Immunotherapy (IMTX) : Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immune Effector Cell (IEC) Patients

BACKGROUND

B cell-targeted chimeric antigen receptor-modified T (CAR-T) cell therapy is a novel treatment for patients with refractory or resistant (R/R) B cell malignancies, including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM).[1–5] Patients treated with CAR-T cell Immune Effector Cell (IEC) have poor immune function due to effects of their malignancy, prior cytotoxic treatments, lymphodepletion therapy including depletion of B cells or plasma cells due to B cell targeted CAR- T cells. CAR-T cells can persist for months to years and result in prolonged B cell or plasma cell depletion with resultant hypogammaglobulinemia and risk for infection.[6–10] Long-term effects of B cell-targeted CAR-T cell therapy on the immune system and risk for infection are not well understood.

After B cell-targeted CAR-T cell therapy:

A. Expert guidelines[11] recommend monthly immunoglobulin G (IgG) monitoring and intravenous immunoglobulin (IVIG) supplementation when IgG <400 mg/dL because neutralizing antibodies provide a first line of defense for pathogens such as encapsulated bacteria and viruses.[12,13] See Standard Practice Guideline "Intravenous Immunoglobulin (IVIG) Replacement for Transplant and B cell and plasma cell targeted CAR T-cell Immunotherapy Patients."

B. Vaccination is considered an important long–term goal after CAR-T therapy, similar to after autologous or allogeneic HCT but with potential differences:

   a. Many patients receiving CAR-T therapy may have undergone prior HCT without completion of routine posttransplant vaccinations. The approach to vaccination among subjects who have received a prior HCT without completing all post-transplant revaccinations is to start over with the whole course of vaccinations when immune function recovered adequately post CAR-T cell therapy.

   b. Patients treated with B cell-targeted CAR-T cell therapy may have reconstitution of normal B cells and plasma cells without relapse of the underlying malignancy.[10] Optimal timing for new vaccinations, the need for re-vaccination with prior vaccines, and the effects of different types of B cell-targeted CAR-T cells are unclear. Studies of B cell depletion after rituximab in non-HCT settings have demonstrated the ability to mount immune responses to vaccines, particularly >6 months after therapy and when conjugated vaccines as opposed to polysaccharide vaccines are used, even in the absence of measurable peripheral blood B cells.[14–16] Our approach to vaccinating individuals after CAR-T cell therapy without a prior HCT, or who have completed a recommended post-HCT series of vaccines allows for the possibility of preserved immunity and/or ability to generate a boosted response with a single vaccination, where applicable. This approach is extrapolated from approaches used in cancer patients and transplant recipients and based on expert opinion, given the lack of data derived from patients after CAR-T cell therapy.

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Immunotherapy (IMTX) : Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immune Effector Cell (IEC) Patients

VACCINATIONS

A. Seasonal Flu (September -March):

All patients will get inactivated influenza seasonal vaccinations after leukapheresis and ≥ to 2 weeks prior to beginning lymphodepletion chemotherapy per Appendix B and C and thereafter yearly post CAR-T cell therapy.

B. SARS-CoV-2

Begin SARS-CoV-2 vaccination starting ≥ 90 days post CAR infusion. See Appendices B and C

C. Other Vaccination Eligibility Criteria

1. Indications

a. Killed/inactivated vaccines
- ≥ 6 months post-B cell-targeted CAR-T cell therapy
- Reasonable to attempt a ≥ 2-month trial off IVIG replacement therapy based on a negative history of chronic or serious bacterial infections in the past 6 months.

b. Live vaccines
- If the patient has a positive vaccine response to killed vaccines (see Appendix A), the patient may be considered for live vaccines if no contraindications as detailed below.

2. Contraindications to Vaccinations

a. Killed/inactivated vaccines
- IVIG supplementation within the past 2 months prior to vaccination.
- Receiving immunosuppressive therapy that reduces T cell or B cell function or have active symptoms of graft-versus-host disease that requires treatment.
- Administration of an anti-CD20 or anti-CD19 antibody agent within the past 6 months prior to vaccination.
- Actively receiving chemotherapy

b. Live and non-live adjuvant vaccines
- Administration of an anti-CD20 or anti-CD19 antibody agent within the past 6 months prior to vaccination.
- ≤ 1 year post-B cell-targeted CAR-T cell therapy.
- ≤ 2 years post-autologous or allogeneic HCT.
- ≤ 1 year off all systemic immunosuppressive therapy.
- ≤ 8 months after last dose of IVIG supplementation or plasma.
- Absolute CD4 T cell count < 200 per microliter.
- Actively receiving chemotherapy

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Immunotherapy (IMTX) : Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immune Effector Cell (IEC) Patients

VACCINATIONS (Continued)

3. Exceptions to Contraindications

Vaccination may be considered in patients who are receiving certain immunotherapies that do not suppress T cell and B cell responses, such as:

- Checkpoint inhibitors (e.g. PD-1 and PD-L1 inhibitors)
- Immunomodulatory agents (e.g. lenalidomide)
- Tyrosine kinase inhibitors
- Other agents, such as Ibrutinib

4. Other Considerations

Patients who flare up with active GVHD after CAR-T cell therapy and are on definitive immunosuppressive therapy (for example, prednisone ≥ 1mg/kg/day or prednisone equivalent), please contact the LTFU Attending for vaccination recommendations.

C. Post CAR-T Cell Therapy:

1. Initial Screening for non influenza and non SARS-CoV-2 vaccinations for all patients

If the eligibility criteria for killed/inactivated vaccines are met, check serology titers (≥ 2 months after last IVIG administration) for:

- *Streptococcus pneumoniae* (23 serotypes) IgG
- Tetanus toxoid IgG
- *Haemophilus influenza* type B (HiB) IgG
- Hepatitis A (HAV) IgG
- Hepatitis B (HBV) surface antigen IgG

Check serum total IgG level

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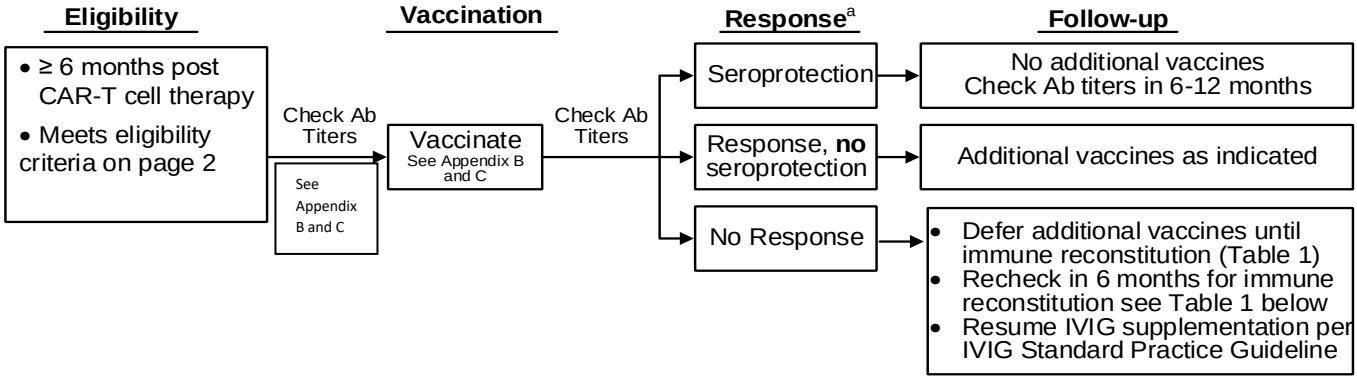
Immunotherapy (IMTX) : Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immune Effector Cell (IEC) Patients

VACCINATIONS (Continued)

2. Post Initial Screening

a. For patients with no history of prior HCT OR who completed the whole series of post-HCT vaccines. (For HCT patients see also "LTFU SECTION IX Vaccinations")

Figure 1. Vaccination approach in patients with no history of prior HCT or who completed post-HCT vaccines, see Appendix B and C



[a] See appendix A for definition of response.

See Appendix B & C

- Month 0: Give one dose each of Prevnar 20, age appropriate Pentacel® (Hib/DTaP/IPV), HAV and HBV, irrespective of preexisting seroprotective IgG. If Pentacel® is unavailable, then can give separate component vaccines (with the DTaP formulation of diphtheria/tetanus/acellular pertussis being preferred over Tdap).

- Months 1-2: Check IgG titers to *Streptococcus pneumoniae* (23 serotypes), tetanus toxoid, HiB, HAV, and HBV.
- Months 2-4:
  - Seroprotective IgG based on reference laboratory guidelines and Appendix A: No additional vaccination. In 6-12 months, recheck IgG titers to *Streptococcus pneumoniae* (23 serotypes), tetanus toxoid, HiB, HAV, and HBV.
  - Response but IgG not seroprotective as per Appendix A: Give additional vaccinations as indicated in Appendix B and C. Check IgG titers to *Streptococcus pneumoniae* (23 serotypes), tetanus toxoid, Hib, Hepatitis A, and Hepatitis B surface antibody 1-2 months after completion of the indicated vaccination series

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Immunotherapy (IMTX) : Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immune Effector Cell (IEC) Patients

VACCINATIONS (Continued)

No response: Additional vaccination should be deferred until all 3 criteria for markers for immune reconstitution are demonstrated as per Table 1 below. Resume IVIG therapy as clinically indicated (see "Intravenous Immunoglobulin (IVIG) Replacement for Transplant and B cell and plasma cell targeted CAR T-cell Immunotherapy Patients Standard Practice Guideline").

Table 1 Markers for Immune Reconstitution
Criteria
• Detectable serum IgA† (> 6 mg/dL) AND
• CD19 or CD20 B cell count ≥ 20 per microliter AND
• $CD4^+$ T cell count ≥ 200 per microliter

†A detectable IgA level indicates potential ability to "class switch"

Additional Vaccines for patients with no history of prior HCT OR who completed post-HCT vaccine series (see Appendix D):

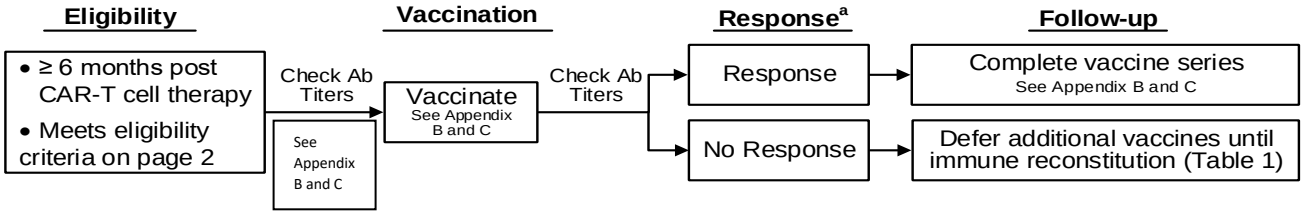
- For patients who responded AND developed seroprotection to *Streptococcus pneuoniae* tetanus toxoid, HiB, and hepatitis A/Hepatitis B surface antibody, consider checking IgG for:
  - Meningococcal ACWY
  - Measles, mumps, rubella (MMR)

- If the patient has seronegative IgG level for any of the above pathogens, consider vaccination. If the patient has a history of being seropositive for VZV, consider vaccination with Shingrix.

Post Initial Screening

b. For patients with a history of prior HCT who did not complete the whole series of post-HCT vaccine (See LTFU Section IX Vaccinations Section):

Figure 2. Vaccination approach in patients with a history of prior HCT who did not complete post-HCT vaccines.



[a] See appendix A for definition of response

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Immunotherapy (IMTX) : Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immune Effector Cell (IEC) Patients

VACCINATIONS (Continued)

- Month 0: Give one dose of Prevnar 20, age appropriate Pentacel ® (Hib/DTaP/IPV), HAV and HBV, *irrespective of preexisting seroprotective IgG.* If Pentacel® is unavailable, then can give separate component vaccines (with the DTaP formulation of diphtheria/tetanus/acellular pertussis being preferred over Tdap).
- Months 1-2: Check IgG titers to *Streptococcus pneumoniae* (23 serotypes), tetanus toxoid, HiB, Hepatitis A, and Hepatitis B surface antibody.
- 3 months or more:
  - Response: Complete series of vaccines (see Appendix B and C). Recheck titers after completion of vaccine per Appendix B and C.

No response: Additional vaccination should be deferred until all 3 criteria for numeric immune reconstitution are demonstrated in Table 2 below. As clinically indicated resume IVIG therapy, See "Intravenous Immunoglobulin (IVIG) Replacement for Transplant and B cell and plasma cell targeted CAR T-cell Immunotherapy" Standard Practice Guideline

Table 2 Markers for Immune Reconstitution
Criteria
• Detectable serum IgA† (> 6 mg/dL) AND
• CD19 or CD20 B cell count ≥ 20 per microliter AND
• $CD4^+$ T cell count ≥ 200 per microliter

†A detectable IgA level indicates potential ability to "class switch"

Additional Vaccines: For patients with a history of prior HCT who did not complete the whole series of post-HCT vaccine (continued). See Appendix D

For patients who responded and developed seroprotection to *Streptococcus pneumoniae* (23 serotypes), tetanus toxoid, HiB, and Hepatitis A/Hepatitis B surface antibody, consider additional vaccinations. There is no need to test baseline or subsequent pathogen-specific IgG for these additional vaccines per Appendix D.

D. Miscellaneous

- **Influenzae vaccination:** Live attenuated influenzae vaccine is not recommended.

- **Smallpox vaccine** is comprised of live vaccinia virus. **Smallpox vaccination is contraindicated in HCT and IEC CAR T recipients** because it may result in development of generalized vaccinia or inadvertent inoculation at other sites such as the face, eyelid, nose, mouth, genitalia, and rectum. Smallpox vaccine should not be administered to any family members or other persons who share living space with the patient during the first year after transplant and beyond one year if the patient continues on treatment with immunosuppressive medications. If smallpox vaccination is administered to these close contacts, then these individuals should be prevented from having close contact with the immunocompromised HSCT recipient. See the CDC website for further detailed information http://www.bt.cdc.gov.

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Immunotherapy (IMTX) : Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immune Effector Cell (IEC) Patients

VACCINATIONS (Continued)

- **Other live vaccines (i.e., BCG, oral polio, yellow fever, typhoid)** should not be administered in patients with active manifestation of GVHD receiving immunosuppressive therapy.

- **Anthrax vaccine** is an inactivated, cell-free filtrate vaccine (e.g., no dead or live bacteria in the preparation). Currently, anthrax vaccination is not routinely recommended for anyone except certain high-risk groups such as persons working directly with the organism in the laboratory or certain military personnel. Recommendations for CAR-T cell recipients would be the same as for other at-risk individuals. Detailed information is available at the CDC website http://www.bt.cdc.gov

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REFERENCES

1. Turtle C, Riddell S, Maloney D. CD19-Targeted chimeric antigen receptor-modified T-cell immunotherapy for B-cell malignancies. *Clin. Pharmacol. Ther.* 2016;100(3):252–258.
2. Frey N V, Porter DL. The Promise of Chimeric Antigen Receptor T-Cell Therapy. *Oncology (Williston Park).* 2016;30(10):.
3. Kenderian SS, Porter DL, Gill S. Chimeric Antigen Receptor T Cells and Hematopoietic Cell Transplantation: How Not to Put the CART Before the Horse. *Biol. Blood Marrow Transplant.* 2017;23(2):235–246.
4. Ali SA, Shi V, Maric I, et al. T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. *Blood*. 2016;128(13):1688–700.
5. Carpenter RO, Evbuomwan MO, Pittaluga S, et al. B-cell Maturation Antigen Is a Promising Target for Adoptive T-cell Therapy of Multiple Myeloma. *Clin. Cancer Res.* 2013;19(8):2048–2060.
6. Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T cell immunotherapy. *Blood*. 2017;blood-2017-07-793760.
7. Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia. *N. Engl. J. Med.* 2011;365(8):725–733.
8. Kochenderfer JN, Dudley ME, Feldman SA, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. *Blood*. 2012;119(12):2709–20.
9. Maude SL, Frey N, Shaw PA, et al. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. *N. Engl. J. Med.* 2014;371(16):1507–1517.
10. Kochenderfer JN, Somerville RPT, Lu T, et al. Long-Duration Complete Remissions of Diffuse Large B Cell Lymphoma after Anti-CD19 Chimeric Antigen Receptor T Cell Therapy. *Mol. Ther.* 2017;25(10):2245–2253.
11. Kansagra AJ, Frey N V., Bar M, et al. Clinical utilization of Chimeric Antigen Receptors T-cells (CAR-T) in B-cell acute lymphoblastic leukemia (ALL) – an expert opinion from the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Blood and Marrow Transpl. *Biol. Blood Marrow Transplant.* 2018;
12. van Vollenhoven RF, Emery P, Bingham CO, et al. Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. *J. Rheumatol.* 2010;37(3):558–67.
13. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. *Medicine (Baltimore).* 2006;85(4):193–202.
14. 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.

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References (continued)

15. Bingham CO, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. *Arthritis Rheum.* 2010;62(1):64–74.

16. Sinisalo M, Aittoniemi J, Oivanen P, et al. Response to vaccination against different types of antigens in patients with chronic lymphocytic leukaemia. *Br. J. Haematol.* 2001;114(1):107–10.

17. Schuster J, Hamdan L, Dulek D, et al. Influenza Vaccine in Pediatric Recipients of Hematopoietic-Cell Transplants. The New England Journal of Medicine. 2023; 388(4): 374-376.

Keywords: Immune Effector Cell (IEC)-vaccines, B cell-targeted CARs

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APPENDIX A

Definitions

For Children:

Positive vaccine response (except for *S. pneumoniae*): ≥2-fold increase in IgG from pre- to 1-2 months post-vaccination OR achieving a seroprotective IgG level at 1-2 months post-vaccination.

Positive vaccine response for *S. pneumoniae*: ≥2-fold increase in IgG from pre- to 1-2 months post-vaccination OR achieving an IgG >1.3 µg/ml for ≥50% of the PCV13 serotypes at 1-2 months post-vaccination.

For Adults:

Positive vaccine response for S. pneumoniae is achieving a seroprotective IgG level in ≥ 15 out of 20 PCV20 serotypes at 1-2 months post-vaccination.

Positive vaccine response for other than S. pneumoniae is based on a positive antibody titer 1-2 months post-vaccination.

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Appendix B. Initial vaccination schema in ADULTS who received B-cell targeted CAR-T cell therapy†

Killed/Inactivated Vaccines[1]	**Pre-CAR**	**≥3m**	**~4m**	**~6m**	**≥6m**	**≥7m**	**≥8m**	**≥10m**	**≥12m**	**≥18m**	**Minimal Time Interval Between Vaccinations**
IIV4, Inactivated influenza quadrivalent (Sep-Mar)	**IIV4**[2]				**IIV4**[2,3]						
Pneumococcal-conjugate (Prevnar 20®)				✓titers[8]	**PCV20**	✓titers[4,8]	**PCV20**[4,8]	**PCV20**[4,8]			
Pentacel® (DTaP/IPV/Hib)[5,6]				✓titers[7,8]	**Pentacel®**[8]	✓titers[7,8]	**Pentacel®**[8]	**Pentacel®**[8]	✓titers[7,8]		1-2 months
Hepatitis A				✓titers[8,11]	**HAV**	✓titers[8,11]			**HAV**[8,]	✓titers[8,11]	6 months
Hepatitis B [9,10]				✓titers[8,11]	**HBV**	✓titers[8,11]	**HBV**[8]	**HBV**[8]	**HBV**[8]	✓titers[8,11]	1-2 months
SARS-CoV-2 (Pfizer or Moderna)		**COVID**[12]	**COVID**		**COVID**[13]		**COVID**[13]				

[1] For inactivated "dead" virus vaccines, vaccination should be at least 2 months post last dose of IVIG.
[2] If patient is going to receive CAR-T cell therapy during influenza season, administer annual inactivated influenza vaccine after leukapheresis and ≥ 2 weeks prior to beginning lymphodepletion chemotherapy, (if not previously administered) Subsequent annual vaccinations can resume > 6 months after CAR T therapy.
[3] If there is an influenza outbreak, IIV4 may be given at 3 months post CAR-T therapy.
[4] Check titers for S. Pneumonia (IgG, 23 serotypes) 1-2 months after each PCV20. A positive response to PCV20 is defined: as achieving a seroprotective IgG level against S. pneumoniae in ≥15 out of 20 PCV20 serotypes at 1-2 months post-vaccination. A positive response requires no further PCV20 vaccinations.
[5] Separate component vaccines (shots) may be used instead for DTaP, IPV, and Hib if Pentacel® is unavailable.
[6] If not using Pentacel® and DTaP is unavailable, then may use Adacel® = Tdap (age ≥ 10 y through 64 y) or Boostrix® = Tdap (age ≥ 10 y).
[7] Check titers to Hib, tetanus toxoid.
[8] For patients with no history of HCT or who completed the whole series of post-HCT vaccines, if the patient has seroprotective titers, **do not** give additional vaccines. For patients with no history of HCT or who completed the whole series of post-HCT vaccines, give additional vaccines **ONLY** if the patient developed a response but did not achieve seroprotection based on reference laboratory guidelines and Appendix A. In patients who did not complete the whole series of vaccinations post-HCT, complete the rest of the series as indicated. Patients who did not respond should defer additional vaccination until documented immune reconstitution.
[9] Hepatitis B vaccination is accomplished preferably with Heplisav-B® based on data extrapolated from patients with chronic kidney disease or on hemodialysis for ESRF. Alternatively, double (40 mcg/dose = 2 mL total) doses of Engerix-B® may be given. Patients who do not respond to the primary vaccine series should receive an additional 1-3 doses of the same vaccine or, alternatively, repeat series with a different vaccine brand (e.g., double doses of Engerix-B® if did not respond to Heplisav-B® or single doses of Heplisav-B® if did not respond to Engerix-B®).
[10] If NOT administering hepatitis B series using Heplisav-B®, Twinrix® can be administered on days when HAV and HBV are given together. (Twinrix® approved for age ≥ 18 y)
[11] Hepatitis A & B surface antigen IgG.
[12] Dose 1 of the SARS-CoV-2 vaccination series should begin at ≥ to day + 90.
[13] Dose 3 is preferably given 2 months after dose 2 but may be given as early as 1 month after dose 2 to avoid a missed vaccination opportunity; Dose 4 is 2 months after Dose 3.

†Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommend that vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated. If syncope develops, patients should be observed until the symptoms resolve.

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Appendix C. Initial vaccination schema in CHILDREN who received B-cell targeted CAR-T cell therapy†

Killed/Inactivated Vaccines[1]	Pre-CAR	≥3m	~4m	~6m	≥6m	≥7m	≥8m	≥10m	≥12m	≥18m	Minimal Time Interval Between Vaccinations
IIV4, Inactivated influenza quadrivalent (Sep-Mar)	**IIV4[2]**				**IIV4[3]**						
Pneumococcal-conjugate (Prevnar 20™)				✓ titers[4,8]	**PCV20**	✓ titers[4,8]	**PCV20**[4,8]	**PCV20**[4,8]			
Pentacel® (DTaP/IPV/Hib)[5,6]				✓ titers[7,8]	**Pentacel®**	✓ titers[7,8]	**Pentacel®**[,8]	**Pentacel®**[,8]	✓ titers[7,8]		1-2 months
Hepatitis A[9]				✓ titers[8,10]	**HAV**	✓ titers[8,10]			**HAV**	✓ titers[8,10]	6 months
Hepatitis B[9,11]				✓ titers[8,10]	**HBV**	✓ titers[8,10]	**HBV**		**HBV**	✓ titers[8,10]	1-2 months
SARS-CoV-2 – **Age ≥ 6 months** (Moderna or Pfizer)		**COVID**[12]	**COVID**		**COVID**[13]		**COVID**[13]				

[1] For inactivated "dead" virus vaccines, vaccination should be at least 2 months post last dose of IVIG.
[2] If patient is going to receive CAR-T cell therapy during influenza season, administer annual inactivated influenza vaccine after leukapheresis and ≥ 2 weeks prior to beginning lymphodepletion chemotherapy, (if not previously administered) 6 months OR 6 and 8 months after CAR T therapy and yearly thereafter.
[3] If there is an influenza outbreak, IIV4 may be given at 3 months post CAR-T therapy.
[4] Check titers for S. Pneumoniae (IgG, 23 serotypes).
[5] Separate component vaccines (shots) may be used instead for DTaP, IPV, and Hib if Pentacel® is unavailable.
[6] If not using Pentacel® and DTaP is unavailable, then may use Adacel® = Tdap (age ≥ 10 y through 64 y) or Boostrix® = Tdap (age ≥ 10 y).
[7] Check titers to Hib, tetanus toxoid
[8] For patients with no history of HCT or who completed the whole series of post-HCT vaccines, if the patient has seroprotective titers, do not give additional vaccines. For patients with no history of HCT or who completed the whole series of post-HCT vaccines, give additional vaccines ONLY if the patient developed a response but did not achieve seroprotection based on reference laboratory guidelines and Appendix A. In patients who did not complete the whole series of vaccinations post-HCT, complete the rest of the series as indicated. Patients who did not respond should defer additional vaccination until documented immune reconstitution.
[9] A combination vaccine is available as Twinrix = HBV/HAV (age ≥ 18 y). If using Twinrix (combination HBV/HAV for age ≥18 y), the dosing schedule is 0, 1 and 6 months apart. Heplisav is the preferred vaccine for HBV (age ≥18 y; dosing schedule is 0, ≥1 month apart) given higher immunogenicity; if unavailable, Recombivax HB for HBV alone (dosing schedule is 0, 1, and 6 months apart) is approved in adults.
[10] Test for hepatitis A and B surface antigen IgG.
[11] Patients who do not respond to the primary vaccine series should receive a second 3 dose series (either double the age-appropriate dose of Engerix, Recombivax; or single doses of Heplisav B if age ≥18 y).
[12] Dose 1 of the SARS-CoV-2 vaccination series should begin at ≥ to day + 90.
[13] Dose 3 is preferably given 2 months after dose 2 but may be given as early as 1 month after dose 2 to avoid a missed vaccination opportunity; Dose 4 is 2 months after Dose 3.

†Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommend that vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated. If syncope develops, patients should be observed until the symptoms resolve.

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Appendix D. Subsequent vaccination schema in ADULTS AND CHILDREN who received B-cell targeted CAR-T cell therapy and completed the initial vaccine series with evidence of serologic response †

Killed/Inactivated Vaccines[1]	**≥17m**	**≥18m**	**≥20m**	**≥24m**	**≥26m**	**Minimal Time Interval Between Vaccinations**
Meningococcal ACWY (Menactra, Menveo, MCV4)[2]	✓ titers	**MCV4**	**MCV4**			2 months
Meningococcal Group B (Bexsero®)[3,4]				Bexsero®	Bexsero®	≥ 2 months
HPV (Gardasil), 9-45 years		**HPV**	**HPV**	**HPV**		2 m after 1st; 4 m after 2nd dose
Live and Non-Live Adjuvant Vaccines						
Measles/Mumps/Rubella (MMR) [5] < 18 years	✓ titers	**MMR**	**MMR**			
Measles/Mumps/Rubella (MMR) [5] ≥ 18 years	✓ titers	**MMR**				
Varicella-Zoster - Varivax (live): *VZV seronegative only*[5,6]	✓ titers	**VZV**	**VZV**	✓ titers[7]		≥ 1 month
Varicella-Zoster - Shingrix® (non-live adjuvant): *VZV*[6,8] *seropositive only,*[6] ≥ 18 years	✓ titers	**VZV**	**VZV**			1-2 months

[1]For inactivated "dead" virus vaccines, vaccination should be at least 2 months post last dose of IVIG.
[2]Meningococcal vaccination is recommended for individuals at increased risk for meningococcal infection, such as children between 11 and 18 years of age and certain other groups (college freshmen living in dormitories, individuals traveling to countries where Neisseria meningitidis is hyperendemic or epidemic, patients with terminal complement component deficiencies or anatomic or functional asplenia [ie chronic GVHD], and others).
[3]Recommended for patients ≥ 10 years old with anatomic or functional asplenia condition [ie chronic GVHD] or increased environmental risk.
[4]If Bexsero® is not given, Trumenba® can be substituted in patients ≥ 10 years old as 3 doses (0, 2, and 6 months apart).
[5]Not until > 1 year post CAR-T cell therapy, > 2 year post transplant, > 1 year off all systemic immunosuppressive therapy, > 8 months since last dose of IVIG/VZIG or most recent plasma transfusion, and absolute CD4 T cell count ≥ 200 per microliter.
[6]If patient is VZV seronegative, do not give Shingrix.
[7]Check varicella serology 1-2 months after second dose of Varivax to ensure seroconversion of the VZV seronegative patient.
[8]Not until ≥ 1 year post CAR-T cell therapy, ≥ 1 year post transplant, ≥ 8 months off all systemic immunosuppressive therapy for chronic GVHD, and absolute CD4 T cell count ≥ 200 per microliter.

†Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommend that vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated. If syncope develops, patients should be observed until the symptoms resolve.