

## The Origin and Development Status of Smallpox Vaccine

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Journal of Vaccine Research, 2023, Vol.13, No.1 doi: [10.5376/jvr.2023.13.0001](https://doi.org/10.5376/jvr.2023.13.0001)

Received: 08 Jun., 2023

Accepted: 15 Jun., 2023

Published: 20 Jun., 2023

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### Preferred citation for this article:

Wang W., and Jin L.F., 2023, The origin and development status of smallpox vaccine, Journal of Vaccine Research, 13(1): 1-6 (doi: [10.5376/jvr.2023.13.0001](https://doi.org/10.5376/jvr.2023.13.0001))

**Abstract** Smallpox virus (variola, VAR) belongs to the Orthopoxvirus genus and has caused a global smallpox pandemic in history, causing profound disasters to humanity. Since Edward Jenner (1749~1823), a famous British doctor, scientist, and founder of modern immunology, discovered the subtle connection between cowpox and smallpox and carried out the first vaccination in the 18th century, many domestic and foreign scholars have devoted themselves to the research of smallpox vaccines, saving millions of lives. The emergence and elimination of smallpox virus is a long process. The effectiveness of traditional smallpox vaccines has been fully verified, but they can cause many side effects, requiring the development of safer and more effective smallpox vaccines. This review summarizes the origin of smallpox and the current development status of smallpox vaccines by reviewing domestic and international literature related to smallpox vaccines. Expanding the stockpile of smallpox vaccines has become a global need, and the development of new smallpox vaccines is of great significance in increasing user compliance, improving vaccine immunity and safety.

**Keywords** Smallpox vaccine; Development; Smallpox virus (*variola*)

Smallpox virus (Variola) is a DNA virus belonging to the Poxviridae and Orthopoxvirus genus. There are 14 species belonging to the same genus with smallpox virus, all of which are mammalian viruses. They are closely related. In addition, the smallpox virus has large particles and complex structure, and its complete form can be seen by using a high-precision optical microscope, which provides convenience for the isolation and research of smallpox virus. The smallpox virus can be transmitted in the air through saliva droplets, and it can also be transmitted through bodily fluids and contact. The onset period can be as long as 2 weeks or even longer. In ancient times, when medical and health conditions were not well-developed, its transmission was impossible to prevent. According to literature records, the mortality rate of smallpox virus can be as high as 50%, and as low as over 10%.

In ancient times, symptoms caused by smallpox could cause severe skin rashes and pustules all over the body. If a patient survived with luck, the pustules could gradually scab and eventually leave irregular circular scars on the entire body. Rashes and pustules were called pox because they resemble beans. In ancient China, various diseases could cause pox, but it was not until in the literatures of the Ming and Qing dynasties that people could clearly distinguish whether the recorded pox is smallpox or not (Wang, 2003).

Domestic and foreign researchers have developed various types of smallpox vaccines, including live virus vaccines by cell culture, attenuated live vaccines in forms of replication and replication defects, protein subunit vaccines, DNA subunit vaccines, vector subunit vaccines, etc. Compared to the traditional vaccines, attenuated live vaccines have higher safety, but their immunogenicity is relatively low. Currently, research on subunit smallpox vaccines is still in its infancy, and more and more in-depth research is needed to verify the feasibility of their clinical application.

Vaccines are currently the most cost-effective product for human prevention of infectious diseases. Expanding the stockpile of smallpox vaccines has become a global need. Given the safety issues of traditional smallpox vaccines, it is necessary to develop safer and more effective smallpox vaccines (Guan, 2007). Since the birth of smallpox

vaccines in the 18th century, vaccine research and development has gone through hundreds of years of development. With the development of reverse vaccinology and other technologies, vaccine research and development has ushered in new and broad development prospects. This review briefly introduces the origin of smallpox and the development prospects of smallpox vaccines.

## 1 The Origin of Smallpox

Smallpox originated in the Old World of Asia and Africa. After the geographical discovery, it was introduced by European colonizers to the Americas and Australia, causing a large number of deaths among indigenous residents and leaving many pockmarks on their faces. As to the disaster of "smallpox", archaeological discoveries have found that the face, neck, and shoulders of the mummy of Ramesses V in ancient Egypt all have scars caused by smallpox. This is the earliest case of smallpox in human history, with a history of over 3 000 years. As a plague, smallpox once brought great disaster to people.

Smallpox is a highly contagious disease circulating in ancient China. Over the centuries, the widespread of smallpox has made people tremble with fear and turn pale when it comes to smallpox. Smallpox has the characteristic of "everyone is equal", and its pathogen, the smallpox virus, has extremely strong infectivity and reproductive ability. After the patient dies, the virus can still survive for several months, making it possible for anyone to contract smallpox, regardless of race, status, age, or gender.

The average incubation period after infection with smallpox virus is about 12 d (7~17 d). The initial symptoms after infection include high fever, fatigue, headache, accelerated heartbeat and back pain. After 2~3 d, there will be a typical smallpox rash clearly distributed on the face, arms and legs (Figure 1). In the early stages of rash, there will also be a light red block area accompanying the rash. The lesion began to suppurate a few days later and began to scab until the second week. Over the next 3~4 weeks, it gradually develops into scabies and then gradually peels off. Smallpox is caused by infection with the pox virus, and may leave pockmarks on patients' faces after recovery, hence the name "smallpox".



Figure 1 Marked red rash after diagnosis of smallpox

## 2 Development of Smallpox Vaccines

### 2.1 The traditional smallpox vaccine-variolation

Smallpox is an ancient disease, and we have found traces of it in both ancient books and archaeological discoveries. The earliest clear record of smallpox in China is Zhouhou Jiuzu Fang (The Handbook of Prescriptions for Emergencies), the work of the famous medical expert Ge Hong of the Jin Dynasty. The book records: "In recent years, there has been a prevalence of a disease. When it breaks out, people develop pimples on their heads, faces, and bodies. In an instant, their whole body is covered with pimples, shaped like blisters caused by burning,

all with white pus, which may end life at any time. If the treatment is not timely, most severe cases will die. If not treated well, it will leave black scars. This is a vicious aura that takes about a year to dissipate". This is highly consistent with the description of clinical manifestations of smallpox in modern medicine.

Until the Ming and Qing dynasties, the vaccination method for smallpox in China gradually matured, with three common methods: placing smallpox lesions or scabbed pus into the nostrils of healthy children; or dress healthy children in clothes worn by infected individuals; alternatively, dry powdery smallpox scabs from the late stage of the patient's illness can be blown into the nasal cavity through a silver tube. Children who have been vaccinated with smallpox may experience fever within approximately 7 days, but most cases only show mild smallpox symptoms. Through such an artificial infection process, children can be prevented from contracting smallpox again.

## 2.2 The first generation smallpox vaccine-vaccination with cowpox

From the current perspective, the vaccine for "variolation" is still an active smallpox virus after all, or a virus that has not been completely inactivated, so the risk is still very high. Many people may have died because of variolation, and the proportion of people accepting it at that time was not very high. The emergence of vaccination with cowpox has completely changed this situation. After the advantages of cowpox were confirmed, it quickly replaced "human pox" and became the first choice for humans to prevent smallpox. But when vaccinated on a large scale, the vaccinia solution used as a vaccine is not sufficient. Therefore, humans have had to intentionally inoculate animals such as cows and sheep with the virus, so that humans can harvest more cowpox virus by infecting livestock with the virus.

Later, the production of vaccine was transferred from the field of farms and individual doctors to the industrial field, and a more sophisticated and large-scale production method was adopted, namely, scratch inoculation was carried out on the epidermis of calves, sheep or buffaloes, and then the virus was isolated from the skin scrapes containing pus, serum and squeezed lymph. By the 1950s, it had gradually become more systematic and standardized, and the use of lyophilized formulations instead of liquid lymphatic vaccines made them easier to preserve.

After the 20th century, the vaccine commonly used to prevent smallpox was no longer the cowpox virus that Jenner originally used, but a close relative called vaccinia virus. This virus is a unique species of Orthopoxviridae, and this close relative is neither the cause of smallpox nor the cause of cowpox. The source of the orthopoxvirus is not clear, and people speculate that it may be because the cowpox vaccine recombines with the smallpox virus during the vaccination process, or the virus mutated to adapt to a new host during virus culture of other animal smallpox viruses. Anyway, like cowpox, vaccinia virus provides strong cross protection immunity against smallpox (Figure 2).



Figure 2 Doctors vaccinate cowpox on children

### 2.3 The modern smallpox vaccines

With the advancement of medicine, it has been discovered in the research process that smallpox live virus vaccines can be activated through guidance, leading to the emergence of subunit vaccines that can produce induced protective antibodies. Protective antibodies transmit protein antigens to the immune system through induction. The current subunit smallpox vaccine mainly includes protein subunits, DNA, and vector smallpox vaccines. In recent years, this new type of smallpox vaccine has attracted the attention of scientists, as its protein tissue can reduce the number of infectious antigens and control the spread of the virus in the body. DNA protein vaccines are obtained by recombining DNA plasmids, which has multiple advantages over protein vaccines.

Vector vaccines are proteins required by transmission through non pathogenic viruses or bacteria. Protein vaccines and DNA vaccines require several injections to achieve protective immune effects, while vector vaccines only require one injection to achieve immune effects. The new generation of smallpox vaccine not only achieves immune effects on specific people, but also increases immunity for reinjecting people who have received the vaccine. Currently, such vaccines are only in the preclinical research and development stage, and it is expected that at least one new generation vaccine will enter clinical trials in the coming years.

Smallpox is unique not only in that it was the first human infectious disease to be controlled through immunization, but also in that it has been eliminated through our own efforts so far. From any perspective, smallpox vaccination will become the benchmark for evaluating future vaccines and the starting point of our "Vaccine History" series (Figure 3).

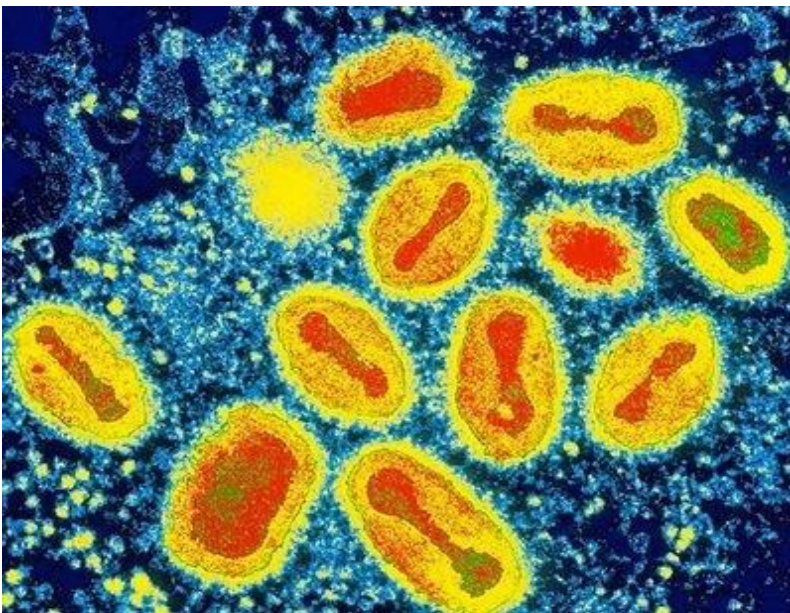


Figure 3 Microscopic smallpox virus

### 3 The Eradication of Smallpox and Its Significance

The widespread vaccination of smallpox vaccine worldwide has greatly reduced the incidence rate of smallpox. In 1980, the World Health Organization announced that smallpox had been eradicated worldwide. So far, there has been no specific method to treat smallpox globally, and vaccination is a simple and effective measure to prevent and control smallpox. The WHO Advisory Committee on Variola Virus Research believes that the best smallpox prevention and control measure is immunization, which has been successfully applied in eradication plans. However, the current smallpox vaccine can cause many side effects. This indicates that although the current vaccine is effective, there is still a need for improvement, especially in terms of safe and effective immunization for vulnerable populations (immune deficiency, elderly, pregnant women, and children with eczema).



The eradication of smallpox is a huge success for public health, and the decisive factor for its success is global solidarity. In the face of sudden public health emergencies, the world needs to unite more than ever before. The successful experience of eradicating smallpox reminds countries that when the world is united, everything is possible. The successful eradication of smallpox mainly relies on technological inventions and progress. From variolation to vaccination with cowpox, from only knowing what it is to wanting to know why, an emerging medical discipline - immunology - has gradually emerged. If variolation has opened the door to human empirical immunology, then vaccination with cowpox has opened a new chapter in classical immunology, and the achievements have laid a solid foundation for modern immunology and current immunology (Deng, 2021).

#### 4 Summary and Outlook

As people gradually forget about the outbreak of smallpox in the last century, the discovery of monkeypox disease similar to smallpox in many regions and the attempts of terrorists to use microorganisms such as anthrax as biological weapons have once again sounded the alarm bell. Terrorists may also use modified recombinant viruses as biological weapons through various channels. In this situation, it is very important for China to understand the genes related to smallpox virus, which can prepare for future genetic testing of the virus and prevent potential risks.

The development of medical care has enabled humans to cure most diseases, alleviate the torment of illness, reduce the duration of illness, maintain long-term health, and avoid the risk of extinction caused by infectious diseases. The eradication of smallpox has brought us experience in the development of medicine, and we will not be at a loss when encountering similar conditions (Fan et al., 2022).

Nowadays, medicine is not only a natural science, but also a symbol of human social progress. With the continuous progress of Chinese medical system and the continuous improvement of laws, China has established the first fundamental and comprehensive law in the field of health and wellness, Law of the People's Republic of China on the Promotion of Basic Medical and Health Care. This law covers basic medical and health services, medical and health institutions and personnel, drug supply security, health promotion, financial security, and other aspects. It embodies the concept of "ensuring the basic rights of the people, strengthening the construction of basic-level, and promoting health education and health management" in the form of laws. China has also continuously demonstrated its style as a major country. In accordance with the 14th Five-Year Plan and the Long-Range Objectives Through the Year 2035, the continuous deepening of the reform of the medical and health system has accelerated the resolution of the problem of "difficult and expensive medical treatment" for the people. National policies will become more deeply rooted in people's hearts and bring more convenience to the people.

#### Authors' contributions

WW was responsible for the relevant literature and material researching, organizing, and the writing for the first draft of this review; JLF participated in discussions and paper revisions; JLF was the person in charge of this review, guiding the writing and revision of the paper. Both authors read and approved the final manuscript.

#### Acknowledgments

This research was funded by "Cuixi Innovation Research and Development Project Fund" of Zhuji Cuixi Academy of Biotechnology.

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