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ВЕТЕРИНАРИЯ

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БОДО МАЛДЫН КУРГАК УЧУГУНА КАРШЫ ВАКЦИНА

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ВАКЦИНА ОТ ТУБЕРКУЛЕЗА КРУПНОГО РОГАТОГО СКОТА

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BOVINE TUBERCULOSIS VACCINE

УДК: 68.41.35

Бодо малдын кургак учугу бодо малдын жугуштуу оорусу. Аны Mycobacterium bovis (M. bovis) бактериясы козгойт, ал түрлөр аралык тосмодон өтүп, башка көптөгөн жапайы жана үй жаныбарларын булгап, ооруну жаратат. Бул бодо малдын респиратордук инфекциясы, бирок клиникалык белгилери сейрек кездешет. Бодо малды эмдөө жолу менен эмдөө, спецификалык жана сезгич диагностикалык тесттер менен айкалыштырып, бодо малдын кургак учугу менен күрөшүүнүн эң эффективдүү стратегиясы катары сунушталат. Учурда адам жана бодо малдын кургак учугу үчүн жеткиликтүү жалгыз вакцина - бул тирүү аттенуацияланган Bacille Calmette Guerin (BCG). Бирок, бул вакцина тарабынан кургак учукка каршы корголгон коргоо ар кандай, жана бүгүнкү күнгө чейин, БЦЖ ийгиликтүү жана ийгиликсиз себептери түшүнүксүз. Ошондуктан, БЦЖ вакцинасына караганда туруктуу коргоону сунуш кылган вакциналарды иштеп чыгуу актуалдуу. Бирок, ар кандай жаңы вакцина же эмдөө стратегиясы негизинен BCG вакцина технологиясына негизделген. Ал эми бул серепте биз кургак учуктун алдын алуу жолдорун жана адабияттан алынган маалыматтардын негизинде дүйнөдө колдонулган бодо малдын кургак учугуна каршы вакциналардын түрлөрүн баяндайбыз.

Негизги сөздөр: *үй жаныбарлар, бодо мал, туберкулез, вакцина, ремпиратодук инфекция, диагностикалык тесттер, эмдөө.*

Туберкулез крупного рогатого скота – это хроническое инфекционное заболевание крупного рогатого скота (КРС). Возбудителем болезни является бактерия Mycobacterium bovis (M. bovis), которая, преодолел межвидовой барьер и может вызывать туберкулез параллельно с КРС у многих других диких и домашних животных. У КРС болезнь в основном протекает, как респираторная инфекция, но клинические признаки проявляются редко. Иммунизация КРС путем вакцинации в сочетании с более специфическими и чувствительными диагностическими тестами предлагается в качестве наиболее эффективной стратегии борьбы с туберкулезом КРС. Единственная вакцина, доступная в настоящее время против туберкулеза человека и КРС – это живая аттенуированная бацилла Кальметта Герена (БЦЖ). Однако защита от туберкулеза, обеспечиваемая данной вакциной, варьируется, и на сегодняшний день причины успехов и неудач БЦЖ не ясны. Следовательно, необходимость в разработке вакцин, обеспечивающих более высокую и более устойчивую защиту, чем вакцина БЦЖ является актуальной, однако, любая новая вакцина или стратегия вакцинации основаны в основном на технологию вакцины БЦЖ. И в этом обзоре мы описываем пути профилактики туберкулеза, а также разновидности вакцин против туберкулеза КРС, используемых в мире на основе данных из литературы.

Ключевые слова: *домашние животные, крупный рогатый скот, туберкулез, вакцина, ремпиратодная инфекция, диагностические тесты, вакцинация.*

Bovine Tuberculosis (bTB) is an infectious illness of cattle. It is caused by the bacterium Mycobacterium bovis (M. bovis), which can cross the interspecies barrier, contaminate and cause disease in numerous other wild and domestic animals. It is a respiratory infection in cattle, but clinical signs are uncommon. The immunezation of cattle by vaccination, in combination with more specific and sensitive diagnostic tests, is suggested as the most effective strategy for bTB control. The only vaccine currently available for human and bTB is the live attenuated Bacille Calmette Guerin (BCG). However, the protection provided by this vaccine against tuberculosis varies, and to date, the reasons for the success and failure of BCG are unclear. Therefore, developing vaccines that offer more sustainable protection than the BCG vaccine is relevant. However, any new vaccine or vaccination strategy is based mainly on BCG vaccine technology. And in this review, we describe ways to prevent TB and the types of vaccines against bTB used in the world based on data from the literature.

Key words: *pets, cattle, tuberculosis, vaccine, respiratory infection, diagnostic tests, vaccination.*

Bovine tuberculosis is an infectious disease of cattle. It is caused by the bacterium *Mycobacterium bovis (M. bovis)* [1]. The bacterium can also infect and cause illness in domestic and wild animals. More than 55 species of domestic and wild animals and about 25 species of birds are susceptible to tuberculosis. Sick animals are the primary source of infection of tuberculosis [2-8]. TB is primarily a chronic respiratory disease in cattle, but clinical signs are rare [9,10].

BTB is a zoonotic disease, which can be naturally transmitted from animals to humans under certain conditions [11-13]. With a comprehensive TB eradication plan in place in the world, human cases of TB caused by *M. bovis* infection are rare. Still, it can cause significant problems in developing and developed countries [15-18].

The disease pathogen is a strictly aerobic bacterium, which is immobile, does not form spores, and is resistant to acids [17,18]. Due to fatty elements, *M. bovis* has a

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strong resistance to the external environment and the effects of disinfectant substances [19,20].

The latest data on the worldwide status of bovine TB is from 2018. Forty-four percent of countries reported bTB via the OIE World Animal Health Information System (WAHIS) between January 2017 and June 2018. Only a quarter of the affected countries applied all the relevant control measures. Improved surveillance and accurate reporting by a country's Veterinary Services contribute to preventing and controlling bTB at the animal source. From January 2017 to June 2018, of the 188 countries and territories reporting their bTB situation to the OIE, 82 countries (44%) were affected, which demonstrates the widespread distribution of the disease (Fig. 1) [21].

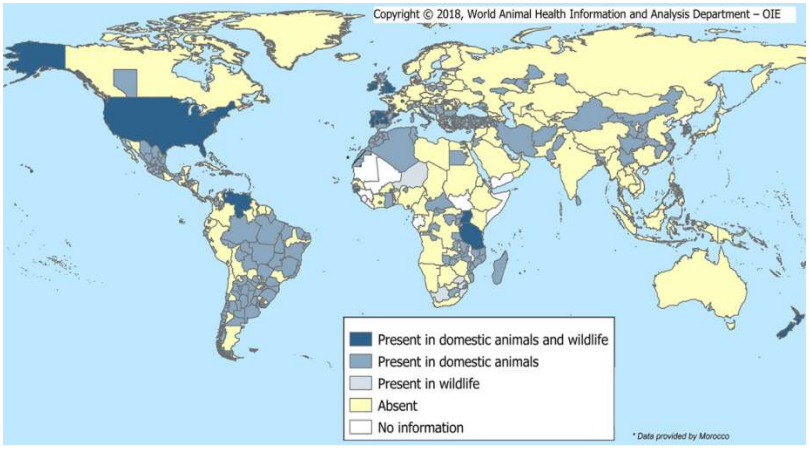

Figure 1. Map of the global distribution of bovine tuberculosis according to the latest dates of OIE World Animal Health Organization [21].

Among the 82 affected countries, 29 (35.4%) countries reported the presence of bTB in both livestock and wildlife. Two (2.4%) countries reported bTB present only in the wilderness, compared to 51 (62.2%), which indicated that only livestock was affected. Moreover, among these 82 affected countries, 66 (80.5%) provided quantitative data for outbreaks via WAHIS, demonstrating relatively good reporting of the global situation of this disease. The persistence of the infection in wildlife poses challenges for disease control in some countries due to the potentially significant impact of nature as reservoirs and spillover hosts [22].

In many industrialized countries, prevention based on regular tuberculin testing and removal of infected animals has effectively eradicated or notably decreased bovine tuberculosis from cattle herds [23]. These preventions are not affordable or acceptable in many parts of the world, particularly in these areas where bovine tuberculosis constitutes a public health risk [24]. More than 94% of the world's population lives in countries in which the control of bovine tuberculosis in cattle or buffaloes is limited or absent.

The primary goal of bTB control is to eliminate the risk of infecting humans. In developed countries, ideally, the goal of vaccinating livestock should be to prevent the establishment of infection [25]. This is an overwhelming challenge because the purpose of the vaccination program for most human and animal pathogens is to prevent clinical disease, not the infection itself. Since vaccination of cattle is unlikely to be fully effective, ancillary diagnostic tests related to vaccination are necessary for cattle, and vaccinated animals should not react to tuberculin or alternative diagnostic tests. The vaccines can be injected into livestock, and animals can be re-vaccinated if necessary, so that a variety of vaccines can be considered, including live vaccines and inactivated vaccines. Vaccines must be safe and acceptable in countries where meat and dairy products are imported.

Worldwide, various evidence points to serious problems related to the host of bovine tuberculosis, involving different host species under other geographic conditions. Well-known wild animal hosts of M. bovis have been identified in some regions [26-31].

Vaccination. Despite vast differences in vaccination efficacies with *M. bovis* BCG in cattle and humans, it is still the only commercially available vaccine candidate with potential benefits in reducing the prevalence and spread of bTB in the cattle population and the severity of a herd breakdown [32, 33]. One problem with using BCG in cattle is that vaccinated animals may respond to tuberculin skin tests [34].

The only potential vaccine currently available for bovine and human tuberculosis, BCG, is unlikely to meet the criteria for an ideal bovine vaccine. However, BCG remains the yardstick for judging the efficacy of any new vaccine or strategy. Calmette and Guerin obtained the BCG vaccine in 1921 by continuously passing *M. bovis* from glycerin-soaked potato slices. Like human trials, cattle challenges and field trials have shown that the ability of BCG to prevent infection with *M. bovis* (or *M.*

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tuberculosis in humans) varies widely [35]. The main characteristic of livestock protection is to reduce the degree of pathology rather than immunological sterilization. Furthermore, BCG vaccination failed to protect against natural infections [36]. As of 2018, more than 10 BCG vaccines have been grown worldwide, all based on attenuated strains of *M. bovis* grown by Calmette and Guerin in 1913 [37]. To avoid further deviation from the original BCG, since 1956, WHO has kept vaccine strains from freeze-dried seed lots. In terms of efficacy, no strain of BCG has apparent advantages over other strains. There is no global consensus on which BCG strainis the most suitable for general use [37]. 90% of BCG vaccines were produced using six common strains of mycobacteria (table 1).

Table 1

Widespread strains of Mycobacterium bovis.

Strain name	Manufacturer
Pasteur 1173 P2	France
Danish 1331	Denmark
Glaxo 1077	derived from Danish, manufactured by Glaxo
Tokyo 172-1	Japan
BCG-1	Russia
Moreau RDJ.	Brazil

In the last years, much knowledge about BCG use has been gained by coordinating challenge models, BCG strains, and doses. The challenge model approach uses 10^3 to 10^4 colony forming units (CFU) of *M. bovis* with a low challenge dose, by intrabronchial inoculation or aerosol administration, to reproduce natural diseases in the respiratory tract [38].

According to Buddle B.M. et al., BCG was more effective when administered subcutaneously at relatively low doses (10^4 to 10^6 CFU) [39]. In Wedlock D.N., et al. research, it is said that vaccination was effective at orally administered within relatively low doses (10^4 to 10^6 CFU) [40]. It also shows research on using different strains of BCG progeny (Pasteur and Denmark) [41]. Vaccination of very young calves (one less than one month) can induce a higher protection level than the 6-month vaccination. According to reports, previous sensitization to environmental *Mycobacterium* prevented calves from causing BCG protection [42]. At the same time, in another study, there is evidence that exposure to *M. avium* causes a certain degree of resistance to *M. bovis*. Protection from infection may mask BCG's subsequent induction of immunity [43,44].

Another study showed that calves vaccinated with BCG at birth and revaccinated six weeks later had reduced protection compared to calves vaccinated once. This result suggests that revaccination, when the calf is still developing an antigen-specific solid immune response, may induce an inappropriate immune response, so the timing of revaccination may be critical [45]. Field trials conducted in Mexico, Ethiopia, and New Zealand have proved that the BCG vaccine can protect cattle from natural exposure to *M. bovis*. In tests in Mexico and Ethiopia, the BCG vaccine was vaccinated under calfskin and then mixed with cows from tuberculosis reactors and unvaccinated control calves. In the Mexican study, after 12 months, compared with the unvaccinated group, the number of animals vaccinated with BCG was significantly less than the number of bTB who had a positive diagnostic test [46]. The results of the Ethiopian study were similar. Compared with the control group, the number of animals vaccinated with BCG after 10 to 22 months was significantly reduced, and the pathology or culture of *M. bovis* was positive. The BCG field trial has just been completed on an isolated farm in New Zealand, and *M. bovis* infection is prevalent in wild animals (possums, ferrets, wild boars, and wild deer). Approximately half of the around 1300 test-negative cattle received oral BCG mixed in a lipid matrix (Liporale, University of Otago, New Zealand) between 6 months and 2.5 years of age, and the remainder were not vaccinated. When these animals were slaughtered after reaching the target weight of beef cattle (3-4 years), preliminary analysis showed that the percentage of vaccinated animals infected with *M. bovis* (approximately 4%) was significantly lower than the corresponding unvaccinated group of animals [47].

BCG is currently the yardstick for judging all other vaccines, and two general ways can be used to develop vaccines that will have more robust protection against TB in cattle than BCG. One way is to increase the level of protection that BCG provides through complementary or booster vaccines. The other way is to develop a vaccine that completely replaces BCG. One of the most effective vaccination examples against bovine tuberculosis is priming the immune system with BCG and then boosting it with a subunit vaccine containing the protective antigens present in BCG (heterologous booster strategy). Subunits are based on DNA or viral vector booster vaccines. A variant of this theme is the simultaneous vaccination of BCG and subunit vaccines [48-50].

To reduce the tuberculin skin test response and create a safer vaccine for people with weakened immune functions. An auxotrophic mutant of BCG has been produced, which has mutations in genes involved in the

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metabolism of leucine and methionine. These mutants can no longer grow on a minimal medium and only grow when the appropriate amino acids are added. Their ability to grow in the body is also reduced. Vaccination of mice with these auxotrophic mutants has induced resistance to *M. tuberculosis* infection. Cattle vaccinated with the BCG leucine auxotrophic mutant will not cause a skin reaction to bovine PPD; however, the protective effect on bovine tuberculosis has not been evaluated. One of the most consistent and successful ways to improve the effectiveness of BCG against experimental challenges is to boost vaccines with viral vectors. The data generated in the past eight years showed that this replication-deficient human recombinant adenovirus type 5 vaccine expressing mycobacterial antigen 85A could repeatedly improve the efficacy of BCG in vaccinated cattle when applied to the BCG main/booster vaccine program. Compared with only BCG vaccination, the increase in the proportion of vaccinated animals with no visible tuberculosis lesions and the decrease in general pathology and histopathology demonstrate this improvement over BCG [51,52]. Another way to solve problems is to replace BCG to support attenuated *M. bovis* strains or transgenic BCG strains with improved immunogenicity because BCG is generated empirically, and recent genetic analysis has shown that BCG contains many gene deletions compared to virulent strains of *M. bovis* or *M. tuberculosis*. It should be possible to enhance BCG by eliminating *M. bovis* or strains of *M. bovis*. Specific genes are involved in virulence or enzymes that encode essential metabolic pathways. These mutants may be closer to the strain than BCG in terms of antigen precursor and antigen expression and, therefore, may have higher vaccine efficacy. Molecular biology techniques, including transposon mutagenesis, illegal recombination, and allelic exchange, have now been developed to inactivate genes in *M. bovis*, and screening techniques have been established to identify attenuated mutants. The atenuated vaccine used for the field requires two different genes, which causes it to be attenuated to eliminate the possibility of any back-mutation to a virulent strain. It would be advantageous if an immunological screening test could be developed to distinguish between vaccinated cattle and cattle infected with mycobacteria. Suppose the new vaccine strain also has more missing genes that induce DTH or other testable immune responses. In that case, an immunological test can be developed to distinguish vaccinated and infected animals. In preliminary studies, the esat6 gene has been removed from the wild-type *M. bovis* strain. Guinea pigs vaccinated with this mutant did not respond to ESAT6 protein in the skin test but had a solid response to bovine PPD. In contrast, animals inoculated with wild-type *M. bovis* strains responded strongly to ESAT6 and PPD. For example, *M. bovis* WAg500 and WAg501 strains that have been attenuated by chemical mutagenesis can protect cattle previously exposed to environmental mycobacteria from *M. bovis*, and BCG does not [53]. However, these vaccines have not been further developed due to undefined mutations. The RD1 deletion mutant identified based on *M. bovis Ravenel* also has a protective effect on cattle. In addition to attenuation, the deletion of the RD1 region also allows the use of RD1-encoded antigens, such as ESAT6 and CFP10, as DIVA antigens. However, the efficacy of this vaccine is comparable to that of the BCG vaccine, so it does not improve its effectiveness compared with BCG [54]. Recently, a study in cattle described better protection than BCG of *M. bovis* vaccine strains lacking the mce2A and mce2B genes. However, due to the presence of the RD1-encoded antigen, the vaccine will not diagnose DIVA immediately. Another strategy used is the overexpression of antigens in BCG, such as Ag85B, which can also improve the protection of cattle against tuberculosis [55]. Another method is to increase the efficacy of BCG itself by genetic modification to increase the immunogenicity of BCG; an example is the deletion of zinc metalloproteinase 1, which is encoded by the zmp1 gene. Bovine BCGzmp1 has been shown to induce a more significant immune response than BCG. The vaccine is currently being tested for its efficacy in vaccination and challenge experiments [56,57].

Nutritional deficiencies or the inability to grow in minimal media indicate that the strain has lost some metabolic functions. Method of attenuation of virulent *M. bovis* strains has been used successfully for several bacterial pathogens to develop attenuated strains with vaccine properties. As a first step in determining the efficacy of this method, several attenuated strains of *M. bovis* were developed using nitrosoguanidine to perform chemical mutagenesis in liquid cultures. After selecting the auxotrophic strains, the virulence of the auxotrophic bacteria was tested in guinea pigs. Two of these auxotrophic strains of *M. bovis* were tested, in guinea pigs was attenuated to protect cattle from bovine tuberculosis. After previous vaccination, calves in this trial had a high cIFN response to avian PPD, indicating exposure to environmental mycobacteria. Compared with control and BCG-vaccinated animals, vaccination with either of the two auxotrophic *M. bovis* strains resulted in a significant decrease in the number of animals with tuberculosis. The reason why BCG did not protect this experiment may be the result of previous exposure of the calves to environmental mycobacteria. The number of viable colonies in the vaccine prepared from the auxotrophic strain was 1-2×10^{-6} CFU/dose, which was higher than that of the BCG vaccine. This is unlikely to help improve the vaccine's efficacy because a BCG dose of 10^{-4}-10^{-6} CFU can induce a similar level of protection. Overall, it is encouraging that the newly derived attenuated *M. bovis* strain appears to perform better than BCG in this situation. Molecular biology techniques have been used to generate new attenua-

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ted strains of *M. bovis* with definite gene deletions. Vaccination with some of these strains induced protection against virulent *M. bovis* in guinea pigs and opossums, the same as the protection induced by BCG. These vaccines have not been tested in cattle [57].

In general, there is currently no vaccine candidate that can produce 100% immunity cattle to bTB. However, significant progress has been made in the past years. As the understanding of protection-related immune responses continues to deepen, a successful vaccination strategy is now a realistic goal.

Conclusion. Significant progress has been made in the development of tuberculosis vaccines for cattle. Most importantly, while progress is being made in human and bovine tuberculosis vaccine development, vaccine strategies are now being considered to supplement rather than replace BCG. Possible methods include the development of recombinant BCG vaccines, genetically attenuated *M. tuberculosis* vaccines, atypical mycobacterial vaccines, auxotrophic vaccines (transposon mutagenesis), or inactivated vaccines based on immunogenic proteins (such as ESAT6, Ag85 complex) subunit vaccine. The discovery of subcutaneous injection of plasmids expressing DNA-encoded antigens into muscles is potentially revolutionary. When this technology was applied to *M. tuberculosis*, many protective antigens were discovered, including Ag85, and the use of DNA vaccines as a possible treatment for tuberculosis opened a new avenue of research.

As mentioned above, the research and development progress of the tuberculosis vaccine has made people more optimistic that the vaccine will play an essential role in controlling and eradicating bovine tuberculosis.

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