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Application Performance of Mumps Vaccine in Mumps

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Abstract. Mumps a highly contagious disease, and it is caused by mumps virus. This research analyzed analyzes the research progress of mumps vaccine, and discussed the main problems faced by mumps vaccine. The live attenuated mumps vaccine has been used in most countries and regions for nearly 50 years since its introduction. Although mumps vaccination was able to greatly reduce the incidence of mumps in the past, in recent years there are many cases of mumps around the world, indicating a tendency for mumps disease to recrect. The reason is prolonged use of the mumps vaccine has led to some problems. The main problem is the vaccine is not effective enough, and the immune effect become weaker with time. Because mumps is highly contagious and can cause many very serious sequelae, so it is important to prevent mumps disease. The most useful way to control mumps disease is still mumps vaccine. Changing the injection schedule, increasing the number of injections, and designing new vaccines with other genotypes mumps virus as vaccine strains may solve the main problem faced by the current mumps vaccine.

Keywords: Mumps; Mumps vaccine; Application.

1. Introduction

Mumps is a highly infectious disease, which can spread via direct contact or droplet. The mumps virus usually lies dormant for two to three weeks after it enters the body. It is possible to get mumps all around year in tropical climates, but mumps incidence is concentrated in temperate climate in winter and spring [1]. The main symptom of mumps infection is swelling with pain of one or both cheeks. A variety of other inflammatory responses, such as meningitis, orchitis, encephalitis, may be also caused by mumps disease [2]. Most patients with mumps recover spontaneously within a few weeks after the onset of symptoms, but some patients may leave epilepsy, deafness, paralysis and other sequelae [3]. The first description of mumps disease appeared in *Epidemics* which is written by Hippocrates in the fifth century BC. Johnson and Goodpasture find mumps virus (MuV) cause mumps disease via experiment in the 1930s [4]. MuV belongs to the paramyxovirus family, and it is an enveloped virus with unsegmented RNA molecule inside. MuV contain nucleocapsid (NC) protein, fusion (F) protein, haemagglutinin-neuraminidase (HN) protein, phosphoprotein (P protein), small hydrophobic (SH) protein, large (L) protein, and matrix (M) protein. NC protein wrap RNA molecule to form virus core. HN protein and F protein are membrane protein, they play a role in MuV infects host cell. HN protein fix MuV to the surface of host cell by combining with sialic acid on the cell surface, and then HN protein and F protein fuse the cell membrane with the MuV membrane to infect host cell by passing virus core into cell. P protein and L protein combine together to form RNA polymerase to replicate the genetic information of MuV in infected cell. M protein is structure protein which plays a key role in virus budding process. SH protein plays a key role in in evading the host's antiviral activity [3].

For MuV, the natural host is only human [1]. Antibodies are produced by immune system in response to MuV stimulation to protect the body after MuV enter body. Antibodies combine with proteins of MuV surface, and bring MuV into macrophage which can eliminate MuV. Immune system mainly produces two kinds of antibody, including IgG and IgM. IgG antibodies are rapidly produced to a high titer after infection and persist for at least 3 months, during which time there is no change in titer. IgM antibodies were also rapidly produced, with a titer slightly lower than that of IgG antibodies, and decreased slowly with time, vanishing almost completely after 50 days of infection [5], which means

that IgG plays a key role in the whole process of against MuV and IgM only works at early period. In order to against mumps disease, the first mumps inactivated vaccine was developed in 1951 [6], but this vaccine cannot prevent mumps disease perfectly because it only provides short-term immune protection and low protective efficacy [1]. In 1963, Maurice Hillerman used the Jeryl Lynn (JL) strain to develop an attenuated mumps vaccine, which was grown in chicken embryo cells. Attenuated vaccine has used around the world after this. Jeryl Lynn strain which approved by American government in 1967 extracted from a female who has infected mumps disease, and named after her. Except Jeryl Lynn strain, other countries and areas in the world also developed mumps attenuated vaccine by other vaccine strain, such as Rubini strain and Urabe strain. Urabe strain and JL strain are used as vaccine strains in the vast majority of current MuV vaccines [7].

Originally, mumps vaccine was produced and used as a monovalent vaccine, and then mumps vaccine was proved it could safely use with measles vaccine and rubella vaccine [8]. Thus, trivalent measles-mumps-rubella (MMR) vaccine was developed, and mumps vaccine was produced and used as a component of MMR vaccine. Until now, more than 120 countries and areas in the world use MMR vaccine [7]. Anders Hviid claims live attenuated mumps vaccine is present in all currently available mumps vaccines [6], which means all vaccine can prevent mumps disease in the world is attenuated vaccine. Compare with mumps inactivated vaccine, mumps attenuated vaccine can provide long-term immune protection and strong protective efficacy. A study of children vaccinated mumps attenuated vaccine in Finland shows that serum conversion rate of one dose of vaccine is 86%, two does is 95%, and attenuated vaccine could provide immune protection at least 9 years [9]. This research will discuss the specific application performance and existing problems of mumps vaccine, providing a design approach for the future development of new vaccines.

2. Mumps vaccine application

The existing research has determined the appropriate age for the second MMR vaccination by investigating the mumps immunity status of children aged 2-5 years after the first MMR vaccination in Jiangsu Province, China [10]. Although MMR vaccination can reduce the incidence of mumps, recently, many studies have shown that there are many factors that contribute to the poor control of mumps incidence with only one MMR vaccination. In China, children aged 1.5 to 2 years are only vaccinated once with MMR vaccine, and the infection rate of mumps in children has increased significantly since 2010. Therefore, in order to reduce the infection rate of mumps, a second MMR vaccination schedule is necessary. Multi-stage stratified cluster sampling method was used to select and collect serum samples from 4033 children in Jiangsu province in 2015. The blood samples were collected from 2 to 5 years old healthy children with at least one MMR vaccination in different regions of Jiangsu Province. Enzyme-linked immunosorbent assay (ELISA) was used to detect the concentration of MuV IgG antibody in serum samples. Subsequently, concentrations ≥108mIU/ml were considered positive, concentrations <90mIU/ml and negative. The incidence data from the National Notifiable Disease Reporting System (NNDRS) were used to analyze the data with 95% confidence interval (CI). Children have a high incidence of mumps and the incidence increased with age.

The total seropositive rate of mumps antibody among 4033 children in this study was 79.0%. The seroprevalence of mumps antibody in children varied significantly by gender, region, age and vaccination history: children in the southern region has higher seroprevalence than in the northern and central regions, 4-year-olds children has higher seroprevalence than 2-and 3-year-olds children, girls have higher seroprevalence than boys, and children who received two doses of MMR vaccine has higher seroprevalence than single dose. One MMR vaccination could not provide good immune protection, and children aged 2 to 5 years were still at high risk of mumps infection, as shown in Figure 1. Two-dose MMR vaccine is necessary [10].

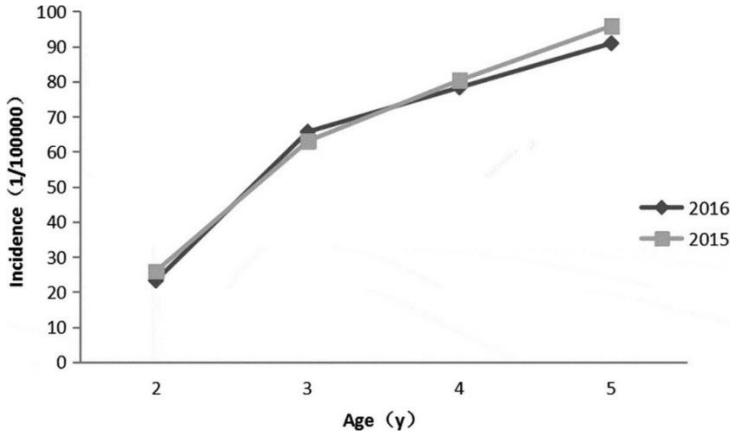

Figure 1. Incidence rate of mumps in children aged 2-5 years [10]

The relationship between the third MMR vaccination and immunity to mumps disease was also investigated [11]. Reduced vaccine efficacy is considered to be an important reason of why vaccinated young people still develop mumps. Therefore, the authors investigated the IgG antibody response and neutralizing antibody responses of JL vaccine strain which is A genotype virus, and the wild-type outbreak strain, MuVi/Utrecht.NLD/40.10, which is G genotype virus. The authors recruited 150 healthy young adults aged 18 to 25 years who had received two MMR vaccines and was not infected by MuV between October 2016 and April 2017. They were given third MMR vaccination which containing the JL mumps virus strain. Blood samples were collected before vaccination, one month and one year after vaccination, and tested these samples. IgG antibody levels were measured with the use of a fluorescent bead-based multiplex immunoassay. Neutralizing antibody titers were subsequently determined by focal reduction neutralization assay (FRNT). The authors used antibody levels in the outbreak population, obtained from 745 students affected by a mumps outbreak at the university between 2009 and 2012, to predict the antibody cutoff for protection against MuV infection. One month after the third MMR vaccination, the neutralizing antibody titers of MMR vaccine strain and outbreak strain were 1.65 times, 1.34 times and 1.35 times higher than those before vaccination, respectively. One year after vaccination, antibody levels were still higher than baseline but had declined. The successive third doses of MMR vaccine can boost immunity against mumps disease in young adults and provide longer duration of immune protection against mumps disease. [11]

In addition, the reported work studied mumps cases identified in Canada from 2002 to 2020 and explored the genotypes of MuV causing these cases [12]. Although routine mumps vaccination has been in place in Canada for decades, mumps cases and outbreaks still occur periodically. The authors therefore hoped that by testing for mumps to determine the cause of the infection, the efficacy of the vaccine would be better explored. The authors analyzed a total of 7395 cases of mumps identified in Canada from 2002 to 2007. Case data were obtained from the Canadian Notifiable Disease Surveillance System (CNDSS). They also derived the incidence of mumps using Canadian population estimates from Statistics Canada, stratified by age, sex, and time period. The groups were then statistically compared within 95% confidence intervals. Women were statistically less likely to develop mumps than men, people aged 60 years and older had the lowest risk but the highest hospitalization rate, adolescents and young adults aged 15 to 29 had the highest risk but the lowest hospitalization rate, and the risk of mumps was lower with two vaccine doses than with one dose. A total of 3378 cases contributed viral specimens, all from the Laboratory Information and Data System (LIMS) of the National Microbiology Laboratory (NML) of the Public Health Agency of Canada. All specimens were genotyped by RT-PCR and Sanger sequencing. A total of 3095 viruses belonged to the G sequence, and 38% of the other genotypes were associated with travel, but only 1.3% of the cases with the G genotype had a travel history. The MuV of genotype G is the endemic virus in Canada. It is not a lack of immunization that causes regular mumps cases and outbreaks, but rather a potential immunogenic mismatch between the vaccine strain of genotype A and the virus strain of

genotype G. This mismatch can be exacerbated by waning immunity and increasing exposure intensity [12].

The immunogenicity and longevity of a vaccine designed based on G genotype MuV was explored. Although the occurrence of mumps cases reduced a lot since MMR vaccination strategy is used, outbreaks still occur, especially in recent years many mumps cases are reported. The reason is that the MMR vaccine contains the JL strain, an A genotype virus. Although A genotype viruses were widespread in the past, currently the most common strain types are genotype G, such as IA/06. Here, the authors describe a new vaccine and explore its immune activity and longevity, as well as its neutralizing effect against G-genotype viruses. The NP, P and L gene fragments of IA/06 strain were inserted into pCAGGS plasmid by gene cloning technology, and then the RNA of JL strain is used as a template to produce recombinant JL virus (rJL): rJL(ΔSH, IA-F), rJL(ΔSH, IA-HN), and rJL(ΔSH, IA-F/HN) viruses. These recombinant viruses were then used to infect cells to obtain a large number of recombinant virus samples, which were detected by RT-RNA technology. Mice were infected with these recombinant viruses by intranasal immunization to test the immunogenicity and longevity of the recombinant viruses against genotype A and G viruses. The results showed that the immunity elicited by JL virus had a lower neutralizing titer against the G genotype virus. IA virus elicited immunity with higher neutralizing titers against the G genotype. The neutralization titer of rJL (ΔSH, IA-HN) virus was significantly lower than that of other viruses. The immunity elicited by rJL (ΔSH, IA-F/HN) had the highest neutralizing titer against the G genotype. ELISA was used to detect the antibodies against the A and G genotype antigens in the serum of mice in each group on days 56 and 364 after inoculation, and the neutralizing ability of antibodies against the A and G genotype viruses was also detected.

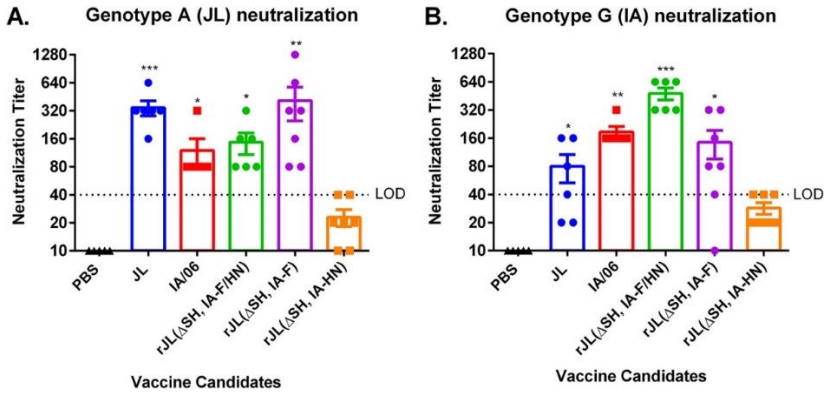

Figure 2. Neutralizing titers in mice immunized with vaccine candidates [13]. Reduction of plaque neutralizing titers for genotype A (JL) virus (A) and genotype G (IA) virus (B)

The total amount of antibody did not decrease within 1 year. JL virus showed a significant increase in neutralizing titer against genotype A. rJL (ΔSH, IA-F/HN) showed the highest neutralizing titer against the G genotype, and the titer increased with time, as shown in Figure 2. Finally, the authors tested whether a booster dose of the G genotype vaccine could enhance virus neutralizing titers in JL-vaccinated mice. Mice were immunized by intramuscular injection and boosted one month after immunization with the same dose. Neutralizing titers of A and G genotype viruses were detected at 2.5 months after immunization. This was followed by booster immunization with JL, rMuV(ΔVΔSH), or rJL(ΔSH, IA-F/HN) at month 3 and by testing for neutralizing titers of A and G genotype viruses at months 3.5 and 6. The results showed that all groups had high neutralizing titers against A genotype virus at 2.5 and 3.5 months of age. Compared with that at 2.5 months, the neutralizing titer of G genotype virus at 3.5 months increased significantly after booster vaccination. The neutralizing ability of the antibody was still maintained at the sixth month. G genotype-based vaccine will increase neutralization against G genotype viruses, and humans who have developed immunity against genotype A MuV can be induced to develop immunity against genotype G MuV with a vaccine designed based on the G genotype, at the same time, the immunity against genotype A virus did not

decrease. Therefore, for better prevention of MuV disease, a third dose of G genotype-based vaccine is necessary. [13]

The efficacy of inactivated vaccines made using different genotypes of MuV for the prevention of mumps disease was analyzed. There are two main speculations about this, namely the decline of vaccine immunity and the antigen of vaccine strain did not match the antigen of wild virus strain. The authors explored the immune efficacy of inactivated MuV vaccines with different genotypes against various MuV genotypes. The JL vaccine strain and MuV of F, I, H, and G genotypes were obtained and cultured in Vero cells. Plaque formation assay was used to determine virus concentrations. These MuVs were purified and inactivated to make inactivated vaccines. Humoral immunity was tested in mice. The results showed JL group has the highest total IgG response, but mumps vaccines of F and G genotypes showed high neutralizing titers against various MuV genotypes. Therefore, F and G genotypes were tested as vaccine candidates. The authors used mice to conduct animal experiments to test the effects of the candidate vaccines. Mice were divided into three groups: experimental group, negative and positive control group. Two inactivated mumps vaccine (MuV of JL, F, G genotypes) were injected into experimental group by intramuscular injection, and the negative and positive control groups received the same dose of phosphate buffer solution and live MuV (F and G genotypes) in the same way. The second injection occurred three weeks after the first injection. Blood samples were collected at weeks 3,6, and 9 after injection. At the end of the experiment, the authors used FRNT to examine the relative cross-genotypic protection provided against the JL, F, I, H, and G genotypes in the experimental group, followed by the detection and quantification of cytokines. The levels of cytokines in JL group were lower than cytokines in F group, and the titers of cross neutralizing antibodies against MuV of JL group is also lower than F, H and G genotype. Humoral immunity induced by inactivated F genotype mumps vaccine persisted for at least 9 weeks. The inactivated F genotype mumps vaccine has stronger immunogenicity against multiple circulating MuV compared to the JL attenuated vaccine [14].

3. Conclusion

This research discusses the application performance of mumps vaccine in treatment and analyzes its specific effects. It can be seen the main problem with the current mumps vaccine is the vaccine has insufficient immune efficacy, and the immune efficacy become weaker with time. There are two reasons for this problem. The first is that the vaccine does not properly activate the human immune system due to the insufficient injection dose of the vaccine, and the second is the antigenic difference caused by the genotype difference between the vaccine strain currently used to make the vaccine and the wild virus strain. At the same time, other genotypes of MuV can be used as vaccine strains to develop new vaccines. These approaches have a great potential to solve the problem with mumps vaccines.

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