Biol Blood Marrow Transplant 25 (2019) e321–e330

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Position statement

Preventing Measles in Immunosuppressed Cancer and Hematopoietic Cell Transplantation Patients: A Position Statement by the American Society for Transplantation and Cellular Therapy

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Article history:
Received 26 July 2019
Accepted 29 July 2019

Keywords:
Measles
Vaccination
Outbreak
Hematopoietic cell transplantation
MMR

A B S T R A C T

Until recently, measles exposures were relatively rare and so, consequently, were an afterthought for cancer patients and/or blood and marrow transplant recipients and their providers. Declines in measles herd immunity have reached critical levels in many communities throughout the United States due to increasing vaccine hesitancy, so that community-based outbreaks have occurred. The reemergence of measles as a clinical disease has raised serious concerns among immunocompromised patients and those who work within the cancer and hematopoietic cell transplantation (HCT) community. Since live attenuated vaccines, such as measles, mumps, and rubella (MMR), are contraindicated in immunocompromised patients, and with no approved antiviral therapies for measles, community exposures in these patients can lead to life-threatening infection. The lack of data regarding measles prevention in this population poses a number of clinical dilemmas. Herein specialists in Infectious Diseases and HCT/cellular therapy endorsed by the American Society of Transplant and Cellular Therapy address frequently asked questions about measles in these high-risk cancer patients and HCT recipients and provide expert opinions based on the limited available data.

INTRODUCTION

Measles cases have surged across the globe, with a 30% year-over-year increase in the number of reported infections worldwide [1]. In developed countries, a large portion of this increase is attributed to the rise of the antivaccine movement [2]. Vaccine hesitancy poses a complex threat to the preservation of herd immunity against measles and has become a serious public health challenge. In 2019, the World Health Organization (WHO) recognized vaccine hesitancy as among the top 10 current threats to global health [3]. Frequent large outbreaks in regions in which measles is considered eliminated pose a major threat to immunocompromised patients. This is especially relevant for HCT recipients, who lack immunity to vaccine-preventable diseases. For HCT recipients and other immunocompromised cancer patients, reliance on herd immunity is the sole layer of protection from measles.

In the last decade, the reemergence of measles, a vaccine preventable illness, has been an unwelcome development in the United States [4]. Public health experts have warned that

Financial disclosure: See Acknowledgments on page e327.

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https://doi.org/10.1016/j.bbmt.2019.07.034
1083-8791/

US vaccination rates have declined, and areas of the country with lower rates of vaccination and high population densities, including New York City, Seattle, Houston, and Detroit, are at risk for measles outbreaks [5]. Since endemic measles was officially declared eliminated from the United States in 2000, unvaccinated visitors or travelers returning from areas of the world where measles transmission is ongoing, such as Israel, Japan, Madagascar, the Philippines, Ukraine, and other locations throughout Europe, are the sources of most outbreaks in North America [6]. When those who acquire the disease abroad return to communities with low vaccination rates (ie, low herd immunity), an increasing phenomenon in the United State, large chains of transmission can occur. Significant outbreaks have occurred at Disneyland in California [3], Minneapolis [7,8], and more recently in Clark and King County, Washington [9] and areas of Brooklyn and Rockland County, New York [10]. Through August 28, 2019, more than 1200 cases of measles have been recorded in the United States, the greatest number of cases seen in any year reported since 1994 [11]. To date, 30 states have reported measles cases in 2019, with the majority occurring in New York and Washington states, areas with both a relatively low community vaccination rate and a high frequency of international travel [12].

Measles is caused by the measles (rubeola) virus, an RNA virus that is a member of the *Morbillivirus* genus in the Paramyxoviridae family. Measles is one of the most contagious human pathogens, with an attack rate of 90% in susceptible persons. The virus spreads by airborne routes when an infected person releases infectious droplets by coughing, sneezing, or simply breathing. The incubation period is 10 to 14 days after exposure, but longer incubation periods of >20 days have been reported [13]. Initial symptoms are similar to those of common upper respiratory viral infections, with cough, coryza, and conjunctivitis. Around day 4, fever and a prototypical rash, starting from the hairline/face and progressing downward, are prominent, often leading patients to seek medical care. Infected patients are contagious several days before and after the development of rash. Transmission before characteristic symptoms develop, late presentation to a healthcare provider or a delayed diagnosis, and high transmissibility lead to a high potential for community spread, particularly in areas where vaccination rates are low [14].

To protect communities from sustained measles transmission, the vaccination threshold needs to exceed 95% coverage [15]. Unfortunately, the rise in nonmedical exemptions (eg, family history of allergies or autoimmune diseases), religious exemptions [16], vaccine hesitancy, a lack of state and national regulations requiring vaccination of school-aged children, as well as inadequate compliance with the second dose of the vaccine, have led to a loss of herd immunity in several hot spots that are particularly vulnerable to measles spread [2,5,17,18]. Insufficient community vaccination rates are of major concern for immunocompromised patients, who are at the greatest risk for measles-related complications [14].

Cancer therapy has advanced rapidly during an era in which measles was an afterthought. Consequently, not only is there limited clinical experience with measles disease manifestations, but there is therapy-related loss of immunity and, most importantly, a need to (re)vaccinate patients receiving newer, more durably immunoablative oncologic therapies. For example, it is known that children undergoing therapy for acute lymphoblastic leukemia (ALL) have low measles antibody levels following chemotherapy despite prior vaccination; limited humoral responses may be most profound in children under 5 years of age [19-21]. Protective levels of measles antibody range between 13% and 70% in children with ALL and appear to depend on the age of the child and the chemotherapeutic regimen [22-25]. Data on adults with leukemia are even less well described but may be somewhat better than in children [26].

Recipients of autologous and allogeneic hematopoietic cell transplantation (HCT) require revaccination [27-29]. Post-transplantation measles immunity varies among HCT recipients depending on the source of pretransplantation immunity (vaccine versus wild-type infection) and is likely affected by graft source type (cord blood versus peripheral blood), T cell depletion, and such post-transplantation factors as T and B cell immunosuppressive or depleting therapies, maintenance therapy, and/or graft-versus-host disease (GVHD) [28,30,31]. Novel targeted therapies, including venetoclax (Venclexta), ibrutinib (Imbruvica), ruxolitinib (Jakafi), checkpoint inhibitors (PD-1/PD-L1), tumor necrosis factor inhibitors (eg, infliximab), and CD19-targeted chimeric antigen receptor T cell (CAR-T) therapies (Yescarta, Kymriah), and their effects on vaccine-related immunity have not been assessed. Suggested negative effects, such as promotion of viral replication (eg, ruxolitinib) [32] and increased risk of vaccine-related side effects (eg, PD-1 inhibitors) [33], are additional factors to consider in the use of live-virus vaccines for these patients.

The fundamental challenge for patients undergoing cancer chemotherapy or HCT in the present era of measles resurgence is that immunosuppression has remained, without caveats, a contraindication to vaccination with live-virus vaccines like the measles, mumps, and rubella vaccine (MMR), or MMR-varicella (MMR-V), because of the risk of developing vaccine-associated measles [34-36]. The Infectious Disease Society of America, the American Society for Transplant and Cellular Therapy, and the European Conference on Infections in Leukemia do not recommend MMR for patients who are immunosuppressed [28,37-39]. Although limited studies suggested that MMR can be safely given to children receiving active treatment for ALL with or without interruption of chemotherapy, and after in adults receiving lenalidomide or bortezomib maintenance therapy after autologous HCT and late post-allogeneic HCT recipients. There remain major gaps in our knowledge of the safety and timing of MMR after HCT [22,40-43]. To date, data on the safety and effectiveness of MMR in patients with HIV with CD4 recovery have informed vaccination practices after HCT [44-46].

In this report, we address frequently asked questions (FAQs) based on the limited published data on measles that are relevant to oncology or HCT or that have been extrapolated from analogous immunocompromised populations. Owing to the paucity of published data, these recommendations are based mostly on expert opinion, but are supported by the American Society for Transplant and Cellular Therapy.

FAQ1: HOW DOES MEASLES PRESENTATION DIFFER AMONG IMMUNOSUPPRESSED CANCER PATIENTS AND HCT RECIPIENTS FROM THE GENERAL POPULATION?

The majority of cancer patients who develop measles present with high-grade fever, cough, coryza, and conjunctivitis (less common), followed by rash [14]. However, with increasing levels of immunosuppression, some of these patients may present with atypical signs and symptoms. Studies have noted that more than 50% of cancer patients present with atypical rash (maculopapular, transient/evanescent, or severe and desquamative) and pattern of distribution [47-50]. Furthermore, as many as 20% may present without rash and are diagnosed only after developing severe complications (eg, encephalitis) or at autopsy [47,48,51,52]. Cancer patients may also present

without fever and/or viral upper respiratory symptoms, making the diagnosis quite challenging. A rare form of subacute encephalitis due to viral persistence may present in immunosuppressed patients at weeks to months after primary exposure and be without classical prodromal symptoms [53-55].

The key to diagnosis of measles in cancer patients is an awareness of community and epidemiologic risk. Patients with concerning symptoms and exposure to a known measles case (or a history of being in a location during the exposure window of a known measles case) without evidence of immunity should be immediately isolated and tested for measles. Those with documented exposures should be excluded from public locations and from contact with persons susceptible to measles (see FAQ2) for a minimum of 21 days.

FAQ2: HOW DO YOU DEFINE A MEASLES EXPOSURE?

Any patient who has shared the same airspace with a person with measles during the period when they are known to be contagious (4 days before until 4 days after rash onset) is considered to have been possibly exposed to measles. Measles can be spread through direct contact with infectious droplets; when contaminated hands touch mucous membranes of the eyes, nose, or mouth; or by airborne spread from patients who are coughing, sneezing or breathing [56]. The measles virus can live for up to 2 hours in an airspace in which an infected person has coughed or sneezed. Therefore, when considering exposures, those who were in the same space (eg, playroom, household, clinic, waiting room) as the contagious patient for up to 2 hours after that patient was present should be considered at risk for measles exposure [57,58]. Risk increases with exposure time, intensity of the source patient's illness (and production of respiratory droplets), proximity to the contagious patient, and vaccination status of the exposed person. It is also important to keep in mind that immunosuppressed patients who develop measles may shed for prolonged periods when compared with normal hosts [59].

FAQ3: HOW SHOULD PATIENTS WITH MEASLES EXPOSURE AND/OR SYMPTOMS BE ISOLATED?

In an area with ongoing measles transmission, screening and precautions should be undertaken at points of entry to the health care facility for suspected cases of measles with compatible symptoms and/or exposure. Patients who screen positive should be promptly isolated and undergo additional assessment. During large community outbreaks, preappointment phone screening can be considered to identify possible symptomatic patients before arrival. Transplant recipients should be educated to report any suspected measles exposure and should always be asked to come in for evaluation after discussing the need for limiting additional exposures with the caregiver/family. A patient with known exposure should notify clinic personnel about exposure and/or symptoms before arriving at the clinic, and clinic staff should discuss each scenario with their center's designated Infection Prevention experts.

A patient with concerning symptoms should be met outside the facility if possible, masked immediately, and then moved to a nearby negative-pressure isolation room with airborne precautions, if available. Rooms in which patients are seen should be cleared of other patients, left empty for 2 hours after use, and then terminally disinfected. Portable negative-pressure isolation systems can be used when available to minimize exposures during larger outbreaks or if there are limited airborne isolation rooms. All staff entering the room, regardless of immunity, should wear a fitted N-95 mask or a powered air purifying respirator in addition to taking standard precautions. Staff without documented evidence of measles immunity should not enter the room of a patient with proven or suspected measles, unless no other staff members are available. If a negative-pressure room is unavailable, the patient should be masked and placed in a single room with the door closed to limit potential exposures. Accompanying visitors should be clinically screened for measles and wear a mask. For confirmed cases, all visitors should be restricted to those with proof of measles immunity.

Any time a patient is considered to have measles, local public health departments/jurisdictions should be contacted immediately. During periods of high community risk, cancer centers and healthcare centers with large at-risk populations may need to consider targeted screening for signs, symptoms, and possible measles exposures at points of entry to the facility. Airborne isolation precautions should be maintained for a minimum of 21 days after exposure and for 28 days for those who receive postexposure prophylaxis with intravenous immunoglobulin (IVIG).

FAQ4: HOW IS MEASLES DIAGNOSED IN IMMUNOCOMPROMISED PATIENTS?

Many US healthcare providers have seen few if any measles cases, and thus a review of clinical findings in immunosuppressed patients is important (see FAQ1). To avoid delayed diagnosis associated with atypical clinical features, patients presenting with upper respiratory symptoms (including conjunctivitis) with or without fever and with a known history of exposure, or those who present with rash with or without a known exposure during a measles outbreak, should be appropriately isolated (see FAQ2) before undergoing laboratory testing. Measurement of measles-specific serology (serum IgM and IgG antibodies) and measles virus by real-time polymerase chain reaction (RT-PCR) from upper respiratory viral specimens are commonly recommended for initial diagnosis [14,60].

RT-PCR is more sensitive than serology for the initial diagnosis [61], especially in immunosuppressed patients who have a reduced ability to produce antibodies. In addition to respiratory secretions, throat or nasopharyngeal secretions (and sometimes urine) are recommended for RT-PCR testing. In patients with an atypical presentation, particularly with isolated pulmonary and/or central nervous system signs, bronchoalveolar lavage fluid and/or cerebrospinal fluid also should be sent for RT-PCR testing [56]. Measles virus also can be detected in tissue biopsy specimens on the basis of characteristic histopathological findings (eg, giant cells, inclusion bodies). Testing should be done in collaboration with public health departments, which often can expediate measles RT-PCR results and facilitate molecular epidemiologic testing when appropriate.

Serologic assays have limited utility early in diagnosis and should not be used alone, because antibodies may be negative for approximately 4 days after rash appears and long after patients are contagious, previously vaccinated individuals may not mount an IgM response, and antibody-based diagnostic testing for measles (and other viral exanthems) can yield false-negative results in HCT recipients [62,63].

FAQ5: WHAT ARE THE OUTCOMES OF ACUTE PRIMARY MEASLES INFECTION AMONG IMMUNOSUPPRESSED PATIENTS?

Measles-related complications are more likely among patients who are immunocompromised, and the risk is thought to increase with increasing level of immunodeficiency. Available studies and case reports of measles among cancer patients demonstrate that approximately one-half of hematology-oncology patients with infection develop life-threatening measles

complications such as pneumonia, liver failure, and encephalitis, a much higher frequency than that seen in normal hosts [48-50,55,64-71]. Case fatality rates in children with leukemia in published studies range from 13% to 83%, related primarily to lethal pneumonia and encephalitis [47,49,64,65]. Studies among HCT recipients are limited. One study from Brazil suggested less severe outcomes among multiyear transplantation survivors, who generally are not on immunosuppression and thus are likely to be at lower risk than early post-transplantation survivors [50]. Notably, 2 patients in that study developed measles at around 1 year post-transplantation, including 1 who was on immunosuppressive therapy for extensive chronic GVHD and developed measles pneumonia; both patients survived. In Shanghai, China, 2 previously vaccinated pediatric transplant recipients acquired measles during a hospital outbreak. The time after transplantation was unclear; both patients survived, although 1 developed pneumonia [64]. Data are unavailable for most other cancer populations and patients receiving new chemotherapy regimens and other treatment modalities.

FAQ6: ARE THERE ANY LONG-TERM COMPLICATIONS OF ACUTE MEASLES IN IMMUNOSUPPRESSED PATIENTS?

Infection sequelae among survivors of measles infection may include severe neurologic complications, particularly in children with encephalitis [47,48]. Acute measles is known to lead to periods of altered immunity following primary infection which has been associated with an increased risk for other infections following the acute illness in healthy children that can persist for years [72,73]; vaccination with the live attenuated MMR virus does not cause similar findings [72]. Subacute sclerosing panencephalitis (SSPE) is a late complication of measles virus reactivation in the central nervous system that had been on the decline in the United States due to extensive vaccination. SSPE is rare but universally fatal for patients who survive initial infection and is typically seen in older children who were infected with measles at a young age [74]. Whether cancer patients and HCT recipients who develop measles are at increased risk for SSPE is unknown.

FAQ7: WHAT ARE AVAILABLE TREATMENT OPTIONS FOR IMMUNOCOMPROMISED PATIENTS WITH ACUTE MEASLES?

No currently licensed treatments or investigational drugs in humans are available, and thus treatment is primarily supportive. Oral and i.v. formulations of ribavirin have been used during measles outbreaks among cancer patients. Retrospective data indicate potential benefits for those treated with ribavirin [55,65], but success remains mixed, likely dependent on the severity of the initial presentation and the level of underlying immunosuppression. Intravenous ribavirin is available in the United States only through an emergency investigational new drug application and cannot be routinely recommended due to significant adverse side effects associated with its use, including life-threatening hemolytic anemia [75]. Limited observations from case reports have suggested potential benefit from gamma- and alpha-interferon therapies, particularly for patients with encephalitis [76-78]. Novel therapies, such as fusion inhibitors, short interfering RNA (siRNA), and small-molecule inhibitors, have shown some efficacy in animal models but are not yet available for clinical use [78-80]. Whereas the use of IVIG is recommended for postexposure prophylaxis, its use likely provides no additional benefit during active measles treatment. The WHO currently recommends vitamin A therapy for all children with measles, and due to the risk of severe disease but low risk of this treatment, there appears to be a limited downside to routinely prescribing vitamin A for immunocompromised patients. Vitamin A is administered once daily for 2 days at the following doses: 200,000 IU for children age $\geq$12 months, 100,000 IU for infants age 6 to 11 months, and 50,000 IU for infants age $<$6 months [81].

FAQ8: WHEN IS IT TRADITIONALLY CONSIDERED SAFE TO VACCINATE IMMUNOSUPPRESSED CANCER PATIENTS AND HCT RECIPIENTS WITH THE MMR VACCINE?

The current live attenuated MMR vaccine uses the Edmonston-Enders strain of measles (a live attenuated strain) and has been used in the US since 1986. It is combined with live attenuated rubella and mumps viruses, and one dose elicits $>$93% protective immunity in normal hosts. The current recommendation for 2 doses of MMR in immunocompetent children was made in 1989 to improve protective immunity [81]. A third dose of MMR has not been shown to improve the immune response against measles [82].

MMR vaccine is contraindicated for patients receiving exogenous immunosuppression, because it contains live-attenuated viral strains that can lead to acute disease in patients with weakened immune systems [35,36]. The timing of MMR vaccination has been described for patients with hematologic malignancies and HCT recipients when there is no increased risk from community clusters or outbreaks. In patients with leukemia, MMR is recommended to be given at least 3 months after the end of chemotherapy and at least 6 months after receipt of anti-B cell antibodies (eg, rituximab) [38,39]. MMR and other live attenuated vaccines can be administered beginning 24 months transplantation in autologous or allogeneic HCT recipients who are off immunosuppression and/or not receiving certain relapse prophylaxis or maintenance therapies [28]. In allogeneic HCT recipients at more than 24 months post-HCT who required prolonged immunosuppressive therapy for chronic GVHD, MMR can be administered once off immunosuppressive therapy for at least 8 to 11 months [28,37,39,83]. MMR is not recommended for patients receiving rituximab (Rituxan) maintenance, although limited data suggest that MMR may be safe for patients receiving other agents, such as bortezomib (Velcade) and/or lenalidomide (Revlimid) [40,84]. The timing of IVIG and MMR needs to be considered; vaccination is not recommended within 8 to 11 months after IVIG replacement, because IVIG may inhibit the viral replication necessary for generating the measles-specific vaccination response [85]. The rates of seroconversion in HCT recipients vary among studies and are affected by timing of vaccine, age of population vaccinated, and both acute and chronic GVHD status; overall vaccine responses are less robust among post-HCT recipients compared with normal hosts [31].

FAQ9: SHOULD HEALTHCARE PROVIDERS DEVIATE FROM TRADITIONAL MMR VACCINATION RECOMMENDATIONS IN IMMUNOSUPPRESSED CANCER PATIENTS AND HCT RECIPIENTS DURING INCREASED MEASLES TRANSMISSION AND/OR OUTBREAKS IN THE COMMUNITY?

During large community clusters or outbreaks, the risk of developing clinical measles may outweigh the risk of potential vaccine-related complications, particularly in this subset of immunosuppressed hosts. We advise considering vaccination earlier than the standard 2-year post-transplantation recommendation for HCT recipients on a careful case-by-case basis for patients on minimal immunosuppressive therapy

who are at least 1 year post-transplantation and in the presence of arbitrarily defined "reasonable" numeric immune reconstitution. One Australian pediatric center administered MMR to 79 pediatric autologous or allogeneic HCT recipients as early as 12 months after transplantation (median time to vaccination from HCT, 13 months), provided that they were without GVHD and off immunosuppressive therapy for ≥3 months. There were no serious complications, and only 1 child who was vaccinated at 24 months post-transplantation developed transient rash and fever at 1 week after vaccination [86]. Among 44 patients with available serology results, 35 were measles-seronegative before MMR, of whom 16 (46%) seroconverted after vaccination. The seroconversion rate was 78% for those vaccinated at ≥15 months (versus 35% in those vaccinated at <15 months), similar to rates obtained by vaccination at 2 years or later after HCT [86,87]. MMR vaccination at >1 year after liver transplantation also appeared to be safe and modestly efficacious among 39 children in a Japanese study who had not received systemic steroids to treat rejection within the last 6 months, and were receiving only tacrolimus with a serum trough level <5 ng/mL [88].

Given the limited studies in these patient populations, our recommendations are based on available data about safety and efficacy. When moving MMR vaccination to an earlier time point in the preexposure setting, we consider the following (see also Table 1):

Allogeneic HCT recipients

- A minimum of 1 year post-transplantation
- On single-agent tacrolimus with a serum trough level <5 ng/mL, cyclosporine with a serum trough level <120 ng/mL, or sirolimus with a serum trough level of <2 ng/mL
- On ≤5 mg prednisone equivalent once daily (for secondary adrenal insufficiency, not for GVHD)
- No active systemic GVHD requiring immunosuppression beyond topical agents
- A total lymphocyte count of $\geq 1 \times 10^3$ μL, or CD4 cells >200/μL and CD19 cells >20/μL
- Unsupported IgG >400 mg/dL and measurable IgA >6 mg/dL

Autologous HCT recipients

- A minimum of 1 year post-transplantation
- On ≤5 mg prednisone equivalent once daily (for secondary adrenal insufficiency)
- No post-transplantation chemotherapy, unless receiving lenalidomide or bortezomib for maintenance therapy; because no data exist for novel chemotherapy agents (eg, ibrutinib [Imbruvica]), vaccine should not be given to patients on these therapies
- A total lymphocyte count of $\geq 1 \times 10^3$ μL, or CD4 cells >200/μL and CD19 cells >20/μL
- Unsupported IgG >400 mg/dL and measurable IgA >6 mg/dL.

A second dose of MMR in immunocompromised patients can be arranged no sooner than 1 month after the first dose and at least >15 months post-HCT, or at a time more consistent with standard recommendations [28]. This second MMR dose is important, because early vaccine (before 15 months post-HCT) may be less likely to seroconvert than vaccine given later [86].

FAQ10: WHAT IS THE VALUE OF CHECKING MEASLES (RUBEOLA) TITERS IN IMMUNOSUPPRESSED PATIENTS BEFORE OR AFTER VACCINATION?

Checking serologic responses to measles can be considered for those who are less than 2 years post-HCT and are being considered for early vaccination. It also is important for providers to recognize that serologic diagnostic testing has limitations even in healthy patients [89]. Plaque reduction neutralization, the most sensitive assay for measuring measles immunity, is not readily available in most settings. Serologic

Table 1
Criteria for Early MMR Vaccine among High-Risk HCT Recipients and Patients Receiving CAR-T Cell Therapy*

Criteria	Allogenic HCT	Autologous HCT	CAR-T Cell Therapy
Timing	>1 year post	>1 year post	>1 year post, but can consider as early as 6 months in the context of acute community clustering or during outbreaks
Immunosuppressive therapy	Single agent: tacrolimus with serum trough level <5 ng/mL *or* cyclosporine with serum trough level <120 ng/mL *or* sirolimus with serum trough level of <2 ng/mL	No post-transplantation chemotherapy, unless lenalidomide or bortezomib for maintenance therapy • no data exist for novel chemotherapy agents (eg, ibrutinib) • risk for agents such as rituximab	No post-CAR-T cell therapy chemotherapy • no data exists for novel chemotherapy agents (eg, ibrutinib) • risk for agents such as rituximab
Steroid use	≤5 mg prednisone daily (for secondary adrenal insufficiency; not for GVHD)	≤5 mg prednisone daily (for secondary adrenal insufficiency)	≤5 mg prednisone daily (for secondary adrenal insufficiency)
Cell counts	Total lymphocyte count of $\geq 1 \times 10^3$ μL *or* CD4 >200/μL and CD19 > 20/μL	Total lymphocyte count of $\geq 1 \times 10^3$ μL *or* CD4 >200/ μL and CD19 >20/μL	Total lymphocyte count of $\geq 1 \times 10^3$ μL *or* CD4 >200/μL and CD19 >20/μL
Immunoglobulin level	Unsupported IgG >400 mg/dL and measurable IgA >6 mg/dL	Unsupported IgG >400 mg/dL and measurable IgA >6 mg/dL	Unsupported IgG >400 mg/dL and measurable IgA >6 mg/dL
Additional	No active systemic GVHD requiring immunosuppression beyond topical agents		Patients who received allogeneic or autologous HCT before CAR-T cell therapy should meet both the HCT and CAR-T cell parameters.

* Early vaccine should be considered only in the presence of increased community clustering or outbreaks.

testing using enzyme-linked immunosorbent assay (EIA) methods might not detect protective levels of antibody but is the community standard of care.

In addition, providers should be aware that even apparently protective measles titers obtained before post-transplantation revaccination will decline, and at some unpredictable time point become nonprotective without post-transplantation MMR vaccination [27,90]. Revaccination is the current standard of care in these patients based on this issue of waning titers [28]. There are concerns that positive/protective post-transplantation titers for those <2 years out from HCT and who have not yet been revaccinated may lead some providers, based on current levels of protection, to delay or skip opportunities for early vaccination for those at risk. Furthermore, measles titers should be used with caution for patients who have been exposed to determine any potential interventions (see FAQ 12).

In the setting of ongoing measles transmission, we recommend post-vaccination measles titers at 6 to 8 weeks following receipt of the second post-transplantation MMR vaccine. Repeat vaccination could be considered for those vaccinated before 2 years and with low or absent titers following the intended 2-dose MMR series.

FAQ11: WHEN SHOULD RECIPIENTS OF CAR-T CELL IMMUNOTHERAPIES BE CONSIDERED FOR MMR VACCINATION?

B cell-targeted CAR-T cell therapy is a novel treatment for patients with refractory or resistant B cell malignancies, including ALL, chronic lymphocytic leukemia, large B cell lymphomas, and multiple myeloma (MM) [91-95]. Patients treated with CAR-T cell immunotherapy have poor immune function due to effects of their malignancy, previous cytotoxic treatments, and depletion of B cells due to on-target off-tissue effects of CAR-T cells. CAR-T cells can persist for months to years and result in prolonged B cell depletion with resultant hypogammaglobulinemia [96-100]. Notably, a large proportion of patients receive CAR-T therapy as a bridge to HCT or as treatment of post-transplantation relapse without ever having completed recommended vaccinations after HCT. The long-term effects of B cell-targeted CAR-T cell therapies on the immune system and risk for infection are not well understood; however, patients treated with B cell-targeted CAR-T cell therapy may have reconstitution of normal B cells [96]. Moreover, because B cell-targeted CAR-T cells do not deplete preexisting plasma cells, antibodies to pathogens for which the patient was vaccinated even years before CAR-T therapy may continue to be produced [101]. The optimal timing for vaccinations after CAR-T cell therapy to balance safety and efficacy is unknown, but a rational approach can be extrapolated from strategies described above (see FAQ 9) to include the following parameters in those without protective measles antibody titers outside of a known exposure:

CAR-T cell therapy

- A minimum of 1 year post-CAR-T cell therapy, but can be considered as early as 6 months in the context of acute community clustering or during outbreaks
- On ≤5 mg of prednisone daily (for secondary adrenal insufficiency)
- No post-CAR-T cell therapy chemotherapy; because no data exist for novel chemotherapy agents (eg, ibrutinib), vaccine should not be given to patients on these therapies
- A total lymphocyte count of $\geq 1 \times 10^3$ μL, or a CD4 cells >200/ μL and CD19 cells >20/μL
- Unsupported IgG >400 mg/dL and measurable IgA >6 mg/dL
- Patients who underwent allogeneic or autologous HCT before or after CAR-T cell therapy should meet both the HCT and CAR-T cell therapy parameters.

FAQ12: IF AN IMMUNOCOMPROMISED PATIENT HAS BEEN POTENTIALLY EXPOSED TO MEASLES AND THERE IS A CONTRAINDICATION TO VACCINATION, WHAT OTHER OPTIONS EXIST FOR PROTECTION?

In the absence of antiviral therapy options, the only option available for preventing measles in those who are ineligible to receive MMR is IVIG or intramuscular immunoglobulin (IMIG); IMIG is not recommended for patients weighing >30 kg. IVIG or IMIG is recommended to be given within 6 days of the exposure and regardless of titer [60]; benefits of IVIG therapy beyond 6 days are unknown. Testing for measles antibodies before administration of IVIG or IMIG should be considered, because dosing will alter measles antibody results for up to 3 to 11 months [81]. Because immunoglobulin is not 100% effective at preventing measles, exposed patients given IVIG should be monitored for a minimum of 28 days and excluded from school, work, and other public locations within the community and from contact with susceptible persons during this period. Exposed patients who receive IVIG should mask when entering the clinic, bypass the waiting room, and be rapidly and directly escorted into a negative pressure room. The patient, family, and caregivers should be educated for signs and symptoms of measles; exposed patients should be managed in airborne precautions until the exclusion period ends.

Any patient considered to have an exposure, even those who have received immunoglobulin, should be instructed to call ahead before being seen in clinical spaces if they develop upper respiratory symptoms, conjunctivitis, fever, and/or rash. Immunoglobulin replacement is likely less effective in patients with low cell counts, because without adequate cellular responses, antibodies alone may be insufficient to limit viral replication [102]. Patients receiving routine IVIG replacement do not need additional IVIG unless they are >3 weeks from their last dose [81].

FAQ13: WHAT OTHER RECOMMENDATIONS SHOULD BE GIVEN TO IMMUNOCOMPROMISED CANCER PATIENTS AND HCT RECIPIENTS?

Patients who are immunosuppressed due to chemotherapy or disease-related complications or those who are post-HCT should avoid travel to areas where measles is endemic or where there are measles outbreaks. In communities with ongoing measles transmission, limiting interactions by practicing social distancing may help prevent possible exposures. The benefits of wearing facemasks to prevent measles have not been established for respiratory pathogens in the community setting and are not recommended by the WHO for large outbreaks of respiratory viruses such as measles, especially in open areas [103]. It is unlikely that wearing a surgical mask in the community will provide any direct protection for patients, but doing so may aid in social distancing, which can help prevent possible exposures.

Most importantly, family members, caregivers, and other close contacts should ensure that they are up to date on MMR (as age-appropriate). There are no reports of the transmission of the vaccine strain of measles being transmitted to other household contacts following vaccination [104,105], so those close contacts who have not been vaccinated should receive vaccination at any point during the post-transplantation period. No special precautions or visitation restrictions are

necessary for recently vaccinated individuals. Healthcare providers should have targeted discussions with family members and caregivers about the known risk of all communicable vaccine-preventable diseases in HCT recipients and play an active role in promoting vaccination among those in close contact with the patient. Early vaccination can also be considered (as noted above) for patients who are returning to employment where risk of measles exposure is increased (eg, healthcare worker, daycare worker). The role of IVIG for preexposure prophylaxis in high-risk patients has not been established, although use in special settings (eg, unavoidable travel to areas with ongoing measles transmission) and individual risk in outbreak settings could be considered to offer short-term protection.

Finally, in the healthcare setting, visitor restriction for those residing in counties with ongoing measles transmission and without proof of immunity has been implemented in select high-risk healthcare settings (eg, neonatal intensive care unit, transplantation and oncology units) in the current New York City outbreak [106].

FAQ14: HOW SHOULD I COUNSEL AN IMMUNOCOMPROMISED CANCER PATIENT OR HCT RECIPIENT REGARDING RISK VERSUS BENEFIT OF EARLY MMR VACCINATION?

During community outbreaks, patients are increasingly concerned about measles, and the desire to receive the MMR vaccine will be high. The provider is faced with a risk-benefit assessment that warrants explanation for the patient. With live attenuated MMR, the theoretical risk for severe or life-threatening vaccine-associated measles complications cannot be completely erased, yet for the scenarios outlined in FAQ9, this risk is expected to be very low. In the unlikely event that a patient develops more severe vaccine-associated measles symptoms or complications, consultation with local infection disease and/or prevention specialists to discuss clinical management and isolation is recommended. It is difficult to quantify the potential benefit to MMR immunization during a measles outbreak because of unknowns related to the uncertain immunogenicity of MMR in the setting of diverse immune-compromising factors and unknowns related to exposure risk. Figure 1 illustrates 4 different scenarios that clinicians are likely to encounter during ongoing measles transmission.

In scenario A, a provider would counsel the patient not to receive MMR because the patient is not yet far enough post-HCT, has a low CD4 count, is still receiving IVIG replacement, and is on too high a dose of systemic immunosuppression to have reasonable reassurance that live attenuated MMR would be safe or that a protective serologic response would be attainable. The patient resides in an area in which herd immunity is well below the desirable threshold of 90% to 95%. Checking the measles titers might have provided some reassurance but is not possible due to the IVIG replacement therapy that contains measles antibodies. Finally, IVIG therapy is a contraindication to MMR vaccination, because it interferes with the viral replication necessary to establish immunity. In the event of an exposure, another dose of IVIG would be offered to patient in scenario A depending on the timing of the last dose.

In scenario B, the patient no longer receives exogenous immunosuppression, has no GVHD, and has evidence of adequate immune reconstitution. Reflecting the practices of several centers that have already safely administered MMR vaccine at as early as 12 months post-HCT, offering early MMR vaccination could be considered regardless of herd immunity levels.

In scenario C, the patient is 3 years post-HCT and resides in an area with very low local herd immunity but, importantly, requires robust dosing of exogenous immunosuppression to control GVHD. As a result, MMR vaccination is deemed unsafe.

Scenario D is similar to scenario B, except that the patient is 4 months further out from transplantation with very mild GVHD. The GVHD is occurring at a single body site managed with topical steroids and is receiving only low-dose tacrolimus with subtherapeutic levels in the range of where some groups

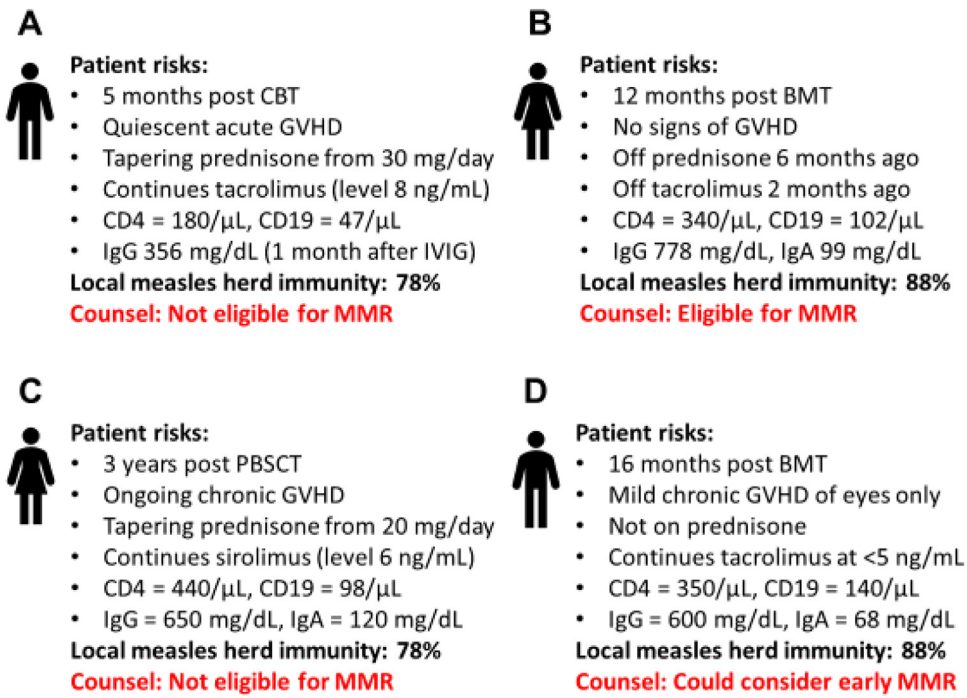

Figure 1. Counseling based on possible clinical scenarios.

have safely administered the MMR vaccine to other immunosuppressed patient populations [86,88,107].

Patients should be counseled regarding the theoretical risks associated with MMR vaccination and informed that there are limited data available to guide decision making. Ultimately, it is a case-by-case decision between the patient and counseling physician that requires shared decision making until more data emerge, or until this problem is more appropriately mitigated by restoration of community-wide herd immunity.

FAQ15: WHAT ELSE CAN HEALTHCARE CENTERS AND PROVIDERS WHO CARE FOR IMMUNOSUPPRESSED PATIENTS DO TO PROTECT PATIENTS FROM MEASLES?

In the absence of an effective nonlive measles vaccine, promoting the importance of routine vaccination of all community members and bolstering public health policy, school immunization policies, and patient education may be the only recourse. The fundamental problem that has led to the current measles resurgence is a breakdown of vaccination coverage in the community, resulting in a decrease in the herd immunity that protects immunosuppressed patients who cannot be vaccinated and rely on this protection.

Large healthcare centers that care for cancer and HCT recipients, as well as other immunosuppressed populations, should ensure that their clinical staff are protected from measles. It is important that healthcare centers know which providers are potentially susceptible to measles. Providers caring for high-risk patients should have either documented evidence of measles protection (through laboratory-based documentation of previous measles infection) or documentation of receipt of 2 doses of MMR vaccine. Importantly, a self-reported history of measles infection or vaccination is not acceptable as proof of immunity. Currently 15 US states have laws related to vaccination of healthcare workers with medical exemptions; other states permit religious exemptions. Importantly, healthcare workers who either do not have evidence of protection (in accordance with Centers for Disease Control and Prevention criteria, including in outbreak situations) or refuse vaccination should not provide direct care to patients with confirmed or suspected measles [108]. If exposed, MMR and IVIG can be offered based on existing guidelines; however, even if these are administered, such employees must be furloughed from spaces with potential patients from 5 days after first exposure to 21 days after last exposure. Healthcare workers with known primary vaccine failure ($\sim$ 3% after 2 doses of MMR) should be considered susceptible. Healthcare workers with negative serologic titers many years after vaccination should be offered another dose of MMR if they have received only 1 dose or have and unknown vaccination history. Those with credible evidence of 2 MMR vaccinations in the past and negative titers by EIA are considered immune [89]. Center-based conditions for employment that require evidence of measles immunity, except among those with a documented medical reason for nonvaccination, should be considered in transplantation centers.

Finally, there is a need for those who care for cancer and HCT recipients to be vaccine advocates. As members of the medical community, we take active roles in prevention, treatment, and survivorship of cancer patients. The potential devastation that measles can cause on individual, center, and national bases is palpable. It is our duty to talk to our patients, their families, caregivers, and the community at large about the importance of vaccination. Despite clear scientific evidence of the life-saving benefits and safety of vaccination, there continue to be those individuals and organizations who question vaccines. Healthcare workers caring for those at greatest risk for vaccine-preventable infections need to take an active role in advocating for vaccines along with our colleagues in public health, primary care, and infectious diseases to once again raise herd immunity. The recommendations presented in this article grew out of our desire to protect our patients; however, they are presented with a tremendous sense of sadness based on the realization that despite the innumerable lives saved by vaccines, we once again find it necessary to develop strategies to protect the most vulnerable against a disease that is preventable.

DECLARATION OF COMPETING INTEREST

There are no conflicts of interest to report.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

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