Immunotherapy (IMTX): Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immunotherapy 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 immunotherapy have poor immune function due to effects of their malignancy, prior cytotoxic treatments, lymphodepletion therapy including depletion of B cells due to B cell targeted CAR-T cells. CAR-T cells can persist for months to years and result in prolonged B 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, expert guidelines11 recommend monthly monitoring of immunoglobulin G (IgG) levels and intravenous immunoglobulin (IVIG) supplementation for patients with severe hypogammaglobulinemia (i.e. IgG <400 mg/dL), as 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 Immunotherapy Patients." Vaccination is considered an important long-term goal after CAR-T therapy, similar to after autologous or allogeneic HCT. Notably, a large proportion of subjects receiving CAR-T therapy may have had a prior HCT without completion of the subsequently recommended vaccinations. Studies of patients with 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 Furthermore, patients treated with B cell-targeted CAR-T cell therapy may have reconstitution of normal B 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 not clear.

These guidelines are 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. The approach to vaccination after CAR-T cell therapy among individuals who have not had a prior HCT or who have completed post-transplant the standard recommended series of vaccines is designed to allow for the possibility of preserved immunity and/or the ability to generate a boosted response with a single vaccination, where applicable. 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.

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.

(continued on the next page)
B. 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 they do not have any 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.
      - ≤ 5 months after last dose of IVIG supplementation.
      - Absolute CD4 T cell count ≤ 200 per microliter.
      - Actively receiving chemotherapy

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.

(continued on the next page)
C. Post CAR-T Cell Therapy:

1. Initial Screening for non influenza 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

2. Post Initial Screening

   a. For patients with no history of prior HCT OR who completed the whole series of post-HCT vaccines. For additional information for transplant patients see “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 A response is defined: as achieving a seroprotective IgG level against 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 AND also achieving a seroprotective IgG level against the other non S. pneumoniae vaccines ≥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.
Immunotherapy (IMTX): Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immunotherapy Patients

Post Initial Screening (Continued)

See Appendix B & C

- **Month 0:** Give one dose each of Prevnar conjugate vaccine (PCV13), HiB, HAV and HBV and age-appropriate formulations of diphtheria/tetanus/acellular pertussis (DTaP preferred over Tdap), irrespective of preexisting seroprotective IgG.
- **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, HAV, and HBV 1-2 months after completion of the indicated vaccination series.
  - 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 Immunotherapy Standard Practice Guideline”).

<table>
<thead>
<tr>
<th>Table 1 Markers for Immune Reconstitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
</tr>
<tr>
<td>- Detectable serum IgA⁺ (&gt; 6 mg/dL) AND</td>
</tr>
<tr>
<td>- CD19 or CD20 B cell count &gt; 20 per microliter AND</td>
</tr>
<tr>
<td>- CD4⁺ T cell count &gt; 200 per microliter</td>
</tr>
</tbody>
</table>

*⁺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 PCV13, DTaP/Tdap, HiB, and HAV/HBV, 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.

(continued on the next page)
**Immunotherapy (IMTX): Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immunotherapy Patients**

Post Initial Screening (Continued)

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.

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>Vaccination</th>
<th>Response*</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 6 months post CAR-T cell therapy</td>
<td>Check Ab Titers</td>
<td>Vaccinate See Appendix B and C</td>
<td>Response</td>
</tr>
<tr>
<td>Meets eligibility criteria on page 2</td>
<td>Check Ab Titers</td>
<td>No Response</td>
<td>Defer additional vaccines until immune reconstitution (Table 1)</td>
</tr>
</tbody>
</table>

*A response is defined: as achieving a seroprotective IgG level against *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 AND also achieving a seroprotective IgG level against the other non *S. pneumoniae* vaccines ≥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.

- **Month 0:** Give one dose each of Prevnar conjugate vaccine (PCV13), HiB, and age appropriate formulations of diphtheria/tetanus/acellular pertussis (DTaP preferred over Tdap) and HAV/HBV irrespective of preexisting seroprotective IgG.
- **Months 1-2:** Check IgG titers to *Streptococcus pneumoniae* (23 serotypes), tetanus toxoid, HiB, HAV, and HBV.
- **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 Immunotherapy” Standard Practice Guideline

<table>
<thead>
<tr>
<th>Table 2 Markers for Immune Reconstitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
</tr>
<tr>
<td>Detectable serum IgA† (&gt; 6 mg/dL) AND</td>
</tr>
<tr>
<td>CD19 or CD20 B cell count &gt; 20 per microliter AND</td>
</tr>
<tr>
<td>CD4⁺ T cell count &gt; 200 per microliter</td>
</tr>
</tbody>
</table>

†A detectable IgA level indicates potential ability to “class switch”

(continued on the next page)
Immunotherapy (IMTX): Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immunotherapy Patients

Post Initial Screening (Continued)

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 PCV13, DTaP/Tdap, HiB, and HAV/HBV, consider additional vaccinations. There is no need to test baseline or subsequent pathogen-specific IgG for these additional vaccines per Appendix D.

D. Miscellaneous

- Inactivated vaccine injections should be used for family members who need vaccinations against polio. Isolation is necessary if live (oral) polio vaccine is administered to family members or other persons in close contact with patients during the first year after a HCT or at any time during treatment with immunosuppressive medications. The virus can be shed for 8 to 12 weeks after vaccination.

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

- Smallpox vaccine is comprised of live vaccinia virus. Smallpox vaccination is contraindicated in HCT and Immunotherapy 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.

- 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


(continued on the next page)
Immunotherapy (IMTX): Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immunotherapy Patients


Keywords: Immunotherapy-vaccines, B cell-targeted CARs
Immunotherapy (IMTX): Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immunotherapy Patients

APPENDIX A

Definitions

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.
## Immunotherapy (IMTX): Vaccination after B cell-targeted CAR-T cell therapy for Adult and Pediatric Immunotherapy Patients

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

<table>
<thead>
<tr>
<th>Killed/Inactivated Vaccines¹</th>
<th>Pre-CAR</th>
<th>&gt;6m</th>
<th>&gt;6m</th>
<th>&gt;7m</th>
<th>&gt;8m</th>
<th>≥10m</th>
<th>&gt;12m</th>
<th>≥18m</th>
<th>20m</th>
<th>Minimal Time Interval Between Vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (inactivated, Sep-Mar)</td>
<td>Flu²</td>
<td>Flu²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>Pneumococcal-conjugate (Prevnar 13™)</td>
<td>✓ titers³ PCV13 ✓ titers³,⁴ PCV13 PCV13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>Pneumococcal-polysaccharide (Pneumovax)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>Diphtheria, tetanus, and acellular pertussis</td>
<td>✓ titers⁵ DTP ✓ titers⁶,⁷ DTP⁶ DTP⁶ ✓ titers⁸</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>H. Influenza type B</td>
<td>✓ titers HiB ✓ titers⁸ HiB HiB ✓ titers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>Hepatitis A⁶,⁷</td>
<td>✓ titers⁸ HAV ✓ titers⁸ HAV⁴ ✓ titers⁸</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 months</td>
</tr>
<tr>
<td>Hepatitis B⁶,⁷,⁹</td>
<td>✓ titers⁸ HBV ✓ titers⁸ HBV HBV⁴ ✓ titers⁸</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 months</td>
</tr>
</tbody>
</table>

¹For inactivated “dead” virus vaccines, vaccination should be at least 2 months post last dose of IVIG.

²If 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.

³Check titers for S. Pneumoniae (IgG, 23 serotypes).

⁴For 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.

⁵Preference is DTaP but Tdap can be substituted.

⁶A combination vaccine is available as Twinrix = HBV/HAV (age ≥ 18 y).

⁷If 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.

⁸Hepatitis A & B surface antigen IgG.

⁹High dose (40mcg/dose) hepatitis B vaccination is recommended in immunocompromised or hemodialysis patients. Patients who do not respond to the primary vaccine series should receive a second 3 dose series.

¹⁰Check anti-tetanus toxoid titer.
## Appendix C. Initial vaccination schema in CHILDREN who received B-cell targeted CAR-T cell therapy

<table>
<thead>
<tr>
<th>Killed/Inactivated Vaccines</th>
<th>Pre-CAR</th>
<th>≥6m</th>
<th>≥6m</th>
<th>≥7m</th>
<th>≥8m</th>
<th>≥10m</th>
<th>≥12m</th>
<th>≥18m</th>
<th>≥20m</th>
<th>Minimal Time Interval Between Vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (inactivated, Sep-Mar)</td>
<td>Flu&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>1-2 months</td>
</tr>
<tr>
<td>≥ 6 months and &lt; 9 years</td>
<td>Flu&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>1-2 months</td>
</tr>
<tr>
<td>&gt; 9 years</td>
<td>Pneumovax</td>
<td>Pneumovax</td>
<td>Pneumovax</td>
<td>Pneumovax</td>
<td>Pneumovax</td>
<td>Pneumovax</td>
<td>Pneumovax</td>
<td>Pneumovax</td>
<td>Pneumovax</td>
<td>1-2 months</td>
</tr>
<tr>
<td>Pneumococcal-conjugate (Prevnar 13™)</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td>1-2 months</td>
</tr>
<tr>
<td>Pneumococcal-polysaccharide (Pneumovax)</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>1-2 months</td>
</tr>
<tr>
<td>Diphtheria, tetanus, and acellular pertussis (DTaP&lt;sup&gt;5,6&lt;/sup&gt;)</td>
<td>HAV</td>
<td>HAV</td>
<td>HAV</td>
<td>HAV</td>
<td>HAV</td>
<td>HAV</td>
<td>HAV</td>
<td>HAV</td>
<td>HAV</td>
<td>6 months</td>
</tr>
<tr>
<td>H. Influenza type B</td>
<td>HiB</td>
<td>HiB</td>
<td>HiB</td>
<td>HiB</td>
<td>HiB</td>
<td>HiB</td>
<td>HiB</td>
<td>HiB</td>
<td>HiB</td>
<td>1-2 months</td>
</tr>
<tr>
<td>Hepatitis A&lt;sup&gt;8,10&lt;/sup&gt;</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>2 months</td>
</tr>
<tr>
<td>Hepatitis B&lt;sup&gt;5, 8, 9,11&lt;/sup&gt;</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>2 months</td>
</tr>
</tbody>
</table>

<sup>1</sup>For inactivated “dead” virus vaccines, vaccination should be at least 2 months post last dose of IVIG.

<sup>2</sup>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.

<sup>3</sup>Check titer for S. Pneumoniae (IgG, 23 serotypes).

<sup>4</sup>For patients with no history of HCT or who completed the whole series of post-HCT vaccines, if the patient has seroprotective titer, 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.

<sup>5</sup>Combination vaccines are available for certain age groups: Pentacel = DTaP/HiB/IPV (age < 4 y), Infanrix and Daptacel = DTaP (age < 7 y), Pediarix = DTaP/HPV/IPV (age ≤ 7 y).

<sup>6</sup>DTaP (Daptacel, Infanrix) is the recommended vaccine in children ages < 7 years old. In children and adults ≥ 7 years old with a history of cancer, DTaP may be more effective than Tdap (Adacel) due to higher antigen loads of diphtheria and acellular pertussis.

<sup>7</sup>Check anti-tetanus toxoid titer.

<sup>8</sup>A combination vaccine is available as Twinrix = HBV/HAV (age ≥ 18 y).

<sup>9</sup>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.

<sup>10</sup>Test for hepatitis A and B surface antigen IgG.

<sup>11</sup>High dose (40mcg/dose) hepatitis B vaccination is recommended in immunocompromised or hemodialysis patients. Patients who do not respond to the primary vaccine series should receive a second 3 dose series.

**Appendix C**
## Appendix D. Subsequent vaccination schema in ADULTS AND CHILDREN who received B-cell targeted CAR-T cell therapy and responded to initial vaccine series (Pneumococcal-conjugate, tetanus, H. Influenza, Hepatitis A and B)†

<table>
<thead>
<tr>
<th>Killed/Inactivated Vaccines¹</th>
<th>&gt;17m</th>
<th>&gt;18m</th>
<th>&gt;20m</th>
<th>&gt;22m</th>
<th>&gt;24m</th>
<th>&gt;26m</th>
<th>&gt;27m</th>
<th>Minimal Time Interval Between Vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningococcal ACWY (Menactra, Menveo, MCV4)²</td>
<td>✓ titer</td>
<td>MCV4</td>
<td>MCV4</td>
<td>Bexsero®</td>
<td>Bexsero®</td>
<td>2 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal Group B (Bexsero®)³,⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 2 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polio (inactivated)</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td></td>
<td>1-2 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV (Gardasil), 9-45 years</td>
<td>HPV</td>
<td>HPV</td>
<td>HPV</td>
<td></td>
<td></td>
<td>2 m after 1st; 4 m after 2nd dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Live and Non-Live Adjuvant Vaccines⁵</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles/Mumps/Rubella (MMR)</td>
<td>✓ titer</td>
<td>MMR</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Varicella-Zoster</td>
<td>VZV</td>
<td>VZV</td>
<td></td>
<td>✓ titer⁷</td>
<td>≥ 1 month</td>
<td></td>
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<tr>
<td>- Varivax (live): VZV seronegative only⁶</td>
<td></td>
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</tr>
<tr>
<td>Varicella-Zoster</td>
<td>VZV</td>
<td>VZV</td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Shingrix® (non-live adjuvant): VZV seropositive only,⁷ ≥ 50 years</td>
<td></td>
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</tbody>
</table>

¹For inactivated “dead” virus vaccines, vaccination should be at least 2 months post last dose of IVIG.
²Meningococcal 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).
³Recommended for patients > 10 years old with anatomic or functional asplenia condition [ie chronic GVHD] or increased environmental risk.
⁴If Bexsero® is not given, Trumenba® can be substituted in patients > 10 years old as 3 doses (0, 2, 6 months apart).
⁵Not until > 1 year post CAR-T cell therapy, > 2 year post transplant, > 1 year off all systemic immunosuppressive therapy, > 5 months since last dose of IVIG/VZIG or most recent plasma transfusion, and absolute CD4 T cell count ≥ 200 per microliter.
⁶Based on pre-HCT or pre-CAR-T cell test serological results.
⁷Check varicella serology 1-2 months after second dose of Varivax to ensure seroconversion of the VZV seronegative patient.

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†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.