

# **Timing of vaccination in children after intravenous immunoglobulin therapy for Kawasaki disease**

## *Abstract*

The present study investigates the timing of vaccination in children after intravenous immunoglobulin therapy for Kawasaki disease. The specific type and timing of vaccinations following IVIG usage have been extensively studied both domestically and internationally, but there exist some discrepancies in live attenuated vaccines (LAVs). Based on the analysis of recent research findings both domestic and international, we propose that for Kawasaki disease (KD) children receiving IVIG treatment, the recommended vaccination interval for LAVs. The diagnosis and treatment of KD in foreign countries mostly refer to the Sixth Revision of the Japanese Kawasaki Disease Diagnostic Guidelines, while China follows the Expert Consensus on the Diagnosis and Acute Treatment of Kawasaki Disease. At six months after IVIG therapy, the seroconversion rate for measles, mumps, rubella (MMR), and varicella after the initial vaccination was 88%, 6%, 78%, and 16% respectively, but at 9 months the seroconversion rate were over 90%. Therefore, the recommended vaccination interval for LAVs (MMR vaccine, MMR varicella, and varicella vaccine) should be 9 months in KD children.

*Keywords:* immune-assessed serum, Kawasaki disease, vaccination,

clinical practice.

### ***Introduction***

Kawasaki disease (KD) is a systemic vasculitis that primarily affects children under the age of 5. The etiology remains unknown, and potential triggering factors may be associated with infection and immune response. It is widely recognized that the administration of intravenous immunoglobulin (IVIG) in KD has a temporal correlation with vaccination using various types of vaccines. Vaccination is primarily linked to IVIG containing pathogen-preventing antibodies, as well as the dosage and half-life of IVIG. The specific type and timing of vaccinations following IVIG usage have been extensively studied both domestically and internationally, but there exist some discrepancies. Based on the analysis of recent research findings both domestic and international, we propose that for KD children receiving IVIG treatment, the recommended vaccination interval for LAVs (MMR vaccine, MMR varicella, and varicella vaccine) should be 9 months. Inactivated vaccines (IV) and oral live vaccines can be administered at any time before or after IVIG treatment, which will provide valuable guidance for clinical practice.

KD also known as mucocutaneous lymph node syndrome, is a vascular inflammatory disease that seriously affects children's health. It often occurs in children under 5 years old, and it is prone to common

complications such as coronary artery damage, liver function and coagulation function damage. Severe complications such as macrophage activation syndrome and Kawasaki shock syndrome can also be seen, and the incidence is increasing year by year<sup>[1-2]</sup>. Some children may be complicated by giant coronary artery aneurysm or coronary artery thrombosis and extend to adults, causing angina or myocardial infarction, so active treatment is needed. The first-line treatment of KD is IVIG combined with aspirin, which has a significant clinical effect, and the incidence of coronary artery damage can be reduced from 25% to 5%<sup>[3]</sup>.

Currently, there are numerous reports available regarding the types and timing of vaccination in children with KD following IVIG treatment. It is recommended to administer inactivated vaccines, oral vaccines such as oral rotavirus vaccine and oral typhoid vaccine, live intranasal vaccine, BCG vaccine, and yellow fever vaccine at any time before or after treatment. However, there is still no consensus on the optimal immunization interval for LAVs like MMR or Measles, mumps, rubella and varicella vaccine (MMRV), as well as Varicella vaccine (V) . Reported intervals range from 3 months to 12 months both domestically and internationally which can cause confusion in clinical practice. Based on recent advancements in understanding KD pathogenesis, treatment approaches, and latest research findings, it is expected that a reliable time interval for administering LAVs and inactivated vaccines (IVs) after IVIG

treatment will be proposed to address this issue.

### **1. Pathogenesis and first-line treatment of KD**

The etiology of KD remains unclear, however recent studies have revealed that certain small RNAs may play an essential role in the central pathogenesis of KD through differential expression and other mechanisms, including immune regulation, inflammatory response modulation, and vascular dysfunction<sup>[4]</sup>.

The diagnosis and treatment of KD in foreign countries mostly refer to the Sixth Revision of the Japanese Kawasaki Disease Diagnostic Guidelines, while China follows the Expert Consensus on the Diagnosis and Acute Treatment of Kawasaki Disease<sup>[5]</sup> (referred to as the Consensus). According to the Consensus, IVIG is considered as the primary treatment for children with KD during the acute phase. The recommended dose is 2g/kg·d with an intravenous infusion time of 10-12 hours. For children with a higher body weight, a dose of 1g/kg · d should be administered over a period of two days<sup>[6]</sup>. The mechanism behind IVIG's effectiveness in treating KD involves various factors. It is generally believed that IVIG can inhibit immune complexes-induced antigen-specific CD4+T cell response, leading to a reduction in antigen-specific T cells count. However, this process does not directly inhibit or stimulate CD4 + T cell function or decrease total molecules CD80 / CD86 expression in APCs. Instead, it reduces immune complex

binding by decreasing Fc gamma R expression on APC surfaces<sup>[7]</sup>.IVIG has a generalized anti-inflammatory effect including the enhancement of regulatory T cell activity (transforming growth factor), neutralization of bacterial super-antigens or other unknown pathogenic agents, regulation of cytokine production, suppression of antibody synthesis and inflammatory markers, nitric oxide, and inducible nitric oxide synthase expression),the provision of antiidiotypic antibodies, the Fc-gamma receptor and balancing the T helper (Th) Th1/Th2 immune responses<sup>[8]</sup>.

## **2. The current status and correlation of vaccine administration after IVIG treatment for KD**

### **2.1 Current vaccination status after IVIG treatment for KD**

Vaccination is a crucial method for establishing artificial immunity, as it can passively provide antibodies that inhibit the active immune response, effectively preventing the occurrence of diseases. This approach is considered the most cost-effective means to control and potentially eliminate diseases<sup>[9]</sup>. KD triggers may be widely distributed in the human body, leading to an attack on the immune response. After IVIG treatment, KD may inhibit neutrophils, mononuclear macrophages, NK cells, and other nonspecific immune cell activation and secretion. It also regulates inflammatory mediators to reduce autoantibody production by modulating B cell responses. Additionally, it plays a pharmacological role by inhibiting Th1 and Th17 cells while enhancing Treg cells and

suppressing vascular endothelial cell activation <sup>[10]</sup>. The administration of high doses of IVIG significantly impacts LAV vaccination not only due to IVIG half-life but also to the dosage used. Therefore, children with KD who receive IVIG treatment should have a reasonable time interval before receiving attenuated vaccines. However, different countries have varying recommendations regarding the delay in vaccination for children with KD after IVIG treatment. For instance, Japan recommends a 6-7 month interval between measles vaccination and 2 g/kg IVIG treatment for KD children; whereas for those treated with 4g/kg IVIG, an interval no longer than 11 months is recommended (with 9 months being appropriate). If there is an imminent risk of measles exposure, it is suggested that the time interval can be appropriately shortened since direct access to antibodies may not completely prevent infection <sup>[11]</sup>. The American Academy of Pediatrics recommends that children with KD who receive 2g/kg IVIG should be administered the measles vaccine at least 11 months after treatment. However, there are no specific guidelines regarding the timing of measles vaccination for children receiving 4g/kg IVIG. Some scholars speculate on the appropriate timing for measles vaccination in children treated with 2g/kg IVIG. For those receiving 4g/kg IVIG, the recommended interval for measles vaccination should be extended accordingly, although a specific timeframe has not been established. In regions where measles has been eliminated, such as the

United States, vaccination can be delayed; however, countries experiencing frequent outbreaks require earlier immunization. European guidelines recommend a 6 months interval due to endemicity of measles in this region. Conversely, Japanese guidelines suggest that KD patients vaccinated with LAV within 6 months after IVIG treatment require a booster dose <sup>[12]</sup>.

## **2.2 Vaccination mechanism and its correlation with KD**

### **2.2.1 The measles vaccine**

Measles vaccine is LAV, and both humoral and cellular immunity are involved in the response after vaccination. B cells on the surface of the BCR to specific recognition, activate the B cell signal, leading to B cell activation, proliferation and differentiation, a measles specificity immune globulin IgM antibody in the blood, whereas IgA antibodies in the mucous secretions, IgG antibody can persist for many years in the blood, Measles vaccination can also induce the production of measles virus-specific CD4<sup>+</sup> and CD8<sup>+</sup>T lymphocytes. Studies have shown that the dominant T cells of measles vaccinated children are CD4<sup>+</sup>T cells, and the CD45RA<sup>+</sup> naive T cells are as high as 70%-80%, and the CD4<sup>+</sup> memory T cells are as high as 28%-29% <sup>[13]</sup>. Measles vaccination can induce the differentiation of measles-specific CD4<sup>+</sup> and CD8<sup>+</sup>T lymphocytes, while the stimulation of measles vaccination can significantly activate Th1 cells, and there is still a high protective

antibody level in the long term after measles vaccination <sup>[14]</sup>. High-dose IVIG can inhibit the immune response of KD children, inhibit the activation of non-specific immune cells, and reduce the secretion of inflammatory mediators <sup>[15]</sup>. Moreover, it can regulate the response of B cells and inhibits the activation and proliferation of B cells <sup>[16]</sup>. Therefore, the KD children treated with high dose IVIG should be vaccinated with measles vaccine at a certain interval, otherwise there may be no immune response after measles vaccination, and it cannot prevent measles virus.

### **2.2.2 Mumps and rubella vaccine**

The vaccines commonly used in our country currently contain components for measles, rubella, and mumps, Measles and rubella combined attenuated live vaccine (MR), MMR, Mumps attenuated live vaccine (MuV) for the prevention of measles, rubella and/or mumps. The MMR vaccine strains are different in different countries. At present, measles vaccine strain Shanghai-191, MuV strain S79 and rubella vaccine strain BRD-II are used in China <sup>[17]</sup>.

Recent studies have shown that compared with the measles and rubella, mumps memory B cells frequency lower affinity mature mumps IgG index is 40-60%, lower than the average measles IgG affinity index 80%. In the United States, mumps vaccine was introduced in 1967 and recommended for routine use in 1977. MMR was first used in the United States in 1971. For the first time after the MMR vaccine and second

MMR vaccine, mumps antibody protective effect were 78% (49-91%) and 88% (66-95%), make the mumps vaccine effect is the worst of trivalent MMR vaccine. Immunization coverage rate is estimated at 79-100%, and is considered to be the necessary condition to herd immunity. Despite a sharp decline in mumps cases in the United States with coverage > 90% for both doses, mumps has made a comeback in the United States and in the other two countries with high dose coverage. Decreased humoral immunity and antigenic variation in circulating wild-type fungal strains may play a role in susceptibility and are thought to contribute to mumps recurrence <sup>[18]</sup>.

The first attenuated rubella vaccine was developed by Parkman and Meyer in 1966; In 1969, HPV77.DE5 and Cendehill vaccine strains were licensed in the United States <sup>[19]</sup>. Currently, rubella vaccine is a live virus preparation (strain RA 27/3) grown in human diploid cell culture, which is immunogenic in 98% of recipients and provides lifelong immunity to more than 90% of recipients <sup>[20]</sup>.

### **2.2.3 Varicella vaccine**

Varicella vaccine is also LAV, the most widely used strain for vaccine production is Oka strain, which was isolated by Dr. Riaki Takahashi in 1971. Imported varicella attenuated live vaccine (VarV) was marketed in China in 1997. After 2000, a number of domestic VarV were marketed in China, using Oka strain consistent with foreign VarV.

Immunization with live attenuated varicella vaccine alone and/or in combination with MMR can provide effective protection against varicella [21-22]. Live varicella vaccines were prepared from attenuated varicella strains, which reduced the pathogenicity but still had the ability to induce immune responses. The safety and efficacy of varicella vaccine have been widely recognized at domestic and international [23]. Most patients can obtain protective antibodies through vaccination, thereby reducing the incidence of the disease and relieving the clinical symptoms of infected patients. Currently, it is widely acknowledged that the preventive mechanism of varicella vaccine involves the induction of humoral immune response, leading to the production of protective antibodies. Following vaccination, the body develops immunological memory cells specific to the virus, enabling rapid recognition and targeted elimination upon subsequent viral invasion, thereby effectively combating viral infection. In addition, varicella vaccination can also produce herd immunity, improve herd immunity, form an immune barrier, and prevent the outbreak of varicella. That is, by improving the immunity level of the whole population, it can protect the unvaccinated or uninfected people, and thus effectively control the outbreak of varicella [24]. High dose IVIG has pharmacological effects of inhibiting immune response and inhibiting the activation of vascular endothelial cells. Studies have shown that early immunization with varicella vaccine can suppress serological responses

in KD children treated with high dose IVIG. It is recommended that KD patients receive two vaccinations, especially varicella and mumps vaccines, within 6 months after IVIG treatment. If it is not feasible to administer multiple doses of the vaccine within the immunization program, a post-vaccination blood test can be conducted. In case of a negative result, booster vaccination should be administered <sup>[12]</sup>. The seroconversion rate for varicella after the initial vaccination was 16%, the seroconversion rate after a booster vaccination was 77% for varicella <sup>[12]</sup>.

### **2.3 KD occurred after vaccination**

Miron et al. reported the first case of KD after vaccination in 2003, and Nataliya et al. reported that a 3-year-old boy was diagnosed with KD after vaccination with polio vaccine in 2020<sup>[25-26]</sup>. Subsequently, many countries have reported that children with KD after vaccination. In recent years, our country also has occurred after vaccination cases of KD. Although KD occurs after vaccination, there is still a lack of sufficient evidence to confirm that the vaccine causes KD. Due to the obvious abnormal immune regulation in the acute phase of KD, and the vaccination itself also induces the body's autoimmune response, and the KD high-risk population is precisely in the age group with the most concentrated vaccination programs in various countries, the relationship between vaccine and the occurrence of KD has become a hot topic of clinical attention in recent years. For patients with KD, it is recommended

to assess the antibody titers of relevant vaccines within a specific timeframe following high-dose IVIG treatment. If necessary, administration of booster vaccinations should be considered <sup>[10]</sup>.

### **3.Current status of vaccination after IVIG treatment of KD in China**

Studies have found that domestic IVIG in the treatment of KD can produce inhibition of nonspecific immune cell activation and secretion of inflammatory mediators, adjust B cell response while reducing autoantibodies, affect the T cells subgroup and restrain the pharmacological effects of vascular endothelial cell activation<sup>[27]</sup>. Matysiak-Klose D et al. pointed out that the level of measles virus-specific immune antibodies in the population has decreased since the global adoption of standard active immunization of measles and the corresponding reduction of virus circulation <sup>[28]</sup>. In 1994, the American Academy of Pediatrics recommended that after receiving high-dose IVIG (2g/kg), the interval between vaccination of MMR, MMRV and V vaccines should be delayed for 11 months. At present, Chinese expert consensus continues this view and recommends that the interval between vaccination of KD with high-dose IVIG should be 8 months to 11 months<sup>[2]</sup>.

2014 Shanghai immune abnormalities children vaccine expert consensus, points out that IVIG can inhibit the measles and rubella

vaccine immune response for 3 months or more, of mumps and varicella vaccine immune response inhibition is still unclear. IVIG use does not affect oral Ty21a typhoid vaccine, yellow fever vaccine, attenuated influenza vaccine, herpes zoster and rotavirus vaccine inoculation, when gamma globulin use a dose of 2 g/kg, 11 months, chicken pox, measles vaccine recommended. According to the 2019 expert consensus on vaccination of children with special health status, intravenous IVIG can be used to vaccinate other vaccines except measles-containing vaccines, and it is recommended to delay the vaccination of measles-containing vaccines until 8-9 months after receiving high-dose (2g/kg) IVIG. In 2020, the Pediatrician Branch of Guangdong Medical Doctor Association pointed out that the immune response to live parenteral viral vaccines (such as live attenuated Japanese encephalitis vaccine, live attenuated hepatitis A vaccine, live vaccine containing measles and varicella) may be inhibited, and the interval between the administration of live attenuated parenteral vaccine and IVIG is still 3-11 months. The administration of oral live vaccines, such as poliovirus vaccine and rotavirus vaccine, remains unaffected. However, when IVIG is used for KD treatment at a dosage of 1600-2000mg/kg, it is recommended to observe an interval of 11 months before administering attenuated live vaccines via the gastrointestinal route <sup>[29]</sup>.

#### **4.Impact of antibody titer on vaccination efficacy after IVIG**

## **treatment in Kawasaki disease**

Prospective studies have shown that patients with KD do not respond well to vaccination after 6 months of IVIG treatment. The administration of LAV in KD patients 6 months after IVIG treatment resulted in seroconversion in 88%, 6%, 78%, and 16% of patients with measles, mumps, rubella, and varicella, respectively. Booster vaccination after 12 months resulted in serologic responses in all patients with measles and rubella, 97% of those with mumps, and 77% of those with varicella <sup>[11-12]</sup>.

The present study is the first survey of antibody concentration change and children of all four vaccine immune response. Like previous studies, the rubella vaccine immune response is relatively strong; However, this study found that response to measles vaccine was stronger than previous studies, the less response to the mumps vaccine <sup>[30-31]</sup>. This difference may be influenced by the amount of specific antibody contained in IVIG or the method used to measure the antibody titer or the vaccine strain. IVIG were acquired from blood donors and their immune features may affect the results. Studies have found that varicella vaccine is considered as affected by IVIG and the MMR vaccine. Seroconversion rates for measles, mumps and rubella increased to 86%, 71% and 95%, respectively, after booster vaccination among non-responders to primary vaccination. In the present and previous studies, seroconversion was

observed in almost all patients vaccinated with the MMR booster vaccine and in almost 80% of patients vaccinated with the varicella booster vaccine. 12 months after IVIG treatment to strengthen the vaccination is effective, because the residual antibody is eliminated, strengthen the vaccination is effective or both <sup>[12]</sup>.

In KD patients received IVIG treatment for 6 months, the residual antibodies for measles and chickenpox were found to be 9% and 6%, respectively, while mumps and rubella were negative in all patients. In KD patients treated with an average dose of 1.3 g/kg of IVIG, the antibodies turned negative after 6-7 months <sup>[11]</sup>. Similarly, in patients treated with two doses of 2g/kg of IVIG (totaling 4 g/kg), the antibodies became negative after 9 months. The dose of IVIG in the current study was 2g /kg, but the HI titer results for measles were similar. It showed that in 6 months after IVIG treatment the existence of residual antibodies may affect the effectiveness of the LAV. The timing of vaccination depends on the vaccination schedule in each country. In the United States and Japan, LAV is targeted at young children over the age of 1, but in many countries, LAV was conducted in 9 months old, our country MMR vaccination for eight months. In areas where measles virus has been eradicated, such as the United States, the risk of contracting the disease is low and vaccination can be delayed, whereas in countries with frequent outbreaks, earlier vaccination is required. After initial vaccination,

enzyme-linked immune-assessed serum response rates for measles and rubella were 88% and 78%, respectively, but vaccination may be considered 6 months after IVIG treatment in areas with frequent epidemics. The effectiveness of MMR vaccination in children with KD who received high doses of IVIG was analyzed in a retrospective study conducted by Tacke. Among the 92 patients vaccinated before IVIG, similar rates of protective antibodies against MMR were observed compared to healthy controls. In cases where vaccination occurred 6-9 months after IVIG treatment, the proportions of obtained protective antibodies were found to be 35%, 70%, and 100% respectively. However, for cases inoculated after more than 9 months, the proportions of obtained protective antibodies were determined as 90%, 90%, and 95% respectively. Based on these findings, it is suggested by researchers that MMR vaccination should be delayed until at least 9 months after IVIG treatment<sup>[31-32]</sup>. If early vaccination, the serological assessment should be from now on, so that the reaction of the subjects to vaccination. Vaccination of children for many times, even for vaccination for the first time in six months, can also get immunity by vaccination again<sup>[11]</sup>. Recent studies have shown that specific measles antibodies can be maintained in the blood for 9 months after IVIG 2g/kg treatment<sup>[29]</sup>.

## **5. Conclusion**

In conclusion, children with KD can be effectively prevented from

the formation of coronary aneurysms after treatment with high-dose IVIG, a therapeutic preparation containing pooled antibodies from plasma of different blood donors. One study analyzed 38 batches of IVIG preparation, all containing antigens of tetanus, diphtheria, chickenpox, and measles <sup>[33]</sup>. So the IVIG treatment of children with KD in LAV is should be a certain amount of time intervals, and the interval of vaccination time is too short may reduce the effectiveness of the vaccine, but the interval time is too long may increase the risk of infection <sup>[10]</sup>. Children and the safety of the society, therefore, in order to determine appropriate vaccination timing is crucial. Comprehensive research at home and abroad, we believe that the interval of 9 months vaccination LAV is reasonable; IV and oral live vaccine in IVIG-treated any time before and after treatment can be vaccinated. At the same time, our team suggests that the national database of KD children treated with IVIG should be improved, and the vaccination time of live attenuated vaccine should be calculated according to the frequency, dose, and duration of IVIG treatment, so as to guide the scientific vaccination of KD children. This way of unified, standardized management, not only can reduce the vaccine caused by careless families of children with delay or ahead of time, provide data for clinical and scientific research better.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as

Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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