Policy Forum

Immune Control Strategies for Vaccinia Virus-related Laboratory-acquired Infections*

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While presenting biological characteristics of vaccinia virus and laboratory-acquired infections during related research processes, this paper focuses on benefits and risks of vaccinia virus immunization in relation to laboratory-acquired infections, describes characteristics and the adaptation of vaccinia virus vaccine, analyses the role vaccinia virus immunization plays in the prevention and control of laboratory-acquired infections, and finally proposes solutions and countermeasures to further promote and implement immune control strategies. The problem related to immune strategy and laboratory-acquired infections which is being raised, analyzed and explored plays an active and instructive role in vaccinia virus related researches and laboratory-acquired infections, and also helps to recommend and develop relevant immune strategy for future vaccine control of such infections.

In May of 1980, the World Health Assembly certified that the world was free of naturally occurring smallpox, and since then routine smallpox vaccinations have been discontinued across the world[1]. Now, work with the virus is only confined to two World Health Organization-sanctioned sites under biosafety level 4 conditions. With the emergence of monkey pox in the USA in 2003 and owing to international concerns over the potential use of smallpox virus as a bioterrorism agent, poxviruses have received renewed attention from all parties interested, and, as a result, related researches have been further strengthened[2].

Vaccinia virus, the orthopoxvirus used in smallpox vaccine, is increasingly and widely used in molecular biology and vaccinology research laboratories[3]. Thus, laboratory-acquired vaccinia virus infections are commonly stemmed from the research process. Therefore, young laboratory researchers and students who are born after the cessation of routine vaccinations against the virus may be at a risk of acquiring vaccinia virus infections[4]. Since most unintentional vaccinia virus infections occur through direct contact with the skin and eye of a susceptible individual, they can lead to a very serious public health security problem if laboratory-acquired infections begin to appear and are subsequently spread through close contact. Therefore, health professionals and administrative authorities should pay greater attention to the prevention of the spread of vaccinia virus infections from laboratory.

Smallpox is a vaccine-preventable disease and has been eliminated. With the global elimination of smallpox virus among the general population, the approach to immunizing special occupational groups so as to control the risk of transmission as a possible result of laboratory infections is of great significance. Despite the benefits of vaccination, various adverse reactions may occur after vaccination using the vaccinia virus. This means that those engaged in vaccinia virus-related research are unwilling to be vaccinated, although they understand that exposure to vaccinia virus can cause laboratory-acquired infections[5]. Therefore, by providing further explanation of the characteristics of vaccinia virus vaccine and the appropriate way to adapt the vaccination process, this paper elaborates on the role of vaccinia virus immunization in the prevention and control of laboratory-acquired infections and proposes meanwhile strategies and countermeasures for the control and prevention of other laboratory-acquired vaccine-preventable disease-related infections in China.

Vaccinia Virus Vaccinia virus belongs to the poxvirus family, which is well-known for its widespread use as the vaccine that eradicates the smallpox virus infection across the world. However, the origin of vaccinia virus and its natural host are still unknown. Vaccinia virus is a large, complex, double-stranded DNA virus, with genomes

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approximately 200 kb[6].

The pathogenicity of different strains of vaccinia virus is variable from individual to individual and can be divided into two categories according to its replication in mammalian cells, namely non-highly attenuated strain and highly attenuated one. The non-highly attenuated strain can still be replicated in mammalian cells, and the most typical strain is selected by serial intracerebral passage in mice for neurotropic potential, which is called Western reserve (WR) strain[3]. Conversely, if the virus cannot be replicated in mammalian cells, it is a highly attenuated strain. Highly attenuated virus strains include MVA, NYVAC, ALVAC, and TROVAC strains[7]. Although the vaccinia virus is widely used as a viral agent for smallpox vaccination, the non-highly attenuated vaccinia virus strain is still a potential pathogen in human beings, and caution should be taken in its handling[8].

The virulence of different strains of vaccinia virus is variable, and laboratory personnel engaged in research into non-highly attenuated and highly attenuated viruses should follow different laboratory biosafety requirements. Non-highly attenuated vaccinia virus-associated (including WR strain) laboratory activities are required to be conducted under biosafety level 2 conditions, while other highly attenuated vaccine strains-associated laboratory activities can be conducted under biosafety level 1 conditions. Inadvertent exposures occur through needles tick accidents or splashes to the eye area, therefore, by using proper personal protective equipment and complying with good operating procedures, safety glasses should be worn when working with vaccinia virus[9].

History of Vaccination As a highly effective immunizing agent, vaccinia virus has played an important historical role for the global eradiation of smallpox although its origin remains unknown. Neutralizing antibodies against vaccinia virus are genus-specific, and can provide cross-protection from other orthopoxviruses, and the antibody levels are sustainable for a long time. Epidemiological studies have shown that an increased level of protection against smallpox can persist for <5 years after primary vaccination and substantial but waning immunity can persist for >10 years[10]. After percutaneous vaccination using the standard dose of vaccinia virus vaccine, 95% of primary vaccine recipients will produce neutralizing antibodies or hemagglutination inhibition antibodies at a titer of more than 1:10[10].

Taking into account specific situations in various countries, different immunization strategies are implemented. In 1971 the USA stopped routine vaccination in the general population, however the vaccination in the health-care staff was not stop until 1976. The vaccination was continued in the army until 1990[10]. China used its own vaccinia virus of Tiantan strain (TTV), and the second-generation of TTV smallpox vaccine derived from the TTV has successfully eradicated smallpox in China[11].

Side Effects and Contraindication The vaccinia virus used in vaccination is a non-attenuated live virus. It is, therefore, prone to different adverse reactions. After vaccination, the expected response is the development of a papule within 2-5 d, and it may develop into a vesicle after 8-10 d, followed by a pustule. Scabs fall off 14-21 d after inoculation, leaving a scar after recovery[12]. In addition to reactions at the site of vaccination, fever is more likely to develop in children than in adults[13]. Inadvertent inoculation, which results from autoinoculation of vaccinia virus transferred from the site of vaccination, is the most common complication, accounting for about 50% of the total complications in primary immunization and revaccination. Face, eyelids, nose, mouth, genitals, rectum, and other areas are the most frequent sites of complication[14].

In addition to common mild adverse reactions after vaccination, moderate to severe symptoms of adverse reactions may develop, including eczema vaccinatum, generalized vaccinia, progressive vaccinia, and postvaccinal encephalitis. More severe adverse reactions can occur, and some even result in death. However, the incidence of death is relatively rare, about 1 death per million primary vaccinations. The incidence rate of death during revaccination is about 0.25 deaths/million, indicating that the risk of adverse reactions after primary vaccination is more than 10 times that of revaccination and is more common in infants than in children and adults, and the vast majority of serious cases appear during primary immunization[10]. It was reported that non-serious adverse reactions occurred in 722 out of 37 901 volunteers after vaccination[15].

Another concern is possible transmission of the virus from people receiving vaccinia virus vaccine to a susceptible person, with whom they have close contact. The USA survey of 10 states in 1968 found that the risk of transmission via close contact with others was 27 infections per million, 44% of the cases were children under five years and 60% of the

cases occurred due to inadvertent inoculation[16]. Prior to 1990, a case was reported in which one vaccine recipient had infected 6 people among the vaccinated military recruits[17].

Vaccinia Virus Related Laboratory-acquired Infections Vaccinia virus is commonly used in molecular biology research, as it can infect a variety of cell types and result in high levels of protein expression. Vaccinia virus WR strain is one of the more commonly used strains, while the vast majority of cases related to the reported laboratory-acquired vaccinia virus infections are also caused by the use of WR strain virus[18]. Characteristic analysis of 17 cases of the reported laboratory-acquired vaccinia virus infections from 1985 to 2010 displayed that 52.9% of the cases were resulted from accidental needle inoculation during animal experiments, and symptoms occurred 5.1 d after vaccination on average. Laboratory infections may involve local swelling, pustules and nodules with pain accompanying fever or other symptoms. Severe cases may cause infection in fingers or eyes and can subsequently co-infect the face, jaw, knees, chest, shoulders, arms, legs, and other areas. Other syndromes like enlargement of armpit lymph nodes may also occur[19].

Vaccination Requirements Since non-highly attenuated vaccinia virus can cause infections in laboratory staff, and people born after vaccination termination are susceptible to poxvirus , the US Advisory Committee on Immunization Practices (ACIP) has released a guidance for vaccinia virus (smallpox) vaccination. The ACIP recommended that high-risk groups engaged in non-highly attenuated vaccinia virus research should receive smallpox vaccination[10]. Since 1983, the US CDC has provided vaccination for laboratory staff engaged in non-highly attenuated vaccinia virus researches, and added a requirement that personnel engaged in work with animal-contaminated or animals infected with non-highly attenuated vaccinia virus should also be vaccinated[20]. In 1991, the ACIP guidance once again expanded the scope of vaccination, and required that staff in clinical contact with vaccinia virus vaccine should also be vaccinated. The above persons should be revaccinated at least every 10 years, and staff exposed to smallpox virus, camel pox virus or monkey pox virus in laboratory experiments should be revaccinated at least every 3 years. On the other hand, laboratory and other health-care personnel who work with highly attenuated vaccinia virus are not required to receive routine vaccination[10].

Vaccination Status In contrast to the US ACIP recommendation to vaccinate laboratory workers, advisory committees in other countries have come to different conclusions and do not recommend routine vaccination. The UK Committee has concluded that the risk of complication and serious side effects outweigh the benefits of routine vaccination in workers handling vaccinia virus[21]. Due to the lack of monitoring and reporting systems, the real vaccination status is still unknown due to unavailable accurate laboratory staff vaccination statistics. Indirect or retrospective studies may reflect real status quo to a certain extent. Data analysis of 17 cases of laboratory-acquired infections in 1985-2010 showed that 52% were never vaccinated with vaccinia virus vaccine, and 82.4% were never administered with vaccinia virus during 10 years of research[19].

In 2005, Noelle carried out a survey to determine laboratory workers' adherence to the ACIP recommendations, and assessed potential barriers to vaccination, which showed that 92 researchers engaged in vaccinia virus research in 11 Institutes of University of Pennsylvania were contacted, and 45 responded. Of them 87% received a smallpox vaccination in their lifetime, 73% received the vaccine in the past 10 years, and 70% of the respondents worked with non-highly attenuated vaccinia virus. At the same time, the survey also did a comparative analysis to try to perceive which specific adverse outcomes were more likely to occur following vaccination versus accidental infection, namely, 'swelling of glands' (91% *vs* 51%), 'feeling bad enough to miss work' (53% *vs* 29%) and 'accidental infection of someone with whom you are in close contact' (26% *vs* 13%), and 31% of laboratory workers were also aware of laboratory infections and knew someone who was infected, indicating that laboratory staff were more concerned with the side effects of vaccination than with the accidental infection. The survey showed that 59% of people were vaccinated to meet the requirements of an institution, and 76% were vaccinated for safety consideration[5].

The above discussion showed that it was controversial to assess the risks and benefits of routine vaccination in laboratory or healthcare workers handling non-highly attenuated vaccinia virus. Even though the ACIP recommends laboratory personnel engaged in non-highly attenuated vaccinia virus research to be vaccinated, some organizations

or individuals believe that the risk of vaccination outweighs the potential benefit of protecting themselves from accidental exposure which will result in an infection. Meanwhile, information also shows that the symptoms of unvaccinated individuals are relatively mild in cases of laboratory infections and need no hospital care. Some data indicate that vaccination on the first day of exposure to vaccinia virus can reduce symptoms or prevent the disease. However, once vaccinia virus is frequently used in laboratories, and laboratory-acquired vaccinia virus infections still exist, appropriate countermeasures should thus be taken and implemented, and the positive role of immunization in control of laboratory infections should be considered.

Screening Staff with Contraindications Graduates who are currently engaged in laboratory studies are mostly born after 1980, and have never been vaccinated. Epidemiological surveys have confirmed that primary immunization usually leads to severer adverse reactions, and strict screening should therefore be carried out during primary immunization so as to screen people affected with eczema, atopic dermatitis, immunodeficiency and other high-risk populations to avoid the occurrence of serious adverse reactions. Health surveillance, infection control, and timely vaccination are the preferable measures to alleviate their symptoms. Patients with contraindications or in poor health should be transferred from their current posts.

Adjustment of Vaccination Strategies Non-replicative vaccinia virus vectors can improve the vaccinia virus vector immune effectiveness and reduce its virulence, thus providing a new solution for the vaccinia application. MVA is a kind of replication-defective smallpox vaccine, which is derived from vaccinia virus Ankara strain. MVA reduces the virulence and side reactions of the virus by maintaining its biological characteristics. However, its titer is not high and large doses of the vaccine need to be administered. Primary immunization of MVA, followed by inoculation of the first generation vaccine, can obviously alleviate skin reactions. It was reported that MVA, combined with the first generation of vaccine, could improve the effect of immunity and reduce the adverse reactions, supporting that MVA could be used as a vaccine in the general population to improve their immunity to orthopoxvirus[22].

Development of New Vaccines From the first generation vaccines produced from bovine lymphoid tissue, to the second generation vaccines prepared in cell culture, the natural passage attenuated third generation vaccines, and the ongoing genetically engineered highly attenuated vaccines, research staff have been looking for a new generation vaccine which can maintain the immunogenicity and reduce the side effects. The reduced side effects of new vaccines will promote the vaccination in laboratory staff[11].

Vaccine-preventable diseases refer to certain human infectious diseases that can be prevented by vaccination or immunization. Vaccine immunization can prevent such diseases, improve the immunity of the population, reduce the susceptibility of the population to pathogens, cut off the transmission and eliminate the source of infection. With the immunization strategies for vaccine-preventable diseases, some infectious diseases have been effectively controlled, or even eliminated, such as smallpox and polio. Since viruses will be widely present in laboratory conditions, research needs to be going on, the laboratory has become the major target of infection and the main source of biorisk. Therefore, it is increasingly important to control the transmission of laboratory-acquired vaccine-preventable infectious diseases outside of the laboratory. Regulations on Pathogenic Microorganisms Laboratory Biosafety have been available and more attention has been paid to biosafety and laboratory-acquired infections in China since 2004[21]. Referring to related US or European practices, measures should be taken for the prevention and control of laboratory infections and the elimination of the risk of transmission derived from laboratory exposure.

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