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Overview

Vaccinating an Immunocompromised Child

ALENKA GAGRO

Children's Hospital Zagreb
Klaićeva 16, 10000 Zagreb
E-mail: alenka.gagro@gmail.com

Abbreviations:
PID – primary immunodeficiencies
MMR – measles, mumps, and rubella
HSCT – hemopoietic stem cell transplantation
GVHD – graft-versus-host disease
Hib – Hemophilus influenza type B

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Abstract

Any illness associated with possible immune dysfunction during childhood requires a decision on the start and/or continuation of ongoing vaccination program according to national guidelines, as well as the decision on possible booster vaccination and vaccination with additional, registered vaccines. It is widely accepted that if a child with presumed or proven immune disorder might benefit from vaccination, this should not be delayed if its application is safe. Children with immune disorders vary in the degree of immunosuppression, susceptibility to infections and immune reactions after vaccination. Besides these, there are certain groups of children with diseases that increase their risk of infectious diseases even in the absence of specific immune disorders. In this article, we discuss the basic principles that should guide decisions for immunization of children with suspected or proven immune system disorder (primary or secondary).

During childhood, we obtain the largest number of vaccines. Immune disorders resulting from inherited errors of immune system are rare diseases and very heterogeneous in their degree and type of immunosuppression, ranging from mild defects in immune function to severe, life-threatening conditions that usually affect multiple arms of the immune system *(1)*. However, the advances of modern medicine made in treatment of malignant and inflammatory diseases and resulting in improved survival and morbidity rates, increased the proportion of children who have special vaccination needs *(2)*. Regardless of the origin of immune dysfunction, primary or secondary, children vary in the degree of immunosuppression, susceptibility to infections and immune reactions after vaccination. These differences emphasize the necessity of careful examination of all three issues of importance in the vaccination of children: vaccine safety, vaccine efficacy and the potential benefit of particular vaccines in unique medical circumstances of each immunocompromised child *(3)*.

UNDERSTAND YOUR PATIENT'S CONDITION AND PERFORM CAREFUL ASSESSMENT OF RISKS VERSUS BENEFITS

To clarify a given child's immune status, his or her underlying diagnoses need to be considered and the degree of immunosuppression must be determined. There are at least six different groups of conditions and treatments that should be taken into account prior to any decision to vaccinate a child:

1) Primary immunodeficiency
2) Malignant and other diseases treated with chemotherapy and/or hemopoietic stem cell transplantation

3) Solid organ transplantation
4) Inflammatory disease treated with immunosuppressive therapy
5) HIV infection, and
6) Other conditions that increase the risk of infectious diseases even in the absence of specific immune disorders (ie, asplenia/hyposplenism, malnutrition and chronic disease, nephrotic syndrome, children born prematurely, etc).

Primary immunodeficiency

Primary immunodeficiencies (PID) are a heterogeneous group of inherited disorders. Classification of PIDs needs to be constantly updated as novel developments in gene discovery and increased knowledge in the mechanisms that govern immune system development and function help us in the identification of novel PIDs. The most recent classification of PID recommended by the International Union of Immunological Societies Expert Committee on Primary Immunodeficiency recognizes eight groups of these disorders: 1) combined immunodeficiencies, 2) well-defined syndromes with immunodeficiencies, 3) predominantly antibody deficiencies, 4) diseases of immune dysregulation, 5) congenital defects of phagocytic number, function or both, 6) defects in innate immunity, 7) autoinflammatory disorders , and 8) complement deficiencies (for details see 4). Figure 1 shows a simplified algorithm for evaluation of a child with suspected PID based on thorough history as well as clinical presentation. It should be stressed that not all immunodeficiencies are alike and each presents different issues related to the risk and benefits of vaccines. Furthermore, the definitive diagnosis of PID that requires the confirmation of genetic defect if discovered is often not known at the time of immunization. Only rarely is immunity so compromised that active immunization is unsafe, ineffective and/or inappropriate. From the immunization point of view, PIDs can be subdivided into three categories: severe, moderate and non-specific. Some general recommendations regarding the immunization practice in PID patients are shown in Table 1 *(1, 4, 5)*. Live attenuated vaccines are contraindicated for all patients who have combined and T cell mediated disorders. Children with B cell disorders could be immunized against measles, mumps, and rubella (MMR), but immunogenicity of this vaccine is decreased as these children are scheduled to receive immunoglobulin regularly *(5, 6)*. Other live viral vaccines are contraindicated in patients with this disorder, except in immunoglobulin A deficiency. Many experts believe that live-virus vaccines are safe to administer to children who have disorders of phagocyte or complement function.

Taking into account Mandatory Childhood Vaccination Program in Croatia, it should be emphasized that BCG vaccination should be delayed in every newborn with a family history of primary immunodeficiency until the condition has been ruled out (7). Furthermore, if a child with a strong clinical and laboratory suspicion of severe and/or combined PID has been immunized with

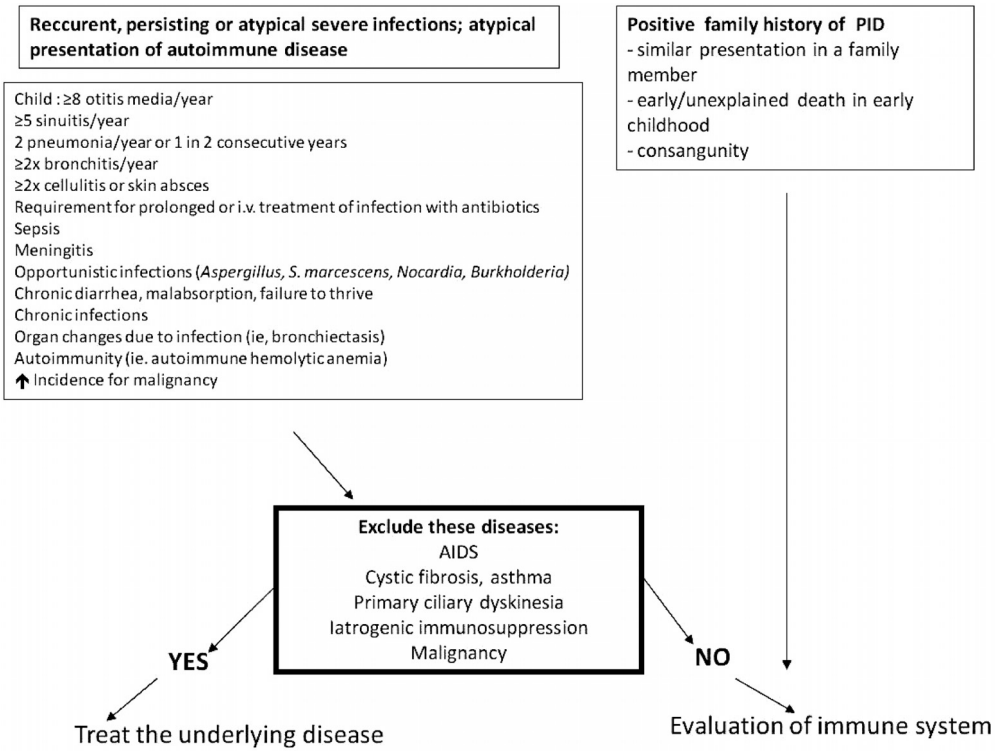

Figure 1. *A simplified algorithm for evaluation of a child with suspected PID based on thorough history, as well as clinical presentation. PID = primary immunodeficiency.*

TABLE 1

General recommendations for immunization in some PIDs based on severity of presentation.

Common presentation of immune disorder	Examples of PID	General recommendations
severe	Severe and other combined immunodeficiencies (ie SCID) Leukocyte adhesion deficiency Hyper IgM syndrome Chronic mucocutaneous candidiasis (APECED syndrome) X linked agammaglobulinemia di George syndrome* Wiskott Aldrich syndrome* Ataxia telangiectasia* Hyper IgE syndrome* Common variable immunodeficiency (CVID)*	1. No live vaccines (including rotavirus vaccine) except for some patients with PIDs indicated by asterisks since its severity is variable 2. those with mild phenotype might be immunized with MMR but it is recommended to monitor specific antibody response after vaccination 3. questionable vaccine response in those on immunoglobulin replacement
Moderate	IgA deficiency Most IgG subclass deficiencies Failure of antibody production to specific vaccines	1. No absolute contraindications for immunization 2. Consider vaccines such as pneumococcal and influenza vaccines
Non-specific	Chronic neutropenia Chronic granulomatous disease (CGD) Complement deficiency diseases Other opsonisation defects	1. BCG vaccine is contraindicated for CGD 2. Other live vaccines seem to be safe 3. Consider vaccines such as pneumococcal and influenza vaccines 4. consider meningococcal vaccine for patients with deficiencies of terminal complement components

* Or equivalent doses of other steroids

BCG vaccine, tuberculous prophylaxis with at least two drugs should be started without delay while awaiting exact diagnosis of immune disorder *(8)*.

Malignant and other diseases treated with chemotherapy and/or hemopoietic stem cell transplantation (HSCT)

The degree and type of impairment of immune system function during and after treatment for malignant and other diseases treated with chemotherapy and/or hemopoietic stem cell transplantation vary considerably among patients. Factors that should be taken into account are the nature of disease, type of treatment and the presence of a functional spleen *(9)*. Regarding children with malignant disease, no live vaccines should be given: 1) to those undergoing chemotherapy, 2) within six months following completion of chemotherapy, and if 3) tumor/disease is not in remission. MMR vaccination should be further postponed if these children received additional therapy such as blood derivates and immunoglobulins (Table 2). A possible exception are children with acute lymphatic leukemia who might be immunized against varicella three months after completion of therapy if they are in remission and have no anti-varicella specific antibodies (two doses of vaccine are recommended), but recently this approach has been questioned regarding its safety *(10, 11)*.

At six months following completion of treatment, it is recommended for most of the children in this group to receive an additional booster of diphtheria (DI), tetanus (TE), and acellular pertussis if they are less than 8 yrs old, or DI-TE pro adultis for those =8 years *(3)*. Other inactivated vaccines should also be given, especially including pneumococcal vaccine and conjugated vaccine against Haemophilus influenza type B (Hib) if children are less than 5 years old or were splenectomized. Subse-

TABLE 2

Recommended postponement of MMR-vaccine in children following treatment with different blood derivates.

Type	Postpone for (in months)
RBC	5
FFP, platelets	7
Hyperimmune tetanus or varicella serum	3–5
Hyperimmune HBV serum	3
Immunoglobulins (depends on dosage)	8–11

HBV – hepatitis B virus

quent routine booster doses (e.g. pre-school) are usually not necessary if they are scheduled to be administered within one year of the additional dose that has been given six months after treatment completion *(3, 9)*.

The degree and kinetics of immune function recovery following HSCT are determined by many factors such as the primary disease, type of conditioning regimen (especially if T cell depletion was performed), graft types (autologous or allogeneic), source of cells (bone marrow, peripheral blood, umbilical cord blood), HLA-compatibility between a donor and a recipient, and the degree of chimerism. Furthermore, most children usually receive immunosuppressive drugs in order to control graft-versus-host disease (GVHD). These factors contribute to weak or even absent immunity in the recipient. Studies indicate that administration of non-live vaccines such as diphtheria and tetanus toxoids to the donor before organ harvest and to the recipient after transplantation can facilitate response to these antigens. The use of non-live vaccines is recommended if the patient is not receiving immunoglobulins. However, the use of live vaccines is potentially dangerous until the child has been off all immunosuppressive treatment for at least 12 months and has no evidence of active chronic GVHD. Some vaccines are not recommended due to the lack of data regarding safety and immunogenicity (i.e. intranasal influenza vaccine, cholera vaccine, oral typhoid vaccine, zoster vaccine, rotavirus vaccine), while some are strictly contraindicated (BCG, oral Polio). The frequency and severity of loss of immunity appear to be lower in children who have received an autologous HSCT. However, it has being shown that these children often become seronegative so they should be considered for a re-immunization program also, usually starting one year post-HSCT. An interested reader will find more details in recently published joint guidelines by the European Group of Blood and Marrow Transplantation (EBMT) and the Centers for Disease Control (CDC), by the Infectious Diseases Society of America (IDSA) and by the American Society for Blood and Marrow Transplantation (ASBMT) published in 2009 (12).

Solid organ transplantation

Children being considered for solid organ transplantation should be up to date with routine primary immunizations or scheduled to receive age-recommended immunizations prior to transplantation if possible *(3)*. Live virus vaccines should be administered at least 4 weeks before organ transplantation to minimize the potential for post-transplant vaccine-related illness. Some experts recommend the evaluation of antibody titers to MMR and varicella to determine if these vaccines are needed before solid organ transplantation. Liver-transplant candidates should be immunized against hepatitis B and possibly hepatitis A because of the more rapid and severe course of infection in comparison to other children *(13)*.

After solid organ transplantation, children receiving chronic immunosuppressive treatment should be given non-live vaccines normally according to the national immunization schedule, but should not receive live vaccines. Most experts recommend waiting at least 6 months after solid organ transplantation for the resumption of immunization schedules, but this should also be evaluated individually *(13, 14)*.

Inflammatory disease treated with immunosuppressive therapy

Patients with many inflammatory diseases, irrespective of their autoimmune or autoinflammatory etiology, are generally considered to be at increased risk of infection due to either the nature of their disease or type of treatment. As in all other immunocompromised children, safety of vaccination is in addition to efficacy of unquestionable importance *(15)*. Whether or not vaccination raises the incidence of autoimmune diseases or presents a risk of coincidental temporal association is still under debate *(16, 17)*. Vaccination should ideally be administered during stable disease. Live-attenuated vaccines should not be administered if patients are on high-dose steroids, disease-modifying drugs or biological drugs. The cut-off values for these drugs are mostly made on consensus and not occurrence of infections *(18, 19)*. The dose and duration of systemic steroid treatment that results in significant immunosuppression are usually considered to include prednisolone (or equivalent doses of other steroids) 2 mg/kg/day or equivalent to a total of at least 20 mg/day for children who weigh more than 10 kg for more than one week, or 1 mg/kg/day for more than one month. These children are often on additional or alternative immunosuppressive drugs, such as azathioprine, cyclosporin A, methotrexate, and biological agents which may further compromise the immune function. Table 3 shows recommendation, based on the currently

TABLE 3

Consensus-based recommendation to withhold live-attenuated vaccines in pediatric patients with inflammatory diseases treated with high dosages of common immunosuppressive drugs.

Drug	Cut-off values of immunosuppressive drugs
Prednisolone*	≥ 2 mg/kg (≥ 20 mg/day if body mass >10 kg) ≥ 2 weeks or 1 mg/kg/day for more than one month
Methotrexate	15 mg/m^2/week
Cyclosporin A	2.5 mg/kg/day
Sulphasalazine	40 mg/kg/day – 2g/day
Azathioprine	1–3 mg/kg
Cyclophosphamide	0.5–2.0 mg/kg/day orally
Leflunomide	0.25–0.5 mg/kg/day
6-mercaptopurine	1.5 mg/kg/day

* Or equivalent doses of other steroids

available evidence and expert opinion recently formulated by an EULAR task force, when to withhold live-attenuated vaccines in pediatric patients with inflammatory diseases if they are treated with high dosages of common immunosuppressive drugs *(19)*. Vaccine schedules should be postponed until corticosteroids have been discontinued for at least 3 months. The safety and efficacy of live-attenuated vaccines administered concurrently with other immunomodulators is unknown and until additional information becomes available, avoidance of live vaccines is generally recommended. This is especially important for BCG in patients receiving anti-TNF drugs as well as in patients with active Kawasaki disease.

Patients treated with methotrexate and/or anti-TNF therapy have an increased risk of severe disseminated primary varicella infection or zoster infections *(10)*. It is important that evaluation of possible candidates for such a treatment include careful history of possible infection in the past. If this history is negative or inconclusive, it is advised to first assess humoral immunity and immunize a child if specific antibodies are negative. The recommended consensus-based guideline is to wait up to 4 weeks before starting treatment with DMARD and/or anti-TNF therapy. If a child acquires varicella, therapy with acyclovir and/or varicella-zoster hyperimmune globulin might be necessary.

Non-live vaccines are generally recommended especially for these groups although some exceptions in terms of their efficacy are well-known.

However, influenza vaccination and pneumococcal vaccination should be strongly considered and it seems that, in comparison to high or prolonged treatment with glucocorticoids, their use in patients treated with DMARDs and TNF-inhibitors, but not rituximab, could be recommended according to available guidelines *(20)*. Routine vaccination should be finished at least two weeks prior to initiation of therapy. Table 4 shows available data regarding safety in patients treated with different immunosuppressive drugs. Vaccination against human papilloma virus seems to be safe in patients with juvenile idiopathic arthritis *(19)*. It is also advised to immunize adolescent girls with stable systemic lupus erythematosus with this vaccine, although a caution is necessary as HPV-vaccine has been linked to increased incidence of venous thromboembolic events *(21)*. A recent study performed in adults 18–35 years old showed that this vaccine is well tolerated and reasonably effective in patients with stable SLE and does not induce an increase in lupus activity or flares *(22)*.

In conclusion, it is recommended to keep to expert consensus guidelines while maintaining strict surveillance and submitting reports of possible side effects following any vaccine administration.

HIV infection

A decision to immunize a HIV-positive child should be based on child's age, numbers of CD4+ T cells and risk for infection *(2, 3)*. It seems that most of the non-live vaccines are efficacious if children are undergoing therapy, have un detectable or low copy HIV number, no lymphopenia and no decreased number of CD4+ T cells. Subunit influenza vaccine seems to be safe even in symptomatic patients although reports of increased HIV viral copies have been described following influenza vaccination. Data from the literature shows that some live-attenuated vaccines such as MRP and VZV are safe if a child has normal number of CD4+ T cells, but BCG vaccine is usually contraindicated *(23)*.

Other conditions that increase the risk of infectious diseases even in the absence of specific immune disorders

Many conditions pose a risk of infection for a child. This is particularly important for children with functional or anatomic asplenia who are at increased risk of invasive infections with encapsulated bacteria such as *Streptococcus pneumonia, Neisseria meningitidis* and Hib. Therefore, these children should be immunized with the Hib-vaccine as well as pneumococcal (depending of child's age 7-heptavalent conjugate pneumococcal vaccine before age 2, or the 23-valent pneumococcal polysaccharide vaccine for older children) and meningococcal vaccine. If

TABLE 4

Safe non-live vaccines in patients with inflammatory diseases undergoing therapy.

Drug	Safety demonstrated for the following vaccines
Glucocorticosteroids[1]	HBV, influenza, pneumococcal
Methotrexate[2]	HBV, influenza, TT*
Anti-TNF-alpha	Influenza, pneumococcal
Rituximab[3]	Influenza, pneumococcal, TT
Tocilizumab (anti-IL-6)	Influenza

[1] studied in children treated with maximum dose of 10 mg/day of prednisolone
[2] < 15 mg/m^2/week
[3] it is highly recomended to immunize a child BEFORE therapy with rituximab; immunization with influenza and TT should be postponed six months after completion of therapy
* TT = tetanus toxoid vaccine

an elective splenectomy is planned, it is important to ensure that the child is up to date with Hib and meningococcal C conjugate vaccinations, and has received pneumococcal vaccination as far in advance as possible *(24)*. Children with chronic disease and malnutrition such as those with cystic fibrosis or children with nephritic syndrome should also receive pneumococcal vaccine, as well as influenza vaccine. Children with the nephrotic syndrome often receive corticosteroids or other immunosuppressive treatment so, for them, similar recommendations as described for children with inflammatory diseases should be applied. Children born prematurely respond appropriately to most immunizations, but there is some evidence that a minority may fail to respond adequately to hepatitis B immunizations if this vaccine is given at birth to infants under 2 kg birth weight *(25)*. Premature infants 6 months of age or older and experiencing chronic lung disease have to be vaccinated against influenza *(24)*.

UNDERSTAND THE VACCINE AND KNOW THE CURRENT VACCINE RECOMMENDATIONS

Understanding immunization principles and strategies for children who are immunocompromised is critically important to maximize protection against preventable diseases. The most up-to-date recommendations on vaccinations in immunocompetent children are easily accessible on several international web-sites such as the web-site of Centers for Disease Control and Prevention. However, this is not the case for all immunocompromised patients. In addition to immunogenicity, recommendations concerning the immunization of immunocompromised children must take into account safety profile, possible effect on the underlying disease and control of infections (Table 5). Most recommendations are consensus based, as controlled studies especially in terms of possible safety profile of particular vaccine, are absent. Many issues regarding possible effect of therapy are also unresolved. For example, it is not known to what extent and which dosage of immunoglobulin supplementation interferes with vaccine immunogenicity *(5)*. This is particularly important for patients with B cell disorders as regular immunoglobulin therapy is the mainstay for prevention of infection in this group of immunocompromized patients. Correlates of immunological response following vaccination, as well as the development of memory cells have not been established for all vaccines and a simple measurement of specific antibodies is not sufficient for evaluation of vaccine efficiency. The necessity to re-immunize children because of waning immunity is also unresolved for many immunocompromised children. A recent introduction of a rotavirus vaccine once again raised the level of awareness regarding safety of vaccines. Postmarketing reports have described severe gastroenteritis with vaccine viral shedding in infants who received rotavirus vaccine and were later diagnosed with severe combined immunodeficiency *(26)*. Timely identification of children with severe types of primary immunodeficiency (e.g., from expanded newborn screening or improved clinical awareness) could prevent unsafe live vaccine administration and many complications linked to vaccine-related illness. As stressed already in this article, it is important to keep to expert consensus guidelines if they exist while maintaining strict surveillance and submitting reports of possible side effects. This is particularly important because of possible changes in national vaccination program as well as emerging results from studies about safety and efficacy of existing and new vaccines.

TABLE 5

Special considerations in immunocompromised children for inactivated (non-live) vaccines (adopted from Nield SL, Troischt MJ. Vaccinating the Immunocompromised Child, 2009. »New Football Recruits.« Northwestern Football. Ed. Alex Shokey. 2004. Northwestern University. 2 Oct 2009 <http://www.pediatricsconsultantlive.com/display/article/1803329/1466353 >)

Type of licenced vaccine	Special considerations in immunocompromised children
Di-Te-aP	Tetanus toxoid less efficient in children with AIDS?
Hib	Recommended for children with asplenia
HAV	Immunize seronegative patients, liver transplant recipients and those with chronic liver disease
HBV	Immunize seronegative patients, liver transplant recipients and those with chronic liver disease
HPV	Children with syndrome WHIM
Influenza	Use subunit vaccine Immunize infants ≥ 6 months of age
iPolio	
Meningococcal	Recommended for children with asplenia and deficiencies of terminal complement components
Pneumococcal	<10 yrs 7vPCV
	≥ 10 yrs 23vPCV

WHIM – warts, hypogammaglobulinemia, myelokathesis; CVID – combined variable immunodeficiency; 7vPCV – 7-valent Pneumococcal Conjugated Vaccine; 23vPCV – 23-valent Pneumococcal Conjugated Vaccine

IMMUNIZE CONTACTS

One strategy worth emphasizing is the protection of immunosuppressed children from vaccine-preventable diseases by immunization of household contacts, particularly other children and adolescents in the family *(27)*. Annual influenza vaccination of all family members with inactivated influenza vaccine is recommended in addition to ensuring routine immunization of all other recommended vaccines. MMR, varicella, and rotavirus vaccines, although live viral vaccines, are recommended for immunocompetent household contacts because transmission of the virus is rare. However, one should bear in mind that house-hold contacts must be properly informed when and how the transmission could take place. For example, varicella virus can be shed through a post-immunization vesicular rash so a contact with an immunocompromised child should be strictly avoided until the rash resolves. For the rotavirus vaccine, an immunocompromised child should at least one week after vaccination not be in in contact with the stool of a vaccinated household contact so that hand hygiene is of utmost importance. Other live-attenuated vaccines, especially BCG, are contraindicated for household contacts *(27)*.

WHENEVER IN DOUBTS, CONSIDER A SUBSPECIALIST

Even if recommendations for a particular group of immunocompromised children are up-to-date, primary care physicians are placed under great pressure when a decision to immunize a child should be made. As we often see in everyday clinical practice, a subspecialist included in the specific treatment of a child as well as other subspecialists are usually consulted in order to define an optimal individual vaccination plan. This approach is welcome in order to determine the child's actual risk of acquiring natural infection and of experiencing complications from a vaccine-preventable infection, as well as the risk associated with vaccine administration. It is necessary to emphasize that a particular child with immune disorder has the benefit of vaccination, so it cannot be delayed or not implemented, provided that its application is safe. Besides the application of existing vaccines, immunocompromised children need vaccines with improved immunogenicity, as well as new vaccines against several microorganisms that cause a disease in immunocompromised host. It is also necessary to introduce better correlates of immunity after vaccination and develop methods for their analysis that are applicable in clinical practice.

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