Quality control and evaluation of vaccines in China

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I was born in Luoyang in 1963, a city in China with thousands of years’ history. The city is the eastern starting point of the Silk Road (BC 206–260 AD), a famous and long trade route in human history. Living in this ancient city, I grew up under the influence and impact of Chinese traditional culture. When I was a teenager, I once read a book “Yellow Emperor’s Inner Canon” (Huang Di Nei Jing, written about 5th century BC), which is the oldest extant classic of traditional Chinese medicine. I was immediately attracted by an idea in it “prevention is better than cure,” which is mean that the highest level of medical treatment is not to cure a disease, but to prevent the occurrence of diseases. I think even in the modern society, this is still the highest realm of medical treatment. Inspired by this view, I developed a strong interest in preventive medicine and majored in it during my college years. With an increasingly deeper understanding of preventive medicine, I gradually realized the importance of epidemiology and vaccinology in preventing infectious diseases. Fortunately, in 1991 I entered the group of professor Zhuang Hui in Peking University Health Science Center for a doctorate degree in epidemiology. Professor Zhuang who is an academician of the Chinese Academy of Engineering not only taught me how to do research, but showed me how to act like a scientist. I benefited greatly from his rigorous attitudes toward life and research. During this period, I focused on transmission routes of hepatitis C virus which made me increasingly recognized the great harm of hepatitis in China. It is well known that more than three-quarters of all liver cancer cases are thought to be attributable to hepatitis B or C. In China about 110 000 people die from liver cancer each year, accounting 45% of the total number of deaths caused by liver cancer worldwide.

The discovery of vaccines can be described as a milestone in the human history. In a sense, the history of human thriving is the history of human fighting diseases and natural disasters. The most important means of controlling infectious diseases is prevention, and vaccination is considered the most effective preventive measure. The smallpox which had threatened human was eliminated due to the application of vaccine. This is the first victory over infectious diseases with vaccines. However, the development and application of vaccines were not easy. There have been repeatedly serious adverse events because of vaccine quality. In addition, vaccines are the most special class of drugs in the pharmaceutical field. It is used to immunize healthy people, especially healthy infants. Therefore, to ensure the safety and effectiveness of vaccines is particularly important, and the quality control and the evaluation of vaccines is one of the most important part. Aware of this, I set quality control and evaluation of vaccines as my career. Fortunately, in 1994 I became a member of the National Institutes for Food and Drug Control (NIFDC) which was formerly named China’s National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) after obtaining my doctorate degree. I was in charge of the quality control and evaluation of hepatitis vaccines and enterovirus vaccines such as hepatitis A vaccines, hepatitis B vaccines (HB vaccine), hepatitis E vaccines and a

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newly-developed enterovirus 71 vaccine (EV71 vaccine).

Quality Control and Evaluation of Hepatitis B Vaccine

Which type and what dose of recombinant vaccine should be chosen in China from the view of vaccine’s quality control and evaluation in 1990s

Hepatitis B can cause chronic liver disease and chronic infection and puts people at high risk of death from cirrhosis of the liver and liver cancer, which usually brings heavy economic burden to both family and society. Therefore, the control of hepatitis B epidemic is the focus of China’s Ministry Of Health. Hepatitis B vaccination is the most effective measure to control hepatitis epidemic. In the 1990s, HB vaccine available on the Chinese market was plasma-derived vaccine, while at that time recombinant HB vaccines were started to use in other countries, the main expression system of which were yeast and Chinese hamster ovary (CHO) cells. Compared with plasma-derived hepatitis vaccine, recombinant hepatitis B vaccines have the advantages of higher output, lower cost and no safety harm to blood donors. However, which type and what doses of recombinant vaccine should be chosen in China to replace plasma-derived vaccine are the problems we faced at the time. Supported by national research projects, I led the group to compare the antigenicity, immunogenicity and immune effects of different hepatitis B vaccines including saccharomyces cerevisiae (S. cerevisiae) vaccines, CHO vaccines and plasma-derived vaccines with different dosages. The protective efficacy of mother-to-infant transmission interruption of HBV was compared in 140 newborns and the antibody response of different vaccines was compared in 2291 children. Beside these studies, immunological mechanisms of vaccination were also researched. The protective efficacy of transmission interruption from mother to infant with 5 μg yeast-derived hepatitis B vaccines (YHBV) made in China was as same as YHBV produced in other counties (87. 29%; 90. 40%), and was significantly higher than other glycosylated vaccines such as CHO vaccine (74. 64%, 10 μg/ml) and plasma-derived vaccine(54. 41%, 10 μg/ml). Our results showed that immunogenicity of the vaccines was related to the expression system and glycosylated degree of the antigen. The epitope density was significantly different between non-glycosylated antigens (yeast) and glycosylated antigens (plasma and CHO). Non-glycosylated antigens had an advantage to induce earlier cellular immunity of Th1 cells and high protective efficacy, however, the activation of B cell stimulated by CHO and plasma antigens was relatively stronger. It is concluded that 5 μg YHBV for children is the vaccine formulation suitable for China’s newborns. The vaccine dose of other populations was also set to 5 μg/dose because of the insufficient vaccine supply caused by the discontinued production of plasma-derived HB vaccine. According to this conclusion, China began to promote the use of 5 μg saccharomyces cerevisiae HB vaccine because this kind of vaccine had good immunogenicity in people and finally stopped the production of plasma-derived HB vaccine in 1998. Owing to the application of HB vaccine for decades, the hepatitis B surface antigen carrier rate in Chinese children under 5 y of age has dropped to less than 1%. Since 1992, Chinese hepatitis B surface antigen carriers reduced 16 million to 30 million, and the population infected with hepatitis B virus reduced 200 million. For the research on HB vaccines, I have received the second prize of Science and Technology achievement given out by Chinese Medical Association and the second prizes of the Chinese Medical Award in 2001 and 2008 (Chinese Medical Association) and the China National Science and Technology Progress Award (State Council of China) in 2002. He serves on several national councils and committees engaged in the prevention and control of hepatitis, and he is a member of the Expert Steering Committee for adverse events following immunization (AEFI) monitoring of the Chinese Medical Association. His research has resulted in over 200 papers in well-established international scientific journals, including Lancet among others.

About Dr Liang

Dr Zheng-lun Liang earned his Bachelor of Medicine in 1985 from Henan Medical University (China), followed by a Master of Medicine in 1990 from Xi’an Medical University (China). In 1994 he completed his MD at Peking University Health Science Center. Subsequently, he joined the National Institutes for Food and Drug Control (NIFDC), where he serves as Director of the Division of Hepatitis Viral Vaccines.

Dr Liang’s research has mainly focused on the quality control and evaluation of hepatitis B vaccines, and more recently on the development of vaccines against enterovirus 71 (EV71), the pathogen that causes human foot and mouth disease (HFMD).

For his research on hepatitis B vaccines, Dr Liang received several awards and honors, including second prizes of the Chinese Medical Award in 2001 and 2008 (Chinese Medical Association) and the China National Science and Technology Progress Award (State Council of China) in 2002. He serves on several national councils and committees engaged in the prevention and control of hepatitis, and he is a member of the Expert Steering Committee for adverse events following immunization (AEFI) monitoring of the Chinese Medical Association. His research has resulted in over 200 papers in well-established international scientific journals, including Lancet among others.
vaccine companies and two Hansenula HB vaccine companies; the other two are recombinant CHO cell HB vaccine manufacturers. The number of Chinese HB vaccine batch release is about 300 batches per year, with quantities of more than 100 million doses, of which about 80% are yeast vaccines. Although hepatitis B recombinant vaccines have already been widely used, it is still urgent to resolve a lot of key technical issues in the aspect of immunization strategy because these problems will directly affect the control of hepatitis B virus. Whether existing commercial HB vaccines could prevent the infection of viral mutant strains; what is the boost strategy for different people and what are the impact factors on HB vaccines’ effects. To solve these issues, we developed a sensitive, specific and rapid gene chips for screening prevalent point mutations of HBV on a large scale, polymerase chain reaction (PCR) for detection of genotypes and mutations in pre-core and basic-core promoter. It is concluded that the existing HB vaccines can be used for interrupting the transmission of “a” determinant’s 126- and 145-point mutants from mother to child, indicating unnecessary to develop a new type of vaccine against “a” determinant’s 126- and 145-point mutants. The results showed that the infants born to mothers with HBV of C genotype had a significantly higher non-response rate to HB vaccination as compared with those born to mothers with HBV of other genotypes. It suggested that failure to interrupt mother-to-infant transmission by HB vaccine may be related to HBV genotypes. The subjects successfully immunized with initial dosage were boosted at their 18 years of age. Most of them (90%) had a good immune memory after the boost while 10% individuals lost their immune memories after the successful initial immune response. We found that the newborn infants born to mothers with both HBSAg and HBeAg positive had a high risk of HBV infection, and most of them became HBSAg positive at the age of 2–3 y old. Therefore, it was suggested to increase HB vaccine dose for the initial immunization, and to provide a boost at the age of 1–2 y old. Furthermore, we have performed re-evaluation of lyophilized recombinant yeast HB vaccine reference materials, and established reference materials for recombinant Hansenula HB vaccines and recombinant CHO vaccines. Results have been included in the Chinese Pharmacopoeia (2010 Edition, Part III). These efforts mentioned above have been taken to guarantee the quality of vaccines and provide the proper immunization strategy for people.

**Quality control and evaluation for a newly-developed EV71 vaccine**

While the application of HB vaccine has received a great success in China, enterovirus 71 (EV71) which used to be a modest and self-limited virus, gradually attracted public concern in the 1990s in the West Pacific region. It is one of the major pathogens associated with human foot and mouth disease (HFMD). Children under five years old are the susceptible population of EV71. It outbreaks in Taiwan in 1998 when 129,106 cases of HFMD and herpangina, 405 cases of neurological and cardiopulmonary complications, and 78 deaths were reported. Since then, EV71 infection has become endemic in Taiwan and caused >40, >40, and 14 deaths in 2000, 2001, and 2008, respectively. And 42 deaths have been reported in China by June in 2008. In addition, the number of reported HFMD cases in Mainland China was 1,619,706 in 2011 and 2,168,737 in 2012, leading to 509 and 567 deaths, respectively. In 2013, there were 1,855,457 reported cases of HFMD, including 260 deaths. Therefore, HFMD caused by EV71 has become a serious public health problem in the Western Pacific Region. As a newly-developed vaccine, there is no experience that could be referred to in the R&D of EV71 vaccine. To facilitate the development of EV71 vaccine, since 2008, I led the group to carry out the cross-protective study of EV71 vaccine candidate strains from different Chinese companies. This study provided a basis for the selection and determination of the appropriate vaccine strains in preclinical stage for manufacturers. We also established EV71 antigen quantitative standard and neutralizing antibody quantitative standards, which can be used to unify the vaccine dosage from different manufacturers and also to evaluate immunogenicity of vaccines. Furthermore, we performed the research on clinical sample testing method to ensure the immunogenicity results of vaccine accurate and reliable. These efforts accelerated the development process of inactivated EV71 vaccines in China. Currently there are three companies that completed the phase III clinical trials of whole virus inactivated vaccines. The results have shown that the vaccine had good safety, and the protection rate for HFMD caused by EV71 was over 90% for the three vaccines. So the vaccine is expected to become the world’s first HFMD vaccine available on market.

**Conclusion and Opinion**

As a constituent part of regulatory science, the quality control and evaluation of vaccine is important for further promoting the quality of existing vaccines and accelerating the R&D of new vaccines. To be an expert on vaccine quality control and evaluation, man needs a strong background and rich experience in medical and other related scientific areas, and should be familiar with the relevant laws, regulations and technical guidelines. To be an expert, man also should own enthusiasm and persistent attitude to his career, demand respect for his profession and be highly responsible for his occupation. It is gratifying that research on the quality control and evaluation of hepatitis B vaccine I have engaged in ensures the quality of Chinese HB vaccines, and plays a role in the control of hepatitis B epidemic in China. Due to the good effect in Phase III clinical trials, EV71 vaccine is expected to control the epidemic of serious HFMD in China and worldwide. I hope that the quality of vaccine is good enough to realize the idea “prevention is better than cure.”