**Supplemental information- Supplemental Tables 1-7**

**Supplemental Table 1.** **Overview of the phenotypic descriptions used in the reviewed articles.** Only unique phenotypic descriptions are shown. Of note, several publications used overlapping phenotypic descriptions, but different population names. Therefore, some here-reported B-cell populations have high overlap in their phenotypic description. In cases where phenotypic descriptions were identical, both names were put in the same cell.

|  |  |
| --- | --- |
| **Regular B-cell populations** | **Phenotypic description used by reviewed articles** |
| Total B cells | CD19+CD20+CD19+CD20+CD19+CD45+HLA-DR+ |
| B1 B cells | CD19+CD5+ |
| Transitional/Immature B cells | CD19+CD10+CD20+CD10+CD19+CD27-IgD-CD19+CD24hiCD38hiCD19+IgMhiCD38hiCD19+CD21intIgMhiCD38hiCD19+CD20-CD21-CD27-CD19+CD20+CD27+/-IgD+CD38+/-CD19+CD27-IgD+IgM+/-CD38+CD19+CD20+CD10+CD23+CD5+CD38+ |
| Naive B cells/Mature Naive B cells | CD19+CD27-CD19+CD27-IgD+CD20+CD27-IgD+CD19+CD27-IgM+CD19+CD27-IgM+IgD+CD19+CD27-CD21+CD38+CD19+CD20+CD27-IgD+CD38-CD19+CD27-IgG-IgA-CD19+CD10-CD21+CD27-CD19+CD10-CD20+CD21+CD27-CD19+CD10-CD24+IgD+CD38- |
| Memory B cells | CD19+CD27+CD20+CD27+CD19+CD20+CD27+CD19+CD27+CD10-CD20+CD27+CD10-CD20+CD21hiCD27+CD10- |
| Unswitched Memory B cells (of note, high overlap with phenotypic description of IgM memory B cells between publications) | CD19+CD27+IgM+CD19+CD27+IgMhiCD19+CD27+IgMhiIgD- CD20+CD27+IgM+IgD+CD19+CD20+CD27+IgD+CD38- |
| Marginal zone (like) B cells/Natural effector B cells | CD19+CD27+IgMhiIgD+CD19+CD27+CD38-IgM+IgD+CD19+CD27+IgM+IgD+ |
| IgM memory B cells/IgM only memory B cells | CD19+CD27+IgD+ CD19+CD27+IgM+CD19+CD27+IgM+IgD+CD19+CD27+IgMhiIgD- CD19+CD27+IgMhiIgDloCD21hiCD19+CD10-CD27+CD21hiIgM+CD19+CD27+IgD+IgG-IgA- |
| IgD memory B cells | CD19+CD27+IgD+ CD19+CD27+CD38loIgD+ |
| Switched Memory B cells | CD19+CD27+IgD-CD20+CD27+IgD- CD19+CD27+IgM-CD19+CD27+IgM-IgD-CD19+CD20+CD27+IgD-CD19+CD27+CD38loIgD-CD19+CD20+/-CD27+IgD-CD38-CD19+CD27+IgG+/IgA+CD19+CD27+CD21+IgM-CD19+CD27+CD38+IgM-IgD‑CD19+CD10-CD27+CD21hiIgM- |
| Resting memory B cells | CD19+CD10-CD20+CD21+CD27+CD19+CD21+CD27+ |
| Activated memory B cells | CD19+CD10-CD20+CD21-CD27+CD19+CD21-CD27+ |
| Activated (mature) B cells | CD20+CD21loCD27-CD10+ CD19+CD10-CD21- CD19+CD38+HLA-DR+ |
| Plasmablasts | CD19+CD27hiCD38hiCD45+HLA-DR+CD19+CD10-CD20-CD27hiCD38hiCD19+CD27++CD20- (and Ag-specific)CD19+CD27+CD38+CD19+CD27hiCD38hiCD19loCD27hiCD38hiCD20loCD27hiCD38hiCD19+CD27+CD38+CD24-CD19loCD21intCD38hiIgM-(+)CD19+CD27+CD38+IgD-CD21-CD20loCD27+CD21+CD38+Ki67-CD20-CD27+CD21loCD10-Ki67+ |
| Antibody secreting cells | CD19+CD20-CD27hiCD38hiCD19+CD20loCD27hiCD38hi |
| **Aberrant or immune senescence-related B-cell populations** |  |
| Atypical memory B cells | CD19+CD10-CD20+CD21-CD27- |
| Age-associated B cells | CD19+CD21-T-bet+CD11c+CD27+ ‘memory’ CD19+CD21-T-bet+CD11c+CD27- ‘atypical memory’ |
| Late/exhausted memory B cells/ double negative B cells | CD19+CD27-IgD- CD19+CD27-CD21loCD19+CD20+CD27-IgD-CD38-CD20+CD27-IgD-CD19+CD27-IgD- |
| Anergic B cells/CD21lo B cells | CD19+CD21loCD38loCD19+CD21loCD38loIgM-CD19+CD21-/loCD38-CD19+CD27-CD21loCD38lo |
| Tissue-like (exhausted) memory B cells | CD20+CD10-CD21loCD27-CD19+CD21-CD27-IgD-CD38+CD19+CD21-CD27-CD19+CD20+CD21-CD27-CD19+CD10-CD21-CD27- |

In cases where ‘++’ was used to indicate high marker expression, this was replaced by ‘hi’ to make phenotypic descriptions more consistent.

**Supplemental Table 2.** **Overview of vaccines evaluated in reviewed studies.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Overall vaccine group name** | **Commercial name(s)** | **Manufacturer(s)** | **Vaccine content (only the antigens are listed in this table)** |
| Mengingococcal vaccine- CRM carrier **(MenC-CRM)** | Menjugate® | Novartis vaccines and Diagnostics, GSK | *N. meningitidis* group C (strain c11) oligosaccharide (10µg), conjugated to CRM197 protein (12.5-25.0 µg) in 0.5 mL |
|  |
| Pneumococcal conjugate vaccines **(PCV)** | Prevnar 7®/ Prevenar 7® | Pfizer, Wyeth | Polysaccharides of 7 *S. pneumoniae* serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), conjugated with diphtheria proteins (CRM197); 2mg of each (except for 6B, of which 4mg is present, 20mg of CRM197 |
| Prevnar 13®/ Prevenar 13® | Pfizer, Wyeth  | Polysaccharides of 13 *S. pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), conjugated with diphtheria proteins (CRM197); 2.2mg of each (except for 6B, of which 4.4mg is present), 34mg of CRM197 |
| Pneumococcal polysaccharide vaccines **(PPV)** | PneumovaxPneumovax 23®,Pneumo 23®, Pneumovax II, Pnu-Immune® | Merck, MSD,Merck, MSD, Sanofi PasteurAventis PasteurAventis Pasteur, Sanofi Pasteur MSDLederle Laboratories, Wyeth | Polysaccharides of 23 *S. pneumoniae* serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F), 25mg of each |
|  |
| Influenza vaccines | Pandemrix® | GSK | Monovalent: A/California/7/2009 (H1N1)-like virus; 3.75mg HA per 0.5ml |
| Fluarix®, TIV 2010-2011,TIV 2011-2012Fluzone®, TIV 2011-2012Fluvirin®, TIV 2010-2011Vaxigrip®, TIV 2010-2011 | GSKNo manufacturer indicatedNo manufacturer indicatedSanofi PasteurNovartisSanofi Pasteur | Trivalent, (1) A/ California/7/2009 (H1N1), (2) A/Perth/16/2009 (H3N2), (3) B/ Brisbane/60/2008, 15mg HA per 0.5ml |
| Flucelvax®, TIV 2014-2015 | Novartis | Trivalent, (1) A/Brisbane/10/2010 (H1N1, A/California/7/2009-like virus), (2) NYMC X-223A (H3N2, A/Victoria/361/2011-like virus), (3) B/Massachusetts/2/2012  |
| Fluvirin®, pH1N1 2009, TIV 2013-2014, QIV 2015-2016,  | Novartis | Monovalent: A/California/7/2009 (H1N1)-like virus; 15mg HA per 0.5mlTrivalent, in 2013-2014 season: (1) A/Christchurch/16/2010 (H1N1); (2) A/Texas/50/2012 (H3N2); (3) B subtype virus, B/Massachusetts/2/2012Quadrivalent, in 2015-2016 season: (1) A/Christchurch/16/2010, (2) NIB74 (H1N1, A/California/7/2009 pdm09-like virus), (3) NIB-88 (H3N2 A/Switzerland/9715293/2013-like virus), (4) B/Phuket/3073/2013. |
| Agriflu® | Novartis | Trivalent: (1)A/H1N1 (2007), (2) A/H3N2 (2007), (3) B/Brisbane |
| Intanza®, TIV 2010-2011 | Sanofi Pasteur | Trivalent: (1) A/California/7/2009 (H1N1), (2) A/Perth/16/2009 (H3N2), (3) B/Brisbane/60/2008 (18 µg per antigen per dose) |
| Vaxigrip®, TIV 2012-2013, pH1N1 2009 | Sanofi Pasteur | Monovalent: A/California/7/2009 (H1N1)-like virus; 15mg HA per 0.5mlTrivalent: (1) A/California/7/ 2009 (H1N1) pdm09-like virus, (2) A/Victoria/361/2011 (H3N2)-like virus, (3) B/Wisconsin/1/2010-like virus; 15mg HA per 0.5ml |
| Vaxigrip®, TIV 2005-2006 | SBL Vaccin AB | Trivalent, (1) A/New Caledonia/20/99 (H1N1), (2) A/California/7/2004 (H3N2), (3) B/Shanghai/361/2002; 15mg HA per 0.5ml |
| Fluvax®, TIV 2015-2016 | bioCSL | Trivalent: (1) A/California/7/2009-like virus (H1N1), (2) A/Switzerland/9715293/2013 (H3N2)-like virus and (3) B/Phuket/3073/2013-like virus; 15mg HA per 0.5ml |
| Influvac®, TIV 2007-2008 | Solvay | Trivalent, (1) A/Wisconsin/67/2005-like virus (H3N2), (2) A/Solomon Islands/3/2006-like virus (H1 N1), (3) B/Malaysia/2506/2004-like virus, 15 mg HA per 0.5ml |
| Inflexal V®, TIV 2008-2009 | Crucell | Trivalent, (1) A/ Brisbane/10/2007 (H3N2), (2) A/Brisbane/59/2007 (H1N1), (3) B/Florida/4/ 2006, 15 mg HA per dose |
| Focetria® | Novartis | Monovalent MF-59–adjuvanted vaccine: A/California/7/ 2009(H1N1) pdm09  |
| Fluad® | Novartis | Trivalent, (1) A/Brisbane/10/2007 (H3N2), (2) B/Brisbane/60/2008 (B), (3) A/Brisbane/59/2007 (H1N1), 15 mg HA per 0.5ml |
| TIV 2006-2007 | Sanofi Pasteur | Trivalent, (1) A/New Caledonia/20/99 (H1N1), (2) A/Wisconsin/67/2005 (H3N2), and (3) B/Malaysia/2506/2004, 15 mg HA per dose |
| TIV 2009-2010 | No manufacturer indicated | Trivalent, A/Brisbane/ 59/2007 (H1N1)-like virus; A/Brisbane/10/2007 (H3N2)-like virus; B/Brisbane/60/2008-like virus.  |
| TIV 2014-2015 | No manufacturer indicated | Trivalent, (1) A/California/7/2009, (2) A/Texas/50/2012, (3) B/Mass/12 |
| QIV 2015-2016 |  No manufacturer indicated | Quadrivalent, (1) A/California/7/2009, (2) A/Switzerland/9715293/2013, (3) B/Phuket/13, (4) B/Brisb/08 |
| QIV 2016-2017 | No manufacturer indicated | Quadrivalent, (1) A/California/7/2009, (2) A/Hong kong/4801/2014, (3) B/Phuket/13, (4) B/Brisb/08 |
|  |
| Hepatitis vaccines | Engerix-B® | GSK | Hepatitis B surface antigen (HBsAg) recombinant (yeast) vaccine; typically 10 or 20mg per 0.5ml dose |
| Recombivax-HB® | MSD | Hepatitis B surface antigen (HBsAg) synthetic; 10-20mg per 1ml dose |
| Twinrix® | GSK | Hepatitis A (inactivated) and hepatitis B (rDNA) (HAB) vaccine; 720 ELISA Units hepatitis A virus (inactivated) and 20mg hepatitis B surface antigen per 1ml dose |
| Havrix® | GSK | Hepatitis A Vaccine 1440 Units per 1ml dose  |
|  |
| Combination vaccines | Pentavac® | Sanofi Pasteur | Diphtheria (≥30 IU), tetanus toxoids (≥40 IU), acellular pertussis adsorbed (25 ug of pertussis toxoid, 25 ug of filamentous haemagglutinin (FHA)), inactivated poliovirus (40 U type 1, 8 U type 2, 32 U type 3) and *H. influenzae type b* vaccine (10 ug); 0.5 ml dose |
| Tetagrip® | Sanofi Pasteur | Tetanus toxoids and trivalent influenza vaccine; (1) A/New Caledonia/20/99 (H1N1), (2) A/Wisconsin/67/2005 (H3N2), and (3) B/Malaysia/2506/2004, 15 mg HA per 0.5 ml dose |
| Decavac® | Sanofi Pasteur | Tetanus (5 Lf) and diphtheria (2 Lf) per 0.5 mL dose |
| Duplex® | SBL | Diphtheria (30 Lf/mL) and tetanus toxoids (7.5 Lf/mL), 0.25 ml dose |
| Boostrix ® | GSK | Tetanus (≥5 Lf), diphtheria (≥2.5 Lf), acellular pertussis (8 ug pertussis toxoid, 8 ug FHA, 2.5 ug pertactin) adsorbed per 0.5 ml dose |
|  |
| Tick-borne encephalitis vaccines | FSME Immun® | Pfizer | Inactivated tick-borne encephalitis virus strain Neudörfl vaccine; 2.4 ug per 0.5 ml dose |
|  |
| Hemophilus influenzae type vaccines | Act-Hib® | Sanofi Pasteur | *H. influenzae type b* vaccine conjugated to 18-30 ug tetanus toxoid, 10 ug per 0.5 ml dose |
|  |
| Immunocyanin vaccines | Immucothel® | biosyn | Immunocyanin (keyhole limpet hemocyanin) vaccine, 1 mg in 1 ml dose |
|  |
| HPV vaccines | Cervarix® | GSK | Bivalent, HPV16 (20 ug), HPV18 (20 ug) per 0.5 ml dose |

abbreviations: TIV, trivalent influenza vaccine; QIV, quadrivalent influenza vaccine; HPV, human papilloma virus

**Supplemental Table 3.** **Overview of vaccination studies in elderly.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Authors** | **Year** | **Cohort** | **Vaccine** | **Baseline assays** | **Follow-up, incl. timing of measurement** | **Risk of bias** |
| Ademokun et al. | 2011 | 27 elderly, aged 65-89 years39 adults, aged 18-49 years | Influvac (Solvay) +PPV (Pneumovax II®; Sanofi Pasteur MSD) | ELISA, spectratyping | ELISA, spectratypingd7, d28 | low |
| Carson et al. | 2000 | 29 elderly, aged 75-103 years21 adults, aged 25-35 years | PPV (Pnu-Immune; Lederle Laboratories)+Alum-absorbed ultrafine TT+DT vaccine (Wyeth Laboratories Inc.) | FC, nephelometry, ELISA, Antibody avidity, MNC stimulation | ELISA, antibody avidity, MNC stimulationd28 | moderate |
| Kolibab et al. a | 2005 | 20 elderly, aged >65 years20 adults, aged <30 years | PPV (Pneumovax®; Merck & Co. Inc.) | Baseline data reported in Kolibab et al., 2005b | repertoire analysis Ag-specific B cellsw6 | low |
| Kolibab et al. b | 2005 | 20 elderly, aged >65 years20 adults, aged <30 years | PPV (Pneumovax®; Merck & Co. Inc.) | CBC, Blood Chemistry profile, ELISA, IgG antibody avidity, OPK assay | ELISA, IgG antibody avidity, OPK assayw6 | moderate |
| Leggat et al. | 2013 | 14 elderly, aged 64-88 years18 adults, aged 18-30 years | PPV (Pneumovax 23®, Merck) | FC, ELISA, OPK assay | FCd7ELISA, OPK assayd28 | moderate |
| Shi et al. | 2005 | 65 elderly, aged 65-99 years65 adults, aged 21-64 years | PPV (Pneumovax®, manufacturer not specified) | FC, latex agglutination test, ELISA | FC, latex agglutination test, ELISAw4 | low |
| Abreu et al. | 2020 | 35 elderly, aged 65-85 years24 adults, aged 18-34 years | TIV/QIV: 2014, 2015, 2016 (manufacturer not specified) | FC, HAI assay, ELISA | FC, HAI assay, ELISA, isotype-specific antibody fractionationd21/28 | moderate |
| Camous et al. | 2018 | 22 elderly, aged 65-84 years29 adults, aged 23-33 years | Vaxigrip® (Sanofi Pasteur) | FC, HAI assay, microneutralization assay | FCd2, d7, d28HAI assay, microneutralization assayd28 | low |
| Frasca et al.  | 2011 | 9 elderly, aged 65-75 years34 adults, aged 20-64 years | pH1N1 2009 (Novartis, monovalent) /pH1N1 2009 (Sanofi Pasteur monovalent)+ Seasonal influenza vaccine of current and past 3 seasons (not specified) | FC, HAI assay, ELISA, qPCR, RT PCR | FCd7, d28 (w4/6)HAI assay, ELISA, qPCR, RT-PCRd28 (w4/6) | low |
| Frasca et al. | 2017 | 6 elderly, aged > 65 years6 adults, aged 25-55 years | TIV 2011/2012 (manufacturer not specified) | FC, FACS, qPCR, HAI assay, WB | FC, FACS, qPCR, HAI assay, WBd7, d28 (w4/6) | low |
| Kannan et al. | 2015 | 35 elderly, aged 66-88 years28 adults, aged 30-40 years | TIV 2012/2013 (manufacturer not specified) | FC, microneutralization assay, ELISA | FC, microneutralization assay, ELISAd7, d14 | moderate |
| Kurupati et al. | 2013 | 30 elderly, aged 65-87 years15 adults, aged 30-40 | TIV 2011/2012 (manufacturer not specified) | FC, microneutralization assay, ELISpot, ELISA | FC, microneutralization assay, ELISpotd0, d7, d10, d14, d28, d60ELISAd10, d28 | low |
| Nipper et al. | 2018 | 151 elderly, aged 64-95 years55 adults, aged 22-45 years | TIV 2010/2011 or TIV 2011/2012 (manufacturer not specified)  | HAI assay | FC, HAI assaym2-4 | serious |

Abbreviations: CRM, cross-reactive material; TT, tetanus toxoid; DT, diphtheria toxoid; TIV, trivalent influenza vaccine; QIV, quadrivalent influenza vaccine; IIV, inactivated influenza vaccine; Hib, *H. influenzae* type b; RT PCR, reverse transcriptase polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immune absorbent spot; (r)SBA, (rabbit) serum bactericidal activity; FC, flow cytometry; OPK, opsonophagocytic killing; MNC, mononuclear cells; CBC , complete blood count; Ig, immunoglobulin; HAI, hemagglutination inhibition; FACS, fluorescence activated cell sorting; WB, Western Blot; d, days; w, weeks; m, months.

**Supplemental Table 4.** **Overview of vaccination studies in immunodeficient patients.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors** | **Year** | **Cohort** | **Treatment** | **Vaccine** | **Baseline assays** | **Follow-up, incl. timing of measurement** | **Risk of Bias** |
| Cavaliere et al. | 2013 | 125 CVID patients20 healthy controls | SCIG or IVIG (125) | PPV (Pneumovax®, Merck) | FC, ELISA | ELISAd0, d28, d360 | low |
| Gardulf et al. | 2018 | 48 CVID patients (initially 57 recruited) | SCIG (47) IVIG (1) | Pandemrix (GSK) | FC (at diagnosis), HAI assay, ELISA\*, PCR\* | HAI assayd0, m1, m3 | moderate |
| Goldacker et al. | 2007 | 21 CVID patients | Ig substitution therapy (21) | routine vaccines: tetanus and diphtheria, Hib, PPV, hepatitis A/B (Twinrix®, GSK) | FC, PBMC stimulation, analysis of total IgM, IgA, IgG levels, ELISA | ELISAin regular intervals for up to 1y | low |
| Ko et al. | 2005 | 53 CVID patients30 healthy controls | Ig substitution therapy (part of the donors) | PPV (Pneumovax®, Merck) | FC, ELISA | ELISAd0, w4-6 | low |
| Pulvirenti et al. | 2020 | 74 CVID patients20 healthy controls | SCIG or IVIG (all) | PPV (Pneumovax®, Merck) | FC, ELISA | ELISAd0, w4, m36 ± 6 | low |
| Rezaei et al. | 2005 | 12 (pediatric) CVID patients | NI | meningococcal polysaccharide vaccine (manufacturer not specified) | FC, SBA | SBAd0, w3 | low |
| Sharifi et al. | 2018 | 16 CVID patients16 healthy controls | NI | PPV (Pneumovax 23, manufacturer not specified)  | FC, ELISA, PBMC stimulation\*, RT-PCR\* | ELISANI | low |
| Yazdani et al.a | 2017 | 10 CVID patients10 healthy controls | IVIG | PPV (Pneumo 23®, Aventis, Pasteur) | FC, B-cell stimulation, RT-PCR, ELISA | ELISAd0, d21 | low |
| Yazdani et al.b | 2017 | 30 CVID patients30 healthy controls | NI | PPV (Pneumo 23®, Aventis, Pasteur) | FC, ELISA | ELISAd0, d21 | low |
| Abudulai et al. | 2016 | 50 HIV patients20 healthy controls | ART (30) | PPV (Pneumovax®, Merck) | FC, microsphere-based FC assay, analysis of Ig subclasses and serum free light chains | microsphere-based FC assay, ELISpotd0, d7, d28 | moderate |
| Cagigi et al. | 2013 | 54 HIV patients47 healthy controls | ART (37) | Pandemrix® (GSK) | HAI assay, PBMC stimulation, RT-qPCR, FC  | HAI assayd0, m1, m3, m6 | moderate |
| Cagigi et al. | 2014 | 59 HIV patients, 19 controls | ART (59) | Split Virion VAXIGRIP (Sanofi Pasteur) | FC, ELISA  | ELISAd0, d21 | low |
| Chang et al. | 2000 | 12 HIV patients10 healthy controls | ART (6) | PPV (Pneumovax®, MSD) | PCR, PCR ELISA, ELISA | PCR, PCR ELISA, ELISAd0, d7, d28 | low |
| Curtis et al. | 2015 | 90 HIV patients (children and youth) | NI | Fluvirin (Novartis) | FC, ELISA, HAI assay, FluoroSpot | FC, ELISA, HAI assay, FluoroSpotd0, d21-28, d10-14 post dose 2, w28 post dose 1 | moderate |
| Eisen et al. | 2016 | 93 HIV patients51 healthy controls | NI | PPV (Pneumovax 23®, manufacturer not specified) | FC, flow-based multiplex assay, OPK assay | flow-based multiplex assay, OPK assayd0, d28, y1 | moderate |
| Farmaki et al. | 2018 | 40 HIV patients | ART (40) | PCV (Prevenar 13, Pfizer) and PPV (Pneumovax 23, MSD) after 12m | FC, ELISA | FC, ELISAd0, m1 (after each vaccine) | low |
| Hart et al. | 2007 | 84 HIV patients28 CVID patients8 splenectomized patients83 healthy controls | ART (55)Ig replacement therapy (25) | TT (Aventis Pasteur) (14 patients) or PPV (Pneumovax II, Aventis Pasteur) (19 patients) | FC, ELISA | ELISAd0, w4, m3-6 | moderate |
| Johannesson et al. | 2012 | 95 HIV patients | ART (62)impaired ART responders (13) | PCV (Prevnar, Wyeth) 2 doses 3m apart with or without CPG7909 | FC, ELISA | ELISAd0, m3, m4, m9 | moderate |
| Luo et al. | 2016 | 26 HIV patients16 healthy controls | ART (26) | Fluvirin (Novartis) | FC, ELISpot, HAI assay, ELISA, microneutralization assay, qPCR | FC, ELISpot, HAI assay, ELISA, microneutralization assayd0, d7-10, d14-21 | low |
| Milagres et al. | 2018 | 17 (pediatric) HIV patients12 healthy controls  | ART | MenC-CRM (Novartis; C Polysaccharide/CRM197), in patients, booster at y1 | SBA, FC, ELISA, turbidimetry | SBA, FCd0, m1-2, m10-12 (booster), m1-2 (after booster) (controls d0, m1-2 only) | low |
| Pallikkuth et al.a | 2011 | 17 HIV patients8 healthy controls | ART (17) | A/California/ 07/2009 H1N1 vaccine (Novartis Vaccines and Diagnostics Ltd) | FC, ELISpot, ELISA | FC, ELISpot, ELISAd0, d7, d28 | low |
| Pallikkuth et al.b | 2011 | 16 HIV patients8 healthy controls | ART (16) | A/California/ 07/2009 H1N1 vaccine (Novartis Vaccines and Diagnostics Ltd) | FC, ELISpot, ELISA, HAI assay | FC, ELISpot, ELISA, HAI assayd0, d7, d28 | low |
| Paris et al. | 2017 | 20 HIV patients | ART (20) | 20 µg Engerix-B® or 10 µg Recombivax-HB® (0-, 1-, 6-month schedule) (manufacturer not specified) | FC, ELISA, Luminex assay | FC, ELISA, Luminex assayd0, within 12m after the 3rd dose | low |
| Parmigiani et al. | 2013 | 16 HIV patients12 healthy controls | ART (16) | Fluarix® (GSK) | HAI assay, Luminex assay, ELISA, FC, cell co-cultures | HAI assay, ELISA, FCt0, w4 | low |
| Rinaldi et al. | 2017 | 64 HIV patients60 healthy controls | ART (64) | TIV, seasonal influenza vaccination, 2013/2014, 2014/2015 and 2015/2016 (manufacturer not specified) | HAI assay, FC, ELISpot | HAI assay, ELISpotd0, d7, d21 | low |
| Tsachouridou et al. | 2015 | 66 HIV patients60 healthy controls | HAART (35) | PPV (Pneumovax 23®, Merck and Co., Inc.) | FC, ELISA | ELISAd0, w4, w48 | low |
| Van Epps et al. | 2014 | 46 HIV patients30 healthy controls | ART (part) | TT (Aventis Pasteur or Wyeth-Ayerst), hepA vaccine (Smith-Kline Beecham) | FC, ELISA | FC, ELISAd0, w192 | moderate |
| Weinberg et al. | 2009 | 152 (pediatric) HIV patients | NI | Havrix (GSK), two doses 24 weeks apart | ELISA, lymphocyte proliferation assay, Luminex, FC | ELISA, lymphocyte proliferation assay, Luminex, FCd0, w32 (some analysis every 8w) | low |
| Wheatley et al. | 2016 | 26 HIV patients30 healthy controls | ART (26) | 2015 IIV3 (Fluvax, bioCSL) | FC, HAI assay | FC, HAI assayd0, w4 | low |
| Giesecke et al. | 2014 | 6 splenectomized and 3 tonsillectomized patients, 12 healthy controls (additional tissues from non-vaccinated donors) | - | TT/DT (Sanofi Pasteur MSD GmbH) | FC, ELISA | FC, ELISAd0, d7, d14 | low |
| Papadatou et al. | 2014 | 39 patients with β-thalassemia and asplenia | - | PCV13 (previous vaccinations: PCV13, 1-4 doses of PPV23) (manufacturer not specified) | ELISpot, ELISA | ELISpot, ELISAd0, d7, d28 | low |
| Rosado et al. | 2013 | 57 asplenic adults, 21 asplenic children, 47 healthy adults, 19 healthy children | - | PPV or PCV7 (manufacturer not specified), before and/or after splenectomy | NI | ELISpot\*, ELISA\*, FC\*, IHC\*, cell culture\*NI | moderate |
| Wasserstrom et al. | 2008 | 26 splenectomized patients12 healthy controls | - | PPV (Pneumovax 23, Merck) | ELISA, FC | ELISAd0, w4-7 | low |

Abbreviations: CVID, common variable immunodeficiency; HIV, human immunodeficiency virus; NI, not indicated; PPV, pneumococcal polysaccharide vaccine; PCV, pneumococcal conjugate vaccine; TT, tetanus toxoid; DT, diphtheria toxoid; hep, hepatitis; TIV, trivalent influenza vaccine; SCIG, subcutaneous Ig; IVIG, intravenous Ig; Hib, *H. influenzae* type b; RT (q)PCR, real time (quantitative) polymerase chain reaction; HAI, hemagglutination inhibition; SBA, serum bactericidal antibody; ART, Antiretroviral Therapy; HAART, Highly Active Antiretroviral Therapy; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immune absorbent spot; OPK, opsonophagocytic killing; IHC, immunohistochemistry; d, day; w, week; m, month; y, year; \*, not specified whether analysis performed at baseline; follow up or both.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Name |  |  |  |  |
| London | group A | **no** production of **IgM or IgG** upon stimulation *in vitro* |
| group B | production of **IgM**, but **not IgG** upon stimulation *in vitro* |
| group C | production of **IgM** and **IgG** upon stimulation *in vitro* |
| Freiburg\* | group I | **class-switched MBCs** (CD27+IgD-IgM-) **<0.4%** of PBLs | a | **immature CD21-** B cells **>20%** of B cells |
| b | **immature CD21-** B cells **<20%** of B cells |
| group II | **class-switched MBCs** (CD27+IgD-IgM-) **>0.4%** of PBLs |  |  |
|  |  |
| Paris | MB0 | total (CD27+) **MBCs ≤11%** of PBLs |
| MB1 | total (CD27+) **MBCs >11%** of PBLs; **class-switched MBCs** (CD27+IgD-) **≤8%** of B cells |
| MB2 | total (CD27+) **MBCs >11%** of PBLs; **class-switched MBCs** (CD27+IgD-) **>8%** of B cells |
| EUROclass | B- | **B cells** (CD19+) **<1%** PBLs |  |
| B+ | **B cells** (CD19+) **>1%** PBLs | smB- | **class-switched** (CD27+IgD-IgM-) **MBCs ≤2%** of B cells | TRhi | transitional (CD38++IgMhigh ) ≥9% of B cells |
| TRnorm | transitional (CD38++IgMhigh ) <9% of B cells |
| 21low | ≥10% CD21low B cells |
| 21norm | <10% CD21low B cells |
| smB+ | **class-switched** (CD27+IgD-IgM-) **MBCs>2**% of B cells | 21low | ≥10% CD21low B cells |
| 21norm | <10% CD21low B cells |
| B-cell pattern | pattern 1 | B-cell production and germinal center defect |
| pattern 2 | early peripheral B-cell maturation or survival defect |
| pattern 3 | B-cell activation and proliferation defect |
| pattern 4 | germinal center defect |
| pattern 5 | post germinal center defect |

**Supplemental Table 5. Classifications of CVID patients**

**\***, includes only CVID patients with peripheral B-cell numbers above 1% of peripheral blood lymphocytes (PBL)

**Supplemental Table 6. Classification of vaccination responders in CVID**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | vaccine | Responders | London | Freiburg | Paris | EUROClass | B-cell pattern |
| Cavaliere et al. | PPV | 10/125 (IgM and IgA)25/125 (IgM)2/125 (IgA) | - | - | - | - | - |
| Gardulf et al. | influenza | 8/48 | - | Ia:2Ib:5II:1 | MB0:1MB1:6MB2:1 | smB+21low:1smB-21low TRhi :1smB-21norm TRnorm :6 | pattern 1: 2pattern 3: 1pattern 4: 4pattern 5:1 |
| Goldacker et al | PPVHepAHepBTetanusDiphHib | 3/15 (IgM)3/17 (IgG)1/177/17 1/132/146/18 | A:1B:1C:1A:1C:2C:1A:1B:3C:3C:1B:1C:1B:2C:4 | Ib:2II:1Ib:1II:2II:1Ia:1Ib:4II:2II:1Ib:1II:2Ib:3II:3 | MB1:3MB1:2MB2:1MB2:1MB0:3MB1:2MB1:2MB2:1MB1:1MB2:1MB0:1MB1:3MB2:2 | - | - |
| Ko et al. | PPV | - | - | - | - | - | - |
| Pulvirenti et al. | PPV | 14/76\* | - | Ib:27%II:73% | smB+:100% | - | - |
| Rezaei et al. | meningococcalpolysaccharide vaccine | 7/12 |  | Ia:2Ib:3II:2 |  |  |  |
| Sharifi et al. | PPV | - | - | - | - | - | - |
| Yazdani et al.a | PPV | 2/8 | - | - | - | - | - |
| Yazdani et al.b | PPV | 3/25 |  | Ib:1II:1 | MB0:2MB1:1 | smB-21low smB-Trnorm:1smB-21norm smB-Trnorm:1smB+21norm:1 | pattern 3:2pattern 4:1 |

**\***, either 14 or 16 indicated in different sections of the manuscript, due to this inconsistency, number of donors belonging to different classifications expressed as % as it was done in the manuscript

**Supplemental Table 7. Overview of vaccination studies in immunosuppressed patients.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors** | **Year** | **Cohort**  | **Vaccine** | **Timing** | **Baseline assays** | **Follow-up, incl. timing of measurement** | **Risk of bias** |
| Avetisayan et al. | 2008 | 14 post-alloHCT patientsIndication: malignancyImmunosuppression: heterogeneous18 healthy controls | Vaxigrip® (SBL Vaccin AB)  | Variable | ELISpot, HAI assay | w4, ELISpot and HAI assay. | moderate |
| Roll et al. | 2012 | 36 post-alloHCT patientsIndication: heterogeneousImmunosuppression: heterogeneous | Pandemrix® (GSK) | NI | FC, HAI assay | w4-8, HAI assay. | moderate |
| Buckley et al. | 2013 | SCID patients post-alloHCT 61 on IVIG64 off IVIGImmunosuppression: none777 healthy controls | Tetanus, diphtheria vaccine (not specified)Neoantigen phiX174 (0.02 ml/kg intravenously)  | NI | FC | Tanned red cell hemagglutination or ELISA, BCR spectratyping. | moderate |
| Hoshina et al. | 2016 | 8 post-HCT patientsIndication: heterogeneousImmunosuppression: none9 patients on immunosuppressionIndication: heterogeneousImmunosuppression: heterogeneous14 healthy controls | PCV (Prevnar 7®; Pfizer) | NI | FC, OPK assay, ELISA | w4-6. ELISA and multiplexed OPK assay. | moderate |
| Harrison et al | 2020 | 19 post-alloHCT patientsIndication: heterogeneousImmunosuppression: heterogeneous15 healthy controls | FSME Immun® (Pfizer) | m0, w4, m9-12 | FC, neutralization assay | w4, Neutralization assay, ELISA.  | moderate |
| Winkler et al. | 2020 | 27 post-alloHCT patientsIndication: heterogeneousImmunosuppression: heterogeneous13 healthy controls | Pentavac® (Sanofi Pasteur)PCV (Prevenar 13®; Wyeth) | NI | FC, ELISA, ELISpot | w1, w4, w8, w26, w52. ELISA, ELISpot.  | moderate |
| Puissant-Lubrano et al. | 2010 | Post-kidney Tx patients26 on heterogeneous immunosuppression13 on immunosuppression + rituximab30 healthy controls | Tetagrip® (Sanofi Pasteur) | NI | FC, nephelometry, ELISA | m1, ELISA, FC. | moderate |
| Bedognetti et al. | 2011 | 31 NHL patients on heterogeneous immunosuppression + rituximab34 healthy controls | Inflexal V® (Crucell) | Median m29 post-treatment | FC, HAI assay  | w4, FC, HAI assay.  | moderate |
| Pescovitz et al. | 2011 | Diabetes type I patients46 on rituximab29 on placebo | Decavac® (Sanofi Pasteur)Havrix® (GSK)Subset: neoantigen phiX174 (University of Washington) | m12 after treatmentw6, w12, w52 and w58 | FC, ELISA | w4, ELISA for DT and HepA. PhiX194: w1, w2 and w4 after each immunization: phage neutralization assay.  | some concerns |
| Bedognetti et al. | 2012 | 14 NHL patients on rituximab in addition to relatively homogeneous immunosuppression21 healthy controls | Focetria® (Novartis; 2 doses) followed at d28 by Fluad® (Novartis) | NI | FC, HAI assay | w4, HAI assay.  | moderate |
| Eisenberg et al. | 2013 | 25 heterogeneous auto-immune disease patients on rituximab + heterogeneous immunosuppression15 healthy controls | TIV (2006–2007, 2007–2008, 2008–2009, 2009–2010) (manufacturer not specified) | m7-9 after treatment | FC, HAI assay, ELISpot | m2, m6, HAI assay, ELISpot.  | moderate |
| Nazi et al. | 2013 | ITP patients17 on rituximab 7 on placebo | PPV (Pneumovax 23®; Merck)Act-Hib® (Sanofi Pasteur) | m6 after rituximab or placebo | FC, ELISA, SBA (anti-Hib) | w1, w4 and m6, ELISA, SBA (anti-Hib), FC | some concerns |
| Cho et al. | 2017 | 23 pemphigus patients on rituximab28 healthy controls | Flucelvax® (Novartis) or Fluvirin® (Novartis) | NI | FC, ELISpot, HAI assay | d7, ELISpot. d28, ELISpot, HAI assay, MN assay, PCR.  | moderate |
| Ek et al. | 2005 | 31 ALL patients on NOPHO chemotherapy40 healthy controls | Duplex® (SBL)Act-Hib® (Sanofi Pasteur) | m1 or m6 post-treatment | FC  | d7, ELISpot. d21, ELISA. | moderate |
| Chu et al. | 2013 | Ovarian cancer patients 13 on DC vaccine + chemotherapy18 on heterogeneous chemotherapy21 healthy controls | Seasonal inactivated trivalent influenza vaccine (manufacturer not specified) | NI | FC, HAI assay | m3, m4, m9, m12, HAI assay, ELISpot.  | low |
| De Lavallade et al. | 2013 | 51 CP-CML patients on TKI24 healthy controls | 2008/2009 or 2009/2010 influenza vaccine (CSL Biotherapies)2009 pandemic influenza A (H1N1) vaccine Subset: PPV (Pneumovax II®; Sanofi Pasteur) | NI | FC, ELISA | w4, m2, m3, ELISA.  | moderate |
| Kersun et al. | 2013 | 110 ALL patients on chemotherapy67 solid tumor patients on chemotherapy | Seasonal inactivated trivalent influenza vaccine (2006-2007, 2007-2008, 2008-2009 or 2009-2010) (manufacturer not specified) | NI | FC, HAI assay | m2, m4, y1. HAI assay.  | moderate |
| Reilly et al. | 2013 | 8 AML patients on chemotherapyNI healthy controls | Trivalent influenza vaccine (manufacturer not specified) | NI | FC, HAI assay, ELISpot | m2, m4 and y1. HAI assay, ELISpot.  | moderate |
| Koskenvuo et al. | 2016 | 9 ALL patients on NOPHO chemotherapy  | PCV (Prevenar 7®; Wyeth) | m6-12 post-treatment | FC | NI | moderate |
| Goswami et al. | 2017 | 10 AML patients on heterogeneous chemotherapy | TIV 2012–2013 (manufacturer not specified) | NI | FC, MN assay, BCR spectratyping | d30. MN assay, ELISpot. | moderate |
| Struijk et al. | 2010 | Post-kidney Tx patients on prednisolone12 on cyclosporine12 on MPA12 on everolimus13 healthy controls | Immucothel® (biosyn)PPV (Pneumovax®; N/R)Tetanus toxoid (Sanofi Pasteur) | NI | FC, ELISA | d14, ELISA. | low |
| Cowan et al. | 2014 | 22 post-kidney Tx patients on immunosuppression21 healthy controls | Fluvirin® (Novartis) or Fluzone® (Sanofi Pasteur) | NI | FC, ELISpot, ELISA | d7, d14, d28. ELISA, ELISpot, FC. | moderate |
| Egli et al. | 2015 | 47 post-organ Tx patients on heterogeneous immunosuppression11 healthy controls | Intanza® (Sanofi Pasteur) or Vaxigrip® (Sanofi Pasteur) | NI | FC, HI assay | w4. HAI assay.  | moderate |
| Kobie et al. | 2011 | RA, patients61 on anti-TNF 70 on MTX33 untreated97 healthy controls | Seasonal inactivated trivalent influenza vaccine (manufacturer not specified) | NI | FC, HAI assay, ELISpot | d5-7, d8-10, m1 and m6, HAI assay, ELISpot, FC.  | moderate |
| Kamphuis et al. | 2013 | 32 sarcoidosis patients on heterogeneous immunosuppression 28 healthy controls | Agriflu® (Novartis)Focetria® (Novartis)PPV (Pneumo 23®; N/R)Hib vaccine (not specified) | NI | FC, HAI assay, nephelometry | w4, HAI assay, NI for evaluation of other vaccines. | moderate |
| Salinas et al. | 2013 | 41 SpA patients on TNF-blocking immunosuppression 15 untreated SpA patients | Engerix-B® (GSK) + revaccination at W6 and W22PPV (Pneumovax 23®; Merck) | NI | FC, IgκRHEMA assay, ELISA | w6, w10, w22, w26. ELISA. | low |
| Fallahi et al. | 2014 | 18 IBD patients on heterogeneous immunosuppression20 healthy controls | PPV (Pneumo 23®; Sanofi Pasteur) | NI | FC, ELISA | d28, ELISA.  | moderate |
| Heijstek et al. | 2014 | 63 JIA patients on heterogeneous immunosuppression 49 healthy controls | Cervarix® (GSK) | m0, m1, m6 | ELISpot, multiplex assay | m3, m7, m12. Multiplex assay, ELISpot.  | moderate |
| Bingham et al. | 2015 | RA patients on MTX 51 on tabalumab17 on placebo | Boostrix® (GSK) PPV (Pneumovax 23®; Merck) | w24 after drug start | FC, ELISA | w4, ELISA. w28, FC. | some concerns |

Abbreviations: NI , not indicated; alloHCT, allogeneic hematopoietic stem cell transplantation; IVIG, intravenous immunoglobulins; NHL, non-Hodgkin lymphoma; CP -CML, chronic phase - chronic myeloid leukemia; TKI, tyrosine kinase inhibitor; ITP, immune thrombocytic purpura; SCID, severe combined immunodeficiency; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; SpA, spondylarthritis; Tx, transplantation; JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis; MTX, methotrexate; IBD, inflammatory bowel disease; CP, cyclosporine; MPA, mycophenolate sodium; TT, tetanus toxoid; TIV, trivalent influenza vaccine; PPV, pneumococcal polysaccharide vaccine; PCV, pneumococcal conjugate vaccine; Hib, *H. influenzae* type b; FC, flow cytometry; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immune absorbent spot; HAI, hemagglutination inhibition; OPK, opsonophagocytic killing; d, day; w, week; m, month; y, year; BCR, B-cell receptor; DC, dendritic cell.