	Mylotarg®	CD33	Acute myeloid leukemia	Yes
Glofitamab	L01FA80	Columvi®	CD20	Diffuse large B-cell lymphoma	Yes
Golimumab	L04AB06	Simponi®	TNF-alpha	Rheumatoid arthritis, psoriatic arthritis, axial spondyloarthropathy, ulcerative colitis	Yes
Guselkumab	L04AC16	Tremfya®	IL-23	Plaque psoriasis	Yes
Ibritumomab-tuixetan	V10XX02	Zevalin®	CD20	Follicular non-Hodgkin lymphoma	Yes
Idarucizumab	V03AB37	Praxbind®	Dabigatran	Rapid reversal of the anticoagulant effects of dabigatran	No
Inebilizumab	L04AA47	Uplizna®	CD19	Neuromyelitis optica spectrum disorder	Yes
Infliximab	L04AB02	Remicade®, Flixabi®, Inflectra®, Remsima®, Zessly®	TNF-alpha	Rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondyloarthropathy, psoriatic arthritis, psoriasis	Yes
Inotuzumab-ozogamicina	L01XC26	Besponsa®	CD22	Acute lymphoblastic leukemia	Yes
Ipilimumab	L01XC11	Yervoy®	CTLA-4	Melanoma and renal cell carcinoma	No
Isatuximab	L01FC02	Sarclisa®	CD38	Multiple myeloma	Yes
Ixekizumab	L04AC13	Taltz®	IL-17A	Plaque psoriasis and psoriatic arthritis	Yes
Lanadelumab	B06AC05	Takhzyro®	Plasma kallikrein	Hereditary angioedema	No
Lebrikizumab	D11AH10	Ebglyss®	IL-23	Plaque psoriasis	Yes
Loncastuximab tesirina	L01FX22	Zynlonta®	CD19	Diffuse large B-cell lymphoma and high-grade B-lymphoma	Yes
Mepolizumab	R03DX09	Nucala®	IL-5	Refractory severe eosinophilic asthma	No
Mirikizumab	L04AC24	Omvoh®	IL-23	Ulcerative colitis	Yes
Mogamulizumab	L01FX09	Poteligeo®	CCR4	Mycosis fungoides, Sézary syndrome	Yes
Mosunetuzumab	L01FX25	Lunsumio®	CD20 (y CD3)	Follicular lymphoma	Yes
Natalizumab	L04AA23	Tyruko®, Tysabri®	Integrin α4β1	Relapsing-remitting multiple sclerosis	Yes
Nirsevimab	J06BD08	Beyfortus®	RSV F-protein	Respiratory syncytial virus (RSV) pre-exposure prophylaxis in neonates and infants	No
Nivolumab	L01XC17	Opdivo®	PD-1	Melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin's lymphoma, spinous cell carcinoma of the head and neck, urothelial carcinoma	No
Obinutuzumab	L01XC15	Gazyvaro®	CD20	Chronic lymphocytic leukemia, follicular lymphoma	Yes
Ocrelizumab	L04AA36	Ocrevus®	CD20	Relapsing-remitting multiple sclerosis	Yes
Ofatumumab	L01FA02	Kesimpta®	CD20	Relapsing-remitting multiple sclerosis	Yes
Omalizumab	R03DX05	Xolair®	IgE	Allergic asthma, chronic spontaneous urticaria	No
Palivizumab	J06BB16	Synagis®	RSV fusion protein	Prevention of severe RSV disease in high-risk children	No
Panitumumab	L01XC08	Vectibix®	EGFR	Colorectal carcinoma with unmutated RAS (wild type)	No[c]
Pembrolizumab	L01XC18	Keytruda®	PD-1	Melanoma, non-microcytic lung cancer, Hodgkin's lymphoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, renal cell carcinoma	No[c]
Pertuzumab	L01XC13	Perjeta®	HER-2	Breast cancer	No[c]
Polatuzumab-vedotina	L01XC37	Polivy®	CD79b	Diffuse cell lymphoma	Yes
Ramucirumab	L01XC21	Cyramza®	VEGF receptor 2	Gastric, colorectal, hepatocellular, and non-microcytic lung cancer	No[c]
Ranibizumab	S01LA04	Byooviz®, Lucentis®, Ranvisio®, Ximluci®	VEGF-A	Exudative age-related macular degeneration, diabetic macular edema, proliferative diabetic retinopathy, venous occlusion, choroidal neovascularization	No
Ravulizumab	L04AA43	Ultomiris®	C5 (complement)	Paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, generalized myasthenia gravis	Yes
Regdanvimab	J06BD06	Regkirona®	SARS-CoV-2 spike protein	COVID-19	No
Relatlimab-nivolumab	L01XY03	Opdualag®	PD-1 (PD-L1 y PD-L2)	Melanoma	Yes
Reslizumab	R03DX08	Cinqaero®	IL-5	Eosinophilic asthma	No
Risankizumab	L04AC18	Skyrizi®	IL-23	Plaque psoriasis	Yes
Rituximab	L01XC02	Mabthera®, Rixathon®, Truxima®	CD20	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, pemphigus vulgaris	Yes
Romosozumab	M05BX06	Evenity®	Sclerostin	Osteoporosis	No
Sacituzumab-govitecan	L01FX17	Trodelvy®	Trop-2	Triple-negative breast cancer	Yes
Sarilumab	L04AC14	Kevzara®	IL-6 receptors (IL-6 Rα)	Rheumatoid arthritis	Yes
Satralizumab	L04AC19	Enspryng®	IL-6 receptors (IL-6 R)	Neuromyelitis optica spectrum disorder	Yes

(*Continued*)

Table 2. (Continued).

Agent (drug)	ATC code	Tradename	Target antigen	Main clinical indications[a]	IS[b]
Secukinumab	L04AC10	Cosentyx®	IL-17A	Plaque psoriasis, psoriatic arthritis, ankylosing spondyloarthropathy	Yes
Siltuximab	L04AC11	Sylvant®	IL-6	Multicentric Castleman's disease	Yes
Sotrovimab	J06BD05	Xevudy®	SARS-CoV-2 spike protein	COVID-19	No
Spesolimab	L04AC22	Spevigo®	IL-36 R	Generalised pustular psoriasis	Yes
Sulesomab	V09HA04	Leukoscan®	NCA-90 y CEA	Diagnosis of osteomyelitis, including diabetic foot ulceration	No
Sutimlimab	L04AA55	Enjaymo®	C1s (complement)	Cryoagglutinin hemolytic anemia	Yes
Tafasitamab	L01FX12	Minjuvi®	CD19	Diffuse large B-cell lymphoma	Yes
Talquetamab	L01FX80	Talvey®	GPRC5D (y CD3)	Multiple myeloma	Yes
Teclistamab	L01FX24	Tecvayli®	BCMA (y CD3)	Multiple myeloma	Yes
Tezepelumab	R03DX11	Tezspire®	TSLP	Asthma	No
Tildrakizumab	L04AC17	Ilumetri®	IL-23	Plaque psoriasis	Yes
Tislelizumab	L01FF09	Tevimbra®	PD-1 (PD-L1 y PD-L2)	Squamous cell carcinoma of the oesophagus	Yes
Tixagevimab – Cilgavimab	J06BD03	Evusheld®	SARS-CoV-2 spike protein	COVID-19 pre-exposure prophylaxis and treatment for preventing progression	No
Tocilizumab	L04AC07	Actemra®, Tyenne®	IL-6 receptors	Rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis	Yes
Tralokinumab	D11AH07	Adtralza®	IL-13	Atopic dermatitis	Yes
Trastuzumab	L01XC03	Herceptin®, Herwenda®, Herzuma®, Kanjinti®, Ogivri®, Ontruzant®, Trazimera®	HER-2	Breast and gastric cancer	No[c]
Trastuzumab-deruxtecan	L01FD04	Enhertu®	HER-2	Breast cancer	Yes
Trastuzumab-emtansina	L01XC14	Kadcyla®	HER-2	Breast cancer	Yes
Tremelimumab	L01FX20	Imjudo®	CTLA-4	Hepatocellular cancer	Yes
Ublituximab	L04AA57	Briumvi®	CD20	Relapsing-remitting multiple sclerosis	Yes
Ustekinumab	L04AC05	Stelara®	IL-12 and IL-23	Crohn's disease, ulcerative colitis, plaque psoriasis, and pediatric psoriatic arthritis	Yes
Vedolizumab	L04AA33	Entyvio®	Integrin α4β7	Crohn's disease, ulcerative colitis	Yes
Other no-mAbs biological agents of special interest for vaccination					
Abatacept	L04AA24	Orencia®	CD80 y CD86	Rheumatoid arthritis, psoriatic arthritis, polyarticular juvenile idiopathic arthritis	Yes
Abrocitinib	D11AH08	Cibinqo®	JAK1	Atopic dermatitis	Yes
Aflibercept VA	S01LA05	Eylea®, Yesafili®	VEGF	Age-related macular degeneration, macular edema after central vein or branch vein occlusion, impaired vision due to diabetes or myopic choroidal neovascularisation	No
Aflibercept IV	L01XX44	Zaltrap®	VEGF	Colorectal cancer	No[c]
Anakinra	L04AC03	Kineret®	IL-1 receptor 1 (IL-1RI)	Rheumatoid arthritis, periodic cryopyrin-associated syndromes, Still's disease	Yes
Baricitinib	L04AA37	Olumiant®	JAK1/JAK2	Rheumatoid arthritis, atopic dermatitis, alopecia areata	Yes
Belatacept	L04AA28	Nulojix®	CD80 y CD86	Prevention of graft rejection in kidney transplantation	Yes
Deucravacitinib	L04AF07	Sotyktu®	TYK2 (JAK family enzyme)	Plaque psoriasis	Yes
Etanercept	L04AB01	Enbrel®, Benepali®, Erelzi®	TNF-alpha	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial or ankylosing spondyloarthropathy, plaque psoriasis	Yes
Filgotinib	L04AA45	Jyleseca®	JAK1/JAK3	Rheumatoid arthritis, ulcerative colitis	Yes
Luspatercept	B03XA06	Reblozyl®	TGF-β	Transfusion-dependent anemia due to myelodysplastic syndrome, betathalassaemia	Yes
Ritlecitinib	L04AF08	Litfulo®	JAK3 y TEC	Alopecia areata	Yes
Ruxolitinib	L01EJ01	Jakavi®, Opzelura®	JAK1/JAK2	Splenomegaly, myelofibrosis, polycythemia vera, acute or chronic graft-versus-host disease	Yes
Tecnecio 99 Mtc Tilmanocept	V09IA09	Lymphoseek®	CD206	Diagnosis of melanoma, breast cancer, oral squamous cell carcinoma	No
Tofacitinib-citrato	L04AA29	Xeljanz®	JAK1/JAK3/TyK2	Rheumatoid arthritis, psoriatic arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondyloarthropathy, Crohn's disease, ulcerative colitis	Yes
Upadacitinib hemihidrato	L04AA44	Rinvoq®	JAK1/JAK3	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondyloarthropathy, ulcerative colitis, atopic dermatitis	Yes

Adapted and updated from [6]. An actively updated summary of approved MCAs can be found at www.antibodysociety.org. The information presented in this table is available from the Animal Cell Technology Industrial Platform (ACTIP) (13).
[a]Immunosuppression. [b]Most of these indications are only for specific situations (e.g. severe disease, refractory to treatment, etc.). Specific indications are available at EMA technical data sheets (5). [c]Immunosuppression caused by frequent concomitant chemotherapy. [d]Unknown frequency of adverse reactions associated with immunosuppression. It is considered as non-immunosuppressive until more information is available (important to assess concomitant treatments).

immunosuppressive properties and, therefore, generate irrational vaccine overuse. As detailed in Table 2, only around half of the authorized mAbs to date require immunization as part of a risk group. However, it is important to consider the underlying diseases and other concomitant treatments before taking a decision on immunization. Coordination with other services and healthcare professionals is essential to find the best time for initiating vaccination, when possible.

In order to provide appropriate vaccination recommendations, it is essential to know whether these drugs have hepatotoxicity effects and the elimination half-life (pharmacokinetic properties) of each of them. This information and other relevant data (type of immunosuppression and specific vaccine recommendations) included in their technical data sheets for all identified imAbs are presented in Table 3.

3. Prophylactic mAbs for primary and tertiary prevention

Although the objectives of this review are aimed at mAbs with therapeutic indications (which may or may not potentially require specific vaccination), in recent years several mAbs have been authorized with an indication not contemplated to date – prevention. Therefore, in addition to the diagnostic and therapeutic applications already known and approved, we must include in the future panorama the preventive applications of targeted biological therapies. We are therefore witnessing a paradigm shift with respect to the most frequent strategies to date in vaccination consultation (offering mAbs as immunization tool for immunocompromised patients, rather than vaccinating immunocompromised patients due to immunosuppressive mAbs), especially relevant for subjects potentially not-responders to vaccines. This reflects the enormous variability in the current characteristics and uses of mAbs. It is therefore necessary to avoid homogenization of this highly varied group of drugs and to tend toward individualization and specific knowledge of each of them, an objective that this review aims to facilitate.

A representative example of how this paradigm shift has influenced clinical decisions, is that many national vaccine associations and important reviews on the topic suggest changing the name 'vaccine schedules' by 'immunization schedules' (including mAbs at the same level as vaccines) [21].

The first high-impact example of prophylactic mAb was the combination of cilgavimab and tixagevimab, marketed as Evusheld® by AstraZeneca® and initially used in COVID-19 pre-exposure prophylaxis [22]. Nevertheless, as this drug was designed considering the SARS-CoV-2 variants circulating at the time of its development, several countries deauthorized its use subsequently. This decision was based on the frequency of non-susceptible-to-Evusheld® variant strains. For example, when the variant omicron XBB.1.5. exceeded the 60% of cases in the U.S.A., the Food and Drug Administration (FDA) withdrew its commercialization on 27 January 2023 [23]. However, the era of mAbs as prophylaxis tools had already started. Other mAbs were authorized with the same pre-exposure prophylaxis indications (primary and tertiary prevention of COVID-19), like casirivimab + imdevimab (Ronapreve®), apart from other mAbs used for COVID-19 treatment (regdanvimab or sotrovimab) intended to reduce the risk of progression to severe disease.

Another important field in which this indication for mAbs has been developed is the prevention of respiratory syncytial virus (RSV). Palivizumab was, in fact, the first mAb authorized with preventive indications several decades ago, for the prophylaxis of RSV infection in at-risk neonates. Other mAbs with this indication are currently being developed, such as motavizumab, but recently (November 2022) nirsevimab (Beyfortus®) was approved for passive pre-exposure immunization in infants (considered as a vaccine by general population). It should be noted that RSV became, together with influenza, COVID-19, and pneumococcal pneumonia, one of the most frequent causes of respiratory infection in the elderly, so research is also being conducted on the development of immunizations for this group, such as the RSV prefusion protein F vaccine based on adenovirus serotype 26 (Ad26.RSV.preF) [24]. In 2023, some regions of Spain such as Andalusia or Galicia pioneered worldwide a population-based prophylaxis with nirsevimab; the first time a mAb is used as pre-exposure prophylaxis at the population level, analogous to vaccines [25]. In the case of Andalusia, a region in southern Spain with over 8.5 million inhabitants, during the 2023–2024 campaign, systematic administration of this drug was indicated for all children under 6 months of age born between 1 April 2023, and 31 March 2024, as well as for children at high risk of severe RSV disease [25]. In the case of Galicia (northwestern Spain), early results on implementation experience, with excellent results on coverage and safety, have been published [26], although the effectiveness of the measure has yet to be evaluated.

The routine use of this drug for prophylaxis at the population level is a milestone in the use of mAbs, and the evaluation of its impact in the prevention of RSV infection or severe disease in children will be useful in making decisions about extending this practice to other contexts.

These are all examples of the use of the pharmacological technology of mAbs and biological agents for preventive purposes, which are likely to expand in the future and contribute, together with the development of vaccines, to better protection from specific diseases at the population level.

4. Vaccination recommendations for patients under imAb therapies

4.1. Current available evidence and general recommendations

Since the last review published on this topic in 2020 [6], there has been an explosive increasement in the number of mAbs authorized by the EMA (from 72 in 2020 to 114 in 2024) [5], which represents a mean of 10.5 new mAbs each year. Updated recommendations on vaccination of immunocompromised patients in general are available from the Centers for Disease Control and Prevention (CDC) [27,28], but no concrete information is reported regarding patients under imAb treatments to date. More importantly, there is a scarcity of primary studies that rigorously analyze the effectiveness of vaccination at different time periods according to each imAb. Therefore, most current recommendations are mainly based on expert opinions, which are the main source of official documents on this topic [27–30], including those referring to COVID-19 vaccines [31].

The most recent published reviews regarding vaccination of the immunocompromised host [6,32–34] consistently recommend vaccination against influenza and pneumococcal disease, along with appropriate immunization against COVID-

Table 3. Characteristics for vaccination recommendations regarding immunosuppressive monoclonal antibodies (imAbs) and other immunosuppressive biological agents of interest.

Agent (drug)	Type of IS[a]	Elimination half-life ($t_{1/2}$)[b]	Hepatotoxicity	Specific vaccination recommendations in the technical datasheet[c]
Immunosuppressive monoclonal antibodies (imAbs)				
Adalimumab	Moderate	$t_{1/2}$ = 14 days	ELE (very common). Hepatitis, reactivation of hepatitis B, autoimmune hepatitis (rare)	Vaccination during treatment is possible, except in the case of live vaccines.
Alemtuzumab	Severe	$t_{1/2}$ = 5 days	HUS (very common). Cholecystitis, Epstein-Barr hepatitis, autoimmune hepatitis (rare)	Vaccination should be administered at least 6 weeks prior to treatment with alemtuzumab. Life viral vaccines are contraindicated.
Anifrolumab	Moderate	$t_{1/2}$ = 22 days	–	Concomitant use of live or attenuated vaccines should be avoided
Basiliximab	Severe	$t_{1/2}$ = 7 days	–	Contraindication to live vaccines. No evidence on immunization
Belantamab mafotodina	Severe	$t_{1/2}$ = 14 days	ELE (very common)	No specific recommendations on vaccination are reported in the datasheet
Belimumab	Moderate	$t_{1/2}$ = 19 days	–	Vaccination during treatment or within 30 days is not recommended for live vaccines. Evidence on maintaining antibody titers to previous pneumococcal, tetanus, and influenza vaccines [36]
Bimekizumab	Moderate	$t_{1/2}$ = 23 days	–	Vaccination with live vaccines is not recommended during treatment
Blinatumomab	Severe	$t_{1/2}$ = 2 hours	ELE (very common). Hyperbilirubinemia (common)	Vaccination with live vaccines is not recommended in the previous 2 weeks, during treatment or until normal B-lymphocyte levels are restored
Brentuximab-vedotin	Severe	$t_{1/2}$ = 5 days	ELE (very common)	No specific recommendations on vaccination are reported in the datasheet
Brodalumab	Moderate	$t_{1/2}$= $t_{1/2}$= $t_{1/2}$ $t_{1/2}$ =$t_{1/2}$ = 11 days	–	Live vaccines should not be administered during treatment
Canakinumab	Moderate	$t_{1/2}$ = 26 days	–	Live vaccines should not be administered during treatment
Certolizumab-pegol	Moderate	$t_{1/2}$ = 14 days	Hepatitis (common). Cirrhosis, cholestasis, e hyperbilirubinemia, cholelithiasis (rare)	Vaccination during treatment is possible. Live vaccines should not be administered. A clinical trial demonstrated good immunogenicity with pneumococcal and influenza vaccines [37]
Daclizumab	Moderate	$t_{1/2}$ = 21 days	ELE (very common). Autoimmune hepatitis (rare). Fulminant hepatitis (frequency unknown).	Vaccination during treatment is possible. Vaccination with live vaccines during treatment and 4 months after discontinuation is not recommended. An experimental study demonstrated good immunogenicity with influenza vaccine [38]
Daratumumab	Severe	$t_{1/2}$ = 15-23 days	Hepatitis B reactivation (rare)	No specific recommendations on vaccination are reported in the datasheet
Dinutuximab	Severe	$t_{1/2}$ = 8 days	Hepatocellular lesion (rara)	Vaccination is recommended after 10 weeks of the last cycle
Eculizumab	Moderate	$t_{1/2}$ = 11 days	Jaundice (rare)	Vaccination is recommended before starting treatment with eculizumab. Patients should be vaccinated against meningococcal A, C, Y, W, 135 and B at least 2 weeks before the start of treatment. If vaccinated before these 2 weeks, they should receive antibiotic prophylaxis. Children under 18 years of age should be vaccinated against *Haemophilus influenzae*.
Efalizumab	Moderate	$t_{1/2}$ = 5-10 days	ELE (common)	Vaccination with live vaccines is not recommended. Vaccination 2 weeks before or 8 weeks after treatment is recommended.
Elotuzumab	Severe	$t_{1/2}$ = 6-8 days	–	No specific recommendations on vaccination are reported in the datasheet
Epcoritamab	Severe	$t_{1/2}$ = 22-25 days	ELE (common)	Live and/or attenuated vaccines should not be administered at the same time
Gemtuzumab-ozogamicina	Severe	$t_{1/2}$ = 160 hours	ELE, hyperbilirubinemia (very common). Veno-occlusive liver disease, hepatomegaly, jaundice (common). Liver failure, Budd-Chiari syndrome (rare)	No specific recommendations on vaccination are reported in the datasheet
Glofitamab	Severe	$t_{1/2}$ = 1,5 days	ELE (common)	Immunisation with live vaccines is not recommended
Golimumab	Moderate	$t_{1/2}$ = 12 days	ELE (common). Cholelithiasis (rare)	Vaccination is possible during treatment. Avoid use of live vaccines
Guselkumab	Moderate	$t_{1/2}$ = 15-18 days	–	Vaccination prior to treatment is recommended. Live vaccines are not recommended, but if necessary, 2 weeks before or 12 weeks after treatment
Ibritumomab-tuixetan	Severe	$t_{1/2}$ = 28 hours	–	Vaccination with live vaccines is not recommended. No evidence of active immunization during treatment
Inebilizumab	Moderate	$t_{1/2}$ = 18 days	Risk of HBV reactivation has been observed with other antibodies that decrease the number of B-lymphocytes (excluded in trials with this drug)	All immunizations should be administered according to immunization guidelines at least 4 weeks prior to the start of inebilizumab. Immunization with vaccines made with live or attenuated microbes is not recommended during treatment and until B-lymphocyte repletion. Infants born to mothers exposed to inebilizumab during pregnancy should not receive vaccines made with live or attenuated microbes prior to confirmation of recovery of B-lymphocyte counts in the infant. Non-live vaccines, as indicated, may be administered prior to recovery
Infliximab	Moderate	$t_{1/2}$ = 8-9 days	ELE (frequent). Hepatitis, cholecystitis, autoimmune hepatitis, jaundice (rare). Liver failure (frequency unknown).	Vaccination according to local protocols, before starting treatment. Vaccination during treatment is possible. Live vaccines should be avoided

(*Continued*)

Table 3. (Continued).

Agent (drug)	Type of IS[a]	Elimination half-life ($t_{1/2}$)[b]	Hepatotoxicity	Specific vaccination recommendations in the technical datasheet[c]
Inotuzumab-ozogamicina	Severe	$t_{1/2}$ = 12 days	HUS, hyperbilirubinaemia (very common). Veno-occlusive liver disease (frequent)	Vaccination with live vaccines is not recommended. Vaccination is recommended 2 weeks before and, after treatment, when normal B-lymphocyte levels are restored
Isatuximab	Severe	$t_{1/2}$ = 28 days	–	No specific recommendations on vaccination are reported in the datasheet
Ixekizumab	Moderate	$t_{1/2}$ = 13 days	–	Vaccination with live vaccines is not recommended. No evidence on immunization with inactivated vaccines
Lebrikizumab	Moderate	$t_{1/2}$ = 24 days	–	If a patient has received a live virus or bacterial vaccine, it is recommended to wait a minimum of 4 weeks before starting treatment. Treated patients should not receive vaccines made with live microorganisms during treatment or for at least 17 weeks thereafter
Loncastuximab tesirina	Severe	$t_{1/2}$ = 21 days	ELE (very common)	No specific recommendations on vaccination are reported in the datasheet
Mirikizumab	Moderate	$t_{1/2}$ = 9 days	ELE (rare)	Avoiding the use of live vaccines in treated patients
Mogamulizumab	Severe	$t_{1/2}$ = 17 days	Acute hepatitis, hepatitis (rare)	No specific recommendations on vaccination are reported in the datasheet
Mosunetuzumab	Severe	$t_{1/2}$ = 16 days	ELE (very common)	Live and/or attenuated vaccines should not be administered at the same time
Natalizumab	Severe	$t_{1/2}$ = 16 days	ELE (frequent), hyperbilirubinaemia (rare), liver damage (unknown frequency)	Vaccination with live vaccines is not recommended (no evidence of safety). A small study of 60 patients showed no difference in humoral response to diphtheria toxoid compared to untreated patients [39]. Humoral response to mRNA-1273 COVID-19 vaccine is preserved [40]
Obinutuzumab	Severe	$t_{1/2}$ = 26-36 days	HBV reactivation (frequency unknown)	Vaccination is not recommended during treatment or until B-lymphocytes have recovered for live vaccines
Ocrelizumab	Moderate	$t_{1/2}$ = 26 days	HBV reactivation (frequency unknown)	Vaccination is not recommended during treatment or until B-lymphocytes have recovered for live vaccines. There is evidence of a good response to immunization against influenza, pneumococcal-23 [41] and diphtheria toxoid [12]. Influenza vaccination is recommended during treatment with ocrelizumab. Vaccination is recommended at least 6 weeks before starting treatment. Humoral response to mRNA-1273 COVID-19 vaccine can be altered [40]
Ofatumumab	Moderate	$t_{1/2}$ = 16 days	HBV reactivation (frequency unknown)	All immunizations should be administered according to immunization guidelines at least 4 weeks before the start of treatment for live or live attenuated vaccines and whenever possible, at least 2 weeks before the start of treatment with ofatumumab for inactivated vaccines. Ofatumumab may interfere with the efficacy of inactivated vaccines. The safety of immunization with live or live attenuated vaccines following treatment with ofatumumumab has not been studied. Immunization with live or live attenuated vaccines is not recommended during treatment and after discontinuation until B-lymphocyte repletion occurs. Infants born to mothers who have been treated with ofatumumab during pregnancy should not receive live or live attenuated vaccines until recovery of B-lymphocyte counts has been confirmed
Polatuzumab-vedotin	Severe	$t_{1/2}$ = 12 days	ELE (frequent). Hepatocellular damage (frequency unknown).	Live vaccines should not be administered
Ravulizumab	Moderate	$t_{1/2}$ = 50 days	–	Vaccinate all patients against N. meningitidis two weeks before starting ravulizumab treatment and/or receiving prophylactic antibiotic treatment. Patients under 18 years of age should be vaccinated against *Haemophilus influenzae* and pneumococcal infections
Relatlimab-nivolumab	Severe	$t_{1/2}$ = 27 days	ELE (very frequent), hepatitis (frequent), cholangitis (frequent)	No specific recommendations on vaccination are reported in the datasheet
Risankizumab	Moderate	$t_{1/2}$ = 28-29 days	–	Vaccination prior to treatment is recommended. Live vaccines are not recommended during treatment, and if necessary, 4 weeks before or 21 weeks after treatment
Rituximab	Severe	$t_{1/2}$ = 22-32 days (IVR), 30 days (SCR)	HBV reactivation (frequent)	Vaccination is not recommended during treatment or until B-lymphocytes have recovered for live vaccines. Immunization with inactivated vaccines may be less according to [42–44]. Vaccination with inactivated viruses during treatment should be completed at least 4 weeks before the next cycle. COVID-19 vaccines and boosters should be prioritized more than 6 months after receiving the last dose of rituximab [45], or after B cell recovery [46]
Sacituzumab-govitecan	Severe	$t_{1/2}$ = 24 hours	–	No specific recommendations on vaccination are reported in the datasheet
Sarilumab	Moderate	$t_{1/2}$ = 21 days	ELE (common)	Vaccination with live vaccines is not recommended. Vaccination is recommended before the start of treatment

(*Continued*)

Table 3. (Continued).

Agent (drug)	Type of IS[a]	Elimination half-life ($t_{1/2}$)[b]	Hepatotoxicity	Specific vaccination recommendations in the technical datasheet[c]
Satralizumab	Moderate	$t_{1/2}$ = 30 days	ELE, hyperbilirubinemia (common)	Live or attenuated vaccines should not be administered at the same time as satralizumab
Secukinumab	Moderate	$t_{1/2}$ = 27 days	-	Vaccination is possible during treatment. Life-long vaccination is not recommended. Humoral immunity response to meningococcal and influenza vaccines is not suppressed
Siltuximab	Severe	$t_{1/2}$ = 16 days	HBV reactivation (frequency unknown)	Vaccination is not recommended during the treatment of live vaccines
Spesolimab	Moderate	$t_{1/2}$ = 26 days	-	The interval between live vaccines and the start of treatment with spesolimab should be at least 4 weeks. Live vaccines should not be administered for at least 16 weeks after treatment
Sutimlimab	Severe	$t_{1/2}$ = 16 days	-	Patients should be vaccinated as if they are persistently deficient in the complement, including vaccination against meningococcus and pneumococcus. Patients without prior vaccination should receive encapsulated vaccination at least 2 weeks before receiving the first dose
Tafasitamab	Severe	$t_{1/2}$ = 17 days	ELE, hyperbilirubinemia (common)	It is not recommended to vaccinate with live vaccines concomitantly with treatment. In case of exposure during pregnancy, newborns should be monitored for B-lymphocyte depletion and vaccination with live viruses should be postponed until the B-lymphocyte count has recovered
Talquetamab	Severe	$t_{1/2}$ = 12 days	ELE (very common)	Vaccination with live virus vaccines is not recommended for at least 4 weeks before the start of treatment, during treatment and at least 4 weeks after treatment
Teclistamab	Severe	$t_{1/2}$ = 4 days	ELE (common), elevated alkaline phosphatase (very common), reactivation of hepatitis B (frequency unknown)	Vaccination with live virus vaccines is not recommended for at least 4 weeks before the start of treatment, during treatment and at least 4 weeks after treatment
Tildrakizumab	Moderate	$t_{1/2}$ = 23 days	-	Vaccination is not recommended during treatment for live vaccines and, if necessary, 4 weeks before or 17 weeks after treatment
Tislelizumab	Moderate	$t_{1/2}$ = 24 days	ELE and hyperbilirubinaemia (very common), immune related hepatitis (common)	No specific recommendations on vaccination are reported in the datasheet
Tocilizumab	Moderate	$t_{1/2}$ = 8-14 days (IVR), 13 days (SCR)	ELE and hyperbilirubinaemia (frequent). Liver damage, jaundice, hepatitis (rare). Renal failure (very rare).	Vaccination with live vaccines is not recommended. Vaccination prior to initiation of treatment is recommended. In a clinical trial [47], an adequate response to pneumococcal-23 and tetanus toxoid vaccine was demonstrated. Adequate response to influenza vaccine has also been reported [48]. Some studies reported humoral response to COVID-19 vaccination, although lower than in controls [49]
Tralokinumab	Moderate	$t_{1/2}$ = 22 days	–	Vaccines made with live and attenuated microorganisms should not be administered concomitantly (if needed, give them before treatment). Inactivated vaccines can be administered simultaneously (the efficacy of the immune response in meningococcal and tetanus vaccines has been demonstrated).
Trastuzumab-emtansina	Severe	$t_{1/2}$ = 4 days	ELE (very common), hyperbilirubinemia (common). Renal failure, nodular regenerative hyperplasia, portal hypertension (rare).	No specific recommendations on vaccination are reported in the datasheet
Trastuzumab-deruxtecan	Severe	$t_{1/2}$ = 7 days	ELE (very common), hyperbilirubinemia (common)	No specific recommendations on vaccination are reported in the datasheet
Tremelimumab	Severe	$t_{1/2}$ = 14 days	ELE (very common), hepatitis (common).	No specific recommendations on vaccination are reported in the datasheet
Ublituximab	Severe	$t_{1/2}$ = 22 days	–	Vaccination with live or attenuated vaccines is not recommended during treatment or until B-lymphocyte replenishment. All vaccines should be administered at least 4 weeks before the start of treatment for live or attenuated vaccines and, whenever possible, at least 2 weeks before the start of treatment for inactivated vaccines. In infants born to mothers treated during pregnancy, vaccines containing live or attenuated micro-organisms should not be administered before recovery of B-lymphocyte counts has been confirmed.
Ustekinumab	Moderate	$t_{1/2}$ = 21 days	–	Vaccination during treatment is not recommended for live vaccines, but, if necessary, 2 weeks before or 15 weeks after treatment. There is evidence of good response to pneumococcal and tetanus vaccination [50]. Inactivated vaccination is possible during treatment.
Vedolizumab	Moderate	$t_{1/2}$ = 25 days	–	Vaccination is not recommended for live vaccines (no evidence of safety). Vaccination is recommended before starting treatment. There is evidence of response to HBV vaccination [51]
Otros agentes biológicos inmunosupresores de interés				
Abatacept	Moderate	$t_{1/2}$ = 14 days	ELE (common)	Vaccination during treatment is possible, except for live vaccines (3 months after treatment)

(*Continued*)

Table 3. (Continued).

Agent (drug)	Type of IS[a]	Elimination half-life ($t_{1/2}$)[b]	Hepatotoxicity	Specific vaccination recommendations in the technical datasheet[c]
Abrocitinib	Moderate	$t_{1/2}$ = 5 hours	–	Vaccination according to local protocol, prior to initiation of treatment. No live vaccines should be administered during treatment. No evidence of active immunization during treatment
Anakinra	Moderate	$t_{1/2}$ = 4-6 days	ELE (rare). Non-infectious hepatitis (frequency not known)	Vaccination during treatment is not recommended for live vaccines
Baricitinib	Moderate	$t_{1/2}$ = 9-13 hours	ELE (common)	Live or attenuated vaccines should not be used shortly before or during treatment
Belatacept	Severe	$t_{1/2}$ = 9-10 days	ELE (frequent), cholelithiasis (rare), hepatic cyst (rare), hepatic steatosis (rare)	Vaccination during treatment with live vaccines is not recommended. Uncertain clinical relevance of immunization with inactivated vaccines
Etanercept	Moderate	$t_{1/2}$ = 70 hours	ELE, autoimmune hepatitis (rare)	Vaccination during treatment with live vaccines is not recommended. Uncertain clinical relevance of immunization with inactivated vaccine
Deucravacitinib	Moderate	$t_{1/2}$ = 10 hours	-	Live vaccines should be avoided in patients undergoing treatment
Filgotinib	Moderate	$t_{1/2}$ = 7-19 hours	–	Live vaccines should not be administered during treatment.
Luspatercept	Moderate	$t_{1/2}$ = 13 days	ELE, hyperbilirubinemia (very common)	No specific recommendations on vaccination are reported in the datasheet
Ritlecitinib	Moderate	$t_{1/2}$ = 2 hours	ELE (rare)	The use of live or attenuated vaccines should be avoided during treatment. Before starting treatment, it is recommended that patients are up to date with all vaccinations, including prophylactic shingles (zoster) vaccines.
Ruxolitinib	Severe	$t_{1/2}$ = 3 hours	HBV reactivation (rare), ELE (common)	No specific recommendations on vaccination are reported in the datasheet
Tofacitinib-citrato	Moderate	$t_{1/2}$ = 3 hours	ELE (frequent), cholelithiasis (rare), hepatic cyst (rare), hepatic steatosis (rare)	Vaccination according to local protocol, prior to initiation of treatment. Live vaccines should not be administered during treatment. Live vaccines should be administered at least 2 weeks before starting treatment (4 weeks)
Upadacitinib-hemihidrato	Moderate	$t_{1/2}$ = 9-14 hours	–	Vaccination according to local protocol, prior to initiation of treatment. Live vaccines should not be administered during or just prior to treatment.

Adapted and updated from [6]. CTLA4, antigen 4 associated with cytotoxic cytotoxic T-lymphocytes; ELE, elevated liver enzymes; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; FGF, fibroblast growth factor; GD2, carbohydrate disialoganglioside 2; RSV, respiratory syncytial virus; SLAMF7, signaling lymphocyte activation molecule family member 7; TNF, tumoral necrosis factor; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor.

[a]Immunosuppression (IS) classified as severe: very common infections (except upper respiratory tract) or infrequent but relevant infections (HBV reactivation, reactivation and primary infection with tuberculosis virus or JC virus), as well as very common lymphopenia or neutropenia. Moderate IS: very common but mild infections. Some rare but relevant (HBV reactivation, reactivation and/or primary TB or JC virus infection), as well as frequent lymphopenia or neutropenia. With respect to frequency, the following classification of adverse events was considered (according to the label): very common (≥1/10), common (≥1/100 to < 1/10), infrequent (≥1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000) and unknown frequency (cannot be estimated from available data).

[b]Elimination half-lives obtained from pharmacokinetic assays included in the European Public Assessment Report (EPAR) for each medicinal product, European Medicines Agency [12]. In general, it is recommended to wait 5–7 half-lives to eliminate approximately 100% of the drug from the body. Therefore, this column estimates the minimum duration of immunosuppression for each imAb.

[c]Recommendations based on the label of each imAb according to the European Medicines Agency [12]. This information is available publicly. Besides, information of recent COVID-19 vaccine immunization studies was included by the authors.

19. The other inactivated vaccines are recommended only at high-risk specific situations, and live or attenuated vaccines are generally contraindicated (except for very concrete contexts). Clinical trial-based recommendations on the immunogenicity of vaccines in patients under immunosuppressive therapy are very scarce. In most cases, these studies examine only one autoimmune disease (often rheumatological diseases) and the use of a specific vaccine (usually 13-valent pneumococcal conjugate vaccine) in a low sample size and very specific populations. Besides, these studies show variable data on immunogenicity in the first months after treatment with anti-TNFα mAbs, although reasonably good seroconversion rates, but a marked decrease in vaccine response under rituximab treatment [35], as confirmed in a recent meta-analysis [36]. Our review highlights the need for more studies of this nature, not only for pneumococcal vaccines and anti-TNFα mAbs, but for all currently available drugs and vaccines. Besides, most studies published to date did not assess cross-immunity (but only direct protection), or clinical outcomes (but only laboratory data like antibody titers). Thus, rigorous studies that specifically analyze the best vaccination schedule and specific vaccines for each drug and pathology are still required for guiding future recommendations (currently based on expert opinions).

Vaccination recommendations should be based on several aspects. First, the immunosuppressive characteristics of the treatment. Second, the type of vaccines available. Third, the specific context of each patient (epidemiological situation and basement risk factors). Table 3 summarizes the degree of immunosuppression caused by each imAb, and recommendations according EMA datasheets [5], including published studies on immunogenicity and vaccination response for each treatment [37–52].

Figure 1 shows a proposal of an algorithm for vaccination guidance for patients receiving treatment with mAbs. First, the immunosuppressive capacity of the drug should be verified, along with underlying diseases and treatments, to recommend or not specific vaccinations. Once an imAb is detected, the specific vaccines and time schedules could be assessed by consulting Tables 3 and 4 (data based on the technical data

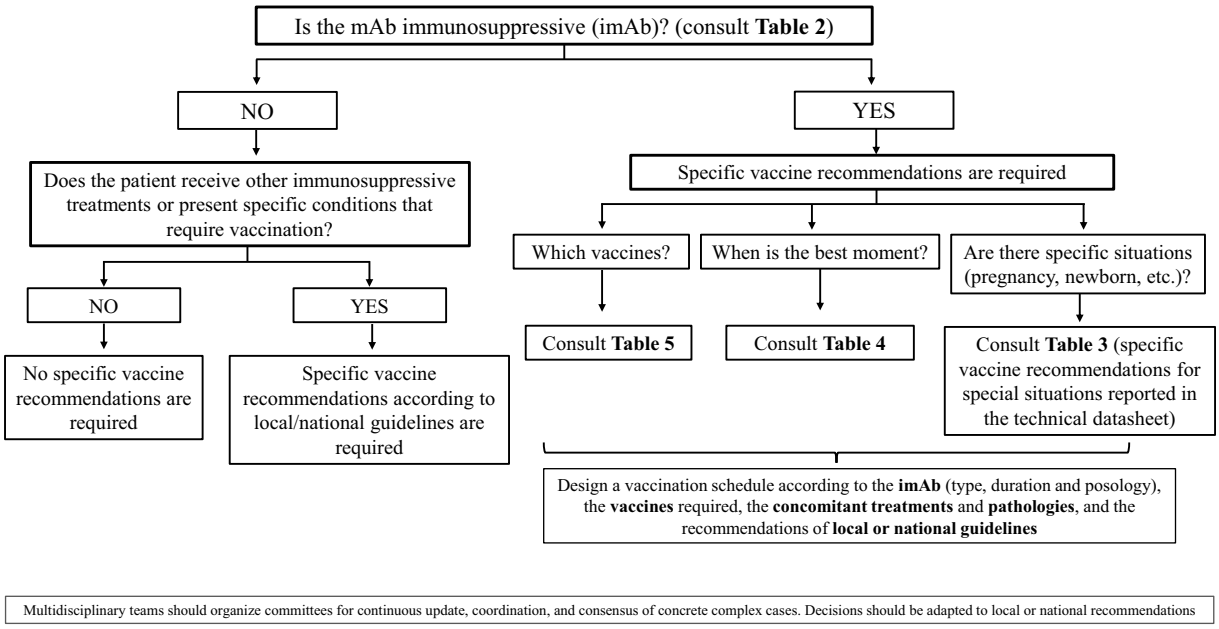

Figure 1. Proposal of an algorithm of vaccination guidance for patients receiving treatment with mAbs (decisions should be adapted according to local or national guidelines).

sheets of all imAbs and current international recommendations). These decisions, however, should be adapted according to local guidelines and policies.

4.1.1. Live or attenuated vaccines

Live or attenuated vaccines are generally contraindicated during treatment with imAbs (Table 3) and should never delay the start of the treatment if it is indicated and urgent. However, if initiation of treatment can wait or is scheduled for a later date, it is advisable to check immunity status against measles, mumps, and varicella prior to treatment. According to serological markers, prior vaccination might be recommended. In general, during the 4 weeks before the start of imAb treatment, live or attenuated vaccines should not be recommended. Table 4 shows the recommended optimal vaccination interval after the end of imAb treatment, based on current available evidence. For example, after anti-TNFα or anti-interleukin treatments, an interval of 3–6 months should be waited before vaccination [53–56], and up to 12 months after imAb targeting B-lymphocyte receptors (ocrelizumab, rituximab, etc.). In cases where there are no specific recommendations, we recommend an optimal waiting time of 5 half-lives for drug elimination, although each situation should be individualized according to treatment, pathology, and vaccination.

4.1.2. Inactivated vaccines

Although inactivated vaccines are not explicitly contraindicated, their effectiveness for immunocompromised patients could be minimal or null if recommended intervals are not followed. In general, vaccination 2 weeks prior to start of imAb treatment is recommended [57]. In certain occasions, this scenario is not possible (the imAb has yet started) and vaccination must be performed during the treatment. In those cases, drug dose and treatment intervals should be considered to decide the best time for vaccination, generally a few days (or hours) before the next dose of imAb [6]. Nevertheless, when this situation happens, revaccination after the end of imAb treatment could be advisable. If vaccination will be performed after imAb treatment, an interval of approximately 3 months is generally recommended. Table 4 shows the recommended optimal intervals for best practice according to the imAbs mechanism of action, pharmacokinetic properties (5 times the half-life of elimination) and is based on previous expert recommendations.

4.1.3. Optimal time for vaccination

As previously highlighted, only imAbs (not all mAbs) require vaccination recommendations by themselves. Nevertheless, choosing the right time and type of vaccine for each situation (according to specific diseases and treatments) remains a challenge. No studies to date have accurately analyzed the effectiveness of each vaccination schedule and recent syntheses show high heterogeneity in the results available [32]. The only consistent recommendation is that vaccination, if possible, should be administered before the start of imAb treatment [58]. Therefore, if the clinician knows that an imAb treatment is to be started on a scheduled basis in the future, early referral to the specific vaccination (e.g. Preventive Medicine service) consultation is necessary. However, vaccination should not delay treatment if treatment is essential [57]. Table 3 shows the minimum duration of the immunosuppression according to the elimination half-life (as the effect may be longer). Table 4 shows the minimum optimal time required for vaccination before and after the end of treatment for each imAb, depending on whether the vaccines are inactivated or live/attenuated vaccines.

4.2. Specific vaccine recommendations

Table 5 shows the specific vaccine recommendations for each type of imAb, according to the results of this review, which should be adapted to local guidelines recommendations.

Table 4. Recommended time intervals for the administration of vaccines in patients treated with imAbs or other biological agents of interest.

Treatment			Live or attenuated vaccines		Inactivated vaccines	
Mechanism of action	imAb (and other biological agents of interest)	Elimination time (5 half-lifes)	From vaccination to start of treatment (BEFORE imAb)	From end of treatment to vaccination (AFTER imAb)	From vaccination to start of treatment (BEFORE imAb)	From end of treatment to vaccination (AFTER imAb)
TNF-α antagonists	Adalimumab	10 weeks	4 weeks	12 weeks	No minimum interval, but vaccine may not be effective. Optimal recommendation: 2 weeks.	No minimum interval, but vaccine may not be effective. Optimal recommendation: elimination time (5 half-lives of elimination) or at least 12 weeks
	Certolizumab-pegol	10 weeks	4 weeks	12 weeks		
	Etanercept	3 weeks	4 weeks	4-12 weeks		
	Golimumab	9 weeks	4 weeks	12 weeks		
	Infliximab	7 weeks	4 weeks	12 weeks		
Anti IL-1	Anakinra	2 days	4 weeks	12 weeks		
	Canakinumab	19 weeks	4 weeks	19 weeks		
IL2 receptor (CD25) blockers	Basiliximab	5 weeks	4 weeks	12 weeks		
	Daclizumab	15 weeks	4 weeks	15 weeks		
Anti IL-6	Siltuximab	12 weeks	4 weeks	12 weeks		
IL-6 receptor blockers	Sarilumab	15 weeks	4 weeks	15 weeks		
	Satralizumab	22 weeks	4 weeks	22 weeks		
	Tocilizumab	10 weeks	4 weeks	12 weeks		
Anti IL-13	Tralokinumab	16 weeks	4 weeks	16 weeks		
Anti IL-17-A	Bimekizumab	17 weeks	4 weeks	17 weeks		
	Brodalumab	8 weeks	4 weeks	12 weeks		
	Ixekizumab	10 weeks	4 weeks	12 weeks		
	Secukinumab	20 weeks	4 weeks	20 weeks		
Anti IL12/23	Ustekinumab	15 weeks	4 weeks	15 weeks		
Anti IL-23	Guselkumab	13 weeks	4 weeks	13 weeks		
	Lebrikizumab	17 weeks	4 weeks	17 weeks		
	Mirikizumab	7 weeks	4 weeks	7 weeks		
	Tildrakizumab	17 weeks	4 weeks	17 weeks		
	Risankizumab	21 weeks	4 weeks	21 weeks		
IL-36 receptor blockers	Spesolimab	18 weeks	4 weeks	16 weeks		
Inhibitors of CD28 and CD80/CD86 union	Abatacept	10 weeks	4 weeks	12 weeks		
	Belatacept	8 weeks	4 weeks	12 weeks		
Inhibitors of IFN-1	Anifrolumab	16 weeks	4 weeks	16 weeks		
BCMA	Belantamab mafotodina	10 weeks	4 weeks	12 weeks		
	Teclistamab	3 weeks	4 weeks	4 weeks	4 weeks	4 weeks
Anti-BLyS	Belimumab	14 weeks	4 weeks	14 weeks	4 weeks	4 weeks
SLAMF7 blockers	Elotuzumab	6 weeks	4 weeks	12 weeks	4 weeks	6 weeks
Integrin α4β1	Natalizumab	12 weeks	4 weeks	12 weeks	4 weeks	12 weeks
Integrin α4β7	Vedolizumab	18 weeks	4 weeks	18 weeks	4 weeks	18 weeks
Anti CD11 and anti LFA-1	Efalizumab	7 weeks	4 weeks	12 weeks	4 weeks	7 weeks
Anti CD19	Inebilizumab	13 weeks	4 weeks	13 weeks	4 weeks	13 weeks
	Loncastuximab tesirina	15 weeks	4 weeks	15 weeks	4 weeks	15 weeks
	Tafasitamab	12 weeks	4 weeks	12 weeks	4 weeks	12 weeks
Anti CD19 and anti CD3	Blinatumomab	1 día	4 weeks	12 weeks	4 weeks	4 weeks
Anti CD20	Epcoritamab	18 weeks	4 weeks	12 months	4 weeks	18 weeks
	Glofitamab	8 days	4 weeks	12 months	4 weeks	4 weeks
	Ibritumomab-tuixetan	6 days	4 weeks	12 months	4 weeks	4 weeks
	Mosunetuzumab	12 weeks	4 weeks	12 months	4 weeks	12 weeks
	Obinutuzumab	19 weeks	4 weeks	12 months	4 weeks	6 months
	Ocrelizumab	26 weeks	4 weeks	12 months	4 weeks	6 months
	Ofatumumab	12 weeks	4 weeks	12 months	4 weeks	6 months
	Rituximab	23 weeks	4 weeks	12 months	4 weeks	6 months
	Ublituximab	16 weeks	4 weeks	16 weeks	2 weeks	16 weeks
Anti CD22	Inotuzumab-ozogamicina	9 weeks	4 weeks	12 weeks	4 weeks	9 weeks
Anti CD30	Brentuximab-vedotin	4 weeks	4 weeks	12 weeks	4 weeks	4 weeks
Anti CD33	Gemtuzumab-ozogamicina	5 weeks	4 weeks	12 weeks	4 weeks	5 weeks
Anti CD38	Daratumumab	17 weeks	4 weeks	17 weeks	4 weeks	17 weeks
	Isatuximab	20 weeks	4 weeks	20 weeks	4 weeks	20 weeks
Anti CD52	Alemtuzumab	4 weeks	6 weeks	12 months	6 weeks	6 months

(*Continued*)

Table 4. (Continued).

Treatment			Live or attenuated vaccines		Inactivated vaccines	
Mechanism of action	imAb (and other biological agents of interest)	Elimination time (5 half-lifes)	From vaccination to start of treatment (BEFORE imAb)	From end of treatment to vaccination (AFTER imAb)	From vaccination to start of treatment (BEFORE imAb)	From end of treatment to vaccination (AFTER imAb)
Anti CD79	Polatuzumab-vedotin	9 weeks	4 weeks	12 weeks	4 weeks	9 weeks
Anti GD-2	Dinutuximab beta	6 weeks	4 weeks	12 weeks	4 weeks	6 weeks
CCR1	Mogamulizumab	12 weeks	4 weeks	12 weeks	4 weeks	12 weeks
Anti CTLA-4	Tremelimumab	10 weeks	4 weeks	10 weeks	4 weeks	10 weeks
HER-2	Trastuzumab-emtansina	3 weeks	4 weeks	12 weeks	4 weeks	3 weeks
	Trastuzumab-deruxtecan	5 weeks	4 weeks	5 weeks	4 weeks	5 weeks
Anti-GPRC5D	Talquetamab	8 weeks	4 weeks	4 weeks	4 weeks	4 weeks
Anti PD-1	Relatlimab-nivolumab	20 weeks	4 weeks	20 weeks	4 weeks	20 weeks
	Tislelizumab	17 weeks	4 weeks	17 weeks	4 weeks	17 weeks
Anti TFG-β	Luspatercept	9 weeks	4 weeks	9 weeks	4 weeks	9 weeks
Anti Trop-2	Sacituzumab-govitecan	5 days	4 weeks	12 weeks	4 weeks	4 weeks
Complement C1 factor	Sutimlimab	12 weeks	4 weeks	12 weeks	2 weeks	12 weeks
Complement C5 factor	Eculizumab	8 weeks	4 weeks	8 weeks	2 weeks	8 weeks
	Ravulizumab*	36 weeks	4 weeks	36 weeks	2 weeks	36 weeks
Anti-JAK	Abrocitinib	1 day	4 weeks	4 weeks	4 weeks	4 weeks
	Baricitinib	3 days	4 weeks	4 weeks	4 weeks	4 weeks
	Deucravacitinib	2 days	4 weeks	4 weeks	4 weeks	4 weeks
	Filgotinib	4 days	4 weeks	4 weeks	4 weeks	4 weeks
	Ritlecitinib	2 days	4 weeks	4 weeks	4 weeks	4 weeks
	Ruxolitinib	1 day	4 weeks	4 weeks	4 weeks	4 weeks
	Tofacitinib-citrato	1 day	4 weeks	4 weeks	4 weeks	4 weeks
	Upadacitinib-hemihidrato	3 days	4 weeks	4 weeks	4 weeks	4 weeks

Recommendations summarized by the authors based on the of the European Medicines Agency (EMA) datasheets [12], the elimination half-life of the drug (Table 3) and previous recommendations of the Spanish government [57].
*Ideally, meningococcal vaccination should be administered 2 weeks prior to treatment with ravulizumab.

4.2.1. Influenza vaccination

Inactivated influenza vaccines are proven to be safe in patients under immunosuppressive treatments [59], including anti CD20 imAbs [60], and in patients diagnosed with immunosuppressive diseases [60,61]. Nevertheless, the quantity and quality of current evidence on vulnerable populations are still lacking. Adequate intervals might be essential for reaching greater response, increasing immunogenicity from 25% to 80% in certain cases [62]. Influenza vaccine, although less immunogenic than other vaccines, has proven to reduce the severity of the disease in immunocompromised patients. However, the effectiveness of this vaccine widely varies according to the population, being very low (50% at best) for hematopoietic stem cell transplant recipients [63] – better for the adjuvanted MF59 vaccine – [64], or organ transplant recipients (especially low for lung transplantation) [65]. For these patients, greater immune response has been reported for double-dose vaccination strategies [66]. For patients diagnosed with inflammatory conditions under imAb therapies, some influenza strains produce lower serological response [67]. Other influenza vaccines have been developed in the last years. For example, high-dose influenza vaccine has shown more effectiveness than standard-dose vaccines for certain populations [68]. Nevertheless, as happens to MF59, these vaccine strategies have been eminently tested in older adults, but studies specifically conducted in immunocompromised patients, or patients under imAb treatment, are still lacking. Besides, live attenuated, adjuvated and potentiated influenza vaccines have been developed and could be useful for immunocompromised patients, although not enough studies have been developed to reach definite conclusions.

Inactivated influenza vaccination has proven to be safe for immunocompromised patients and somehow effective for preventing influenza-like disease [69], and cellular memory after vaccination has been associated with better response to non-vaccine influenza mutations [70]. Finally, as the effectiveness of influenza vaccination is not optimal, relatives and healthcare professionals attending immunocompromised patients should be vaccination during each season for increasing the protection of this vulnerable population.

Based on the literature search, we recommend annual influenza vaccination (inactivated vaccine) for all patients receiving imAb treatments.

4.2.2. Pneumococcal vaccination

Pneumococcal vaccination is also routinely recommended for all immunocompromised patients [6,26,58,60]. The sequential pneumococcal vaccination strategy (pneumococcal conjugated vaccine 13, PCV-13, followed by pneumococcal polysaccharide vaccine 23, PPSV-23) was classically recommended given the immunogenicity (generation of antibodies for one year at least) proven in clinical trials [71]. These vaccines are safe [72] in patients under imAb therapies, but the immunogenicity might be compromised if the level of

Table 5. Recommended minimum vaccines for patients on treatment with imAbs and other immunosuppressive biological agents of interest.

	Vaccines[a]							
Agent (imAbs and other biological agents of interest)	Influenza[b]	Pneumococcal[c]	COVID-19[d]	HBV[e]	HAV[f]	Meningococcal	HiB	Zoster (shingles)[g]
Abatacept	✓	✓	✓	✓	✓			[a]
Abrocitinib	✓	✓	✓	✓				✓
Adalimumab	✓	✓	✓	✓	✓			[a]
Alemtuzumab	✓	✓	✓	✓	✓			[a]
Anakinra	✓	✓	✓	✓				
Anifrolumab	✓	✓	✓	✓				[a]
Baricitinib	✓	✓	✓	✓	✓			✓
Basiliximab	✓	✓	✓	✓				
Belantamab mafotodina	✓	✓	✓	✓	✓			
Belatacept	✓	✓	✓	✓	✓			[a]
Belimumab	✓	✓	✓	✓				[a](only for lupus nephritis)
Bimekizumab	✓	✓	✓	✓				
Blinatumomab	✓	✓	✓	✓	✓			
Brentuximab-vedotin	✓	✓	✓	✓	✓			[a]
Brodalumab	✓	✓	✓	✓				
Canakinumab	✓	✓	✓	✓				[d]
Certolizumab-pegol	✓	✓	✓	✓	✓			[a]
Daclizumab	✓	✓	✓	✓	✓			
Daratumumab	✓	✓	✓	✓	✓			[d]
Dinutuximab beta	✓	✓	✓	✓				
Deucravacitinib	✓	✓	✓	✓				✓
Eculizumab	✓	✓	✓	✓		✓	✓	
Efalizumab	✓	✓	✓	✓	✓			
Elotuzumab	✓	✓	✓	✓				[a]
Etanercept	✓	✓	✓	✓				[c]
Epcoritamab	✓	✓	✓	✓	✓			[a]
Filgotinib	✓	✓	✓	✓				✓
Gemtuzumab-ozogamicina	✓	✓	✓	✓	✓			
Glofitamab	✓	✓	✓	✓	✓			[a]
Golimumab	✓	✓	✓	✓	✓			
Guselkumab	✓	✓	✓	✓				
Inebilizumab	✓	✓	✓	✓	✓			[a]
Ibritumomab-tuixetan	✓	✓	✓	✓				
Infliximab	✓	✓	✓	✓	✓			[d]
Inotuzumab-ozogamicina	✓	✓	✓	✓	✓			
Isatuximab	✓	✓	✓	✓				[a]
Ixekizumab	✓	✓	✓	✓				
Lebrikizumab	✓	✓	✓	✓				
Loncastuximab tesirina	✓	✓	✓	✓	✓			
Luspatercept	✓	✓	✓	✓	✓			
Mirikizumab	✓	✓	✓	✓	✓			[b]
Mogalumizumab	✓	✓	✓	✓	✓			
Mosunetuzumab	✓	✓	✓	✓	✓			
Natalizumab	✓	✓	✓	✓	✓			[a]
Obinutuzumab	✓	✓	✓	✓	✓			[a]
Ocrelizumab	✓	✓	✓	✓	✓			[a]
Ofatumumab	✓	✓	✓	✓	✓			
Polatuzumab-vedotin	✓	✓	✓	✓	✓			
Ravulizumab	✓	✓	✓	✓		✓	*	
Relatlimab-nivolumab	✓	✓	✓	✓	✓			
Risankizumab	✓	✓	✓	✓				
Ritlecitinib	✓	✓	✓	✓				✓
Rituximab	✓	✓	✓	✓	✓			
Ruxolitinib	✓	✓	✓	✓	✓			✓
Sacituzumab-govitecan	✓	✓	✓	✓				
Sarilumab	✓	✓	✓	✓	✓			[d]
Satralizumab	✓	✓	✓	✓	✓			
Secukinumab	✓	✓	✓	✓				
Siltuximab	✓	✓	✓	✓	✓			
Spesolimab	✓	✓	✓	✓				
Sutimlimab	✓	✓	✓	✓		✓	✓	[a]
Tafasitamab	✓	✓	✓	✓	✓			
Talquetamab	✓	✓	✓	✓	✓			
Teclistamab	✓	✓	✓	✓	✓			
Tildrakizumab	✓	✓	✓	✓				
Tislelizumab	✓	✓	✓	✓	✓			
Tocilizumab	✓	✓	✓	✓	✓			[a]
Tofacitinib citrato	✓	✓	✓	✓	✓			✓
Tralokinumab	✓	✓	✓	✓				
Trastuzumab-emtansina	✓	✓	✓	✓	✓			
Trastuzumab-deruxtecan	✓	✓	✓	✓	✓			
Tremelimumab	✓	✓	✓	✓	✓			

(*Continued*)

Table 5. (Continued).

Agent (imAbs and other biological agents of interest)	Vaccines[a]							
	Influenza[b]	Pneumococcal[c]	COVID-19[d]	HBV[e]	HAV[f]	Meningococcal	HiB	Zoster (shingles)[g]
Ublituximab	✓	✓	✓	✓				
Upadacitinib hemihidrato	✓	✓	✓	✓				✓
Ustekinumab	✓	✓	✓	✓				
Vedolizumab	✓	✓	✓	✓				[b]

[a]The MMR (or varicella-zoster virus) vaccine should be administered if the patient is susceptible, regardless of the type of drug. This will require following the vaccination instructions for live attenuated vaccines. Diphtheria and tetanus vaccination should be evaluated every 10 years, and 5 doses should be administered if the patient is not adequately vaccinated and immunized.
[b]Evaluate inactivated influenza vaccination in all vaccination campaigns.
[c]Sequential vaccination (23-valent polysaccharide vaccine and, 12 months later, 13-valent conjugate vaccine), or conjugated 20-valent pneumococcal vaccination, depending on the individual patient's vaccination schedule, previous vaccination and local recommendations.
[d]COVID-19 adequate immunization is recommended for all patients receiving imAbs. The type and moment of vaccination will depend on current local guidelines (regarding type of vaccine, number of boosters, circulating variants.
[e]In all cases, assess whether the patient has received an HBV vaccination regimen and request serology including surface antibodies (HBsAb). Depending on the result, consider primary vaccination, revaccination, or nothing.
[f]Assessment of HAV vaccination is included in at-risk patients who are on treatment with an imAb that either causes HBV reactivation as a described side effect or causes frequent hepatitis or transaminase increases (see Table 3).
[g]At present (January 2024), vaccination against herpes zoster is indicated in patients treated with anti-JAK drugs in several settings [57]. However, we include information on those drugs that cause reactivation of herpes zoster according to the technical data sheet, as well as the described frequency of this problem, in order to facilitate subsequent evaluations of the indications for this vaccine. [a]Very common adverse reaction (≥1/10) or common according to the data sheet (≥1/100 to < 1/10), [b]Infrequent adverse reaction (≥1/1,000 to < 1/100), [c]Rare adverse reaction (≥1/10,000 to < 1/1,000), [d]Adverse reaction of unknown frequency (some cases reported, but with no plausible causal relationship or without sufficient data to establish the frequency). The rest of the drugs (no letter assigned) do not show any frequency of herpes zoster reactivation reported in the data sheet.
*Vaccination against *H. influenzae* and pneumococcus 2 weeks prior to start of treatment only in children under 18 years of age. In adults, vaccination with meningococcus without *H. influenzae*.

immunosuppression is too high. This situation has been widely studied mainly for patients with rheumatoid arthritis under rituximab (anti-CD20) treatment (25% response rate, compared with 90% response rate without this treatment) [35,73]. Similarly, the response rate of patients with inflammatory bowel disease under anti-TNF-α therapy might be also reduced (60%) [74].

Evidence on other imAbs suggest an impaired serologic response to pneumococcal vaccines (especially conjugated vaccine) [75], but data on the concrete effect of certain imAbs is still insufficient. Other studies conducted on new imAbs such as belimumab in patients with autoimmune diseases reported adequate response rates [76]. For each specific case, pneumococcal and influenza vaccination should be administered considering the immunosuppression characteristics of each imAb, as summarized in Table 5. As for the high-dose influenza vaccine, several expert opinions recommend a two-dose regimen of conjugate pneumococcal vaccines for immunosuppressed patients (e.g. patients treated with ibrutinib or splenectomized patients). Again, not enough specific studies are available to reach definite conclusions, and future studies should focus on evaluating the impact of such interventions.

It is important to highlight the potential role that new conjugate vaccines (15-, 20- or 21-valent) with experience of use in countries such as the United States may acquire in the immediate future [77,78]. The extent to which 13-valent conjugate vaccine and the 23-valent polysaccharide will change their indications and how this may affect vaccination schedules in patients treated with imAbs will be the subject of research and evaluation in the near future. For example, in Belgium, the use of the 20-valent conjugate vaccine has been proposed as the preferred option for vaccination in adults in at-risk groups with comorbidities and in patients aged 65–85 years [79], and cost-utility was reported for this intervention [80]. In Andalusia (Southern Spain), the 20-valent conjugate vaccine (VNC20), Apexxnar®, is recommended in the general population aged 60–73 years who have not received previous pneumococcal conjugate vaccination, and in at-risk groups [81]. Besides, 15-Valent pneumococcal conjugate vaccine V114 has proven safety and immunogenicity in a recent clinical trial conducted on allogeneic hematopoietic cell transplant recipients [82]. Nevertheless, despite all recommendations of pneumococcal vaccination for patients under immunosuppressive treatment, compliance with this vaccination schedule is yet far from the desirable [83].

Based on the literature search, we recommend pneumococcal vaccination for all patients receiving imAb treatments.

4.2.3. COVID-19 vaccination

Since the start of the COVID-19 pandemic, a large number and types of vaccines have been developed to optimize prevention strategies [84]. Virus-like particles (VLPs), protein subunit vaccines, DNA, RNA-based and viral vector-based, inactivated, and live-attenuated vaccines are the most frequent strategies developed in current clinical trials, although protein subunit, RNA-based and non-replicating viral vector-based platforms have been majorly used worldwide [84]. Since its development, in contrast to research on other vaccines over the last decades, much interest was put into evaluating the effectiveness of these vaccines in immunocompromised patients, given the disproportional impact of the pandemic in this population [30]. For example, despite lower than in healthy controls, humoral vaccine response to mRNA COVID-19 vaccination was evident for patients receiving anti-IL-6 receptor imAbs, stronger than those receiving anti CD20 therapies [85]. Something similar was reported for patients receiving natalizumab (preserved response) compared with ocrelizumab (altered response) [41]. Several studies have been conducted

regarding response in patients under anti CD20 imAbs [7–9] but, in general, COVID-19 vaccines and boosters should be prioritized in this subgroup, more than 6 months after receiving the last dose of treatment [46], or after recovery of B lymphocytes level [47].

The optimal interval before receiving COVID-19 vaccines for these patients (under anti CD20 imAb treatments) was reported to be, at least, 5.5 months after the last dose of treatment [9]. Currently, an additional dose of COVID-19 is recommended in several countries in immunocompromised patients if they have not been infected or vaccinated within the last 3 months (regardless of previous infections or doses received).

Some studies reported humoral response to COVID-19 vaccination in patients receiving tocilizumab (an imAb that was indicated for COVID-19, to prevent the development of severe disease), although lower than in controls [50]. Also, prophylactic mAbs for preventing COVID-19 severe outcomes are also being developed and studied [10,11].

Despite all these studies, precise data to guide vaccination and treatment approaches in immunocompromised people are generally lacking and extrapolated from other populations, so research in this field, along with the effectiveness of each vaccine on current circulating variants, is still needed [31].

Based on the literature search, we recommend COVID-19 vaccination for all patients receiving imAb treatments, according to local guidelines (considering the circulating variants, previous COVID-19 vaccines, and current local recommendations).

4.2.4. Meningococcal vaccination

Humoral immunity, spleen function and the activity of the complement system are immunologically relevant for the adequate response to encapsulated bacteria. The ACWY meningococcal vaccination (2 doses with a 4-week minimum interval) and the B serogroup vaccination (2 doses with a 4-week minimum interval) are recommended for patients with functional or anatomical asplenia [27] and for patients with deficiencies in the complement pathway, including imAbs that specifically affects the complement (eculizumab, ravulizumab or sutimlimab). As for pneumococcal vaccination, some experts suggest the use of a two-dose regimen of conjugate meningococcal vaccines for immunosuppressed patients (e.g. splenectomized patients) although specific studies on this topic are still lacking.

Based on the literature search, we recommend meningococcal vaccination of patients under treatment with eculizumab, ravulizumab or sutimlimab, with appropriate booster schedules.

4.2.5. Haemophilus influenzae B vaccination

Similar to meningococcal vaccines, for patients with functional or anatomical asplenia [27], and with complement pathway deficiency (i.e. patients under treatment with eculizumab, ravulizumab or sutimlimab), *Haemophilus influenzae* type B vaccine (single dose) should also be included. This is due to the increased risk of encapsulated bacterial infections in this population subgroup. *H. influenzae* type B vaccine is also recommended for patients undergoing chemotherapy for malignant neoplasms [27], for hematopoietic stem cell transplant recipients [86], and could also be recommended for patients with inflammatory bowel disease under immunosuppressive treatment [29], although this indication is not entirely clear. In the recent years, several studies have reported the need for developing optimal non-typeable *H. influenzae* vaccines in a few current clinical trials, due to the emergence of these pathogens [86,87].

Based on the literature search, we recommend vaccination against *H. influenzae* type B in patients treated with eculizumab, ravulizumab or sutimlimab, with appropriate booster vaccination schedules.

4.2.6. Hepatitis B vaccination

Hepatitis B vaccines have proven to be among the safest both for general population [88] and for patients under imAb treatment [89]. In some specific vulnerable populations such as patients under antineoplastic treatments, these vaccines have shown efficacy [90]. Nevertheless, their effectiveness might decrease in patients with autoimmune or chronic diseases and especially in transplant recipients, where efficacy is less than 50% [89,91]. Approximately 5% of general population are non-responders to the vaccine, and this percentage is much higher in at-risk groups (mainly dialysis-dependent and immunocompromised patients) [92]. It has been recently suggested that adjuvanted AS04C vaccine (Fendrix®), currently recommended for patients with kidney diseases, produces an adequate immune response in patients with immunosuppressive biological therapies [93]. Nevertheless, the decision on whether to vaccine or not against hepatitis B always depends on the context (age, epidemiologic risk factors, etc.) so individualization is required for this immunization.

Several schedules have been recommended, with differences in the dose (20 or 40 mcg), and in time between doses (generally 3–4 doses for 6 months or during 4 months in accelerated schedules). Given the higher non-response rates in immunocompromised patients, some studies propose high-dose (40 mcg) strategies for transplant recipients [94] or for patients under certain imAb treatments. Besides, adjuvanted vaccines are generally preferred given that booster vaccination could restore antibody titers if they are decreased [95], then offering a potentially adequate solution for non-responders. Although the best recommendation is one-dose revaccination, some studies analyzed a second 3-dose vaccine strategy as an alternative, with inconsistent conclusions [96,97]. Intradermal administration, new adjuvants or the use of Toll-like receptor agents, between others, are new strategies that might generate greater immunogenicity. The imAb therapy could worsen the prognosis and outcomes of hepatitis B infection, therefore vaccination should be administered in patients with high-risk exposures [98,99]. The best decision on how to manage non-responders (e.g. high-dose vaccine, intradermal administration, different vaccines or different schedules) will depend on the design of specific studies conducted on immunocompromised patients.

Besides, patients under potentially hepatotoxic imAb therapies should also receive this vaccination. Evidence suggest that hepatitis B vaccination should be administered to patients with inflammatory bowel disease [32] or multiple sclerosis [100,101] under imAb treatments. To sum up, hepatitis B vaccination seems recommendable for most patients under imAb therapy if antibody titers are not sufficient. Hence, pre-treatment serological tests are needed (HBsAg, anti-HBc and anti-HBs), and also after vaccination, as several therapies may affect the response to the vaccine.

Based on the available literature, hepatitis B vaccination is recommended for all patients on imAb treatment and with unknown or negative serology.

4.2.7. Hepatitis a vaccination

Vaccination against hepatitis A would be reasonable in at-risk groups [6], especially in those under treatment with hepatotoxic imAbs [102]. Ideally, as for the other vaccines, vaccination should be administered before the start of immunosuppressive treatment. Table 3 shows the imAbs (and other immunosuppressive biologic agents of interest) for which an increased risk of hepatitis B reactivation (adalimumab, daratumumab, obinutuzumab, ocrelizumab, ofatumumumab, rituximab, ruxolitinib and siltuximab) or acute hepatitis (mogamulizumab) has been described in the data sheet. Of these, only rituximab showed a high frequency of this problem (between 1 in 100 and 1 in 1,000). In addition, Table 3 shows those drugs that frequently produce elevated liver enzymes or liver inflammation (abatacept, alemtuzumab, baricitinib, belantamab-mafodotin, belatacept, blinatumomab, brentuximab-vedotomab, brentuximab-vedotomab, mogalumizumab, mogamulizumab, brentuximab-vedotin, certolizumab-pegol, daclizumab, efalizumab, epcoritamab, gemtuzumab-ozogamicin, glofitamab, golimumab, inebilizumab, infliximab, inotuzumab-ozogamicin, loncastuximab tesirin, luspatercept, mirikizumab, mosunetuzumab, natalizumab, polatuzumab-vedotin, relatlimab-nivolumab, sarilumab, satralizumab, tafasitamab, talquetamab, teclistamab, tocilizumab, tofacitinib citrate, trastuzumab-emtansine, trastuzumab-deruxtecan and tremelimumab), representing 54% of all imAbs. Although non-immunosuppressive mAb, nivolumab-induced hepatitis has been reported as a rare side effect [103], so hepatitis A vaccination might be also recommendable for patients under this treatment.

Vaccination against hepatitis A, in addition to the aforementioned cases, can also be recommended in patients with inflammatory bowel disease under any immunosuppressive treatment [13,30] who showed effective responses. An extra priming dose of vaccine has also been recommended for immunocompromised patients [104]. Nevertheless, despite recommendations by some experts [54], there is insufficient evidence to support the indication for a booster after completion of the 2-dose primary vaccination series (although it is currently recommended for immunocompromised patients in several countries). Human immunoglobulin, apart from the vaccine, should be administered to patients on imAb treatment that have been potentially exposed to hepatitis A virus [105].

Similar to hepatitis B vaccination, serological response to hepatitis A vaccine should be monitored, 1 to 2 months after the completion of vaccination schedule.

Based on the current available literature, hepatitis A vaccination should be recommended to all patients treated with hepatotoxic imAbs, at risk of hepatitis A exposure or with negative or unknown serology.

4.2.8. Human papillomavirus vaccine (HPV)

According to several national associations [55,103,104], tetravalent HPV vaccines (HPV4) is indicated for patients diagnosed with inflammatory rheumatic diseases and inflammatory bowel diseases [13,55] under imAb therapy. A two-dose immunization schedule (0, 6–12 months) for immunocompromised patients [105] is generally recommended, although in some countries a three-dose schedule is implemented [57]. Some experts have also recommended this vaccine for patients treated with alemtuzumab, preferably women ≤26 years [106].

Nevertheless, currently the nonavalent vaccine (9vHPV) is the only marketed alternative, which is more effective than HPV4 by extending protection against five other oncogenic HPV types [105,107].

According to our literature search, no conclusive evidence has been found to recommend or not recommend HPV vaccination in patients undergoing treatment with imAbs.

4.2.9. Herpes zoster vaccination

Live herpes zoster vaccines are not recommended for patients under imAb therapy. The adjuvanted vaccine (Shingrix®), approved in 2018 by the EMA, is currently indicated for most patients under immunosuppressive treatments. A 2-dose vaccination schedule is safe and effective for hematopoietic cell transplant recipients [108], patients with tumors or receiving chemotherapy [109] and patients' treatment with imAbs, including anti-CD20 drugs [110]. A randomized controlled trial in renal transplant recipients (NCT02058589) also showed promising results.

Its immunogenicity and safety in patients under treatment with JAK-2 inhibitors (baricitinib, tofacitinib, ruxolitinib) has also been demonstrated, as these agents increase the risk of developing herpes zoster reactivation and serious complications such as post-herpetic neuralgia [111]. Recently, the indication for herpes zoster vaccine has been approved in several countries for patients treated with JAK inhibitors (anti-JAK), including abrocitinib, baricitinib, deucravacitinib, filgotinib, rictlecitinib, ruxolitinib, tofacitinib and upadacitinib, which lead to the inclusion of these agents (despite not being imAbs) in this document. Nevertheless, as thoroughly collected in Table 5, high frequency of herpes zoster reactivation has also been reported for several other imAbs (apart from anti-JAK) in the technical datasheet. That reason led some countries (or regions like Andalusia, Spain) to broaden the indications of herpes zoster vaccines to most imAbs [112].

The indicated regimen consists of two doses, with an optimal interval between doses of 2 months, which can be reduced to 1 month in situations of imminent immunosuppression or under clinical criteria [112]. Although no specific recommendations have been found for patients on imAb treatment, patients with solid tumors should be considered, as the relative risk of developing herpes zoster has been reported to be five times higher than in the general population [110]. It is important to emphasize that vaccination is indicated regardless of serology and prior varicella vaccination. Vaccination against varicella is not necessary in patients who are going to be vaccinated against herpes zoster. Finally, recent systematic reviews have highlighted the safety and effectiveness of the recombinant vaccine in immunocompromised patients [113,114].

According to our literature search, herpes zoster vaccination (to prevent herpes zoster infection and post-herpetic neuralgia) is recommended in patients aged ≥18 years with unknown or negative serology, who are 1) hematopoietic

stem cell transplant recipients, 2) patients with solid organ transplant or awaiting solid organ transplantation, 3) treated with anti-JAK, or 4) treated with chemotherapy for solid tumors, hematological malignancies, or HIV infection, according to the recent official recommendations [112,115]. No conclusive evidence was found to whether or not to recommend vaccination against herpes zoster in patients on treatment with imAbs. However, the frequency of herpes zoster reactivation for some imAbs is similar or even higher than for some anti-JAK drugs, which is why we include this information in Table 5.

4.2.10. Diphtheria, tetanus, and acellular pertussis (DTaP) vaccination

Recommendations regarding DTaP vaccination for immunosuppressed patients are the same as for general population. The recommended schedule includes a 3-dose series followed by 2 booster doses. For patients over 65 years old, an additional booster could be necessary. Other strategies propose a booster dose of DT or DTaP each 10 years during all the life [116]. However, the risk–benefit balance must be weighed since the tetanus vaccine has rare but potentially serious adverse effects (e.g. Arthus-type hypersensitivity reactions) [117].

Periodic measurement of antibody titers after vaccination to determine the immune response may help to guide revaccination in immunocompromised children [53], although it is not usually recommended for adult immunocompromised patients [57]. In contrast to non-immunocompromised subjects, biologically treated patients with a tetanus-prone wound should receive an injection of tetanus immune globulin (TIG), regardless of their *C. tetani* immunization status [118].

Based on the literature search, we recommend DTaP vaccination of patients undergoing imAb treatment with the same recommendations as for the general population.

4.2.11. Tuberculosis vaccination

The live attenuated tuberculosis vaccine, bacillus Calmette-Guérin (BCG) is not recommended for patients under immunosuppressive therapy, unless it is administered 4 weeks before the start of treatment. Before solid organ transplantation, BCG vaccination is only recommended in certain situations (endemic areas or when exposure to tuberculosis is not avoidable and preventive measures are not possible) [119]. Evidence suggest that BCG might somehow protect against other *Mycobacterium* species and even other pathogens such as pertussis or pneumococcal antigens [120], therefore reducing the risk of infections [121]. It is also been suggested that it reduces all-cause mortality for children [122] and it might prevent autoimmune conditions [123]. Nevertheless, all these studies have been conducted in healthy infants and are not conclusive for the purposes of this review. Besides, no other tuberculosis vaccines have been approved to date, and it can cause the disease (tuberculosis) in immunosuppressed patients [124].

According to the current literature, there is no sufficient data to recommend BCG vaccination in patients under imAb therapy, and it should be avoided during the treatment.

5. Current discussions and developments

Several imAbs generate a relevant immunosuppression affecting lymphocyte-B-mediated response, thus affecting their capacity to adequately response to vaccination. Besides, some of them require long waiting vaccinating times. For example, anti CD20 imAbs (rituximab, ocrelizumab, obinutuzumab, etc.) require waiting for vaccination at least 6 months after the end of treatment [57]. This fact remarks the importance of guaranteeing vaccination of these patients before treatment. That implies that clinical specialists could help referring these patients to the vaccination consultation before the initiation of imAb therapy, which is the most effective interval even for anti-CD20 imABs [60]. Besides, it is not clear if vaccination during certain treatments (e.g. anti-CD20) is effective, or if these vaccines are being administered without clinical or serological benefits. As no studies have concretely approached this dilemma, clinicians cannot risk not vaccinating. The risk–benefit balance is yet to be established for each type of imAb and vaccine. Similarly, when imAbs are administered together with other chemotherapy drugs or highly immunosuppressing treatments, all vaccines that have been administered during treatment should be repeated after the end of the therapy, when the immune response is recovered. Nevertheless, the immune response may not be optimal and continue to decline [125].

Another issue of particular concern is that of pregnant women requiring treatment with imAbs. There is a need to promote and intensify peer education to instruct other professionals (including gynecologists, pediatricians, and general practitioners) when to refer pregnant women requiring imAb treatment for specialized vaccination consultation. Several imAbs (Table 3) require, according to the technical datasheet, an analysis of B lymphocyte count in the newborns and, in cases of depletion, the use of live or attenuated vaccines should be avoided until normal lymphocyte levels are restored.

Current vaccine recommendations are generally common (equal) for most immunocompromised patients, regardless the specific type of treatment. Moreover, not all mAbs are immunosuppressive (and therefore requiring vaccination); we present a list of non-immunosuppressive mAbs as Supplementary Table S1. Regarding imAbs, their high heterogeneity makes it necessary for vaccine schedules to be adapted. We propose a general decision algorithm in Figure 1, which may vary according to local or national recommendations. Nevertheless, more efforts in individualizing these vaccine strategies are still required.

Other promising area for future research includes the incorporation of different vaccines to official recommendations. As an example, an analysis of the potential benefits of incorporating the 20-valent pneumococcal conjugate vaccine (PCV20) or other new vaccines, compared to previously available vaccines is needed. The high-dose influenza vaccine (currently recommended for the elderly in several countries, because of immunosenescence reasons) could also be recommended for immunocompromised patients (including those under imAb treatment) but, again, safety and effectiveness studies in this population are lacking. The consequences in terms of prevention of invasive pneumococcal disease with PCV20 and RSV infection in children with nirsevimab are two lines of research that will also serve to make decisions regarding the

reinforcement or extension of these preventive measures in other contexts.

Hepatitis B vaccine should also be considered for any patient on imAb therapies, and hepatitis A vaccine should be recommended when hepatotoxic effects have been reported. However, the decision on when to use these vaccines (according to epidemiologic risk factors), the type and doses preferred, and when to perform serologic test to assess the response, are still under debate.

Many other vaccines have been shown to be effective in certain patients and under specific biological treatments (e.g. human papillomavirus vaccine). The indication for herpes zoster vaccination has also been accepted for some particular drugs. Some potential uses of BCG vaccines have been proposed, but as they are live attenuated vaccines, the risk–benefit balance is not clear and, therefore, vaccination cannot be recommended. Future research on this vaccine should be conducted on patients under imAb therapies.

Besides, some relevant but very uncommon adverse events have been associated with several vaccines. For all these cases, the benefits outweigh the potential risks, but patients have to be fully informed, especially at a time when anti-vaccine movements are proliferating. Adequate information on benefits and risks and evidence-based recommendations should guide vaccination consultation decisions.

There are also some 'forgotten' issues regarding protection of immunocompromised patients. First, the vaccination of the domestic environment (co-habitants and close relatives), and other preventive measures rather than vaccination [33]. Future studies analyzing the best way of recruiting such contacts and the adequate required vaccines will be relevant. Health promotion including healthy lifestyles, use of masks in clinical environments and general prevention attitudes, especially during seasonal influenza, RSV and COVID-19, are critical for improving current strategies mainly based on vaccination. Second, the inclusion of other pharmacological preventive measures rather than (or together with) vaccination (e.g. mAb prophylaxis like nirsevimab, pre-exposure prophylaxis – PrEP for VIH, passive immunization with immunoglobulins, etc.).

The use of nirsevimab for prevention of RSV infection in children in some regions of Spain is currently under debate. How this expensive measure is effective at the population level will guide future recommendations on mAb use for prophylactic purposes. In addition, the joint use of imAbs, as authorized in 2023 with the relatlimab-nivolumab combination, opens another door to the pharmacological development of combinations, as occurs with other agents such as antivirals.

New indications are also in constant debate. For example, indications of hepatitis A vaccine for imAbs that presented high frequency of hepatic complications, or indications on exact biological treatments that require herpes zoster vaccination (for the moment, anti-JAKs are the only consistent recommendations). Finally, optimizing COVID-19 vaccine boosters according to imAbs is also needed.

6. Conclusions

In this review, a comprehensive list of mAbs authorized by the EMA as of January 2024 is available, along with their main characteristics and current vaccination recommendations.

The level of immunosuppression, optimal time schedules, and best practice for vaccine schedule organization are approached, and current discussed issues that will lead future research are presented. Injectable influenza, COVID-19, pneumococcal, and hepatitis B vaccination is recommended for all patients on imAb therapy. Hepatitis A vaccination should be considered when the imAb or other immunosuppressive treatments have reported hepatotoxicity. Herpes zoster vaccine should be recommended in patients treated with anti-JAK (which could be broadened in the near future); however, the recommendations given in this review should be considered with caution, as patients should be assessed on an individual basis and according to local guidelines. Concomitant diseases and treatments, the duration, posology, and initiation of imAb treatment, immunosuppression status, clinical history, and local guidelines according to each epidemiologic situation should be considered for individualizing vaccination.

Therefore, this practical review should be considered as a compendium of minimum recommendations, to which further indications should be added depending on the characteristics of each patient. Future studies addressing the current issues discussed in this review will be useful for optimizing the adequacy of vaccination schedules.

7. Expert opinion

Despite the enormous explosion of mAb authorization and commercialization, and the recent advances in vaccine development, most recommendations on vaccination for patients under imAb treatment are based on expert opinions and consensus documents to date [57]. A comprehensive review of the literature identified an alarming absence of studies analyzing adequate vaccine recommendations and immunogenicity for patients under imAbs, except for recent COVID-19 vaccine schedules. These data are, however, essential for guaranteeing safety and infection prevention on especially vulnerable patients.

The wide variety of antigen targets, biological mechanisms of action, elimination time, and effects on immunology, creates great uncertainty for healthcare professionals working in specialized vaccine consultations. Most of these problems would be solved through two strategies: 1) by creating and maintaining multidisciplinary teams continuously updating on imAbs and immunization strategies, and 2) by supporting and investing in specific research projects aimed at analyzing the optimal vaccination schedule for each individualized imAb.

This review and future research on this topic could improve the individualization of vaccinated patients under imAb treatment and homogenize evidence-based vaccination recommendations between different centers and services. To this end, practical guidelines that could be easily implemented in clinical practice according to updated recommendations would be very useful. This would lead

reviews and advances in this topic to impact real-world outcomes (specifically, the adequate immunization of vulnerable patients and the reduction of outcomes caused by preventable infections). Besides, changes can be realistically implemented in clinical practice by continuously updating clinical guidelines through coordinated reviews on the advances in this field.

Nevertheless, the limited number of current original analytical follow-up studies with sufficiently large sample sizes on outcomes regarding vaccination schedules of patients on imAb therapy may delay the adoption of effective preventive measures. In our opinion, it would be essential to promote and finance studies of such design. Several lacks in this field are related to the need of a research agenda funded by Public Trust. It is likely that vaccination industries have low interest in investigating the effectiveness and the immunogenicity of vaccines among immunocompromised people, for absence of relevant commercial return. While these studies are conducted, it is necessary to find the ideal balance between general vaccination recommendations and individualization. The ultimate goal in this field would be to generate continuously updated comprehensive guidelines to help clinicians take the best decision regarding vaccination of patients under any imAb treatment. Ideally, future research projects should be focused on the real response (not only laboratory but also clinical outcomes) to specific vaccination schedules. It is difficult to evaluate real-world outcomes regarding vaccine effectiveness. To define surrogate endpoints for future trials will be essential (e.g. infection case rates, but also hospitalization, ICU admission, mortality or other prognostic endpoints regarding severity of the infection) to correctly evaluate the impact of these vaccines from a clinical point of view.

The conduction of updated periodic reviews on the heterogeneity and variety of imAbs, their characteristics and risks, and the design of studies to evaluate the most adequate vaccination strategies, are essential. These efforts might guide actions in the future years, as this review intend, updating the data previously published in 2020 [6]. Besides, homogenization of the clinical practice regarding vaccination of the immunocompromised patient is necessary, as decision highly vary among countries and hospitals.

It is increasingly essential to update the knowledge and clinical practice according to the current treatments and vaccines. It is possible that in 5–10 years the quantity and variety of approved imAbs will be profuse, as the different vaccine technologies and available options. In the recent years, numerous different technologies have been successfully applied to specific vaccines. It is likely than in the following years a large number of different vaccines (different doses, adjuvanted or not, mRNA technology, adenovirus…) are likely to be approved in the coming years. Decisions on how to manage these data and decide wisely will depend on the design of rigorous longitudinal studies. We believe that the future of this line of research lies in the individualization of vaccination, based on specific treatments and approved vaccines, always based on robust scientific evidence. We encourage researchers to make efforts in this field and share their data with the scientific community. Hopefully, this review may serve as a starting point for facilitating practical tools for vaccine consultations of the immunocompromised patient.

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Author contributions

M Rivera-Izquierdo and MC Valero-Ubierna were involved in the conception and design of the study. A Morales-Portillo, I Guerrero-Fernández de Alba, N Fernández-Martínez, MC Valero-Ubierna, JA Schoenenberger-Arnaiz, and JL Barranco-Quintana were involved in the interpretation of the analysis and ensured its scientific quality, providing expert insight. M Rivera-Izquierdo wrote the first draft of the manuscript. All authors revised the manuscript for important intellectual content and give their approval to the final version of the study to be published and take accountabilities for all aspects of the work.

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ORCID

Mario Rivera-Izquierdo http://orcid.org/0000-0001-6159-6037
Nicolás Francisco Fernández-Martínez http://orcid.org/0000-0001-8257-4304
José Luis Barranco-Quintana http://orcid.org/0000-0002-6925-8363

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers."

1. Castelli MS, McGonigle P, Hornby PJ. The pharmacology and therapeutic applications of monoclonal antibodies. Pharmacol Res Perspect. 2019;7(6):e00535. doi:10.1002/prp2.535
2. Shepard HM, Phillips GL, Thanos C, et al. Developments in therapy with monoclonal antibodies and related proteins. Clin Med (Lond). 2017;17(3):220–232. doi: 10.7861/clinmedicine.17-3-220
3. Buss NA, Henderson SJ, McFarlane M, et al. Monoclonal antibody therapeutics: history and future. Curr Opin Pharmacol. 2012;12(5):615–622. doi: 10.1016/j.coph.2012.08.001

4. An Z. Monoclonal antibodies – a proven and rapidly expanding therapeutic modality for human diseases. Protein Cell. 2010;1(4):319–330. doi: 10.1007/s13238-010-0052-8
5. European Medicines Agency (EMA). European public assessment report. [cited 2024 Jan 1]. Available from: http://www.ema.europa.eu/en/glossary/european-public-assessment-report
•• **Official website of the European Medicines Agency. Data on mAbs regarding authorization, marketing and technical datasheets have been checked on this website.**
6. Rivera-Izquierdo M, Valero-Ubierna MDC, Nieto-Gómez P, et al. Vaccination in patients under monoclonal antibody treatment: an updated comprehensive review. Expert Rev Vaccines. 2020;19(8):727–744. doi: 10.1080/14760584.2020.1800462
•• **The first comprehensive update on vaccination in patients under imAb therapies published in 2020.**
7. Katz Sand I, Gnjatic S, Krammer F, et al. Evaluation of immunological responses to third COVID-19 vaccine among people treated with sphingosine receptor-1 modulators and anti-CD20 therapy. Mult Scler Relat Disord. 2023;70:104486. doi: 10.1016/j.msard.2022.104486
8. Kant S, Kronbichler A, Salas A, et al. Timing of COVID-19 vaccine in the setting of anti-CD20 therapy: a primer for nephrologists. Kidney Int Rep. 2021;6(5):1197–1199. doi: 10.1016/j.ekir.2021.03.876
9. Liu K, Li J, Xu G. The optimal interval before receiving SARS-COV-2 vaccination for patients who have received anti-cd 20 monoclonal antibodies. Virulence. 2022;13(1):2012–2021. doi:10.1080/21505594.2022.2146380
10. Cowan J, Amson A, Christofides A, et al. Monoclonal antibodies as COVID-19 prophylaxis therapy in immunocompromised patient populations. Int J Infect Dis. 2023;134:228–238. doi: 10.1016/j.ijid.2023.06.021
11. Follmann D, O'Brien MP, Fintzi J, et al. Examining protective effects of SARS-CoV-2 neutralizing antibodies after vaccination or monoclonal antibody administration. Nat Commun. 2023;14(1):3605. doi: 10.1038/s41467-023-39292-w
12. European Medicines Agency (EMA). European public assessment report. [cited 2024 Jan 1]. Available from: https://www.ema.europa.eu/en/glossary/european-public-assessment-report
• **Data regarding safety in clinical trials and plans to minimize the risk of infection can be consulted in the European Public Assessment Reports of the EMA.**
13. Animal Cell Technology Industrial Platform (ACTIP). [cited 2024 Jan 1]. Available from: https://www.actip.org/
14. Listing J, Strangfeld A, Kary S, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum. 2005;52(11):3403–3412. doi: 10.1002/art.21386
15. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum. 2007;56(4):1125–1133. doi: 10.1002/art.22504
16. Charan J, Dutta S, Kaur R, et al. Tocilizumab in COVID-19: a study of adverse drug events reported in the WHO database. Expert Opin Drug Saf. 2021;20(9):1125–1136. doi: 10.1080/14740338.2021.1946513
17. Davis JS, Ferreira D, Paige E, et al. Infectious complications of biological and small molecule targeted immunomodulatory therapies. Clin Microbiol Rev. 2020;33(3):e00035–19. doi: 10.1128/CMR.00035-19
18. Margoni M, Preziosa P, Filippi M, et al. Anti-CD20 therapies for multiple sclerosis: current status and future perspectives. J Neurol. 2022;269(3):1316–1334. doi: 10.1007/s00415-021-10744-x
19. Mikulska M, Lanini S, Gudiol C, et al. ESCMID study group for infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). Clin Microbiol Infect. 2018;24(Suppl 2):S71–S82. doi: 10.1016/j.cmi.2018.02.003
20. Sevilla JP. Immunization, not vaccination: monoclonal antibodies for infant RSV prevention and the US vaccines for children program. J Med Econ. 2023;26(1):991–997. doi:10.1080/13696998.2023.2242169
21. Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (tixagevimab-cilgavimab) for prevention of covid-19. N Engl J Med. 2022;386(23):2188–2200. doi: 10.1056/NEJMoa2116620
22. U.S. Food and Drug Administration (FDA). FDA announces evusheld is not currently authorized for emergency use in the U.S. [cited 2024 Jan 1]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-evusheld-not-currently-authorized-emergency-use-us
23. Falsey AR, Williams K, Gymnopoulou E, et al. Efficacy and safety of an Ad26.RSV.preF-rsv preF protein vaccine in older adults. N Engl J Med. 2023;388(7):609–620. doi: 10.1056/NEJMoa2207566
24. Consejería de Salud y Consumo, Dirección General de Salud Pública y Ordenación Farmacéutica, Junta de Andalucía. Programa de prevención de infección VRS con Nirsevimab. Andalucía, campaña 2023-2024 [RSV infection prevention program with Nirsevimab. Andalusia, campaign 2023-2024]. [cited 2024 Jan 1]. Available from: https://www.andavac.es/wp-content/uploads/instrucciones/Instruccion_DGSPyOF-9-2023_Nirsevimab_Andalucia_2023-2024.pdf
25. Martinón-Torres F, Mirás-Carballal S, Durán-Parrondo C. Early lessons from the implementation of universal respiratory syncytial virus prophylaxis in infants with long-acting monoclonal antibodies, Galicia, Spain, September and October 2023. Euro Surveill. 2023;28(49):2300606. doi: 10.2807/1560-7917.ES.2023.28.49.2300606
26. Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). General best practice guidelines for immunization: best practices guidance. Altered immunocompetence. [cited 2024 Jan 1]. Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html
27. Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Immunization schedules. [cited 2024 Jan 1]. Available from: https://www.cdc.gov/vaccines/schedules/hcp/adult.html
28. Infectious Diseases Society of America (IDSA). Clinical practice guideline for vaccination of the immunocompromised host. [cited 2024 Jan 1]. Available from: https://www.idsociety.org/practice-guideline/vaccination-of-the-immunocompromised-host/
29. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):309–318. doi: 10.1093/cid/cit816
30. Shoham S, Batista C, Ben Amor Y, et al. Vaccines and therapeutics for immunocompromised patients with COVID-19. EClinicalMedicine. 2023;59:101965. doi: 10.1016/j.eclinm.2023.101965
31. Lopez A, Mariette X, Bachelez H, et al. Vaccination recommendations for the adult immunosuppressed patient: a systematic review and comprehensive field synopsis. J Autoimmun. 2017;80:10–27. doi: 10.1016/j.jaut.2017.03.011
32. Martire B, Azzari C, Badolato R, et al. Vaccination in immunocompromised host: recommendations of Italian primary immunodeficiency network centers (IPINET). Vaccine. 2018;36(24):3541–3554. doi: 10.1016/j.vaccine.2018.01.061
33. Schreiner D, Zepp F. Allgemeine Prinzipien des Impfens unter Immunsuppression [General principles of vaccination under immunosuppression]. Z Rheumatol. 2020;79(9):848–854. doi:10.1007/s00393-020-00891-3
34. Nguyen MTT, Lindegaard H, Hendricks O, et al. Initial serological response after prime-boost pneumococcal vaccination in rheumatoid arthritis patients: results of a randomized controlled trial. J Rheumatol. 2017;44(12):1794–1803. doi: 10.3899/jrheum.161407
35. Nagra D, Bechman K, Adas M, et al. A systematic review and meta-analysis of Anti-rheumatic drugs and pneumococcal vaccine immunogenicity in inflammatory arthritis. Vaccines (Basel). 2023;11(11):1680. doi: 10.3390/vaccines11111680
36. Chatham WW, Wallace DJ, Stohl W, et al. Effect of belimumab on vaccine antigen antibodies to influenza, pneumococcal, and tetanus vaccines in patients with systemic lupus erythematosus in the

BLISS-76 trial. J Rheumatol. 2012;39(8):1632–1640. doi: 10.3899/jrheum.111587
37. Kivitz AJ, Schechtman J, Texter M, et al. Vaccine responses in patients with rheumatoid arthritis treated with certolizumab pegol: results from a single-blind randomized phase IV trial. J Rheumatol. 2014;41(4):648–657. doi: 10.3899/jrheum.130945
38. Mehta L, Umans K, Ozen G, et al. Immune response to seasonal influenza vaccine in patients with relapsing-remitting multiple sclerosis receiving long-term daclizumab beta: a prospective, open-label, single-arm study. Int J MS Care. 2017;19(3):141–147. doi: 10.7224/1537-2073.2016-026
39. Kaufman M, Pardo G, Rossman H, et al. Natalizumab treatment shows no clinically meaningful effects on immunization responses in patients with relapsing-remitting multiple sclerosis. J Neurol Sci. 2014;341(1–2):22–27. doi: 10.1016/j.jns.2014.03.035
40. Jaber A, Patel M, Sylvester A, et al. COVID-19 vaccine response in people with multiple sclerosis treated with dimethyl fumarate, diroximel fumarate, Natalizumab, ocrelizumab, or interferon beta therapy. Neurol Ther. 2023;12(2):687–700. doi: 10.1007/s40120-023-00448-x
41. Hauser SL, Bar-Or A, Comi G, et al. OPERA I and OPERA II clinical investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2017;376(3):221–234. doi: 10.1056/NEJMoa1601277
42. Eisenberg RA, Jawad AF, Boyer J, et al. Rituximab-treated patients have a poor response to influenza vaccination. J Clin Immunol. 2013;33(2):388–396. doi: 10.1007/s10875-012-9813-x
43. van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. Arthritis Rheum. 2010;62(1):75–81. doi: 10.1002/art.25033
44. Berglund A, Willén L, Grödeberg L, et al. The response to vaccination against influenza (H1N1) 2009, seasonal influenza and streptococcus pneumoniae in adult outpatients with ongoing treatment for cancer with and without rituximab. Acta Oncol. 2014;53(9):1212–1220. doi: 10.3109/0284186X.2014.914243
45. Smith JB, Gonzales EG, Li BH, et al. Analysis of rituximab use, time between rituximab and SARS-CoV-2 vaccination, and COVID-19 hospitalization or death in patients with multiple sclerosis. JAMA Netw Open. 2022;5(12):e2248664. doi: 10.1001/jamanetworkopen.2022.48664
46. Rose E, Magliulo D, Kyttaris VC. Seroconversion among rituximab-treated patients following SARS-CoV-2 vaccine supplemental dose. Clin Immunol. 2022;245:109144. doi:10.1016/j.clim.2022.109144
47. Bingham CO 3rd, Rizzo W, Kivitz A, et al. Humoral immune response to vaccines in patients with rheumatoid arthritis treated with tocilizumab: results of a randomized controlled trial (VISARA). Ann Rheum Dis. 2015;74(5):818–822. doi: 10.1136/annrheumdis-2013-204427
48. Tsuru T, Terao K, Murakami M, et al. Immune response to influenza vaccine and pneumococcal polysaccharide vaccine under IL-6 signal inhibition therapy with tocilizumab. Mod Rheumatol. 2014;24(3):511–516. doi: 10.3109/14397595.2013.843743
49. Schwake C, Pakeerathan T, Kleiter I, et al. Humoral COVID-19 vaccine response in patients with NMOSD/MOGAD during anti-IL-6 receptor therapy compared to other immunotherapies. Mult Scler. 2023;29(6):757–761. doi: 10.1177/13524585221151124
50. Brodmerkel C, Wadman E, Langley RG, et al. Immune response to pneumococcus and tetanus toxoid in patients with moderate-to-severe psoriasis following long-term ustekinumab use. J Drugs Dermatol. 2013;12(10):1122–1129.
51. Wyant T, Leach T, Sankoh S, et al. Vedolizumab affects antibody responses to immunization selectively in the gastrointestinal tract: randomised controlled trial results. Gut. 2015;64(1):77–83. doi: 10.1136/gutjnl-2014-307127
52. American Academy of Pediatrics. Committee on Infectious Diseases. Immunization in special clinical circumstances: Immunization in immunocompromised children. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red Book: 2015 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2015. p. 74–89.
53. Asociación Española de Pediatría (AEP). Comité Asesor de Vacunas. Vacunación en niños inmunodeprimidos o con tratamiento inmunosupresor. Manual de Vacunas en línea de la AEP. Capítulo 14. [Spanish Pediatrics Association (AEP). Vaccine Advisory Committee. Vaccination in immunosuppressed children or children under immunosuppressive therapy. AEP Online immunization manual. Chapter 14. [cited 2024 Jan 1]. Available from: http://vacunasaep.org/print/documentos/manual/cap-14
54. Public Health England. Immunisation against infectious diseases: immunisation of individuals with underlying medical conditions. Salisbury: The Green Book. The Stationary Office; 2016.
55. Australian Technical Advisory Group on Immunisation (ATAGI). The Australian immunization handbook 10th ed (2017 update). Canberra: Australian Government Department of Health. Part 3.3.3 Vaccination of immunocompromised persons; 2017 [cited 2024 Jan 1]. Available from: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part3~handbook10-3-3#3-3-3
56. Rubin LG, Levin MJ, Ljungman P, et al. Infectious diseases society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):309–318. doi: 10.1093/cid/cit816
57. Ministerio de Sanidad, Consumo y Bienestar Social. Vacunación en grupos de riesgo de todas las edades y en determinadas situaciones, del programa y registro de vacunaciones, 2018 [Spanish Ministry of Health, Consumer Affairs and Social Welfare. Vaccination of risk groups of all ages and in specific circumstances, program and registry of vaccinations, 2018]. [cited 2024 Jan 1]. Available from: https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/VacGruposRiesgo/docs/VacGruposRiesgo_todas_las_edades.pdf
- **Detailed advice regarding vaccination of immunocompromised patients according to the Spanish Government.**
58. Liao Z, Tang H, Xu X, et al. Immunogenicity and safety of influenza vaccination in systemic lupus erythematosus patients compared with healthy controls: a meta-analysis. PLOS ONE. 2016;11(2):e0147856. doi: 10.1371/journal.pone.0147856
59. Krajnc N, Bsteh G, Berger T, et al. Monoclonal antibodies in the treatment of relapsing multiple sclerosis: an overview with emphasis on pregnancy, vaccination, and risk management. Neurotherapeutics. 2022;19(3):753–773. doi: 10.1007/s13311-022-01224-9
60. Lebrun C, Vukusic S; French Group for Recommendations in Multiple Sclerosis (France4MS) and the Société Francophone de la Sclérose En Plaques (SFSEP). Immunization and multiple sclerosis: recommendations from the French multiple sclerosis society. Mult Scler Relat Disord. 2019;31:173–188. doi: 10.1016/j.msard.2019.04.004
61. Richi P, Martín MD, Navío MT, et al. Antibody responses to influenza vaccine in patients on biological therapy: results of RIER cohort study. Med Clin (Barc). 2019;153(10):380–386. doi: 10.1016/j.medcli.2019.02.003
62. Bosaeed M, Kumar D. Seasonal influenza vaccine in immunocompromised persons. Hum Vaccin Immunother. 2018;14(6):1311–1322. doi:10.1080/21645515.2018.1445446
63. Natori Y, Humar A, Lipton J, et al. A pilot randomized trial of adjuvanted influenza vaccine in adult allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2017;52(7):1016–1021. doi: 10.1038/bmt.2017.24
64. Manuel O, Humar A, Chen MH, et al. Immunogenicity and safety of an intradermal boosting strategy for vaccination against influenza in lung transplant recipients. Am J Transplant. 2007;7(11):2567–2572. doi: 10.1111/j.1600-6143.2007.01982.x
65. Cordero E, Roca-Oporto C, Bulnes-Ramos A, et al. Two doses of inactivated influenza vaccine improve immune response in solid organ transplant recipients: results of TRANSGRIPE 1-2, a randomized controlled clinical trial. Clin Infect Dis. 2017;64(7):829–838. doi: 10.1093/cid/ciw855

66. Huang Y, Wang H, Tam WWS. Is rheumatoid arthritis associated with reduced immunogenicity of the influenza vaccination? A systematic review and meta-analysis. Curr Med Res Opin. 2017;33(10):1901–1908. doi:10.1080/03007995.2017.1329140
67. Lee JKH, Lam GKL, Shin T, et al. Efficacy and effectiveness of high-dose influenza vaccine in older adults by circulating strain and antigenic match: an updated systematic review and meta-analysis. Vaccine. 2021;39(Suppl 1):A24–A35. doi: 10.1016/j.vaccine.2020.09.004
68. Beck CR, McKenzie BC, Hashim AB, et al. Influenza vaccination for immunocompromised patients: systematic review and meta-analysis by etiology. J Infect Dis. 2012;206(8):1250–1259. doi: 10.1093/infdis/jis487
69. Auladell M, Jia X, Hensen L, et al. Recalling the future: immunological memory toward unpredictable influenza viruses. Front Immunol. 2019;10:1400. doi: 10.3389/fimmu.2019.01400
70. Schmoele-Thoma B, van Cleeff M, Greenberg RN, et al. Persistence of antibodies 1 year after sequential administration of the 13-valent pneumococcal conjugate vaccine and the 23-valent pneumococcal polysaccharide vaccine in adults. Hum Vaccin Immunother. 2019;15(3):575–583. doi: 10.1080/21645515.2018.1538618
71. Rákóczi É, Szekanecz Z. Pneumococcal vaccination in autoimmune rheumatic diseases. RMD Open. 2017;3(2):e000484. doi:10.1136/rmdopen-2017-000484
72. Hua C, Barnetche T, Combe B, et al. Effect of methotrexate, anti-tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2014;66(7):1016–1026. doi: 10.1002/acr.22246
73. Fiorino G, Peyrin-Biroulet L, Naccarato P, et al. Effects of immunosuppression on immune response to pneumococcal vaccine in inflammatory bowel disease: a prospective study. Inflamm Bowel Dis. 2012;18(6):1042–1047. doi: 10.1002/ibd.21800
74. van Aalst M, Langedijk AC, Spijker R, et al. The effect of immunosuppressive agents on immunogenicity of pneumococcal vaccination: a systematic review and meta-analysis. Vaccine. 2018;36(39):5832–5845. doi: 10.1016/j.vaccine.2018.07.039
75. Nagel J, Saxne T, Geborek P, et al. Treatment with belimumab in systemic lupus erythematosus does not impair antibody response to 13-valent pneumococcal conjugate vaccine. Lupus. 2017;26(10):1072–1081. doi: 10.1177/0961203317695465
76. Shirley M. 20-valent pneumococcal conjugate vaccine: a review of its use in adults. Drugs. 2022;82(9):989–999. doi:10.1007/s40265-022-01733-z
77. Wierzbowski A, Pless R, Hildebrand KJ. Summary of the NACI statement on public health level recommendations on the use of pneumococcal vaccines in adults, including the use of 15-valent and 20-valent conjugate vaccines. Can Commun Dis Rep. 2023;49(23):81–86. doi: 10.14745/ccdr.v49i23a08
78. Scheen AJ, Louis R, Moutschen M. Apexxnar®, vaccin antipneumococcique conjugué avec 20 sérotypes [Apexxnar®, 20-valent pneumococcal conjugate vaccine]. Rev Med Liege. 2022;77(11):678–683.
79. Marbaix S, Mignon A, Taelman A, et al. Cost-utility of 20-valent pneumococcal conjugate vaccine compared to no vaccination and recommended alternative vaccines among Belgian adults. Expert Rev Vaccines. 2023;22(1):1008–1021. doi: 10.1080/14760584.2023.2273892
80. Consejería de Salud y Consumo, Dirección General de Salud Pública, Junta de Andalucía. Programa de vacunación frente a neumococo en Andalucía, 2023. [Pneumococcal vaccination program in Andalusia, 2023]. [cited 2024 Jan 1]. Available from: https://www.andavac.es/wp-content/uploads/instrucciones/Instruccion_Vacunacion_Neumococo_Andalucia.pdf
81. Wilck M, Cornely OA, Cordonnier C, et al. A phase 3, randomized, double-blind, comparator-controlled study to evaluate safety, tolerability, and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, in allogeneic hematopoietic cell transplant recipients (PNEU-STEM). Clin Infect Dis. 2023;77(8):1102–1110. doi: 10.1093/cid/ciad349
82. Alvarez CA, Hall RG 2nd, Lin S, et al. Compliance with recommended pneumococcal vaccination schedule in patients treated for rheumatoid arthritis: a retrospective cohort study in the veterans affairs population. Vaccine. 2024;42(3):489–495. doi: 10.1016/j.vaccine.2023.12.075
83. Yadav T, Kumar S, Mishra G, et al. Tracking the COVID-19 vaccines: the global landscape. Hum Vaccin Immunother. 2023;19(1):2191577. doi: 10.1080/21645515.2023.2191577
84. Jalalvand F, Riesbeck K. Update on non-typeable Haemophilus influenzae-mediated disease and vaccine development. Expert Rev Vaccines. 2018;17(6):503–512. doi:10.1080/14760584.2018.1484286
85. Cerquetti M, Giufrè M. Why we need a vaccine for non-typeable Haemophilus influenzae. Hum Vaccin Immunother. 2016;12(9):2357–2361. doi:10.1080/21645515.2016.1174354
86. Thoelen S, Van Damme P, Mathei C, et al. Safety and immunogenicity of a hepatitis B vaccine formulated with a novel adjuvant system. Vaccine. 1998;16(7):708–714. doi: 10.1016/S0264-410X(97)00254-5
87. Intongkam S, Samakarnthai P, Pakchotanon R, et al. Efficacy and safety of hepatitis B vaccination in rheumatoid arthritis patients receiving disease-modifying antirheumatic drugs and/or biologics therapy. J Clin Rheumatol. 2019;25(8):329–334. doi: 10.1097/RHU.0000000000000877
88. Karaman S, Vural S, Yildirmak Y, et al. Assessment of hepatitis B immunization status after antineoplastic therapy in children with cancer. Ann Saudi Med. 2011;31(6):573–576. doi: 10.4103/0256-4947.87091
89. Van Den Ende C, Marano C, Van Ahee A, et al. The immunogenicity and safety of GSK's recombinant hepatitis B vaccine in adults: a systematic review of 30 years of experience. Exp Rev Vaccin. 2017;16(8):811–832. doi: 10.1080/14760584.2017.1338568
90. Saco TV, Strauss AT, Ledford DK. Hepatitis B vaccine nonresponders: possible mechanisms and solutions. Ann Allergy Asthma Immunol. 2018;121(3):320–327. doi:10.1016/j.anai.2018.03.017
91. María FP, María BA, Darío RO, et al. Immunogenicity of the hepatitis B vaccine adjuvanted with AS04C in patients with biological therapies. Vaccine. 2023;41(3):744–749. doi: 10.1016/j.vaccine.2022.12.009
92. Rodrigues IC, Rcmad S, Felício HCC, et al. New immunization schedule effectiveness against hepatitis B in liver transplantation patients. Arq Gastroenterol. 2019;56(4):440–446. doi: 10.1590/s0004-2803.201900000-77
93. Günther M, Neuhaus R, Bauer T, et al. Immunization with an adjuvant hepatitis B vaccine in liver transplant recipients: antibody decline and booster vaccination with conventional vaccine. Liver Transpl. 2006;12(2):316–319. doi: 10.1002/lt.20674
94. Walayat S, Ahmed Z, Martin D, et al. Recent advances in vaccination of non-responders to standard dose hepatitis B virus vaccine. World J Hepatol. 2015;7(24):2503–2509. doi: 10.4254/wjh.v7.i24.2503
95. Choi J, Lim YS. Characteristics, prevention, and management of hepatitis B virus (HBV) reactivation in hbv-infected patients who require immunosuppressive therapy. J Infect Dis. 2017;216(S8):SS778–SS784. doi: 10.1093/infdis/jix178
96. Chen MH, Chen MH, Liu CY, et al. Hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologics treatment. J Infect Dis. 2017;215(4):566–573. doi: 10.1093/infdis/jiw606
97. Epstein DJ, Dunn J, Deresinski S. Infectious complications of multiple sclerosis therapies: implications for screening, prophylaxis, and management. Open Forum Infect Dis. 2018;5(8):ofy174. doi:10.1093/ofid/ofy174
98. Glück T, Müller-Ladner U. Vaccines: vaccination in patients with chronic rheumatic or autoimmune diseases. Clin Infect Dis. 2008;46(9):1459–1465. doi:10.1086/587063
99. Tran-Minh ML, Sousa P, Maillet M, et al. Hepatic complications induced by immunosuppressants and biologics in inflammatory bowel disease. World J Hepatol. 2017;9(13):613–626. doi: 10.4254/wjh.v9.i13.613
100. Mathew Thomas V, Bindal P, Ann Alexander S, et al. Nivolumab-induced hepatitis: a rare side effect of an immune check point

inhibitor. J Oncol Pharm Pract. 2020;26(2):459–461. doi: 10.1177/1078155219837342
101. Rosdahl A, Herzog C, Frösner G, et al. An extra priming dose of hepatitis a vaccine to adult patients with rheumatoid arthritis and drug induced immunosuppression - a prospective, open-label, multi-center study. Travel Med Infect Dis. 2018;21:43–50. doi: 10.1016/j.tmaid.2017.12.004
102. Government of Canada. Update on the recommended use of hepatitis a vaccine. An advisory committee statement (ACS) national advisory committee on immunization (NACI). [cited 2024 Jan 1]. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/update-recommended-use-hepatitis-vaccine.html
103. Wine-Lee L, Keller SC, Wilck MB, et al. From the medical board of the national psoriasis foundation: vaccination in adult patients on systemic therapy for psoriasis. J Am Acad Dermatol. 2013;69(6):1003–1013. doi: 10.1016/j.jaad.2013.06.046
104. Singh JA, Saag KG, Bridges SL, et al. 2015 American college of rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68(1):1–26. doi: 10.1002/art.39480
105. Deeks SL, Tunis MC, Ismail S. National advisory committee on immunization (NACI). Summary of the NACI update on the recommended use of human papillomavirus (HPV) vaccine: nine-valent HPV vaccine two-dose immunization schedule and the use of HPV vaccines in immunocompromised populations. Can Commun Dis Rep. 2017;43(6):138–142. doi:10.14745/ccdr.v43i06a04
106. Meca-Lallana JE, Fernández-Prada M, García Vázquez E, et al. Consensus statement on the use of alemtuzumab in daily clinical practice in Spain. Neurologia. 2020;37(8):615–630. doi: 10.1016/j.nrl.2019.11.003
107. Cuzick J. Gardasil 9 joins the fight against cervix cancer. Expert Rev Vaccines. 2015;14(8):1047–1049. doi:10.1586/14760584.2015.1051470
108. Bastidas A, de la Serna J, El Idrissi M, et al. Effect of recombinant zoster vaccine on incidence of herpes zoster after autologous stem cell transplantation: a randomized clinical trial. JAMA. 2019;322(2):123–133. doi: 10.1001/jama.2019.9053
109. Vink P, Delgado Mingorance I, Maximiano Alonso C, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in patients with solid tumors, vaccinated before or during chemotherapy: a randomized trial. Cancer. 2019;125(8):1301–1312. doi: 10.1002/cncr.31909
110. Parrino J, McNeil SA, Lawrence SJ, et al. Safety and immunogenicity of inactivated varicella-zoster virus vaccine in adults with hematologic malignancies receiving treatment with anti-CD20 monoclonal antibodies. Vaccine. 2017;35(14):1764–1769. doi: 10.1016/j.vaccine.2016.10.055
111. Clark JD, Flanagan ME, Telliez JB. Discovery and development of janus kinase (JAK) inhibitors for inflammatory diseases. J Med Chem. 2014;57(12):5023–5038. doi:10.1021/jm401490p
112. Consejería de Salud y Consumo, Dirección General de Salud Pública, Junta de Andalucía. Programa de vacunación frente a herpes zóster en Andalucía 2023. [Vaccination program against herpes zoster in Andalusia 2023]. [cited 2024 Jan 1]. Available from: https://www.andavac.es/wp-content/uploads/instrucciones/Instruccion_Vacunacion_Herpes_Zoster_Andalucia.pdf
113. Mwakingwe-Omari A, Lecrenier N, Naficy A, et al. Recombinant zoster vaccine in immunocompetent and immunocompromised adults: a review of clinical studies. Hum Vaccin Immunother. 2023;19(3):2278362. doi:10.1080/21645515.2023.2278362
114. Xia Y, Zhang X, Zhang L, et al. Efficacy, effectiveness, and safety of herpes zoster vaccine in the immunocompetent and immunocompromised subjects: a systematic review and network meta-analysis. Front Immunol. 2022;13:978203. doi: 10.3389/fimmu.2022.978203
115. Ministerio de Sanidad, Gobierno de España. Recomendaciones de vacunación frente a herpes zóster, 25 de marzo de 2021 [Herpes zoster vaccine recommendations, March 25, 2021]. [cited 2024 Jan 1]. Available from: https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/programasDeVacunacion/docs/HerpesZoster_RecomendacionesVacunacion.pdf
116. Havers FP, Moro PL, Hunter P, et al. Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: updated recommendations of the advisory committee on immunization practices - United States, 2019. MMWR Morb Mortal Wkly Rep. 2020;69(3):77–83. doi: 10.15585/mmwr.mm6903a5
117. Pool V, Mege L, Abou-Ali A. Arthus reaction as an adverse event following Tdap vaccination. Vaccines (Basel). 2020;8(3):385. doi:10.3390/vaccines8030385
118. World Health Organization. Department of violence and injury prevention and disability. Prevention and management of wound infection. [cited 2024 Jan 1]. Available from: https://www.who.int/hac/techguidance/tools/guidelines_prevention_and_management_wound_infection.pdf
119. Danziger-Isakov L, Kumar D. AST infectious diseases community of practice. Vaccination in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):311–317. doi:10.1111/ajt.12122
120. Zimmermann P, Donath S, Perrett KP, et al. The influence of neonatal bacille Calmette-Guerin (BCG) immunisation on heterologous vaccine responses in infants. Vaccine. 2019;37(28):3735–3744. doi: 10.1016/j.vaccine.2019.03.016
121. de Castro MJ, Pardo-Seco J, Martinón-Torres F. Nonspecific (heterologous) protection of neonatal BCG vaccination against hospitalization due to respiratory infection and sepsis. Clin Infect Dis. 2015;60(11):1611–1619. doi: 10.1093/cid/civ144
122. Butkeviciute E, Jones CE, Smith SG. Heterologous effects of infant BCG vaccination: potential mechanisms of immunity. Future Microbiol. 2018;13(10):1193–1208. doi:10.2217/fmb-2018-0026
123. Kowalewicz-Kulbat M, Locht C. BCG and protection against inflammatory and auto-immune diseases. Expert Rev Vaccines. 2017;16(7):1–10. doi: 10.1080/14760584.2017.1333906
124. Lange C, Aaby P, Behr MA, et al. 100 years of mycobacterium bovis bacille Calmette-Guérin. Lancet Infect Dis. 2022;22(1):e2–e12. doi: 10.1016/S1473-3099(21)00403-5
125. Bühler S, Eperon G, Ribi C, et al. Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases. Swiss Med Wkly. 2015;145:w14159. doi: 10.4414/smw.2015.14159