sFAQ13: What vaccines are needed if a patient travel asks about travel to a developing country?

In general, we recommend that patients still on IST in the setting of allogeneic HCT should avoid traveling to developing countries or areas where typhoid is endemic. Autologous recipients can travel to these areas 3 to 6 months after HCT if their provider agrees it is safe and appropriate. Typhoid fever, caused by Salmonella serotype Typhi, may be serious or even fatal in immunocompromised patients, and areas where this pathogen is endemic frequently pose other serious infectious risks (e.g. malaria or yellow fever) for the patient still on IST. Travel to major cities is generally a less serious issue. The CDC website can be used to determine if a particular area is at high-risk. If a patient must travel to an endemic area, inactivated Typhoid Vi polysaccharide vaccine ( Typhim Vi®, Sanofi Pasteur) is a safe option and preferred to live attenuated typhoid vaccine. Live attenuated yellow fever vaccine is contraindicated in patients with active GVHD or receiving immunosuppressive therapy. However, ASBMT guidelines consider that if more than 24 months out from transplant, with no active GVHD or immunosuppressive therapy, the risk-benefit balance may favor vaccination for patients traveling to endemic areas.

Diphtheria/Tetanus/Acellular-Pertussis (DTaP/Tdap)

sFAQ14: What is the role of antibody titers to diphtheria, tetanus and pertussis in determining response to vaccination or need for booster shots?

There is no true immunologic correlate of protection following pertussis vaccination and it is difficult to obtain serologic assessment of pertussis antibodies from laboratories utilizing standards approved by the FDA (CBER). Therefore, if an individual has received the requisite number of doses of DTaP (or Tdap) and serology shows protective levels of antibody against diphtheria (≥0.10 IU/mL) and tetanus (≥0.16 IU/mL), it is reasonable to assume protection against pertussis. Importantly, pertussis antibodies decline over time even in healthy individuals such that the duration of protection against pertussis is unclear. Tdap vaccines contain smaller amounts of relevant pertussis vaccine antigens but one dose produces an immune response in healthy adults that exceeds that of more than 24 months out from transplant, with no active GVHD or immunosuppressive therapy, the risk-benefit balance may favor vaccination for patients traveling to endemic areas.

Hemophilus influenzae type B (Hib)

sFAQ15: Are Hib vaccine brands interchangeable?

Yes. Hib vaccines are generally considered to be interchangeable, and all Hib vaccines conjugated to tetanus or pertussis would be considered similar except HibOMP (PedVaxHIB, Merck). HibOMP is conjugated to meningococcal protein and actually may be considered to have a different immune mechanism of action. Three doses of all Hib vaccines are necessary to complete the primary post-transplant series since transplant patients are considered to be immunologically similar to "infants". Anti-Hib titers <0.15 mg/L are not protective and >1.00 mg/L are considered desirable for durable protection. Post-vaccination titers can help guide the need for booster immunizations, particularly in patients with active GVHD. Repeat testing every 5 years for maintenance of antibody levels is recommended.

Hepatitis A (HAV) and Hepatitis B (HBV)

sFAQ16: Should hepatitis serology be checked pre- or post HAV and HBV vaccination?

For hepatitis A, the answer is no. For hepatitis B, titers are checked after at least 1 month following completion of the hepatitis B vaccine series. If the post-vaccination Hepatitis B surface antibody titer is <10 mIU/mL, additional doses of HBV vaccine are given; either by repeating a standard 3-dose series of HBV vaccine or, alternatively, by administering 1 standard or higher dose HBV vaccine followed by anti-HBs retesting.

sFAQ17: Is a protective HBV vaccine response durable or are booster shots necessary?

Data suggest that immunologic memory remains intact for at least 20 years among healthy vaccinated individuals who began HBV vaccination > 6 months of age. Cellular immunity appears to persist despite a decline in antibody levels potentially to undetectable levels. However, data in immune compromised individuals is limited.

sFAQ18: How to dose HAV and HBV for patients who are no longer deemed immune compromised?

In children, two 0.5 mL doses (0, 6 months) of the licensed Hepatitis A vaccine (Havrix®, GlaxoSmithKline) are recommended (see Table 1). In adults, two 1 mL doses each provide 1440 ELISA U of HAV for a total of 2880 U per series. A single injection of combined HAV plus HBV vaccination is available for ages ≥18 y as Twinrix® (GlaxoSmithKline). The 3 dose series of Twinrix (given at 0, 2 and 6 months) provides a total of 2160 U of HAV (Table 1). Antibody responses to HAV after 3 dose of Twinrix are not inferior to 2 doses of Havrix despite the 25% lower total HAV dose. Interestingly, 3 standard doses of Twinrix might even lead to higher anti-HAV titers in normal adults.

For Hepatitis B, a 3 dose series (0, 2, and 6 months) is considered standard using currently licensed, HBV-only vaccines, or age-appropriate HBV-containing combination vaccine. Trials of Twinrix in healthy volunteer adults showed that 3 doses of Twinrix were effective in >99% cases.

sFAQ19: How does one best administer HAV and HBV for patients who are still considered immune suppressed?

In contrast to HAV, HBV vaccination doses differ between immune competent and immune compromised individuals. While HAV is not double-dosed, the CDC advises that adult hemodialysis patients require a higher HBV antigen dose to induce protective antibody. By extrapolation, 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 fully 6 months off all IST. Therefore, HBV vaccination may be accomplished by giving an age related double dose of HBV vaccine (Engerix®, GlaxoSmithKline) at 0, 2, and 6 months – See Table 2. These individuals will also need two standard doses of HAV vaccine (Havrix).

The availability of combination vaccines adds more complexity for immune compromised adults. Although separate HAV and HBV vaccinations may be administered as described above, the combination of HepA/Hep B vaccine (Twinrix) can be administered as a double dose of Twinrix at baseline, a double dose of Engerix (HBV only) at 2 months and, finally, a double-dose of Twinrix again at 6 months. The combination DTaP-HepB-IPV vaccine (Pediarix, GlaxoSmithKline) is not advised in this setting because double dosing would provide children with inappropriate doses of the DTaP and IPV vaccines that are also present in Pediarix.

While the CDC does not firmly specify double dosing for immune compromised children and adolescents, Engerix labeling suggests augmented dosing and administration schedules that may be used for specific populations including an additional dose at 12 months; or in adolescents aged 11-19 years, 20 mcg (1 mL) given at months: 0, 1, 6 or, 0, 1, 2, 12. Our approach (Table 2) uses double dosing only for age ≥11 years.

Through experience, despite our answers to FAQ27 and FAQ28 (above) we have learned that clarification is required on the related question: Do two doses of Twinrix in an immune compromised adult provide enough HAV antigen? Twinrix contains lower doses of HAV than Havrix. Only HBV vaccines are ever double dosed in immune compromised patients.
For clarity: when using the combined HBV+HAV vaccine in immune compromised patients, only two doses are given because both HepA and Hep B in the Twinrix will be double-dosed, resulting in 2 x 720 Units HAV which is equivalent to 2 standard 1440 U doses of HAV (Havrix) vaccine. As an aside, patients will need an intervening double-dose of HBV-only vaccine to complete their 3 shot HBV series. Immune competent hosts will instead need 3 shots of Twinrix to provide sufficient total HAV antigen (3 x 720 U = 2160 U) compared to the standard 3-shot series.

sFAQ20: Can HBV vaccine be given concurrently with other vaccines?
Yes, HBV can be given concurrently using separate syringes and body sites for simultaneous administration of injectable vaccines; no interference with hepatitis B vaccine and antibody responses to other vaccines has been demonstrated.

sFAQ21: If there is interruption between doses of the HBV vaccine series does it need to be restarted?
No, the HBV series does not need to be restarted. If delay was as possible but the third dose should still be separated from the second dose by an interval of at least 8 weeks.

sFAQ22: What is the risk of extra doses of HBV or HAV if vaccination history is unavailable?
None.

Human Papillomavirus

sFAQ23: If a PAP smear is positive for HPV in a <26 year old women prior to HPV vaccination, is there any benefit to beginning or continuing Gardasil (Merck) vaccination?
Yes, HPV vaccine is still recommended because multiple HPV types may be responsible for an abnormal PAP smear, and because it is unknown which of dozen or so high risk HPV's may have caused this abnormal PAP smear. There is still potential benefit of HPV vaccine to protect against other HPV types. Similarly, if HPV DNA is detected by PCR, HPV vaccine should still be considered.

Influenza vaccine

Newer “quadrivalent” influenza vaccines (QIV) protect against 2 strains of influenza A and 2 strains of influenza B virus. A variety of flu vaccines are available including: standard IV given in eggs, given IM for age 6-6 months; Intradermal IV (Fluzone Intradermal, Sanofi Pasteur), which uses a much smaller needle and lesser dose than the regular flu shot (age 18-64 years); recombinant egg-free IV (Flublok, Protein Sciences Corp, Meriden, CT) for age 18-49 years; and QIV live attenuated influenza vaccine (LAIV, FluMist, MedImmune) nasal spray (age 2-49 years). These choices come with caveats. LAIV is not given to immune compromised recipients, including BMT recipients. While LAIV is an alternative for 2-8 year old immune competent children, when LAIV is unavailable, a standard IV flu shot should be given to avoid delay. Multidose vials contain thimerosal preservative whereas prefilled single dose syringes do not. Several key flu vaccination questions still arise:

sFAQ24: What time of year is best to give a flu shot?
Flu shots are given early in the fall (ideally by October) in the Northern Hemisphere but as long as flu viruses are circulating, flu vaccine is still offered in the U.S. even in January (when most influenza activity peaks) or later. Here it is helpful to recall that protective antibodies can develop about two weeks after vaccination. Importantly, in other parts of the world these recommendations differ and local epidemiology should be taken into account. In the southern hemisphere, influenza vaccine is recommended prior to the June (winter) flu season. In tropical countries, influenza viruses may circulate nearly year-round and consultation with local experts is recommended.

sFAQ25: What is the role for the low dose Fluzone intradermal IV shot?
Fluzone Intradermal (Sanofi Pasteur) was licensed May 2011 for age 18-64 years; it contains less flu antigens than IM. shots, in only 0.1 mL and can be given with a much smaller needle that might help in needle phobic patients. This has not yet been evaluated in transplant recipients.

sFAQ26: Is the live attenuated influenza vaccine appropriate for family members of BMT recipients?
ACIP previously preferentially recommended LAIV (Flumist, MedImmune) for healthy children aged 2-8 years but as of 2015, LAIV and IIV are considered to be equally effective in children. Because young children are a common community source of infection during flu season, optimally protecting the young family members of BMT patients with a flu vaccine is important. LAIV is cold-adapted, designed to only cause infection at cooler temperatures found within the nose and therefore unlikely to infect the lungs or other areas where warmer temperatures exist, and the risk of transmission of LAIV strains is very low. Our approach is to preferentially recommend IIV for any family member (including those aged 2-8 years) based on newer data showing similar effectiveness of LAIV and IIV in children, in accordance with the ACIP recommendations of February 2015. However, if IIV cannot be given for any reason (e.g. needle phobia) it is preferable to offer family members LAIV rather than no flu vaccine. If LAIV is given, the CDC advises a very conservative 7-day separation from seriously immunocompromised individuals requiring protective isolation.

sFAQ27: Is it safe to administer flu vaccine if the patient has an egg allergy?
Most patients with a history of egg allergies can safely be administered IIV by applying the following algorithm, provided by the ACIP:
1. Can the person eat cooked eggs without reaction? If yes, then ask whether the patient experiences only hives after eating eggs/egg-containing foods. If yes, give the flu shot but observe for at least 30 minutes. If no, then ask does the person experience other (major) symptoms? If yes, refer to a physician with relevant expertise. If there has been a history of severe reaction to IV, the presence or absence of egg allergies is irrelevant and the patient should not get a flu shot. Severe reactions include swelling near the eyes or lips, and significant difficulty breathing that required an ambulance, hospital stay, EpiPen (Mylan Specialty) or another shot.
2. If the patient thinks they are allergic to eggs, then a discussion of the types of reactions experienced to eating various foods can help to determine whether the flu shot is safe. Further investigation might include blood and skin-prick tests. Alternative to applying the ACIP algorithm, adults have the potential option of an egg-free flu vaccine such as RIV3, FluBlok (Protein Sciences) or the cell culture-based ccIIV3, Flucelvax (Novartis).

sFAQ28: Can influenza and pneumococcal vaccines be given at the same time?
Yes, PCV13 or PPSV23 can be given at the same time as the influenza vaccine.

Meningococcus

sFAQ29: When and how should meningococcal vaccination be given after BMT?
Vaccination may begin ≥6 months posttransplant. We offer 1 or 2 doses of MCV4 depending on patient age at the time of vaccination and “high-risk” status (chronic GVHD or otherwise functionally asplenic). Booster shots may be needed because immunity tends to wane within 5 years of vaccination in normal hosts. The decision to offer booster shots falls within the BMT provider’s purview during extended follow-up of patients who want to enter college, join the military, or need protonated GVHD therapy. Data on response to the recently license Men-B vaccines in BMT recipients is lacking, but in healthy individuals, two doses of Bexsero (Novartis) are required and 3 doses of Trumenba
(Pfizer) are required to elicit a protective antibody response. Duration of immunity is not yet well characterized. Table 3 offers suggestions for duration of initial shots and need for boosters.

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

**FAQ30:** Is it safe to vaccinate my child with MMR or MMRV if s/he has an egg allergy?  
There is minimal egg protein in MMR or MMRV vaccines and they are considered safe for all children including those with egg allergies.

**Pneumococcus**

**FAQ31:** What to do if PCV13 and PPSV23 are given out of sequence?  
If a patient receives one or two doses of PCV13 followed by a dose of PPSV23, the patient should subsequently be given the 2nd and/or 3rd doses of PCV13 administered at least 12 months after the dose of PPSV23 and 2 months after the last dose of PCV13.

**FAQ32:** How do I interpret pneumococcal titers?  
Knowing antibody titers to 23-serotype serotypes contained in PPSV23 (includes 12 of the 13 serotypes contained in PCV13) can help assess the need for a subsequent booster immunization. However, defining protective antibody levels or normal ranges for specific pneumococcal IgG antibodies is problematic; protective levels may vary substantially by laboratory or by serotype and may also vary with age. Numerous attempts have been made to assign normal ranges and protective levels to help guide clinical management. A threshold derived from vaccine efficacy in a population(s) cannot be used to precisely discriminate individual people at risk from those who are not. One frequently utilized reference laboratory (Mayo Clinic) utilized normative data from a pre- and post-vaccination healthy adult cohort (N=100) to recommend that protection is adequate when ≥ 50% of individually tallied serotypes are above respective threshold levels. Alternatively, antibody concentrations that increased by 2-fold or greater for ≥ 50% of serotypes when comparing pre- to post-vaccination results could also be considered protective. These recommendations have not been validated in immunocompromised hosts. If a non-heavily immunosuppressed patient develops protective levels to >50% of PCV13 serotypes after 3 doses of PCV13, we consider it reasonable to try to broaden serotype coverage by giving PPSV23.

**Rabies**

**FAQ33:** Can BMT recipients get the rabies vaccine?  
Rabies vaccine is made from killed virus and cannot cause rabies. Rabies vaccination is reasonable beginning at least 6 months after BMT if a patient plans travel to a highly endemic area, or even earlier if actually exposed to a rapid animal.

**Small Pox**

**FAQ34:** Should any BMT recipient get the smallpox vaccine?  
Smallpox vaccination is contraindicated regardless of time after BMT or time off immunosuppression because it contains live vaccinia virus that may result in generalized vaccinia or inadvertent inoculation at other sites such as the face, eyelid, nose, mouth, genitalia, and rectum. Furthermore, BMT recipients should not live in the same household with individuals who have been vaccinated until the vaccination site crusts over. They should not take care of a vaccinated individual until the site crusts over.

**Varicella**

**FAQ35:** Should a transplant recipient who was VZV seropositive pretransplant but VZV seronegative posttransplant be given the varicella vaccine?  
Assays available for determining VZV seropositivity are not equally sensitive. It is possible that with sensitive assays, a patient’s VZV test could be positive before transplant and later negative by a different assay. Among healthy adults, more than 97-99% of those tested with a reliable positive history have VZV antibodies when the best available assays are used. Seroreversion is also seen in some individuals and this does not necessarily imply lack of immunity. If a recipient’s childhood history of chickenpox is clear, then it is appropriate to assume ongoing protection from varicella and that either assay insensitivity or seroreversion accounted for the negative VZV serology. When there is no pre-transplant history of varicella infection or immunization, but the individual is at significant exposure risk, immunization can be offered and follows the “2-1-8” rule.

**FAQ36:** Should siblings of a patient who has recently been transplanted be vaccinated with Varivax®, Merck?  
It is preferable for siblings to get varicella vaccine at the appropriate age and on schedule, rather than to wait because transmission from a healthy child infected with varicella to a susceptible family member occurs at very high rates. By contrast, there have been no documented transmissions of varicella-vaccine virus from healthy individuals to immunocompromised, although transmission has been documented from leukemia patients to healthy siblings. BMT recipients are likely to already be on acyclovir but would need to also be isolated if the vaccinated sibling were to develop a suspicious rash or pox post vaccination.

**Zoster**

**FAQ37:** How does the shingles vaccine (Zostavax®, Merck) differ from the chickenpox vaccine (Varivax®, Merck)?  
Zostavax contains 14 times more virus than Varivax and its use has been associated with a 50% reduction in the rate of shingles and a 67% reduction in the rate of post-herpetic neuralgia among at risk groups.

**FAQ38:** When, if ever, can a BMT recipient get the zoster vaccine?  
The first consideration for receipt of zoster vaccine (Zostavax, Merck) is transplant specific and can be remembered by the “5-1-8” rule which means to not expose BMT recipients to high-tier live attenuated Zostavax until they are at least 5 years after BMT, >1 year off all systemic immunosuppressive therapy, and 8 months out from any prior dose of IVIG. The second criterion is age related. ACIP recommends Zostavax® for those patients ≥60 years, yet FDA licensing allows Zostavax® for those over 50 years of age. From a societal perspective, there is a higher cost per quality-adjusted life years (QALYs) saved when vaccinating at age 50 which results from limited impact on prevention of post-herpetic neuralgia and other complications between ages 50 and 59. In addition, evidence shows that vaccine-attributed protection may wane within 5 years. This increased risk of zoster complications, together with evidence that vaccine-attributed protection may wane within 5 years, helped shape ACIP recommendations for age over 60.

**FAQ39:** Should patients aged ≥60 years without a history of chickenpox get the shingles (zoster) vaccine?  
Serologic surveys indicate that almost everyone born in the U.S. before 1980 has had chickenpox. Therefore, we can assume this age group is, or at least previously was, seropositive. Providing the 5-1-8 rule is followed (see FAQ 63), and no other medical contraindications are present, Zostavax® (Merck) may be given regardless of any memory of having had chickenpox.

**FAQ40:** Should a BMT recipient get shingles vaccine if they have had posttransplant shingles?  
This is probably not necessary in most cases when the shingles episode occurred within approximately 5 years of age 60 because the patient has in effect already been boosted by the increase antigen exposure associated with the episode.
References


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