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Review / Derleme

Vaccination in Individuals with Multiple Sclerosis – Part II

Multipl Skleroz Tanılı Bireylerde Aşılama – Bölüm II

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Abstract

Multiple sclerosis (MS) is an autoimmune and demyelinating disease of the central nervous system. It is a chronic disease, and in the evaluation of all other health and vital processes, decisions about vaccination should be made considering the disease process and the medications used by the patient. Since vaccination can be performed at any stage of life, immune system activity should be reviewed in patients with MS except where it is characteristic of the vaccine. In this review, the applications of different vaccines in patients with MS are discussed in two separate sections (part 1 was published in the previous issue).

Keywords: Multiple sclerosis, vaccination, safety

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Öz

Multipl skleroz (MS) merkezi sinir sisteminin otoimmün ve demiyelinizan hastalığıdır. Kronik bir hastalık olup bireye ait tüm diğer sağlık ve yaşamsal süreçlerin değerlendirilmesinde hastalık seyri, hastanın kullandığı ilaçları göz önüne alarak karar vermek gereklidir. Aşılama, çocukluktan yetişkinliğe yaşamın her döneminde uygulanabildiği için MS tanılı bireylerde de her bir aşının özelliği dışında hastanın immün sistem etkinliği mutlaka gözden geçirilmelidir. Bu derlemede MS tanılı bireylerde farklı aşıların uygulamaları tartışılacak olup, farklı iki bölüm halinde yayınlanması planlanmıştır.

Anahtar Kelimeler: Multipl skleroz, aşılama, güvenlik

Introduction

Vaccination is extremely important in preventing infectious diseases and limiting the problems they may cause. With the invention of vaccination, the prevalence of infectious diseases, which are among the most important causes of mortality, decreased rapidly, with some even reaching the point of eradication. The efficacy and safety of vaccines depend on many factors, such as the age of the patients who are vaccinated, their occupation, the state of their immune system, and the medications they use. The status of the immune system and the immunomodulating or suppressing medications used in patients with autoimmune diseases are also decisive in this regard.

In this review, the principles of vaccination in patients diagnosed with multiple sclerosis (MS), an autoimmune demyelinating disease of the central nervous system (CNS), will be discussed considering current scientific knowledge.

1. Seasonal Influenza Vaccine

Influenza is a disease caused by the influenza virus that affects approximately 3-5 million people worldwide each year. The structure of the influenza virus can easily change, leading to the virus escaping from our immune system. Influenza viruses are typically more commonly active from late autumn to early spring. Influenza infection often resolves without serious complications or sequelae, but it can be associated with serious illness, hospitalization, and death, particularly among older adults, very young children, pregnant women, and patients with certain chronic medical conditions (1). Vaccination is the most effective way to prevent influenza and reduces hospitalizations and death rates during seasonal epidemics. It has also been shown that the vaccination of healthcare workers reduces job losses and nosocomial transmission and decreases mortality rates among hospitalized patients (2). Routine annual influenza vaccination for all persons aged six months or older without contraindications has been recommended since 2010 by the Chronic Disease Committee and the Advisory Committee on Immunization Practices (ACIP) (3).

Influenza vaccines are estimated from strains that had been circulating during the previous influenza season, and the content of the next seasonal vaccine is announced by the World Health Organization's (WHO) vaccine committee in February for the Northern Hemisphere and September for the Southern Hemisphere.

While inactivated (non-living), live, high-dose, and recombinant vaccines approved by the Federal Drug Administration (FDA) are in use around the world; there are triple (trivalent) and quadruple (tetravalent, quadrivalent) inactivated vaccines in Türkiye as of the 2018-2019 season (2). The inactivated vaccine is constructed from viruses produced in pureegg and contains the surface antigen hemagglutinin and small amounts of egg proteins. The influenza vaccine should not be given to those who have previously developed a serious allergy to the vaccine or its ingredients. Furthermore, although there is no harm in giving it to those who are mildly allergic to eggs, those who have a serious allergy should receive the influenza vaccine in health institutions.

Currently, there are four inactivated influenza vaccines (IIV4) containing four influenza virus types in Türkiye (4). Since this is a non-living vaccine, it does not cause influenza. It is offered to at-risk groups in the order determined by the Ministry of Health, and it is given for free in the vaccination units of hospitals or family health centers. For defined at-risk groups, vaccination is provided once a year when prescribed by physicians from all branches, based on a health report stating the patient's disease/pregnancy status. In Türkiye, the influenza vaccine is covered by the Social Security Institution in the following cases:

- Persons aged 65 and older
- Persons staying in an elderly nursing home
- Pregnant women in the second or third trimester of pregnancy
- Patients with chronic lung and cardiovascular disease, including asthma
- Patients with any chronic metabolic disease, including diabetes
- Patients with chronic kidney failure
- Patients with blood diseases, such as hemoglobinopathy
- Patients who have immunodeficiency or receive immunosuppressive treatment
- Children and adolescents aged 6 months to 18 years who are using long-term aspirin

Because the time of onset, peak, and decline of influenza activity varies, the ideal time to start vaccination cannot be predicted every season. For most people, who will only need one dose of influenza vaccine per season, vaccination should ideally be done in September or October. However, vaccination should continue after October and throughout the influenza season as long as influenza viruses are circulating and vaccines that have not expired are available (1). In the planned booster vaccinations for children aged six months to eight years, the second dose should be administered at least four weeks after the first dose (until the end of October). Studies have shown that immunity lasts 6-8 months or longer in healthy adults but may be shorter in the elderly and immunosuppressed individuals. Since influenza infection is a greater risk to pregnant women, the vaccine can be administered in any trimester of pregnancy (2).

The possibility of serious side effects from the influenza vaccine is no different from that of other vaccines. The most common side effect of the vaccine in adults is pain and tenderness at the injection site. This complaint occurs at a rate of 10-64% and disappears within a day or two. Vaccine-related systemic symptoms, such as fever, headache, myalgia, and malaise, occur no more frequently than in other vaccines or a placebo (drug-free) injection.

1.1. Vaccination in Patients with Multiple Sclerosis

The standard-dose inactivated injectable influenza vaccine, which has been extensively studied in patients with MS, is considered safe and recommended for all patients with MS, regardless of the treatment given. However, immune response after vaccination may differ depending on immune therapy. A systematic review of patients with MS following vaccination against influenza subtype H1N1 and/or seasonal influenza examined six studies investigating the risk of developing MS after vaccination. No increase in the risk of developing MS was found in any of the studies (5).

Much of the research on the influenza vaccine (seasonal and H1N1) has focused on the risk of relapse. However, the results are relatively heterogeneous due to the diversity of study designs and the fact that the seasonal influenza vaccine changes each year. One problem is that the characteristics of the vaccine are rarely specified. However, two relatively large studies investigated the effect of H1N1 vaccination on disease activity in patients with MS and did not detect an increased risk of relapse (6,7). Other studies also showed indicated no increase in the risk of relapse after vaccination against seasonal influenza or H1N1 (5).

In a meta-analysis examining the responses of patients with MS to the influenza vaccine (8), no significant difference was found in the immune response of the MS group when compared to healthy controls. Patients with MS were observed to elicit an immune response similar to that observed in healthy controls, with their baseline antibody titers expressing seroconversion or seroprotection. It can be concluded that patients with MS can form an adequate immune response against the influenza vaccine; as such, it would be appropriate to recommend influenza vaccination to patients with MS yearly (9).

1.2. Multiple Sclerosis Treatment and Vaccination

In a study to evaluate the immunogenicity, safety, and predictors of immune response to the seasonal influenza vaccine in a cohort of patients with MS receiving different immunomodulatory/immunosuppressive therapies (10), protection rates of >70% were obtained against each influenza strain. Interferon-treated patients achieved high seroprotection rates (>84%), and glatiramer acetate-treated patients achieved protective rates, although they were lower than those of healthy controls. For influenza subtype H3N2, response rates were low in patients treated with natalizumab and in a small subset of patients treated with fingolimod. Patients with previous disease-modifying therapy and longer disease duration were less likely to produce adequate antibody responses. No serious side effects were reported in the study, and MS disease activity did not increase after a year of follow-up.

Olberg et al. (11) compared 90 patients with MS who received fingolimod, glatiramer acetate, interferon beta-1a/1b, natalizumab, or no treatment with 62 healthy controls. An inactivated virus vaccine was administered to all patients, and serum samples were collected before vaccination and at 3, 6, and 12 months post-vaccination. Vaccine responses were assessed using the hemagglutination inhibition test, with no significant difference in the rates of protection against H1N1 in patients receiving interferon beta 1a/1b and glatiramer acetate compared to healthy controls at 3, 6, and 12 months. Fingolimod was found to provide reduced protection at all time points post-vaccination, while natalizumab showed a reduced response at 3 and 6 months.

In a study conducted to investigate the effect of teriflunomide on the efficacy and safety of the seasonal influenza vaccine, it was found that patients treated with teriflunomide developed a protective immune response, although slightly reduced, against a seasonal influenza vaccine (12).

There are presently no studies evaluating the effect of the influenza vaccine in patients treated with alemtuzumab. The National MS Society recommends that the vaccine be given at least 6 weeks before receiving alemtuzumab (13). There are currently also no vaccine studies evaluating the effect of the vaccine on individuals with MS using oral cladribine or dimethyl fumarate (14).

In a study of patients with MS treated with ocrelizumab (15), patients were shown to retain pre-existing specific humoral immunity to common viral and bacterial agents acquired prior to the initiation of therapy. In the VELOCE study, patients with relapsing-remitting MS (RRMS) were found to have decreased humoral responses to a neoantigen and some vaccines, including the seasonal influenza vaccine, and it was recommended that patients with MS treated with ocrelizumab be vaccinated with inactivated seasonal influenza vaccines. Necessary vaccinations should be performed in patients who are planned to be treated with ocrelizumab, and the vaccination schedule should be completed at least two weeks before the first administration (16). In patients using ocrelizumab, vaccines should not overlap with the infusion, and in the absence of an immunological rationale, a three-month latency is recommended to develop a potentially protective humoral response to the vaccine, even if it is attenuated (17).

Corticosteroids have not been proven to impair immune response following influenza vaccination. Following high-dose corticosteroid therapy, it is recommended that vaccination be delayed for at least two weeks to reduce vaccine-related side effects (18).

The standard-dose inactivated injectable influenza vaccine, which has been extensively studied in patients with MS, is considered safe and recommended for all patients with MS, regardless of the treatment given. Although it is not currently available in Türkiye, the influenza vaccine used in the form of a live nasal spray is not recommended for patients with MS.

2. Herpesviridae Vaccines

Herpesviridae is a large family of DNA viruses with more than 100 subtypes. There are 8 DNA viruses that cause infection in humans; among them, human herpes virus type 1 (HHV-1), HHV-2, and HHV-3 [varicella zoster virus; (VZV)] remain latent in the dorsal root ganglia and cause herpes labialis – herpes encephalitis, genital herpes and chickenpox and shingles, respectively. Meanwhile, HHV-4 (Ebstein-Barr virus) remains latent in lymphoid tissue and causes infectious mononucleosis and lymphoma; HHV-5 (cytomegalovirus; CMV) remains latent in peripheral leukocytes and causes cytomegalic inclusion disease; HHV-6 and HHV-7 remain latent in peripheral leukocytes and cause roseola infantum and pityriasis rosea asymptomatic lymphoreticular diseases, respectively; HHV-8 remains latent in lymphoid tissue and causes Kaposi's sarcoma (19).

The VZV is a ubiquitous neurotropic human herpes DNA virus. Chickenpox presents with vesicular rash and pain, usually in a single dermatome due to the primary infection of the virus. After the disease is healed, the virus remains latent in the body and reactivates at a time when the immune system is suppressed,

causing herpes zoster (shingles zoster; latent VZV reactivation) infection. The overall incidence is 0.3%, and this incidence increases with age, reaching 1% in patients older than 70 years. The infection rate in patients over the age of 85 is 85% (20).

Chickenpox is an important infection that can cause clinical manifestations such as skin rash, pneumonia, and encephalitis. An antibody-mediated immunity of 95-100% can be achieved with vaccination. In addition, the formation of scars after the disease is prevented, and the risks of life-threatening infection and shingles in adulthood are reduced.

There are two VZV vaccines licensed in Türkiye, namely Varilrix, and Okavax. Both are live attenuated vaccines and protect against chickenpox. According to the 2020 vaccination schedule of the Ministry of Health, two doses of VZV are recommended for children, adolescents, adults, and individuals over 65 years of age who have not had chickenpox and have never been vaccinated. Child and adult vaccine doses are the same (21).

The Varilrix vaccine can be administered from nine months of age. While two doses of the vaccine are administered at 3-month intervals in children aged 9–12 months, it is recommended to be administered as two doses at intervals of 4–6 weeks in adults and children older than 12 months. In persons older than 13 years of age, two doses should be administered at least 28 days apart (22).

Salicylate should not be used in the presence of a negative reaction to the dose applied before in disease cases such as lymphoma and leukemia, in which the immune system is suppressed or in patients receiving active immunosuppressive therapy. In addition, pregnancy is not recommended for one month after vaccination. Since chickenpox vaccines are live vaccines, they should be administered prior to immunosuppressive treatments.

In the protection against herpes zoster infection caused by latent VZV reactivation, there are two types of vaccines: Zostavax and Shingrix. Zostavax is a live vaccine licensed for persons above 50 years of age, administered as a single dose, and provides 57% protection according to meta-analysis results. This vaccine, which has a protection rate of 97.4% in persons 60-69 years of age and 91.3% in persons 70 years of age and older, prevents the development of postherpetic neuralgia at rates of 91.2% and 88.8%, respectively, in these two age groups (23). Both vaccines are unavailable in Türkiye. In 2020, Zostavax production was terminated in the USA.

Shingrix is a recombinant vaccine that can provide a protection rate of 89.8% in two doses. Shingrix contains recombinant VZV glycoprotein E. Compared to the live vaccine, it is known to have more side effects, particularly local and systemic reactions. It is estimated that the adjuvant used to increase immunogenicity in this vaccine increases the incidence of local effects (24). If six months have passed since the first dose of Shingrix, the second dose should be given as soon as possible. There is no need to restart the vaccination program. If there are less than four weeks between the first and second dose, the second dose should be considered invalid and should be repeated two months later (25). Although Shingrix has more known side effects, none are serious. The most common side effect is 3-5 chickenpox-like lesions at the injection site or in different regions around the injection site. Pain, swelling, and redness may be observed at the injection site (5-60%). A cold compress and paracetamol are recommended, and side effects generally cease within 48 hours. Very rarely, an anaphylactic reaction can be observed in people who are sensitive to the antigens in the vaccine, but this occurs in only 0-1 cases per million vaccine doses (26,27).

2.1. Vaccination in Patients with Multiple Sclerosis

There are no data showing that varicella vaccination increases the development of MS or the risk of MS attacks (Level B). Although it has been reported that the inactivated vaccine responses of patients with naïve MS are similar to those of the healthy population (28). In patients with MS and those receiving other immunosuppressive therapy, an immunosuppressive agent can be started 15 days after the VZV vaccine program. Patients with MS who are VZV immunoglobulin G (IgG) negative should receive the varicella vaccine, not the shingles vaccine (29). In patients with MS who are planning to receive immunosuppressive therapy, it is recommended that they complete the Shingrix vaccine program 2-4 weeks before the start of treatment to achieve optimal protective efficacy (29). Although it is recommended particularly for persons over 50 years of age, in patients with MS with a history of VZV, a recombinant vaccine (or a live vaccine in cases where a recombinant vaccine is not available) at 2-6 month intervals is recommended by evaluating the benefits and risks (24).

Before starting immunosuppressive therapy, VZV antibody levels should be checked. In cases where there is positivity of both IgG and IgM antibodies, IgM positivity lasting longer than six weeks is considered false positivity and does not prevent the use of immunosuppressive agents (25).

In cases where vaccination is required during treatment, vaccination can be performed if the MS disease course is stable, and the immunosuppressive effect of the given agent is low. It should be considered that the vaccine may show limited efficacy due to treatment (24).

The Shingrix vaccine can be administered regardless of whether the individual to be vaccinated has had a previous herpes zoster infection or a Zostavax vaccine history. No age-specific upper limit has been determined for this vaccine administration (25). Recombinant and live vaccines are currently unavailable in Türkiye.

2.2. Multiple Sclerosis Treatment and Vaccination

Patients who have received corticosteroid therapy for less than 14 days can receive a live vaccination without discontinuing therapy. It has been reported that the risk of VZV infection increases in patients receiving fingolimod, dimethyl fumarate, alemtuzumab, and natalizumab treatment. To develop an adequate immune response against VZV, vaccination should be done at least one month before the administration of fingolimod and other sphingosine receptor modulators and six weeks before the administration of rituximab, ocrelizumab, ofatumumab, cladribine, and alemtuzumab (30,31). In the literature, there are case reports of herpes/zona zoster infections in some patients vaccinated before treatment and in the follow-up of some patients with MS vaccinated while receiving fingolimod and ocrelizumab. A live zoster vaccine (Zostavax) should not be administered to patients with MS who are receiving sphingosine receptor modulators, natalizumab, ocrelizumab, ofatumumab, rituximab, cladribine, and alemtuzumab. A recombinant vaccine can be used for these patients (28,32,33).

3. Human Papilloma Virus Vaccines

Human papillomavirus (HPV) is a small, non-enveloped, double-stranded DNA virus of the papovavirus class. It has an icosahedral capsid structure and comprises a major (L1) and a minor (L2) protein. More than 200 HPV types have been identified to date; 12 HPV types have been defined as high-risk (oncogenic), and it has been stated that they may cause cancer in humans (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) (34). It is the most common viral infection involving the urogenital system. Most HPV infections are asymptomatic and resolve spontaneously, but this infection can also cause persistent diseases. In women, oncogenic HPV types can progress to cervical intraepithelial neoplasia as a persistent infection and then progress to invasive cervical cancer. HPV infection is also associated with cancers of the head, neck, oropharynx, and anogenital region, as well as anogenital warts and respiratory papillomatosis in both men and women (35,36).

The first vaccine used to prevent HPV-related diseases was licensed in 2006. Vaccines for HPV were obtained from purified L1 structural proteins using recombinant DNA and cell-culture technologies. These vaccines do not contain live biological products or viral DNA. All HPV vaccines contain virus-like particles that protect against high-risk HPV types 16 and 18. The use of these vaccines is indicated in women from the age of 9 and up to the age of 26 or 45. Some HPV vaccines are also given to men (37). A quadrivalent HPV vaccine is implemented at 0, 1-2, and 4-6 months.

3.1. Vaccination in Patients with Multiple Sclerosis

The HPV vaccines have been found to possibly trigger demyelinating diseases in some cases (38,39,40,41). Evidence of molecular similarity between various components of vaccines and myelin proteins is also known (42).

In an observational study, it was found that there was no significant increase in the risk of the development of MS and other demyelinating diseases with the routine use of HPV vaccines (43). In a study conducted in Denmark and Sweden, it was reported that the quadrivalent HPV vaccine did not increase the risk of developing MS or other demyelinating diseases in women between the ages of 10 and 44 (44). In another study, the relationship of HPV vaccines with autoimmune diseases, including MS, was evaluated, and no evidence was found that HPV vaccination increased the risk of autoimmune diseases (45).

3.2. Multiple Sclerosis Treatment and Vaccination

There are currently many medication options for the treatment of MS, and their mechanisms differ. This raises questions about the possible interactions of these treatment options with HPV vaccines. It has been reported that fingolimod and alemtuzumab may increase the risk of skin lesions and cervical dysplasia; detailed information about HPV vaccination should thus be given to patients with MS receiving fingolimod or alemtuzumab, and vaccination should be recommended when necessary and appropriate (46).

It can be concluded that the use of HPV vaccines does not increase the risk of developing MS. However, it is very important to determine the most appropriate time for a successful vaccination in a patient with MS who is receiving treatment and to provide detailed information to the patient.

4. Yellow Fever Vaccine

Yellow fever virus (YFV) is a small, enveloped, single-stranded RNA virus in the Flavivirus family that is endemic to Sub-Saharan Africa and Tropical South America. Yellow fever is a vector-borne disease transmitted by the bite of a virus-infected mosquito. It is a potentially fatal disease, affecting approximately 200,000 people a year and causing 30,000 deaths. Symptoms range from presenting as a mild febrile syndrome to severe hepatic and renal dysfunction with jaundice and bleeding diathesis, which can be fatal in up to 50% of cases (47,48). Treatment for yellow fever comprises supportive care, and no specific antiviral therapy is available.

The YFV, developed in 1936 (Yellow fever 17D vaccine), is a live, attenuated vaccine. There are six different YFVs, four of which have been approved by the WHO, and 70-90 million doses are produced per year worldwide (49). This global strategy aims to end yellow fever epidemics by 2026.

According to the United States Centers for Disease Control and Prevention, the United States ACIP, and the WHO, YFV is recommended for travelers and residents of yellow fever-endemic regions areas of Africa and South America (Grade 1A). The vaccine can be administered to persons at least nine months old (50,51).

According to the Travel Health Directive of the Ministry of Health in Türkiye, YFV is administered as a single dose to those living in high-risk countries and those who will travel to them, and it is protective for life. The vaccine should be administered at least 10 days before travel to ensure that the protective action of the vaccination has begun. The vaccine can be recommended for babies aged 6-9 months and pregnant and breastfeeding women but only if the risk of contracting yellow fever due to travel is very high. However, YFV is not recommended for patients with immune system failure (such as patients with HIV and patients receiving chemotherapy and radiotherapy), persons who are allergic to the vaccine's components, persons with an egg allergy, or who have had a serious allergic reaction to YFV in the past, patients with thymus gland diseases, and patients who are not in good health (e.g., those with a high fever). It is recommended that the risk of contracting the disease be assessed for travelers over 60 years of age who have not been previously vaccinated.

Mild side effects (e.g., headache, myalgia, mild fever, and pain at the injection site) and, rarely, anaphylaxis (1.8 per 100,000 cases) have been reported in 10-30% of vaccinated patients (52).

4.1. Vaccination in Patients with Multiple Sclerosis

It is not known how YFV affects the immunological response in patients with MS, and the mechanism by which autoimmune reactions can be triggered by vaccination most likely varies with vaccine type and individual genetic susceptibility (53). Papeix et al. (54) found no difference in terms of first relapse between individuals with a diagnosis of RRMS who were exposed to YFV and individuals with RRMS who were not exposed to it.

A small study of patients with MS in 2007-2009 showed a significant increase in relapse rates within three months following yellow fever 17D vaccination compared to prevaccination (55). In contrast, another small study of patients with MS in Switzerland between 2014-2018 showed no significant association with MS relapses (4 out of 23 patients) following YFV. In addition, although concomitant administration of natalizumab and live attenuated vaccines is not recommended, none of the patients in this study experienced relapses or a YFV-related adverse event (56).

4.2. Multiple Sclerosis Treatment and Vaccination

According to the French MS Society, the current guidelines state that live attenuated vaccines are relatively contraindicated in patients recently treated with immunosuppressive drugs (57). Drugs other than interferons and glatiramer acetate used in the treatment of MS should be evaluated in this category with their immunosuppressive properties.

In the literature, two studies have shown that YFV triggers a MS relapse after fingolimod withdrawal (48,58). Immunogenicity appears satisfactory in patients receiving systemic corticosteroid therapy (mean dose of prednisone 7 mg/day for 10 months), but local reactions may occur more frequently in these patients, and more studies are needed (59). Therefore, in patients with MS who are planning to travel to yellow-fever-endemic regions, the potential risk of relapse associated with vaccination and the possibility of exposure to yellow fever should be carefully evaluated on a case-by-case basis.

5. Smallpox Vaccines

The orthopoxvirus (OPV) genus of viruses includes several species that infect humans, including variola, monkeypox, vaccinia, and cowpox (60). Variola and monkeypox are typically life-threatening, while vaccinia and cowpox are mostly limited to local lesions. The epidemic potential for OPVs is considered to be lower than for respiratory viruses or RNA viruses. Smallpox is a highly contagious virus caused by variola and has a mortality rate of 30-40%. Smallpox was reported by the WHO to have been eradicated on May 8, 1980.

Smallpox infection can be prevented with smallpox vaccines, such as Dryvax and the vaccinia virus vaccine (ACAM2000), which are polyclonal and monoclonal vaccines, respectively. The ACAM2000 vaccine is a live vaccine derived from the vaccinia virus, a smallpox-like but less harmful poxvirus. The protective effect of this vaccine, which has an effectiveness rate of 95%, continues for 3-5 years. The Jynneos® vaccine, developed to prevent smallpox and monkeypox infections in at-risk persons over the age of 18, has been approved by the FDA. Jynneos® is licensed as a two-dose series (SC) administered 28 days apart. Since August 9, 2022, the standard regimen for persons under 18 years of age has also been allowed in cases of emergency. This vaccine can also be administered intradermally, and the results of a clinical study show that a low intradermal dose is not immunologically lower than the standard subcutaneous dose (61).

Smallpox vaccines can be administered regardless of the timing of many other vaccines (https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/jynneos-vaccine.html). They can be administered on the same day as other vaccines, including influenza vaccines, but at different anatomical sites, if possible.

5.1. Multiple Sclerosis and Vaccination

There are no studies demonstrating the efficacy and safety of smallpox vaccines in patients with MS, although some studies have found no increased risk following vaccination (62,63,64,65,66,67). However, since these vaccines are based on a live, attenuated, non-replicating OPV, their use is contraindicated in individuals with severe immunosuppression.

6. Poliovirus Vaccines

Vaccination against poliovirus infection is recognized as one of the most important medical achievements in the world. An inactivated poliovirus vaccine (IPVA) and live attenuated oral poliovirus vaccine (OPV) were produced in the 1950s and implemented in routine childhood vaccination programs all over the world (68). According to data from the WHO, since 1988, the number of patients with polio has decreased by more than 99%, from an estimated 350,000 cases to 6 reported cases in 2021. The IPVA is administered at 2, 4, 6, and 18 months of age in the form of a five-fold mixed vaccine with diphtheria, pertussis, tetanus, and Hemophilus influenzae type b, and is estimated to provide seroconversion in more than 95% of infants (69). According to the vaccination schedule in Türkiye, in addition to this application, the OPA is administered at 6 and 18 months, and a booster dose of IPVA is administered with diphtheria, pertussis, and tetanus at 2 years of age. Although the OPV remains important in poliovirus transmission control due to its lower cost, ease of administration, and ability to induce mucosal immunity, particularly in developing countries, the strategic plan of the Global Poliovirus Eradication Initiative calls for the OPA to be discontinued and replaced with the IPVA once all poliovirus transmission has been eliminated due to vaccine-associated paralytic poliomyelitis cases (70). Since the risk of vaccine-associated paralytic poliomyelitis is highest in those with B-cell immunodeficiency, oral live vaccines are contraindicated in immunosuppressed individuals. No serious adverse events have been reported involving the IPVA, and only mild side effects, such as transient reactions similar to those experienced with a placebo injection (e.g., local pain, redness, and induration), have been observed (71). It is recommended that people who plan to travel to regions with a high risk of poliovirus infection, particularly the eastern Mediterranean and Africa, whose last poliovirus vaccine dose is above the age of should receive a single dose of intramuscular IPVA before travel (57).

6.1. Vaccination in Patients with Multiple Sclerosis

In a newly published study from Austria in which the vaccination status of 424 patients with MS was evaluated, adequate vaccination was defined as follows: being vaccinated for diphtheria-pertussis-tetanus in the preceding 10 years if under the age of 60 or in the past 5 years if over the age of 60; being vaccinated for poliovirus and hepatitis B in the past 10 years; being vaccinated for measles-rubella-mumps at least twice in a lifetime; being vaccinated for tick-borne encephalitis in the past 5 years if under the age of 60 or in the past 3 years if over the age of 60; being vaccinated for influenza and pneumococcus in the preceding season if over the age of 60 (72). In this study, it was shown that only 3% of patients with MS had been adequately vaccinated, although 90% of them were immunized against the poliovirus (72).

In a two-center German study, in which 327 patients with MS were vaccinated against diphtheria-pertussis-tetanus and poliovirus, both the completion status of their vaccinations and their attitudes toward their own vaccination status were evaluated. Although 75.9% of the patients declared that their poliovirus vaccinations were completed, it was determined that 84.8% of the patients had been fully vaccinated against poliovirus; this rate was higher than the average German population and patients with other autoimmune diseases (73). Many studies in the past

two decades have shown that there is no causal relationship between vaccination and the onset or attack of MS (5,74,75). In an Australian study evaluating the association of childhood infections, vaccination, and tonsillectomy with the risk of a first clinical diagnosis of CNS demyelinating diseases, it was found that poliovirus vaccine administration in the preschool period was associated with an increased risk of a first clinical diagnosis of CNS demyelinating disease (76). Since the vaccination information in this study was obtained from the patients' own declarations, it was suggested that this finding should be supported by other studies due to a lack of data on the type of poliovirus vaccine and the low number of controls used in comparison. In a systematic review of 51 studies on vaccination in patients with MS, 9 studies on poliovirus vaccination were evaluated. It was noted that there was no risk of relapse after poliovirus vaccination in any of these studies (5).

6.2. Multiple Sclerosis Treatment and Vaccination

It is recommended that the vaccination status of the patient be reviewed and updated as soon as a diagnosis of MS is made to avoid any delay in initiating treatment (9). It is also recommended that inactivated vaccines be administered at least two weeks before immunosuppressant and immunoreconstructive treatments (77). If it is not possible to immunize using an inactivated vaccine before treatment, vaccination can be made at any time during the treatment, keeping in mind the post-treatment re-immunization. It is not recommended to administer live attenuated vaccines during immunosuppressive/immuneconstructive treatments or less than four weeks before treatment (78). It should be considered that although inactivated vaccines can be administered to people receiving high-dose corticosteroid therapy, the vaccine response may be lower than normal (57). Based on this information, it is possible to state that the IPVA vaccine administered before treatment for poliovirus immunization in patients with MS is safe and effective.

7. Meningococcal Vaccines

Neisseria meningitidis is an encapsulated gram-negative aerobic diplococcus. It is associated with a mortality of approximately 10-14%. Clinically, the most common presentation is meningitis and meningitis with meningococcemia (79). Among the 13 serogroups (A, B, C, D, X, Y, Z, E, W135, H, I, K, and L), the 6 most common that cause disease in humans have been defined (A, B, C, Y, W135, and X) (1). According to data from the WHO, while serogroups B and C are responsible for 85% of cases in Europe, meningitis epidemics occur every 5-10 years in Africa, and serogroup A is the most common cause.

There is an increased risk of meningococcal disease in cases of asplenia, complement deficiency (C3, C5-9, properdin, factor H, and factor D), the use of complement inhibitors (e.g., eculizumab/ravulizumab), and HIV infection (80). Meningococcal vaccines are recommended by the WHO in routine vaccination programs in high-risk (>10 cases/100,000 persons/year) and intermediate (2-10 cases/100,000 persons/year) endemic areas (81). In countries with an incidence of <2/100,000, vaccination is recommended in defined risk groups (e.g., children, teenagers in boarding schools or military units, patients with HIV, patients with asplenia, and travelers to endemic areas). Quadrivalent conjugate vaccines are routinely recommended, while monovalent vaccines are recommended to prevent epidemics (81).

There are polysaccharide and conjugate meningococcal vaccines. The effectiveness of polysaccharide vaccines is above 85% in older children and adults, but they produce a weak immune response in children younger than 24 months. Polysaccharide vaccines create antibodies by stimulating the B-lymphocyte response, but there is no T-lymphocyte stimulation and no memory response in T-cells. Protection is also short-lived. These vaccines provide community immunity. In conjugate vaccines, bacterial polysaccharide structures are attached to a carrier protein, and T lymphocyte-dependent responses can be generated (82). These vaccines provide long-term protection in all age groups, as well as community immunity.

There are three types of quadrivalent conjugate vaccines. First, MenACWY- tetanus toxoid (TT) (Nimenrix-Pfizer) (A, C, W, and Y serogroups and conjugated with tetanus toxoid), which is approved by the European Medicines Agency (EMA) from 6 weeks of age and by Türkiye but is not approved by the FDA. It is administered as a single dose in children who are at least 12 months old. Second, MenACWY-diphtheria toxoid (DT) (Menactra-Sanofi Pasteur) (A, C, W, and Y serogroups and conjugated with diphtheria toxoid), which is approved in Türkiye and is administered as a single dose between 2-55 years of age. finally, MenACWY-CRM197 (Menveo, GSK) (A, C, W, and Y serogroups and covalent binding with the non-toxic diphtheria protein CRM197), which is approved by the FDA and EMA and in Türkiye. It is administered as a single dose above 2 years of age. In addition, the recombinant MenB meningococcal vaccines, MenB-FHbp (Trumenba) and MenB-4C (Bexsero), have been approved by the FDA, and MenB-4C is approved in Türkiye, where doses at 1 month intervals are recommended for persons between 2 months and 25 years of age; 3-4 doses are recommended for younger age groups, based on age range.

According to the recommendations of the Center for Disease Control and ACIP, MenACWY vaccination is recommended for persons aged 2 months or older with the above-mentioned risk factors as teenagers in boarding schools or military units, patients with HIV, patients with asplenia, and travelers to endemic areas (80). Booster vaccinations are recommended for those whose risk continues.

In the Adult Vaccination Practice of the Ministry of Health, it is recommended that meningococcal vaccination be carried out within the scope of soldier vaccinations and hajj and umrah vaccinations (83). According to the Turkish Society of Clinical Microbiology and Infectious Diseases vaccination calendar, there is no specific recommendation for meningococcal vaccination, and it can be adjusted according to the wishes of the physician and the patient (84). However, it has been stated that "those with congenital or acquired immune deficiency, those with cerebrospinal fluid leakage, and patients with sickle cell anemia should be administered (meningococcal vaccination) in two doses at least two months apart in the 18–55 age group" (84). In the Adult Immunization Working Group 2019 Adult Immunization Guidelines, two doses are recommended for at-risk groups that make the Morbidity and Mortality Weekly Report ACIP recommendations (2). Vaccine-related side effects, such as injection-site reaction, headache, weakness, nausea, fever, and myalgia, may occur.

7.1 Vaccination in Patients with Multiple Sclerosis

Although five patients with Guillain-Barre syndrome were reported in 2005 following the administration of meningococcal conjugate vaccines (85), the rate was calculated as 1.5 cases/1,000,000 doses (86). A study conducted on 71 patients with MS (38 using dimethyl fumarate, 33 using interferon) (87) showed that responses to tetanus, diphtheria, pneumococcal serotypes, and meningococcal serotype C vaccines did not differ between the drug groups, and the response to MCV4 meningococcal vaccine, which was used to create a T-cell-dependent humoral response, showed no differences between the drug groups and generated a similar antibody response independent of lymphocyte count (87). In a post-license safety surveillance study of quadrivalent meningococcal DT conjugate vaccines, no finding in favor of myelitis or demyelinating disease attack was reported among the vaccine-related side effects (88).

7.2. Multiple Sclerosis Treatment and Vaccination

For patients with MS, there is no obstacle to vaccination recommendations for non-live, mRNA and vector vaccines (especially non-replicated viral vector vaccines). For patients receiving interferon, glatiramer acetate, dimethyl fumarate, teriflunomide, sphingosine-1-phosphate modulators, or natalizumab, vaccination can be performed at any time, but it should be done 3-6 months after treatment with B-cell depletion agents or alemtuzumab. (89). A mean waiting period of 2 weeks is recommended between the initiation of disease-modifying therapy and vaccination or between cycles with non-live/mRNA/vector vaccines (89).

8. Tick-Borne Encephalitis Virus Vaccination

Tick-borne encephalitis virus (TBEV) is a single-stranded RNA virus in the Flavivirus family with a geographical endemic distribution in Eurasia and the Far East. It is transmitted by the bite of tick vectors of the Ixodes species. This virus and its infection's clinical features were first described by Zilber in 1939 (90). Common clinical features caused by the virus are closely related to three genetic subtypes: European (TBEV-Eu), Siberian (TBEV-Sib), and East Asia (TBEV-FE) types. Although the most common condition after contamination is asymptomatic infection, severe neurological disease may develop in 2-30% of patients (91).

After the incubation period (typically 7-14 days after a tick bite), the first phase, which is caused by viremia, can be characterized by general malaise, fever, and myalgia. The second phase (neurological) occurs in 10% of patients, and the mortality rate is less than 2%. Meningitis, meningomyelitis, and myelitis may be detected, and long-term neurological and neuropsychological sequelae may develop (92).

There is no effective antiviral treatment for TBEV; analgosedation, osmotherapy, and corticosteroids can be used as symptomatic treatment options according to the clinical features (93). Vaccination is of great importance for TBEV, which is a deadly viral infection with no cure. Strains of TBEV that are inactivated with formalin and grown in cell cultures constitute the basic principle of vaccine production. Of the four different TBEV vaccines developed globally, two were produced against the European subtype and two against the Far Eastern subtype. The two vaccines against the European subtype are FSME-IMMUN®/TicoVac® Baxter (Vienna, Austria) and Encepur® Novartis (Marburg, Germany). These are registered by the EMA. The two vaccines against the Far Eastern subtype, TBE-Moscow® (Chumakov Institute, Moscow) and EnceVir® (Microgen, Tomsk), are manufactured in Russia and are not approved by the EMA (94).

In highly endemic areas (≥5 cases/100,000/year), the WHO recommends vaccination to all age groups above one year of age. If much outdoor activity is expected, travelers from non-endemic to endemic areas should be vaccinated (95). Vaccination is highly effective, and the incidence of TBEV has decreased in endemic areas due to successful immunization (96). In addition to creating a strong antibody response, vaccination has been shown to have very low side-effect rates in randomized controlled studies (97,98).

The vaccination schedule for EMA-registered vaccines is commonly created by adding a reminder dose in the third year to the vaccines to be administered at 0, 1, and 9 months. In addition, a rapid vaccination program is applied on days 0, 7, and 21 for Encepur® in cases where rapid protection is required (99).

8.1. Vaccination in Patients with Multiple Sclerosis

In addition to the necessity of administering TBEV vaccines to patients with MS in endemic regions, there are also studies on how the vaccine affects disease activity in MS. In 2003, 15 TBEV-vaccinated patients with MS and expanded disability status scale (EDSS) scores ranging from 1-3.5 and 15 age-sex matched unvaccinated patients with MS were followed for 2 years in the endemic region; no difference in disease activity or progression between the two groups was observed (100).

In a recent multicenter study, 20 patients with MS, who used disease-modifying therapy for at least six months and had been vaccinated with TBEV, were followed up for disease activity for one year (101). Serum TBEV antibody values were measured before and at four weeks after vaccination to evaluate TBEV antibody responses. The annual relapse rate fell from 0.65 in the year before vaccination to 0.21 in the year after, and EDSS scores also remained stable.

8.2. Multiple Sclerosis Treatment and Vaccination

In a study evaluating the efficacy of the TBEV vaccine in patients with MS, protective antibody titers were obtained that exhibited an adequate immune response independent of the underlying disease-modifying therapy (101). It was shown that the lowest serum TBEV antibody values measured in the study group were in patients using fingolimod. Thus, it was concluded that the TBEV vaccine was effective and safe for use in patients with MS, and it was emphasized that the antibody response could change, based on the specific disease-modifying treatment used.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.T., B.P.Ç., Al.S., H.E., Design: B.P.Ç., A.T., A.S., Data Collection or Processing: All authors, Analysis or Interpretation: B.İ.T., B.P.Ç., A.T., Ak.S., H.E., Literature Search: All authors, Writing: B.P.Ç., A.T.

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