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Review Article

Vaccination in Patients with Primary Immunodeficiency Disorders

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Abstract

Primary Immunodeficiency Disorders (PID), are heterogeneous groups of an abnormality in innate and adoptive immune systems. Patients with these disorders, are susceptible to life-threatening infections. Infection control, is an important strategy for improving the quality of life and prognosis. Prophylaxis, intravenous immunoglobulin and antibiotic therapy for a long period of time, is an appropriate option for many patients with PID. But vaccination in immunocompromised patients may play a significant role and various outcomes. Depending on the type of PID, there are different results after the administration of vaccines in patients. In some cases, immune response is perfect and there is a well protection against the syndromes. On the other hand, in some other patients, immune response is impaired, and the vaccination is ineffective or even could lead to severe overwhelming side effects. To date, there are no well-established guidelines about the vaccination of immunocompromised people. In this review, we are going to describe the latest recommendations for the immunization of patients with PID, based on the published literatures.

Keywords: Vaccination; Primary Immunodeficiency; Live-Attenuated Vaccine; Inactivated Vaccine

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Introduction

Primary immunodeficiency disorders, are the results of abnormalities in the development and functions of the immune system components, which is inherited by specific genes. There is a wide variation of the PID's prevalence in different geographic areas and ethnicities. The prevalence of PID, is more than 1/600 individuals in the western countries (1). Patients with PID, have an increased susceptibility to various life threatening viral, bacterial and fungal infections. The most important strategies for the prevention of the infections, are antibiotic prophylaxis, appropriate vaccination, and in some cases, immunoglobulin replacement therapy (2). Vaccination against several microorganisms, is a traditional and effective prevention method for many infectious diseases. Patients with primary immunodeficiency, have an impaired immunologic response, not only to natural infections, but also to vaccination. Vaccines, can be categorized into live attenuated and nonviable agents **(Table 1)**. The viable vaccines, are live attenuated microbes. Therefore, they do not cause any clinical diseases in the immune-competent hosts, but could cause many life threatening disorders in the immunocompromised patients. These vaccines, must be used with caution in these cases. Nonviable vaccines consist of inactivated microorganisms, subunits of organisms and their toxins. These vaccines would not cause any infections or illnesses in any of the patient, even those with primary immunodeficiency. Nonviable vaccines are safe, and can be used for most the PID patients, but in the patients with poor immune response, the vaccination might be ineffective (3-7).

Viable Vaccines

BCG Vaccination

BCG, is a live attenuated mycobacterium bovis that is used in the pediatric group, for the prevention of mycobacterial meningitis and disseminated tuberculosis. Its estimated efficacy is 64% and 78%, respectively. There is a large variation in the BCG's adverse reactions in different geographic regions. The most common complication of the BCG vaccination is, a local non-suppurative lymphadenitis. Infections with varying severity have been reported by BCG vaccine, including bilateral lymphadenitis and disseminated BCG in the distant lymph nodes, bones, livers, and spleen (8). But, the disseminated BCG infection or BCGosis, is a rare adverse reaction to the BCG vaccination, that is reported in some primary immunodeficiency disorders, such as; Severe Combined Immunodeficiency (SCID), chronic granulomatous disease, complete Di George Syndrome (cDGS), the Mendelian Susceptibility to Mycobacterial Disease (MSMD) e.g. INFϒ receptor 1,2 deficiencies, IL12,23 receptor β1 chain deficiency, IL12p40 deficiency, STAT1 deficiency, NEMO deficiency, AIDS(4, 9-11).

The BCG associated-complications, are more prevalent among the SCID patients compared to general population and it is associated with high morbidity and mortality (3, 10-12). Beatriz E. Marciano and collogue showed that the age of BCG vaccination is related to vaccine associated complications. Patients with SCID who receive BCG in the first month of life, have higher rate of complications than those who have been vaccinated after the age of 1 month. Also, they noticed the early BCG vaccination and low T cell number at diagnosis are associated with increased risk of morbidity and mortality. Furthermore, BCG complications in SCID patients may lead to death (4, 10).

Chronic Granulomatous Disease (CGD) is a rare genetic primary immunodeficiency disorder

Table 1. Types of vaccines

Viable vaccines	*Nonviable vaccines*
Adenovirus	Typhoid (inactive)
Influenza (viable)	Tetanus toxin
Measles	Polio (inactive)
Mumps	Rabies
Polio (oral)	Pneumococcus
Rotavirus vaccine	Pertussis (acellular)
Rubella	Meningococcus B
Smallpox	Meningococcus A,C, Y, W-135
Typhoid (oral)	Japanese encephalitis
Varicella/zoster	Influenza (inactive)
Yellow fever	HPV
BCG	HIB
	Hepatitis B
	Hepatitis A
	Diphtheria toxin
	Anthrax

with impaired NADPH oxidase system. The CGD patients are susceptible to mycobacterial infections and catalase positive bacteria. In countries where tuberculosis is endemic and BCG vaccination is performed, mycobacterial infections are more common in CGD patients (13). BCG infections can be seen at high frequency in X-linked and AR forms of Chronic Granulomatous Disease (CGD). Although the first presentation of infections in X-CGD is earlier than AR-CGD, the frequency and onset of BCG infections are similar in both groups (14). In addition to CGD, any immunodeficiency disorder with impaired T cell function and INFϒ pathways (e.g. HIV infection, SCID, and IL12B, IL12RB1, STAT1, IFNGR1, IFNGR2, or CD40/ CD40L deficiencies) should not receive BCG vaccine (4, 13). Administration of some live vaccines such as BCG at birth in some countries, leads to catastrophic out come in the PID patients. So, early screening of PID in neonatal period can prevent the vaccine-associated complications (15). There are several monogenic disorders in INFϒ pathway, which are called Mendelian Susceptibility to Mycobacterial Infections (MSMD). MSMD is a rare PID that is caused by ten genes known to date. Patients with MSMD, are prone to poor mycobacterial infections, such as Attenuated Mycobacterium Bovis (BCG) vaccine, environmental mycobacteria and even mycobacterium tuberculosis. The most common genetic etiology is 12Rβ1 deficiency. These patients may present invasive BCG infections (BCGosis), recurrent severe salmonellosis and candidiasis (16).

Mumps, Measles, Rubella (MMR) and Varicella Vaccines

Serious adverse effects have been reported in patients with cellular immune defect, following the MMR and varicella vaccination. There are no abundant case reports about measles vaccine complications in mild immune-compromises (3, 17). Although the live viral and bacterial vaccines are not advised in T lymphocyte defects, however Perez et al analyzed the adverse effects of MMR and varicella vaccines in patients with mild Di George syndrome. They found that, only 9% of patients have mild complication and none of which was severe. Thus, for reducing the probable risks, the recommendation is, evaluation of T cell number and mitogen responsiveness in the immune compromised hosts, before the administration of varicella and MMR vaccines. Thus patients with ≥500 CD4 cells/ μL, ≥200 CD8 cells/μl, can receive MRR and varicella vaccine (6, 18). The administration of MMR and varicella vaccines in patient with SCID, can cause disseminated vaccine–strain VZV and rubella infection (17). Patients with cellular immune defect such as SCID and Combined Immune Deficiency (CID), have reported disseminated measles vaccine associated infections, and measles inclusion body encephalitis. This means, T cells function is an important factor against the measles vaccine. Primary immune deficiency affecting innate immunity, also can develop measles vaccine infection. In rare cases encephalitis after MMR vaccination and disseminated measles vaccine infection have been reported in AR- STAT1 and STAT2 deficiency. Other innate immune defects with measles vaccine- associated infections are IRF7, IRF9, INFAR1, INFR2 deficiency (18-20).

Patients with minor antibody defects, such as selective IgA deficiency, subclass IgG deficiency, specific polysaccharide antibody deficiency, and Ataxia- telangiectasia, have a mild immune defect that can increase the risk of infections and defective vaccine associated immune responses. However, it has been recommended that the vaccination should be performed same as the schedule for healthy people. Since the complications of varicella and MMR vaccines have not been reported in these patients, we can follow the routine schedule (6, 21). Live attenuated viral vaccines such as MMR and varicella, should not be used in major antibody deficiency. These vaccines do not have any contraindications, and can be used in patients with CGD, congenital neutropenia and cyclic neutropenia (6).

Poliovirus Vaccines

Oral Poliovirus Vaccine (OPV), contains live -attenuated virus. Its replication occurs in gastrointestinal tract and can induce systemic and mucosal antibody. Shortly after the OPV vaccination, the virus replication begins and persists about 2-3 weeks in stool. Several factors are important to virus shedding and replication in people who receive OPV, including maternal

antibody, potency of vaccine, prior immunity and infection with other enteric viruses. Patients with primary antibody deficiency and combined immune deficiency, are susceptible to poliovirus infection and prolonged excretion of the live virus after the OPV vaccination and paralytic disease (22-25).

One study in sir Lanka showed that about 10% of patients affected by primary immune deficiency, have lone time excretion of poliovirus for several months after their vaccination. Furthermore, in developing countries where OPV is used, PID patients may interfere with eradication of poliovirus. Spontaneous mutations can occur in the genome of OPV strains, because its structure is unstable and live excreted polioviruses can revert to wild types, years after the infection (3, 6, 26, 27).

OPV administration in patients with cellular and humoral immune deficiency, have been associated with severe diarrhea and paralysis. So, the inactivated form (IPV) should be administered in these groups (3, 18). During a study that was performed by Mark A. McKinley, from 635 patients with PID who were included in this study, 584 of the patients received OPV at 2 month of age. The most common Primary immune deficiency disorder was CVID followed by agammaglobulinemia, MHC class II deficiency and SCID, respectively. Paralytic disease was seen in 14 patients (1.25% of CVID and 4% of agammaglobulinemia patients), but none of the MHC class II deficiency and SCID had any clinical history of paralytic disorder (25).

SCID and combined immune deficiencies, are prone to Vaccine Associated Poliovirus Paralysis (VAPP) and enteroviral infections. In one study, a third of 107 patients with VAPP, had SCID and CID. AVPP was reported in Patients with MHC II deficiency, Artemis and RAG1 and RAG2 deficiency; although they did not have any genetic diagnosis. In this study, the penetrance of paralysis was incomplete. Furthermore, only a few patients with MHC class II deficiency showed VAPP (18).

X-linked agammaglobulinemia is a humoral immune defect that is caused by BTK mutation. Patients with XLA are susceptible to encapsulated bacterial infections, but generally are not prone to viral infections. XLA patients are vulnerable to severe enteroviral infections, for example; chronic meningoencephalitis due to echovirus and vaccine –associated paralytic poliomyelitis results from OPV. However, the antibody deficiency alone, cannot explain susceptibility to severe enteroviral infections, because enterovirus infection has been reported in XLA patients who have done immunoglobulin replacement therapy. It has been identified; production of INF1, 3 in response to OPV is impaired in monocyte-derived dendritic cells of patients with XLA (28).

Close contacts of the PID patients should not receive OPV, because they may shed the virus and infect the immunocompromised hosts (5).

Influenza Vaccine

The currently seasonal influenza vaccine is categorized into two products: trivalent and quadrivalent influenza vaccine. Trivalent vaccines contain one strain of two subtypes of influenza A virus (A H1N1 and A H3N2) and one of the two co-circulating B virus lineages (B/Victoria or B/Yamagata), but quadrivalent influenza vaccines, contain both influenza A subtypes and influenza B co-circulating lineages (B/yamagata and B/Victoria).

In secondary immune deficiency such as HIV and patients with solid organ transplant, the vaccination was performed with different schedules, with variable out comes. However, there are no comparative studies contributed to PID patients about alternative influenza vaccination protocol. But, the live attenuated influenza vaccine is strongly contraindicated in PID patients. Vaccination with inactivated form, is recommended in household contacts (21, 29). Annual inactivated influenza vaccines are benefitial, and recommended in all PID patients. Some PID patients are unable to produce any response to the vaccine, so maybe, most of the patients don't produce adequate antibody. This has been documented in common variable immune deficiency (3, 26).

Typhoid Vaccine

There are two available typhoid vaccines in the world: A Vi capsular poly saccharide form for parenteral use, and oral live – attenuated vaccine. Both parenteral and oral vaccines are acceptable forms of typhoid vaccine. Indications for the

vaccine administrations are: persons with close contact exposure, travelers to endemic areas, microbiologists and other laboratory workers who are exposed to salmonella cultures.

Ty21a is a live attenuated-vaccine, and is contraindicated in primary immune deficient hosts. But theoretically, Vi vaccine is safe for the immune compromised patients (30). Measurement of the typhi Vi vaccine antibodies, can be a suitable method for the evaluation of polysaccharide antibody response in patients with primary immune deficiency disorders. Since the interpretation is easier than pneumococcal vaccine, post typhi Vi vaccination concentration is significantly lower in PID patients, especially in hypogammaglobulinemia and CVID than control group (31). Healthy immunocompetent people, who live in close contact with immunocompromised patients, can receive live oral typhi vaccine at the time of traveling (21).

Rotavirus Vaccine

Rotavirus is an important cause of gastroenteritis, severe diarrhea and dehydration in infants and young children (32). Rotavirus causes 114 million diarrhea episodes, 600000 deaths and 2.4 million hospitalizations in the world (18). The only method for the prevention of mortality and morbidity of rotavirus gastroenteritis, is vaccination. There are two oral, live attenuated rotavirus vaccines (Rota rix and Rota Teq) in the world (33). Rotavirus vaccines are safe for the HIV infected infants, but administration of vaccine in patients with SCID are contraindicated, as it leads to chronic and severe life-threatening diarrhea and dehydration (21, 34). The evidence shows that the rotavirus vaccines are unsafe in patients with very low T cell number. Although chronic diarrhea is a common manifestation in patients with SCID and antibody deficiency, but wild–type rotavirus gastroenteritis is not a major problem in patients with inborn errors of immunity. Interestingly, only in a few patients with PID, that majority of them had SCID, severe wild-type of rotavirus infection was seen (18). Today, screening of SCID in newborns, can prevent the complications of rotavirus vaccines. Also the academy of American pediatric has recommended that the rotavirus vaccine should be administered at 6-8 weeks of life (3, 5, 35).

Adenovirus Vaccine

Adenovirus is an opportunistic agent in immunocompromised hosts, including; the HIV infection, patients with organ transplantation and congenital immunodeficiency. These patients are susceptible to severe pneumonia and disseminated adenovirus infection (36, 37). In patients with primary immunodeficiency including SCID, severe adenovirus pneumonia and lethal disseminated viral infections are not uncommon. In this setting, fatality rate can reach up to 55%. Adenovirus vaccine is used as live oral enteric coated-tablets, for the prevention and controlling of acute respiratory distress in population with a high risk of exposure. Adenovirus vaccine is also recommended in military populations, who are at risk of adenovirus pneumonia. Administration of this vaccine is not recommended in other populations. Adenovirus vaccine is contraindicated in pregnancy, immunocopromised patients and the people outside the age range of 17- 50 years (36).

Non-Viable Vaccines

Tetanus and Diphtheria Vaccines

DTaP and DT, are purified preparations of diphtheria and tetanus toxoids, accompanied by acellular pertussis that are used at 6 years of age. Adult Td is used for 7 years old children and older.

DPT vaccine might be associated with increased risk of seizure in patients with primary immuno deficiency disorders. But, this warning about DPT vaccine is not included in literatures. Administration of acelluar form of vaccine (DTaP), is an appropriate choice for the PID patients, since there is no association between seizure and the DTaP vaccine (12).

Tetanus and diphtheria toxoids are an important immunogens with high seroconversion rates that can be used for the evaluation of antibody response in the PID patients. Therefore, an initial low level of antibody against tetanus and diphtheria vaccine in fully immunized patients, is a good predictor of primary immune deficiency disorder (3).

Pneumococcal Conjugate and Polysaccharide Vaccines

Ninety serotypes of pneumococcus have

Table 2. Protective levels of vaccines

Vaccine	protective level
Tetanus toxoid	>0.1-0.2 IU/mL (ELISA)
Diphtheria toxoid	>0.1-0.2 IU/mL (ELISA)
Pneumococcal polysaccharide (23-valent) not <2 y	1.3 mg/mL
Meningococcal conjugate (4-valent)	Titer >1:8mg/dl
Vaccine	**protective level**
Pneumococcal conjugate (13-valent)	0.35 mg/mL
HIB	1 mg/mL
HBS antigen	10 mIU/mL

Table 3. Inactivated vaccines in PID patient(7)

	DPT	HBV	Hib	IPV	pneumococcus	meningococcus
CVID, XLA	+*	+*	+*	+*	+*	+*
IgA deficiency	+	+	+	+	+	+
SAD	+	+	+	+	+	+
SCID	-°	-°	+"	-°	+"	+"
CID	+"	+"	+	+"	+	+
MSMD	+"	+"	+"	+"	+"	+"
TLR def	+"	+"	+"	+"	+"	+"
Complement def	+	+	+	+	+	+
Phagocytic defect	+	+	+	+	+	+
IL12/INFY pathway	+"	+"	+"	+"	+"	+"
Complete DGS	-°	-°	+*	-°	+*	+*
Incomplete DGS	+	+	+	+	+	+
Ataxia-telangiectasia	+	+	+	+	+	+
Wiskott-Aldrich	+	+	+	+	+	+
Job syndrome	+	+	+	+	+	+
IPEX syndrome	+	+	+	+	+	+
APECID syndrome	+	+	+	+	+	+

° Not recommended: these vaccines are safe but ineffective.

*may be adminisred when indicated: immune response is impaired and uncertain.

"the respone to these vaccines are likely poor but may be administerd.

been described, with wide geographic variation in prevalence of each type. Twenty-three of the serotypes are the most important types, which can cause illness in humans. Pure pneumococcal poly saccharide vaccines (ppsv) and pneumococcal conjugate vaccines (pcv), contain 23 and 13 serotypes, respectively. The protection level of these vaccines are different, as they stimulate the immune response differently. The protection level of pcv vaccine is 0.35µg/ml, whereas a level of 1.3µg/ml is considered for ppsv **(Table 2)**(3). Therefore, the interpretation of antibody response to ppsv and pcv vaccines may be difficult. To date, there are few studies about antibody response to ppsv and pcv vaccines in the healthy adult population. Because, definition of normal ranges of concentration of ppsv, IgG and normal responses are problematic (38). The US Advisory Committee on Immunization Practices (ACIP), recently advises a routine administration

of PCV13 and PPSV23 in adults of >=65 years (39). An impaired antibody response is an important criterion for the diagnosis of some primary immunodeficiency disorders such as CVID, transient hypogammaglobulinemia of infancy, selective IgA deficiency and selective anti-polysaccharide antibody deficiency. By challenging the patients with capsular polysaccharide pneumococcal antigens in the 23-valent pneumococcal vaccines, we can evaluate the antibody response in the suspected PID patients (40).

Pneumococcal vaccines (PCV and/or ppsv23) especially, are recommended in patients with SCID, CID, CVID, XLA less severe antibody deficiency (IgG sub class deficiency and specific antibody deficiency), less severe impairment of T cell mediated immunity, e.g., partial T cell deficiency (Di George syndrome) and compliment deficiency (26).

Meningococcal, Hib, HBV Vaccines

Meningococcal vaccine contains polysaccharide derived from four strains (ACWY) conjugated to a carrier. Vaccination with tetravalent form of meningococcal vaccines are recommended for microbiologists who are exposed to meningitis-causing bacteria, people traveling to a hyper endemic area, and patients with primary immunodeficiency disorders, for example, Primary complement deficiency (C3,C5-C9, properdin, factor D) (26).

Haemophilus influenza type b (Hib), is one of the most important causes of meningitis, cellulitis, pneumonia, epiglottitis, and arthritis in children. Hib vaccination, is a safe and cost effective strategy for the prevention of infections in children (7, 41, 42). Inactivated vaccines do not cause a significant illness in immunocopromised patients, so Hib vaccine can be administered for the PID patients. Hepatitis B Vaccine (HBV), is an inactivated vaccine and can also be used in PID disorders **(Table 3)**(7, 21).

Conclusion

Vaccination is an important health care measure that protects people against infectious diseases. It seems that immunocompromised patients are highly under vaccinated. Vaccination in PID patients, can improve quality of life and prognosis, and reduce infectious complications. It also could facilitate the diagnosis of primary immunodeficiency diseases. Evaluation of the immune response by specific vaccines could improve the treatment decisions; reduce the complications of disease by early diagnosis and hospitalizations and costs. On the other hand, inappropriate vaccination in patients with PID or other immunocompromised patients, can deteriorate their condition.

Whether to vaccinate or not to vaccinate the, immunocompromised people still is an important question. There is a lack of information about the safety and efficacy of vaccination in PID patients, because of the wide variability of the immune defects among individuals with the same disease.

The decision for the vaccination schedules in patients with PID, should be according to the risk-benefit ratio and clinical and immunological status.

All killed vaccines are safe and can be used in PID patients. But, live vaccines; for example, MMR, BCG, OPV, yellow fever, live influenza, varicella and live typhoid vaccine are contraindicated in severe impairment of immunological function.

Conflict of interest

The author declare that he have no conflicts of interest.

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