HOW I VACCINATE BLOOD AND MARROW TRANSPLANT RECIPIENTS

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Abstract:

Vaccination guidelines for recipients of blood and marrow transplantation (BMT) have been published by three major societies - American Blood and Marrow Transplantation (ASBMT), European Group of Blood and Marrow Transplantation (EBMT), and Infectious Disease Society of America (IDSA). Despite these extensive review articles, clinicians caring for BMT recipients continue to field frequently asked questions (FAQs) regarding the “who, when and how” of feasible and effective posttransplant vaccination, frequently in the absence of adequate data. This may reflect discomfort with a “one size fits all” policy that makes no adjustments for different posttransplant clinical scenarios. Existing guidelines also lack practical dose clarifications when administering vaccines to patients who differ by age, underlying diagnosis, or amount of immunosuppressive therapy. Frequently, little or conflicting guidance is given regarding age-related schedules for certain vaccines (e.g. meningococcal, Tdap, and human papillomavirus vaccines) in addition to time posttransplant or other factors. FAQs and their answers form the body of this article and are shared with readers as a concise practical review, with the intent to facilitate good clinical practice.
Introduction

Three major societies (ASBMT, EBMT and IDSA) have published vaccination guidelines separately or as part of broad practice guidelines for preventing infectious complications among BMT recipients or other immunocompromised hosts. Despite these extensive guidelines, only 17% of anonymously polled participants at a 2015 ASBMT practice guidelines session were aligned with the overarching societal recommendation to begin vaccinations at 6 months for patients without graft versus host disease; 64% of participants requested basic data about the patient’s numeric immune reconstitution which is not recommended by current guidelines. This may reflect a discomfort resulting from “one-size fits all” recommendations, especially when IDSA states upfront that the “Evidence is often limited”. Existing guidelines make little adjustment for whether or not BMT was for primary immunodeficiency disease (PID), or other factors that most providers consider when beginning and dosing vaccines. Other factors generally reviewed in addition to the time after transplant are levels of numeric or functional immune reconstitution (IR), the intensity of recent or ongoing immunosuppressive therapy (IST), and age-related schedules for certain vaccines (e.g. meningococcal, pneumococcal, Tdap, and human papillomavirus).

This “How I Treat” arose from our need for pragmatic institutional vaccination standards while recognizing the dearth of existing data to address many relevant practicalities. The goal for this article was to discuss vaccination clinical cases (Figure 1) and our “Top 20” frequently asked questions (FAQs) about post-BMT vaccination. Supplementary FAQs (sFAQs) that did not make top 20 and those about less common vaccines are found in Supplement 1. Questions came from clinical providers via phone, e-mail, or as “curbside consults” which often began with: “Do you mind if I just ask you a vaccine question?” We share our answers to these FAQs as a concise practical and pragmatic review; the intent is to facilitate good clinical practice in patients of all ages. We also provide an auto-filled Excel immunization schedule table for our recommended BMT approach to early or standard vaccination (hotlink to electronic Supplement 2).

Top 20 Frequently Asked Questions (FAQs)

General:
**FAQ1:** When should vaccinations begin for the typical BMT recipient?  
Consensus guidelines recommend initiating vaccinations at 3-6 months after BMT noting that this lacks prospective validation. Given the variable tempo of IR (see sFAQ1), particularly in patients transplanted for primary immunodeficiency diseases (see FAQ4), the negative impact of moderate to severe GVHD on IR, and potential use of *in vivo* T or B cell depleting therapies, we prefer to select candidates for “early vaccination” at 6 months based on favorable responses to a 6-question algorithm (Figure 2). Any unfavorable response triggers vaccine deferral (except for flu shots) until at least 1 year posttransplant. Our approach takes into consideration that vaccine efficacy depends on at least partial reconstitution of adaptive immunity.  

**FAQ2:** Should BMT recipients be vaccinated if they already have protective titers?  
Yes. Antibody titers to vaccine-preventable diseases decline after autologous (see sFAQ2) or allogeneic BMT despite the fact that most BMT recipients were vaccinated earlier in life. Clinical relevance of declining titers is not immediately apparent because the number of vaccine-preventable diseases reported among BMT recipients is limited. Nonetheless, diseases potentially prevented by vaccines still pose increased risks for BMT recipients until immunity is fully restored. Therefore, with exception of viruses exhibiting latency outside the hematopoietic system (e.g. varicella), BMT recipients should be re-vaccinated against pathogens contained in childhood primary immunization schedules.  

**FAQ3:** Is vaccination appropriate for patients receiving immunoglobulin therapy?  
For inactivated vaccines, recently administered IgG products do not inhibit immune responses (see sFAQ7). However, we do not recommend early vaccination when patients are receiving IVIG replacement therapy because IVIG therapy is a surrogate marker for delayed IR (Figure 2). If a decision is made to vaccinate at 12 months posttransplant, then delaying vaccination after IgG products might create a missed opportunity to vaccinate a patient who is seen infrequently, and immunization in this scenario is therefore recommended.  

In contrast, Advisory Committee on Immunization Practices (ACIP) recommends
deferring live MMR and VZV vaccination no sooner than 3-11 months after receiving the last IgG-containing blood products. This allows sufficient degradation of potential antibodies that could interfere with viral replication, the latter being essential to effective live virus vaccination. Other criteria need to be considered for live virus vaccination in the transplant recipient (FAQs 15, 19 and also sFAQs 30, 35-40).

**FAQ4: Are recipients of allogeneic BMT for primary immune deficiency vaccinated differently than recipients transplanted for other diseases?**

Yes. Because B cell immune reconstitution has been highly variable after BMT in patients with immunodeficiencies, vaccination is delayed until there is robust evidence of functional B cell recovery. Bacteriophage testing may be done when IST is discontinued unless there is a history of anti-CD20 antibody therapy or poor donor B cell engraftment, but results of bacteriophage testing are not the major factor in deciding when to begin vaccination. Except for seasonal flu shots (see FAQ11), routine posttransplant vaccinations are not considered until at least 1 year after BMT and only if the following three criteria are satisfied:

A. Patient is without infections in the past 6 months and so it is reasonable to attempt a 3 month trial off IgG replacement therapy and

B. Low community prevalence of influenza, RSV, human metapneumovirus, or parainfluenza is present during the planned trial off IgG therapy and

C. All the following laboratory criteria are met:

   (i) Trough IgG > 600 mg/dL on standard IgG dosing which suggests numeric IgG reconstitution.
   (ii) Detectable serum IgA (>6 mg/dL) suggesting ability to “Ig class switch”.
   (iii) Donor B cells >200/µL as determined by percent donor B cell chimerism multiplied by the total absolute B cell count. This threshold is arbitrarily set 1-log higher than for non-primary immunodeficiencies diseases.
   (iv) Donor CD4 cells 200/µL as determined by percent donor CD4 chimerism multiplied by the total absolute CD4 T cell count.

Generally, the last criterion is addressed after the first two criteria are met by ensuring that quantitative immunoglobulin testing is timed with the expected IgG nadir following the last dose of IgG therapy. When all three criteria are satisfied, IgG therapy is withheld for 12 consecutive weeks. We begin (Week 0) by giving one dose each of PCV13, HiB,
DTaP (or Tdap age>10) and Hepatitis B. Combination vaccines are preferred in children to limit the number of injections. During weeks 6-8, we repeat the series given at Week 0. At week 12 we check antibody titers to HiB, 23-serotypes of pneumococcus (expecting only a response to PCV13 serotypes), tetanus toxoid and hepatitis B surface antibody. Responders then remain off IgG therapy and proceed with a third dose of each of these vaccines. Patients then receive a standard series of meningococcal, human papilloma virus (HPV), hepatitis A and inactivated polio vaccines. Alternatively, if vaccine response is inadequate, IgG therapy is resumed and further vaccination will be deferred.

**FAQ5:** Why use conjugated vaccines including Hib, PCV13 and MCV4 to initiate early vaccinations?

Due to impaired opsonization, B cell deficient patients are highly susceptible to encapsulated bacteria (*H. influenzae* type B [Hib], *N. meningitidis*, *S. pneumoniae*). BMT recipients without a spleen or with functional asplenia due to chronic GVHD are similarly susceptible (see sFAQ3). Young children are most at risk because of limited capacity to make antibodies to polysaccharide capsules while responding more favorably to protein conjugate vaccines. Similarly, BMT recipients respond to conjugate vaccines as early as 3 months posttransplant and at higher rates than polysaccharide vaccines. [4,5]

**FAQ6:** Can household contacts and healthcare workers who interact with immunocompromised hosts be administered live attenuated vaccines?

Available data supports routine administration of such individuals with injectable live attenuated MMR or varicella vaccine if otherwise age appropriate. However, intranasal live attenuated influenza vaccine should not be given to family members of seriously immunocompromised hosts, such as those requiring protective isolation, because immunocompetent children can shed LAIV for several days. That said, estimated secondary transmission rates of LAIV among immunocompetent hosts are likely <0.001%; LAIV spread from healthy individuals to an immunocompromised patients has not been reported. If a healthcare worker caring for individuals in protective isolation is given LAIV, a 7-day furlough is advised. [10] Live attenuated oral polio vaccine that is still available in some non-U.S. countries should not be used and if inadvertently given to a household contact, a 4-6 week furlough is advised.
**Diptheria/Tetanus/Acellular-Pertussis (DTaP/Tdap)**

Tetanus toxoid revaccination is relevant given the ubiquitous environmental exposure to tetanus and the seriousness of disease due to tetanus toxin. While diphtheria is essentially eradicated, ongoing vaccination is critical for herd immunity and pertussis outbreaks have been prevalent in states where herd immunity has waned. It is important to remember that in the pre-vaccination era (1920s-1940s), annual U.S. death rates for pertussis were 5,000-10,000.

**FAQ7: Should I administer DTaP or Tdap?**

Consensus guidelines favor 3 doses of DTaP regardless of age, although this policy is inconsistent with U.S. recommendations because DTaP is only licensed for <7 years of age. Without data to support DTaP being safe and more effective than Tdap for BMT recipients aged ≥7 years, the Consensus approach needs to be weighed by individual centers. The argument to offer DTaP and not Tdap for older BMT recipients is that 10-fold higher doses of diphtheria and pertussis toxoids in DTaP should elicit better antibody responses. This argument aligns with the fact that early vaccination could include patients who remain on IST (FAQs 1, 4). For reference, the strength of the recommendation for 3 doses of pediatric DTaP vaccine in <7 year-olds is rated by IDSA as “strong” with only “low” quality supporting evidence. In contrast, the same 3 dose DTaP series in ≥7 year-olds (ie. non-FDA-approved use) is rated with a “weak” recommendation and “very low” quality of evidence. Finally, the FDA/ACIP-approved 3-dose series for ≥7 year-olds (Tdap/Td/Td) also carries a “weak” recommendation with “low” rather than “very low” quality evidence. It is unclear whether DTaP side effects are related to higher doses of “D” or “aP” antigens. One study in healthy adults demonstrated that the aP vaccine was safe and relatively non-reactogenic even at high doses.11 Currently, compliance with FDA licensure limits U.S. practice to the potentially inferior Tdap vaccine. If we restrict the use of a 3 shot DTaP series to <7 year olds, the testable question remains whether 3 doses of Tdap would be better than Tdap/Td/Td for those over 7 years of age.

**Hemophilus influenzae type B (Hib)**
Before Hib conjugate vaccines were introduced, *Hib* was the leading U.S. cause of bacterial meningitis among children <5 years old. Hib was also a major cause of other life-threatening infections including pneumonia, epiglottis, bacteremia, and others (See FAQ5, sFAQ3, sFAQ15).

**Hepatitis A (HAV) and Hepatitis B (HBV)**

Hepatitis A infection can be serious and prolonged, particularly in older children, teens and adults. A two shot series is advised to provide durable protective immunity.

Routine U.S. childhood HBV vaccination after 1990 contributed to a >80% decline but incomplete eradication of new acute hepatitis B cases. Thirty to 50% of infected persons aged 5 years and older have initial signs and symptoms for up to 6 months. Fatality rates for CDC-reported acute cases are 0.5%-1% and disease is more severe among older adults. While 95% of adults recover and clear the infection, 90% of infants (and up to 50% aged 1-5 years) will remain chronically infected. Fatality rates for chronic HBV induced cirrhosis or hepatocellular carcinoma are 25% if infection is acquired during childhood and 15% if infected at older ages. There is no treatment for acute infection; chronic infection involves chronic antiviral therapy and regular monitoring to screen for liver damage and cancer. Not surprisingly, broad ACIP HBV vaccine recommendations include immunocompromised individuals.

**FAQ8: How should HAV and HBV vaccines be dosed in BMT recipients?**

HAV vaccination does not differ for immunocompetent and immunocompromised individuals. However, because HBV vaccine antigen doses need to be higher for adult hemodialysis patients to induce protective antibody, the CDC suggests that *higher doses* or *additional doses* of HBV vaccine might also be necessary for other immune compromised individuals. We interpret this to include BMT recipients at least until they reach the milestone of being 6 months off all IST. The nuances of age-related HAV and HBV vaccine dosing and use of combination vaccines are detailed in Tables 1 and 2 (see also sFAQs 16-22).
Human Papillomavirus

**FAQ9: Why is vaccination against HPV advised for young BMT recipients?**
HPV infection is caused by the most common sexually transmitted virus in the U.S., with >50% of sexually active individuals infected (mostly asymptptomatically) during their lifetimes. HPV is responsible for cervical, vaginal and vulvar cancer in women and is the second leading cause of cancer deaths in women worldwide. HPV is also responsible for genital warts and anal cancers in both genders; genital warts can be serious in immunocompromised individuals.

**FAQ10: Which HPV vaccine should be administered after BMT?**
Among three currently available HPV vaccines (4vHPV, 2vHPV, 9vHPV), 9-valent HPV has the potential to prevent approximately 90% of cervical, vulvar, vaginal and anal cancers. It protects against cervical cancer and genital warts. 2vHPV protects against serotypes that are responsible for ~70% of cervical cancer, but does not contain HPV types 6 and 11 that are responsible for over 90% of genital warts. ACIP currently advises vaccination with either 4vHPV or 9vHPV in immunocompromised persons age 9 through 26 years (see sFAQ23). Although two doses may be sufficient for 4vHPV vaccine in healthy individuals, absence of data in BMT leads us to advise three doses be recommended.

Influenza vaccine

Although annual influenza vaccination is a “universal” ACIP recommendation for all individuals age ≥6 months of age, it is especially important for those at high risk for serious flu complications: children aged <5 years or adults aged >65 years and those with “weakened immune systems” including BMT recipients, especially when complicated by chronic lung disease. Even if flu vaccination does not prevent infection with influenza, studies show that it can reduce the risk for hospitalizations and deaths attributable to flu, especially relevant to patients with chronic GVHD because of their risk for bronchiolitis obliterans syndrome and general immune compromise. A variety of flu vaccines are available (sFAQ24-28).
FAQ11: How soon after BMT can I give the flu shot?
Administer at ≥6 months post-BMT regardless of conditioning regimen or BMT type.
During community outbreaks flu vaccine may be given at 3-4 months post-BMT, in which case a second dose is given 1 month later.¹⁴

FAQ12: Is post-BMT flu vaccination different for children compared to adults?
Yes, but only for children aged ≥6 months and <9 years who never had flu vaccine post-transplant; these children need 2 flu shots given ≥1 month apart. One study has not demonstrated further benefit from 2 doses in pediatric BMT recipients who have not received influenza vaccine post-transplant, and therefore just one dose is given annually thereafter.¹⁵ For healthy family members aged 2 to 8 years, live attenuated influenza vaccine (FluMist, MedImmune) or the inactivated flu shot is considered equally effective. LAIV has limited ability to spread from person to person, but in general, patients who require protective isolation or are hospitalized should not be exposed to LAIV. Therefore, persons immunized with LAIV should be separated from patients requiring isolation for at least one week following immunization.

FAQ13: Is flu vaccination different for adults aged ≥65 years?
Intramuscularly administered Fluzone High-Dose (Sanofi Pasteur) contains 4x as much antigen as the standard inactivated flu shot and was shown in one study to improve upon traditionally poor antibody response to standard flu shots in adults ≥65 years and to offer superior protection against influenza.¹⁶ New flu vaccines with adjuvants have been recently licensed; ACIP recommendations for elderly or elderly transplant recipients are not yet available.

Meningococcus

N. meningitides causes <1000 U.S. cases per year of meningococcal disease but the overall case fatality rate exceeds 10% and another 15% suffer permanent complications including neurological impairment, deafness, and limb loss. Several meningococcal vaccines require consideration. Conjugate (MCV4) vaccines or the traditional polysaccharide vaccine (MPSV4) can provide quadrivalent protection against meningococcal serogroups A, C, W, and Y (C, W, Y account for ~70% of U.S. cases). Recently FDA-approved Men-B vaccines now extend protection to serogroup B (up to
33% of U.S. cases). Men-B vaccines are only licensed for individuals 10-25 years of age, and until recently were not commonly utilized outside of outbreak situations. Vaccination strategies first consider that meningococcal disease is most frequent among: infants, pre-teen/adolescents who are the primary focus group for vaccination and, over 65 year-olds among whom 60% of cases are attributable to serogroup Y. Beyond these age groups, other individuals are considered to be at higher risk.

**FAQ14: Who should receive which meningococcal vaccine?**

We advise that all BMT recipients over 9 months of age and ≥6 months posttransplant receive two doses of a T-dependent conjugated quadrivalent vaccine (MCV4) and not the polysaccharide (MPSV4) vaccine because conjugate vaccines are more immunogenic and stimulate long-lived memory B cells. This is congruent with ACIP policy for anatomic asplenia or functionally immunodeficient such as those with chronic GVHD. Regardless of whether one elects to not routinely vaccinate older BMT recipients who have more rapid immune reconstitution and no chronic GVHD, environmental risks (military recruits, college freshmen in dormitories, or microbiologists who handle *N. meningitides*) should be considered.

ACIP recently advised that a multicomponent Men-B antigen vaccine be given routinely to high-risk individuals ≥10 years old, in addition to MCV4, and may be offered on an individual basis to any adolescent or young adult at a preferred age of 16-18 years. This came about due to the availability of safe and immunogenic vaccines and increasing meningococcal B outbreaks. We would consider off-label use for >25 year-olds with functional or anatomic asplenia (e.g. chronic GVHD) or those with work-place risks (see Table 3 and sFAQ29).

**Measles, Mumps, Rubella, Varicella (MMR/MMVR)**

Measles is a highly contagious airborne respiratory disease that caused ~2.6 million deaths globally per year before widespread vaccination. Measles complications include high fever, rash, blindness, life-threatening diarrhea, encephalitis or pneumonia. Mumps complications can be more serious in adults than children and include viral meningitis,
orchitis, oophoritis, mastitis, and deafness. Rubella complications include polyarthralgia, encephalitis, thrombocytopenia, and potentially devastating congenital rubella syndrome.

**FAQ15: When and how should MMR vaccination be given after BMT?**

It is considered safe to give live attenuated MMR when recipients are ≥2 years out from BMT,19 ≥1 year off all systemic immunosuppressive therapy, and ≥8 months out from any prior IVIG dose (the “2-1-8” mnemonic). Relaxation of this rule to some extent is considered when community outbreaks occur. The efficacy of 2 doses of MMR given 1 month apart in immunocompetent children is ~97% for measles, ~88% for mumps and >90% for rubella. Unvaccinated adults need only 1 dose of MMR. Antibody titers are unnecessary before or after vaccination.

**Pneumococcus**

Invasive pneumococcal disease (IPD), caused by *Streptococcus pneumonia*, may result in frequent hospitalizations for fatal pneumonia, bacteremia, or meningitis, and is one of the most common vaccine-preventable infections recorded after BMT. At highest risk are adults aged ≥65, the immunocompromised, or those with chronic health conditions.

**FAQ16: How do the two available pneumococcal vaccines types differ?**

PPSV23 (Pneumovax) is the original polysaccharide capsular vaccine offering protection against 23 serotypes of pneumococcus known to cause disease in humans (Table 4). Twelve of these serotypes plus the 6A serotype not contained in PPSV23 account for >50% of IPD in children and form the basis of the more effective protein conjugated PCV13 vaccine (Prevnar) that was developed originally for young children. Among immunocompromised children, another 25% of IPD cases involved additional serotypes included in PPSV23. Post-2000 herd immunity that followed introduction of the earlier PCV7 vaccine in children also led to a reduction in IPD among older children and adults.

PCV13, a T cell dependent vaccine, is more immunogenic than PPSV23 because it triggers memory response that leads to more durable protection than PPSV23 which confers only 3-5 years of protection. It is worth remembering that PPSV23 is particularly ineffective in young children age <2 years.
FAQ17: What pneumococcal vaccination schedule is ideal after BMT?

Unless a patient is severely immunocompromised, we begin PCV13 vaccination at ≥6 months, with 3 doses, 1-2 months apart (Figure 2). One dose of PPSV23 is then given 6-12 months (minimum 8 weeks) after the last PCV13. The goal is broader coverage to all 23 pneumococcal serotypes (see sFAQs 31, 32). Starting at month 3 versus 9 with PCV7 was equally effective but pneumococcal titers declined faster for the month 3 cohort; therefore a fourth dose is advised. Priming for PPSV23 vaccination was inferior if vaccination began at month 3. PCV13 responses were inferior for older recipients, donors other than matched siblings, and IgG <400 mg/dL. Cord blood or haplorelated grafts were not addressed and extensive chronic GVHD occurred infrequently in both studies.

FAQ18: Are there exceptions or modifications to the pneumococcal vaccination schedule in FAQ17 (Fig 2)?

Yes. When a BMT recipient remains heavily immunocompromised, a fourth dose of PCV13 is given rather than PPSV23 because PCV13 should induce better T cell collaboration and anamnestic response via generation of memory B cells (see FAQ5).

Elderly BMT recipients also need PPSV23 booster immunization because of their increased vulnerability to IPD. The baseline assumption is that these individuals earlier completed 3 post-BMT doses of PCV13 and 1 dose of PPSV23, or 4 doses of PCV13. ACIP recommends one dose of PCV13 for all adults ≥65 who have not yet received this, followed by a booster PPSV23 6 to 12 months later or, a repeat dose of PPSV23, 5 years after the last dose of PPSV23. Injection site reactogenicity to PPSV23 is less of an issue if boosting is done infrequently at a time when antibody levels have waned.

Varicella and Zoster

FAQ19: Who should be offered varicella vaccine and when is it safe to do so?

Vaccination with Varivax® (Merck & Co., Inc) to prevent chicken pox is only recommended for VZV-seronegative recipients without a history of chickenpox or varicella vaccination because BMT does not eradicate latent VZV in the sensory nerve ganglia of previously infected individuals (i.e., those with a history of chicken pox) or
previously vaccinated individuals. Latent VZV is thought to provide ongoing antigen exposure that obviates the need for revaccination with standard Varivax®. However, a history of varicella does not later preclude the need for high-titer Zostavax® (Merck) in ≥60 year-olds for the prevention of shingles (see sFAQs 36-40).

Timing of varicella vaccination can be remembered as for MMR by the “2-1-8” rule (see FAQ15). A second dose of varicella vaccine is needed >1 month after the first.

**Addressing Vaccine Hesitant Patients/Parents**

**FAQ20:** How to address vaccine hesitancy/resistance in patients/parents?

There is no single best way to tackle this problem. Prospective pediatric studies led Opel et al to advise being presumptive (e.g. “It is time to do shots”) rather than being participatory (e.g. “What do you want to do about shots?”). Participatory approaches resulted in more parents verbalizing initial resistance to one or more vaccines, even after controlling for vaccine-hesitancy status. In contrast, when the provider just states which vaccines a child is due to receive, most parents have no issues with vaccines. It’s fine to presume that the parent you are seeing will be one of the majority. Middle ground might include being presumptive while offering parents an opportunity to express their own preference, for example, “Today, Johnny gets his DTaP, Prevnar and Hib. Sound OK?”. If a participatory approach is preferred, commit to pursuing any refusals, concerns or questions knowing that about half of the initially vaccine resistant parents and a quarter of vaccine-hesitant parents will change their mind (see sFAQ4-6).

While there is no evidence for vaccination with anything but the recommended schedule, if we have thoroughly explored the reasons for delaying or refusing vaccination and have been unable to convince them otherwise, we would argue that alternative schedules that at least partially immunize the child (patient) are probably better than the alternative of requesting that the parent (patient) seek care elsewhere.

**Authorship**

Contribution: P.A.C. conceived the FAQ format, wrote the paper. J.A.E. critically read
and edited the manuscript and provided additional in depth expertise on technical and clinical aspects of vaccines.

Conflict-of-interest disclosure: P.A.C. declares no competing financial interests. J.A.E. has been a consultant for Pfizer, Gilead and receives research support from Roche, Pfizer, GSK, Chimerix and Novavax.

References
8. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm#Tab4
12. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6411a3.htm
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Dose of antigen(s)</th>
<th>Schedule (0 m = initiation of vaccination)</th>
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<tbody>
<tr>
<td></td>
<td>Dose 1</td>
<td>Dose 2</td>
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<tr>
<td>Hepatitis A (Havrix, GlaxoSmithKline)</td>
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<tr>
<td></td>
<td>0-18 y 760 U (0.5 mL)</td>
<td>0 m*</td>
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<td></td>
<td>&gt;18 y 1440 U (1 mL)</td>
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<td>Hepatitis B (Engerix, GlaxoSmithKline)</td>
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<td></td>
<td>&lt;19 y 10 mcg (0.5 mL)</td>
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<td>≥20 y 20 mcg (1 mL)</td>
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<td>HepA/HepB (Twinrix, GlaxoSmithKline)</td>
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<tr>
<td></td>
<td>≥18 y 760 U HAV + 20 mcg HBV (1 mL)</td>
<td>*Immune competent adults can alternatively be vaccinated for HAV and HBV with just 3 doses of Twinrix at: 0, 2 and 6 months</td>
</tr>
</tbody>
</table>

*Pediarix (GlaxoSmithKline) can be substituted for age > 6 weeks and ≤ age 7 years and it also contains DTaP and IPV. NA = not applicable. U = ELISA Units of HAV.
**Table 2: Doses of hepatitis vaccines for immune compromised recipients by age**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Dose of antigen(s)</th>
<th>Schedule (0 m = initiation of vaccination)</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
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<tbody>
<tr>
<td><strong>Hepatitis A (Havrix, GlaxoSmithKline)</strong></td>
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<tr>
<td>0-18 y</td>
<td>760 U (0.5 mL)</td>
<td>0 m*</td>
<td>6 m**</td>
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<td>&gt;18 y</td>
<td>1440 U (1 mL)</td>
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<td><strong>Hepatitis B (Engerix, GlaxoSmithKline)</strong></td>
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<tr>
<td>&lt;1 y</td>
<td>10 mcg (0.5 mL)</td>
<td>0 m*</td>
<td>2 m</td>
<td>6 m**</td>
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<tr>
<td>1-10 y</td>
<td>10 mcg (0.5 mL)</td>
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<tr>
<td>11-19 y</td>
<td>20 mcg (1 mL)</td>
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<tr>
<td>≥20 y</td>
<td>40 mcg (2 mL&lt;sup&gt;2,3&lt;/sup&gt;)</td>
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<td><strong>HepA/HepB (Twinrix, GlaxoSmithKline)</strong></td>
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<tr>
<td>≥18 y</td>
<td>1440 U HAV + 40 mcg HBV (2 mL&lt;sup&gt;4&lt;/sup&gt;)</td>
<td>*In adults Dose 1 HAV and HBV may be combined as Twinrix</td>
<td>NA</td>
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<td>**In adults Dose 2 HAV and Dose 3 HBV may be combined as Twinrix</td>
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</table>

1Pediarix (GlaxoSmithKline) can be substituted for age > 6 weeks and ≤ age 7 years and it also contains DTap and IPV. 2Two 1.0 mL doses at one site 3Recombivax HB (Merck) is an alternative dialysis formulation that provides 40 mcg of HBV antigen in just 1.0 mL allowing smaller injection at one site. 4Two 1.0 mL doses at one site at 0, and 6 months

NA = not applicable. U = ELISA Units of HAV
Table 3: Age related schedule of meningococcal vaccination for HCT recipients

<table>
<thead>
<tr>
<th>Age group</th>
<th>Type</th>
<th>Primary doses (N)</th>
<th>Booster</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥6m-23 m</td>
<td>MCV4 (Men-ACWY)</td>
<td>2</td>
<td>3 y later, then every 5 y while still at risk</td>
<td>Menceo preferred for &lt; 2 y old since Menactra may interfere with primary PCV13 series</td>
</tr>
<tr>
<td>2-10 y</td>
<td>MCV4 (Men-ACWY)</td>
<td>2</td>
<td>If last dose was &lt; age 6 then boost 3 y later, then every 5 y while still at risk</td>
<td>Menceo or Menactra, but Menactra may interfere with the immunologic response to PCV13 and so should be separated by at least 4 weeks</td>
</tr>
<tr>
<td>11-12 y</td>
<td>MCV4 (Men-ACWY)</td>
<td>2</td>
<td>Age 16 y</td>
<td>Based on principle that vaccine immunity lasts 3-5 y and highest risk group is age 16-21 y</td>
</tr>
<tr>
<td></td>
<td>Men-B</td>
<td>2 or 3&lt;sup&gt;4&lt;/sup&gt;</td>
<td>No data</td>
<td>Routinely for high-risk groups (see FAQ 14)</td>
</tr>
<tr>
<td>13-15 y</td>
<td>MCV4 (Men-ACWY)</td>
<td>2</td>
<td>Age 16-18&lt;sup&gt;4&lt;/sup&gt;</td>
<td>E.g.: primary doses at age 14.8 y so might give booster at age 16.8 or 17.8</td>
</tr>
<tr>
<td></td>
<td>Men-B</td>
<td>2 or 3&lt;sup&gt;4&lt;/sup&gt;</td>
<td>No data</td>
<td>Routinely for high-risk groups (see FAQ 14)</td>
</tr>
<tr>
<td>≥16 y</td>
<td>MCV4&lt;sup&gt;8&lt;/sup&gt; (Men-ACWY)</td>
<td>2&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Not generally</td>
<td>Exception: occupational exposure or functionally asplenic&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Men-B</td>
<td>2 or 3&lt;sup&gt;4&lt;/sup&gt;</td>
<td>No data</td>
<td>Routinely for high-risk groups and may be offered to 16-23 y (see FAQ 14)</td>
</tr>
</tbody>
</table>

<sup>1</sup> MCV4 is licensed down to 2 months but the earliest we offer vaccination is ≥6 months after HCT. For infants aged 7-23 months, 2 doses of Menceo (MCV4, Novartis) are given with the 2<sup>nd</sup> dose ≥12 weeks after the 1<sup>st</sup> dose AND after the 1<sup>st</sup> birthday.<br><sup>2</sup> A 2<sup>nd</sup> dose (2 mos. after 1<sup>st</sup>) is advised routinely after HCT for age 11-18y (See ref 23). We extend this practice to “high risk” adults with anamotical or functional asplenia (includes those with chronic GVHD).<br><sup>3</sup> Repeat every 5 years if functionally asplenic or occupationally at risk (military, microbiologist)<br><sup>4</sup> Men-B (Bexsero, Novartis) series is 2 doses (0, ≥1 mo later) and Men-B (Trumenba, Pfizer) series is 3 doses (0, 2, 6 mo)
The polysaccharide vaccine, MPSV4 (Menomune, Sanofi Pasteur) is the only licensed vaccine for age \( \geq 55 \) but off label use of MCV4 is advised, especially if previously received MCV4 and/or \( \geq 2 \) doses of meningococcal vaccine are anticipated (as for functional asplenia or occupationally exposed).
Table 4: Pneumococcal vaccines and serotypes associated with invasive pneumococcal disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumovax (PPSV23) contains 23 serotypes: including 11 that are not</td>
<td>1, 2, 3, 4, 5, 6A, 8, 9N, 12F, 14, 17F,</td>
</tr>
<tr>
<td>contained in Prevnar and without one, 6A, that is contained in Prevnar.</td>
<td>19F, 20, 22F, 23F, 6B, 10A, 11A(43), 7F,</td>
</tr>
<tr>
<td>Prevnar (PCV13) contains 13 serotypes (shown in bold)</td>
<td>15B, 18C, 19A, 9V, 33F</td>
</tr>
<tr>
<td>Common serotypes responsible for bad pneumococcal disease</td>
<td>4, 14, 19F, 23F, 6B, 19A, 9V</td>
</tr>
</tbody>
</table>
Figure 1A-F – Posttransplant vaccination case histories

Individualized and autopopulated vaccination schedules are shown for 3 different cases (white boxes).

Case 1, a 19 year-old adolescent, underwent allogeneic BMT on 3/15/2016 for leukemia, did not develop chronic graft versus host disease and, on 9/15/2016 at 6 months posttransplant, had an unsupported IgG level of 780 mg/dL. She was VZV-seropositive pre-transplant. (A) Her schedule for beginning inactivated vaccines at 6 months posttransplant highlights age-related considerations for HPV vaccine (FAQ10) as well as when to offer conjugated quadrivalent and group B meningococcal vaccines (FAQ14). (B) Live vaccines are considered at 2 years posttransplant.

Case 2, a 59 year-old man, underwent nonmyeloablative allogeneic transplant for chronic lymphocytic leukemia on 10/14/2015 but received rituximab early after transplant and thus early vaccination at 6 months was not considered appropriate (FAQ1, Figure 2). He was VZV-seropositive pre-transplant. Posttransplant, his last dose of IVIG was at 11 months, when his B cell count was 80/μL and serum IgG 665 mg/dL. (C) On 10/14/2016 he began inactivated vaccines including 40 μg doses of hepatitis B because he was still on immunosuppressive therapy for mild chronic GVHD (FAQ8, Table 2). At 3 years posttransplant at age 62, he had no signs of chronic GVHD and was off all immunosuppressive therapy. (D) On 10/14/18, he was given the MMR vaccine because he met the “2-1-8” rule (FAQ15). On 10/13/2020, now aged 64, he became eligible to receive the shingles vaccine (FAQ19) and finally at age 67 on 8/09/2022, 5 years after his last dose of PPSV23 (Pneumovax) he received an age-related booster dose of PPSV23 per ACIP recommendations (FAQ18).

Case 3, an 8 month-old boy, underwent myeloablative conditioning (9/15/2015) with antithymocyte globulin and unrelated donor cord blood transplant for severe combined immunodeficiency (SCID). Posttransplant his course was complicated until 2 years by recurrent late acute GVHD. At 2.5 years, lymphocyte counts were CD19 = 3073/μL, CD4 = 955/μL and donor chimerism was 100% for the CD19 and CD4 leukocyte fractions. On 10/3/18 he successfully discontinued his taper of systemic immunosuppressive therapy and except for a rhinovirus infection that cleared within 7 days he remained infection free throughout winter. Subcutaneous immunoglobulin (Hizentra) was discontinued in June 2019 and 6 weeks later the IgG level had only fallen from 1120 mg/dL to 641 mg/dL, at a time when he had a robust IgA level of 60 mg/dL (20-160) and normal IgM, 55 mg/dL (50-199). (E) Because these immune reconstitution data met our standards (FAQ4), inactivated vaccines were initiated in the summer on 7/1/19 at 3.8 years of age, with two doses each of PCV13 and Hib administered. Because of the positive specific antibody responses to these vaccines, he was allowed to remain off Hizentra and proceed with the remaining vaccinations (E, F). On 10/03/19 because he had already been receiving annual posttransplant vaccinations with inactivated influenza vaccine he received just one flu shot for the 2019 flu season. Interactive versions Excel forms that generate these auto-populated vaccination schedules are available in the online Supplement 2.
Footnote: B cell numbers are low in the first 1-2 months and normalize during months 3-12. B cell recovery is delayed by at least 6 months after anti-B cell antibody therapy. Antigen specific responses are impaired also because of limited capacity to undergo somatic mutation and isotype switch during the first year. Normalization of IgA levels can be indicative of isotype switching and is unaffected by IVIG replacement therapy. CD4 counts are generally less than 200/μL during the first 3 months. Thereafter, recovery is highly variable; generally >200/μL by 6-9 months if age <18 years and no chronic GVHD. Adults with chronic GVHD may take more than 2 years. For these reasons, some institutions defer vaccination until the peripheral CD4 count is >200/μL and the CD19 (B cell) count >20/μL. Most circulating T cells at year 1 (especially in adults) are memory/effector T cells derived from infused T cells. These cells can respond to antigens encountered by the donor pre-HCT. Naïve T cells that respond to neoantigens are generated only at 6-12 months (earlier in young children, later in old adults). Only limited data exist for the settings of unrelated cord blood and haploidentical-HCT or after reduced intensity regimens and so, for the sake of simplicity, the algorithm does not make further adjustments on these bases. Which agents are sufficiently immunosuppressive to prevent effective vaccination has not been studied. Other than the seasonal flu shot, most vaccinations are avoided when BMT recipients are receiving azacytidine, lenalidomide or rituximab. We tend to still administer vaccines if patients have little or no chronic GVHD and are on kinase inhibitors (e.g. imatinib or sorafenib).
### Post-transplant Vaccination Schedule - Inactivated Vaccines: To begin vaccination before 24 months

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Contraindicated</th>
<th>Usual timing between shot (and minimum interval between shots)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (IV) (12)</td>
<td>&lt; 9 yrs (September to March) (12)</td>
<td></td>
</tr>
<tr>
<td>Hemophilus Influenza Type B (HIB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesacoccal quadrivalent vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles/Mumps/Rubella (MMR) using the “2-dose” Rule (see FAQ 15)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FAQ 15:** For post-transplant patients, the use of “2-dose” Rule is NOT recommended. The current recommendation is to use the “4-dose” Rule. This can be found on the National Immunization Program's website. **[Click here](https://www.cdc.gov/vaccines/health-professionals/immunization-schedule/hcp-current-schedule.html) for more information.**

### Post-transplant Vaccination Schedule - Live Vaccines: To begin vaccination before 24 months

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<tr>
<td>Influenza (IV) (12)</td>
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### Primary Immunodeficiency Disease: Post-transplant Immunization Schedule - Inactivated Vaccines (8-10)

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<tbody>
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<td>Influenza (IV) (12)</td>
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<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mesacoccal quadrivalent vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
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</table>

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### Primary Immunodeficiency Disease: Post-transplant Immunization Schedule - Live Vaccines (8-10)

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<th>Contraindicated</th>
<th>Usual timing between shot (and minimum interval between shots)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (IV) (12)</td>
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