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Research on the History and Current Status of BCG Vaccine

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Abstract Bacillus Calmette-Guérin (BCG) is a vaccine used to prevent tuberculosis. It is made from a live, attenuated strain of *Mycobacterium bovis*. When injected into the human body, it causes a mild infection that produces immunity to the human strain of the tuberculosis bacterium. The BCG vaccine is primarily used as a preventive measure against tuberculosis in children, and it generates a special resistance to the disease. To honor its inventors, French scientists Calmette and Guérin, the vaccine was named the "BCG vaccine". Currently, most countries around the world have included the BCG vaccine as one of the mandatory vaccines in their immunization programs. This study will focus on the development of the BCG vaccine, exploring its history and current status, including its relationship with pulmonary tuberculosis, research progress, vaccination methods and significance, as well as its future development.

Keywords BGC vaccine; History; Current situation; Tuberculosis (TB); Prevention

The BCG vaccine is a vaccine used to prevent tuberculosis, with a history dating back to the early 20th century. In 1921, French researchers Albert Calmette and Camille Guérin developed the vaccine by cultivating *M. tuberculosis* on the lymph of cattle, creating a weak strain known as the BCG vaccine. This vaccine has been proven to have a protective effect against tuberculosis and is deemed to be highly safe. The widespread use of the BCG vaccine has led to a decrease in the incidence of tuberculosis, making it a preventable and treatable disease.

The BCG vaccine has played an important role in tuberculosis control, but it is not without flaws. There are some controversies and challenges associated with its use. Firstly, the protective immunity provided by the BCG vaccine is relatively short-lived, requiring regular booster shots to maintain immunity. Secondly, the BCG vaccine can cause some side effects, such as local skin reactions and fever. Additionally, the effectiveness of the BCG vaccine varies among different age groups and populations and needs to be chosen based on individual circumstances. Despite these issues, the BCG vaccine is still widely used globally. The World Health Organization recommends the BCG vaccine as one of the first-line preventive measures against tuberculosis and promotes its use worldwide.

Some research teams are working on developing more effective vaccines to improve protection among adults. Other research is focused on developing genetically engineered vaccines to enhance immune response and persistence. However, these studies are still in the laboratory stage and require further clinical trials and validation. The BCG vaccine has achieved significant success in preventing childhood tuberculosis and has been widely used worldwide. However, low vaccination rates still exist in some areas, and efforts are needed to promote and popularize BCG vaccination to improve vaccination rates and better prevent and control the occurrence of pulmonary tuberculosis in the future (Mangtani et al., 2014).

1 The Origin of BCG Vaccine

1.1 From tuberculosis prevention to BCG vaccine

Pulmonary tuberculosis is a major disease with high infectivity, high infection rate, and high mortality. The most important means of preventing tuberculosis in newborns and infants is vaccination with the BCG vaccine. BCG vaccine vaccination can provide newborns with specific immunity to attenuated tuberculosis, thereby preventing

the spread of tuberculosis to the human body and preventing the development of tuberculosis, meningitis, and other military tuberculosis. Generally, newborns need to be vaccinated with the BCG vaccine within 24 hours to effectively achieve passive immunity, improve the success rate of BCG vaccine vaccination, and reduce the incidence of tuberculosis.

Prophylactic vaccination is an important part of tuberculosis prevention and control, and the BCG vaccine, as the only clinically approved vaccine that has been used for nearly a century, has become a mandatory vaccination measure for newborns in high tuberculosis burden countries and regions, showing a certain degree of protection. Tuberculosis is a chronic respiratory infectious disease, with pulmonary tuberculosis being the most common form. According to the World Health Organization's 2019 Global Tuberculosis Report, an estimated 10 million new cases of tuberculosis and 1.5 million deaths due to tuberculosis occurred globally in 2018, with China having the second highest tuberculosis burden in the world. In addition, research estimates that about one-quarter of the global population has tuberculosis infection, indicating that the reactivation of latent infection in the body may pose a greater challenge to tuberculosis prevention and control (Yang et al., 2020).

1.2 Development history of BCG vaccine

In 1921, French physician Vail·Halle first applied this attenuated live vaccine to clinical use. The first person to receive the vaccine was a poor baby whose parents died of pulmonary tuberculosis, and his grandmother who raised him also had pulmonary tuberculosis. If the baby did not enhance his resistance to tuberculosis bacteria, he would also be infected with tuberculosis. In this case, Dr. Vail·Halle decided to give him a preventive vaccination, and the baby was spared the threat of tuberculosis and grew up healthy. Seeing the results of many years of hard work, Calmette and Guérin were also excited. They continued to work hard and conducted more than 300 clinical vaccination experiments in three years, confirming the safety of this attenuated live vaccine.

In 1924, they officially announced this invention. To commemorate the two scientists, this attenuated live vaccine was named "BCG vaccine". Pulmonary tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* and can be transmitted through the air. The BCG vaccine is a vaccine made from a variant of *Mycobacterium tuberculosis* and can prevent tuberculosis. After years of use, the BCG vaccine has been proven to be a safe and effective vaccine that can prevent pulmonary tuberculosis. The use of the BCG vaccine is widespread worldwide. Governments of various countries generally promote BCG vaccination, especially in some high-tuberculosis countries and regions. The efficacy and safety of the BCG vaccine have been widely recognized and are considered one of the effective means of preventing pulmonary tuberculosis.

The preparation of the BCG vaccine requires the cultivation, isolation, and screening of mycobacterium, and then it is made into a vaccine. The preparation process requires strict control of conditions to ensure the quality and safety of the vaccine. After BCG vaccine vaccination, an immune response can be produced, which enables the body to form immunity against *M. tuberculosis* and prevent the occurrence of pulmonary tuberculosis. The protective effect of the BCG vaccine is mainly achieved by activating the body's immune system, promoting the production and activity of immune cells, and resisting the invasion of *M. tuberculosis*. The BCG vaccine is widely used worldwide, especially in some high-tuberculosis areas and countries (Figure 1).

2 Progress in Research on BCG Vaccine

2.1 Research on the function of BCG vaccine

BCG vaccine is a vaccine made from a strain of *Mycobacterium tuberculosis*, the main component of which is mycobacterium with irregular bacilli morphology and positive antacid staining as well as some cell wall components and polysaccharides. The preparation process of BCG vaccine is complex and requires multiple cultures and processing to obtain high preparation purity and activity.

Figure 1 BCG vaccine

The BCG vaccine has been proven to reduce the incidence and mortality of tuberculosis. However, in some areas, the effectiveness of the BCG vaccine is not as expected, which may be related to different strains, vaccination timing, and production processes. Therefore, researchers are working to improve the effectiveness of the BCG vaccine to enhance its role in tuberculosis prevention and control.

Although the BCG vaccine is a relatively safe vaccine, some children may experience mild side effects after vaccination, such as local pain, redness, and swelling. In rare cases, more serious side effects such as skin infections and tuberculosis infections may occur. Therefore, researchers are developing safer BCG vaccines, such as genetically engineered BCG vaccines. Gene engineering technology-based BCG vaccine improvement is one of the hotspots in current BCG vaccine research. Some studies have shown that by modifying BCG vaccine strains through gene engineering technology, better protective effects and fewer side effects can be obtained. For example, the rBCG30 vaccine has been clinically tested in South Africa, and the results show that this vaccine is more effective in preventing tuberculosis than traditional BCG vaccines. BCG vaccine can be used in combination with other vaccines to enhance the protection against tuberculosis. For example, the combined use of BCG vaccine and hepatitis B vaccine can reduce the incidence of tuberculosis in children.

The BCG vaccine is a widely used vaccine that has achieved some success. In the future, researchers need to continue their efforts to further improve the effectiveness and safety of the BCG vaccine to make greater contributions to the prevention and control of tuberculosis. At the same time, the fields of BCG vaccine combination use and genetic engineering improvement are also worth further research and exploration.

2.2 Protective effects and limitations of BCG vaccine

The BCG vaccine is currently the most widely used vaccine for tuberculosis, and its main function is to stimulate the body's immune system to produce antibodies and cellular immune responses against *M. tuberculosis*, thereby enhancing the body's resistance to *M. tuberculosis*. Studies have shown that the BCG vaccine can effectively prevent tuberculosis infection and disease, especially for children and adolescents.

However, the BCG vaccine also has some limitations. First, the BCG vaccine can only provide partial protection, and its protective rate varies with region and age, and its protective effect is poor for adults and high-risk populations. Second, the protective effect of the BCG vaccine is not permanent, and its protective effect gradually decreases over time. In addition, the protective effect of BCG vaccine is also limited for people with HIV infection and immune dysfunction (Fraser, 1996).

2.3 Side effects and safety of BCG vaccine

The side effects of the BCG vaccine are common and mainly include two types: local reactions and systemic reactions. Local reactions include redness and swelling, pain and induration at the injection site, while systemic reactions include fever, fatigue, headache, and nausea. Most side effects are mild and self-resolving, but there are also a few cases of severe allergic reactions and complications.

The safety of the BCG vaccine is also a concern. On the one hand, the preparation and storage of the BCG vaccine need to be strictly controlled to ensure its purity and activity and avoid adverse effects on the vaccinated. On the other hand, the vaccination target of the BCG vaccine needs to be screened strictly to avoid serious adverse reactions after vaccination due to the existence of immune system diseases or other health problems.

In summary, the BCG vaccine is an effective vaccine for preventing tuberculosis, but its protective effect has limitations, and its side effects and safety need attention and management. Future research needs to further explore the protective mechanism of the BCG vaccine and methods to improve its protective effect, while also strengthening the supervision and safety management of the BCG vaccine to ensure its safety and effectiveness in practical applications.

3 Vaccination and Significance of BCG Vaccine

3.1 The recipients and timing for BCG vaccination

Currently, most countries in the world have included BCG vaccine as one of the vaccines that must be immunized in the national vaccination plan. The main recipients of BCG vaccine are newborn infants, and vaccination can prevent childhood tuberculosis, especially those severe types of tuberculosis such as tuberculous meningitis. BCG vaccination is beneficial for the healthy growth of children. BCG vaccination is called the "first shot at birth", so it should be given to newborns in the delivery room or the obstetrics department. If it is not given at birth, it should be given at the tuberculosis clinic or the immunization clinic of the local health and epidemic prevention station before the age of 1 (Figure 2).

Figure 2 The doctor is administering BCG vaccine to the baby

BCG vaccine is a live attenuated vaccine that is typically administered on the first day after birth, with an intradermal injection in the lower part of the deltoid muscle of the upper arm. For premature babies, if they are older than 31 gestational weeks and medically stable, BCG vaccine can be administered. If the gestational age of premature babies is less than or equal to 31 weeks, BCG vaccine can be administered before discharge under the assessment of a professional doctor.

If the vaccine is not given at birth, it can be directly supplemented within 3 months. For children aged 3 months to 3 years who have not been vaccinated, they need to undergo a tuberculin purified protein derivative test or BCG

protein derivative test. Only those who test negative can be vaccinated. Those over 4 years old are not eligible for vaccination. After BCG vaccination, a small red nodule will usually appear locally about 1-2 weeks, which will gradually grow bigger and become slightly itchy but not accompanied by fever. A pustule or ulcer will form after 6-8 weeks, and the scab will naturally heal in an average of two to three months. The scab should be allowed to fall off naturally and should not be scratched off early. After the scab falls off, a small red scar will be left. The redness will gradually turn into skin color, which is a normal reaction. Generally, it does not need to be treated, but local cleanliness and dryness should be maintained to prevent secondary infection, and hot compress should be avoided. Not everyone will have a BCG scar. About 10% of people who receive BCG vaccine will not produce a scar but still have protective effects, so there is no need to supplement the vaccine because of the absence of a scar (Figure 3; Figure 4).

Figure 3 The process of skin changes at the site of BCG vaccination

Figure 4 The scar that appears after BCG vaccination

3.2 Significance and effectiveness of BCG vaccination

BCG vaccination is a method of artificially inducing a mild, non-dangerous primary infection in a body that has not been infected with mycobacterium, so as to induce specific immunity. It is an important part of National Immunization Program of China. Currently, it is believed that after BCG vaccination of newborns and infants, the incidence of tuberculosis is reduced by about 80% compared to the same age group who are not vaccinated (Chang, 2020).

Governments of various countries generally promote the vaccination of BCG, especially in some high incidence areas of tuberculosis. For example, the Chinese government has implemented a free vaccination plan for BCG vaccine nationwide, and many other countries have taken similar measures. The efficacy and safety of BCG vaccine have been widely recognized and are considered to be one of the effective measures to prevent pulmonary tuberculosis.

Although BCG vaccine has a certain effect in preventing pulmonary tuberculosis, its protective effect has certain limitations. For example, BCG vaccine cannot completely protect the vaccinated person from infection, and its protective effect will gradually weaken over time. Therefore, it is necessary to further strengthen the prevention and control of tuberculosis globally, research more effective vaccines and treatment plans, and reduce the incidence and mortality of tuberculosis.

4 Summary and Outlook

BCG vaccine is a vaccine that has a long history and has been developed for many years to prevent tuberculosis. Although there are some problems and challenges in its use, BCG vaccine is still widely used around the world. The development and use of BCG vaccine have made positive contributions to reducing the incidence and mortality of tuberculosis. In the future, we need to continue to conduct in-depth research on BCG vaccine, constantly improve and perfect it, in order to better prevent and control tuberculosis.

The development of BCG vaccine will make significant progress in the next few decades. It has been widely used in tuberculosis control programs in many countries and has become a vaccine recommended by the World Health Organization. BCG vaccine can effectively prevent the occurrence of tuberculosis, especially the protection effect on children is obvious, and BCG vaccine is usually given by intradermal injection in infancy.

Vaccination is the most effective measure in the prevention and control of infectious diseases. Currently, nearly 20 new tuberculosis vaccines have entered phases I-III clinical trials worldwide, but none have been successful and no vaccine has been found to be more protective than the BCG vaccine. Although newborns are vaccinated with the BCG vaccine, its protective effect gradually decreases with age. In high-burden tuberculosis countries, as a result of the abundant presence of infectious sources, with the decreasing efficacy of BCG vaccination and increasing exposure risk to *Mycobacterium tuberculosis* in adolescents and adults, the risk of tuberculosis increases gradually. From the three WHO position papers on BCG vaccine, it can be seen that WHO's attitude towards BCG vaccine has become more positive with increasing research evidence and changing prevention and control situations. Especially in the latest position paper in 2018, BCG vaccination is recommended for adolescents and adults without vaccination history. If we want to further control the prevalence of tuberculosis through strengthening immunization prevention, BCG vaccine is still the only possible choice (You et al., 2018).

Since its application, BCG vaccine has achieved remarkable achievements in the prevention of tuberculosis, and its safety and effectiveness have been widely recognized. With the continuous development of genetic engineering technology, rBCG research will continue to deepen, making it have higher and more stable protection, fully play its advantages such as wide application, strong immunopotentiator, long-lasting immunity, and low production cost, and is expected to be applied as an economic and effective new vaccine for disease prevention and control in the near future (Li and Huang, 2009).

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.

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