



Brucellosis Vaccines: An Overview

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Abstract

Objective: Brucellosis is considered as an important zoonotic and worldwide infection with more than half of million human cases, which it occurs more and more in animals like as wild and live stocks. Sheep, cattle, and goats are animal samples that listed. Symptoms of this disease in human are consisted of: undulant fever, back pains, faint, spondylitis, arthritis and orchitis. This infection causes abortion in livestock, and this point is one of the important economic losses. Reduction in milk production is another problem in this disease too.

Materials and Methods: This study is conducted by reviewing of the literatures, which are related to this concern, and also visiting PubMed, ISI and other websites.

Results: We must pay heed that most zoonoses are maintained in the animal reservoir. These diseases, such as leptospirosis, Q-fever, brucellosis etc. which among them brucellosis can transfer to human via close contact with infected animals or consumption of unpasteurized dairy. Therefore, eradication of this infection in human population is depended on omission of that in possible methods among animals reservoir. Such methods are like test-slaughter and vaccination of livestock. Hence, vaccination is not alone method for controlling, but it is probably economic one.

Conclusion: Nowadays a vaccine which is effective for this disease control in human is not available. Of course presented some different vaccines for this infection in livestock that cleave live attenuated, killed bacteria and sub unit. Therefore, for eradication of this disease some vaccines with more effectiveness protection mid fewer side effects are necessary.

Keywords: Abortion, Brucellosis, Vaccines, Zoonoses

Introduction

Brucellosis is a zoonotic disease which can be created by different bacteria species, this disease has reminded as a serious problem for human and animal health around the world (1). Middle East, Indian subcontinent, and Mexico are some areas that have high consideration for this disease (2,3). Iran is an endemic region for brucellosis. Therefore, this infection is an enormous challenge for health in Iran. Brucella bacterium is a Gram-negative and is considered as an intracellular pathogen for mammals. This bacteria has some species such as: Brucella abortus (mostly case infection in cow),

Brucella melitensis (sheep and goat), Brucella canis (canine), Brucella suis (pig), Brucella ovis (ovine), Brucella neotomae (rat), Brucella pinnipedialis (pinniped), Brucella ceti (marine mammal), Brucella microti (vole) and Brucella inopinata (4,5). The first four specieses are also pathogenic for human and meanwhile it should be remembered that B. melitensis is the most important cause of brucellosis in human for now (6). Brucella bacterium is transferred by connection with infected animals or consumption of non-pasteurized dairy or undercooked meat to human (7). Although some cases of transfer, human to human of this infection

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had been reported (8,9). Wild animals could be proposed as a source of infection for human and domestic animals. Brucellosis disease in human has many appearances that personate from other diseases. The symptoms of this infection in human consist of: undulant fever, malaise, night sweat, lose weight, arthritis, endocarditis and spondylitis (10,11). Common clinical sign of brucellosis in livestock is abortion (12). This abortion is so common in the last trimester of pregnancy period of cows (13). Affected by this disease can cause infertility in livestock (14). Other symptoms of this infection are reduction of milk production in infected cows and hence some studies showed that a reduction in disease prevalence is associated with an increase in milk production (15). It showed be cleared that some symptoms of brucellosis in goat, like abortion and reduction of milk production are the same as symptoms that occurred in cows (16).

Annual estimating of economic losses from brucellosis in cows in Latin America is about 600 million USD (17) which expresses only a small part of effects caused by this disease such as abortion, reduction in fertility and reduction of milk production (18).

With this interpretation, the control programs of brucellosis are due to protection of these losses which brucellosis disease caused in human and animal and can be also caused some economic problems.

In as much as consumption of non-pasteurized dairy is the first common way of infection transition, occupation contingence such as animal husbandry is the second cause of this infection which it is common (19). Hence, pasteurization and occupational exposure control programs which mentioned in before paragraph are important for protection of this infection.

The major necessary programs for elimination of this disease in livestock are: sanitation, test and slaughter and vaccination of livestock. Sanitation programs are mostly consisted of ranchers, producer training to avoid contamination, especially in areas with high prevalence of disease.

Regular programs of test and removal in low level of infection conditions can be used for obtaining disease-free livestock (20). However, this program in high prevalence of brucellosis infection areas might be made unacceptable economic costs, so this reason, makes hard usage of that program (21). Livestock vaccination is a critical factor for controlling of brucellosis in human and animal, so vaccination of suspicious livestock in high prevalence infection areas play an important role in the elimination of this disease (22). In low level of infection areas, elimination, and inadequate vaccination programs and just rely on test and slaughter program can be enhanced disease activity (23). We should pay heed to this point that in some poor countries in which many cases could not compensate costs of infected livestock for owners, so they also could not eliminate them, in this condition

vaccination alone is not applicable (24). A good and ideal vaccine totally has two common features, harmless and effectiveness (25).

Vaccines must have these features:

- It must prevent of infection in both sexes (male and female).
- Prevent of abortion.
- Vaccination just for one time makes long term prevention.
- It should not contaminate milk and meat.
- Free of reversion to virulence.

A pathogen encountered by innate immunity of the host is triggered by pattern recognition receptors (26), among them can be noted to toll-like receptors. These receptors signal through the adaptor molecule MyD88. Moreover had been showed that MyD88-dependent signaling is essential for activation of interferon gamma (IFN γ) cellular producer in Brucella infection (27). IFN γ acts as a macrophage activator for brucellosis control that itself produced by TCD $_4^+$, TCD $_8^+$, T γ λ . Desired protection against intracellular bacteria mostly related to Th1 and production of IFN γ (28). Although the TCD $_8^+$, cells can directly distorted infected cells (29) and T γ λ through cytolytic activity make protection against pathogens (30). In the production of good and ideal vaccine against brucellosis important functions of the immune system must be strengthened and activate. After ruminant's vaccination, IFN γ production by Th1 is reported (31).

Among different vaccines, live attenuated vaccine just by consumption of a dose, has the greatest impact against intracellular pathogens (32) whereas strengthen the cellular immune feature in killed vaccines can be seen so weak. Vaccines which are produced by strain, smooth Brucella can make humoral responses. Body also against O-side chain Brucella bacteria produces antibody, which diagnostic way is based on serological tests. Hence, determination of humoral responses that are due to vaccination and natural response's body against bacteria is difficult (33). According to this point, should pay heed to vaccine production. So based on logical reason that is mentioned in before paragraph, usage of R mutants as a vaccine should have a minimum overlap with serological tests. However, we had some reports based on antibody extension against O-polysaccharide when faced by S brucella in ruminants which vaccinated by R vaccines (34). In the livestock most of vaccination had been done in intramuscular or subcutaneous form, of course, some ways like oral and intraconjunctival has been also used (35).

Recommended vaccines for brucellosis control are various that we will try explaining these varieties in this article.

Evidence Acquisition

Live B. abortus vaccine strain 19 (S19)

S19 is recommended as a live smooth attenuated vaccine for brucellosis control in adult cattle. In 1941

this vaccine introduced for using in the field (36). Strain S19 is smooth, so usage of this vaccine makes problems such as identification by serological test that we explained before. Although there is a method as competitive enzyme-linked immunosorbent assay which can be used in the field and this method serologically offering separation between vaccinated cattle by S19 and infected cattle (37). *B. abortus* S19 vaccination makes high immunity against abortion in cattle (38). However in pregnant cows, it causes abortion (39) and it should be mentioned that possibility in the last trimester of pregnancy is higher than other times (40). Reduction of milk production had been also reported after usage of this vaccine (34). This vaccine is virulent for human and infection caused by this vaccine, especially for a person who involving in cattle vaccination can be transferred by injured skin and dust (41,42). In countries with high prevalent of brucellosis infection, this vaccine is a choice (43).

H2>Live B. abortus vaccine strain RB 51

B. abortus strain RB51 used for a vaccine that is protective against cattle brucellosis (44). This vaccine is a Rough attenuated mutant of *B. abortus* strain 2308 which is as an alternative vaccine for live *B. abortus* vaccine strain 19. Because RB51, unlike S19, is rough and has a minimum rate for expressing Lipopolysaccharide O-side chain, so doesn't led antibody to presentation against this *Brucella* LPSO antigen which is identifiable by common serological test like tube agglutination test and complement fixation (45-47). RB51 against virulent strain 2308 introduces a protective cell-mediated immunity response (48). This vaccine against abortion has the same protective performance as S19 vaccine (46). However, usage of this vaccine in pregnancy period of cattle causes abortion (34), however reduced dose of this vaccine which is used for pregnant cattle is harmless (49). RB51 vaccine pathogenic for human, especially for veterinarians who are involving in cattle vaccination as unintended inoculation form to human (42). In some countries which have a low prevalence, usage of RB51 vaccine is preferable to S19 vaccine (43).

Live B. melitensis vaccine strain Rev-1

Rev-1 vaccine is as the best vaccine for brucellosis control in sheep and goat that offered by some organizations such as World Health Organization (WHO) and the World Organization for Animal Health (OIE) (50,51). This vaccine derived of a virulent *B. melitensis* which is a passage on the media containing streptomycin. Therefore strain Rev-1 obtains streptomycin-resistant (52). So as a conclusion of these passages strain Rev-1 doesn't have reverse as pathogenic effect. *B. melitensis* Rev-1 is a smooth strain (53). Usage of this vaccine in subcutaneous form because creates serological immune responses namely titer antibody enhancement against O antigen. Makes interference in interpretation of serological tests especially in the identification

between vaccine animals and natural infection animals. Whereas vaccination in conjunctival method decreased these serological meddler responses in serological tests which are explained before. In other words, conjunctival method accompany with brucellosis control program in small ruminants has more prosperity than other methods (54,55). It is necessary to explain that although usage of this vaccine is recommended for protection of Rams of *B. ovis* infection. But, antibody meddler problem is also considered in this case, the same as other cases which we explained before (56,57). Rev-1 vaccine is hindering abortion in vaccine livestock which was infected (58). Usage of completed dose or reduced dose of this vaccine in pregnant sheep and goat makes abortion risk in high level (59,60). Of course, vaccination with low dose recommended by some researchers for abortion problem in pregnancy period (61), however this issue is controversial. Rev-1 vaccine causes brucellosis infection in human that is risk-related occupations and is considered as accidental inoculation (62). Usage of Rev-1 vaccine in cattle makes better protective effect than S19 vaccine against *B. melitensis* (63). Brucellosis prevalence rates in boars in some areas of the world are high, so it makes domestic animal in high risk of disease (64). However, prevalence of this disease in pig in more areas of the world is low. Vaccination with RB51 strain in oral or intramuscular form or usage of killed *B. suis* as vaccine has a protective function for pig against infected boars to brucellosis (31,65).

45/20

Heat-killed *B. abortus* strain 45/20 vaccine introduced for consumption in 1920s (66) which is the kind of rough strain, so for this reason does not have interference with serological diagnostic tests. Of course this vaccine cannot be used as an alive vaccine, because in in vivo environment back to its smooth form (67). Vaccines which are produced by killed *Brucella* make insufficient immunity and by using of these vaccines in inoculation place use local reaction that all of these points are disadvantages of them. Uses of adjuvant can be effective for some problems (68). This vaccine is useful for pregnant livestock (34).

Sub unit vaccine

A vaccine which makes a protective and effective immunity against all types of *brucella* is introduced as an ideal one. The researcher could also reach to this aim by producing a Rough strain of *Brucella*. However, this kind of vaccine is explained before had some shortcomings. The subunit vaccines are introduced as a valuable replacement for other conventional vaccines, because they have some features such as: noninfectious and virulent (69). For producing of this vaccine used of purified proteins or DNA. Some reports had been showed that omp₃₁ is considered as nan outer membrane protein of *Brucella* can make protective effect infection in some

mouse models (70). Usage of unlipidated forms of outer membrane proteins and omp₁₉ for subunit vaccine make protective response from Th1 cells, which it shows the possibility of usage of this kind of protein in this type of vaccine (71). Omp₂₅ is also as a 25 k dalton outer membrane protein, which is introduced for usage in this kind of vaccine (72). DNAK as a cytoplasmic protein and SurA as a Periplasmic peptidyl prolyl cis-trans isomerase have been also evaluated in subunit vaccine, because they have the ability to introduce a humoral immunity and rich cytotoxic response (73). Some of these researches showed that liposomized proteins L7/L12 by effects like producing of Th1 cytokines make effective cell's immune and humoral responses (74). Besides of that cases other purified recombinant antigens as subunit vaccines have been studied and could make protective effect against brucellosis. These kinds of antigens consist of: Brucella lumazine synthase (BLS) which is a cytoplasmic protein and periplasmic binding protein (p39) which is as a periplasmic protein (75). DNA vaccines are rich inducer and produce long-lived cell immune responses such as Th1 and CTL and also humoral responses against pathogenic intracellular bacteria, especially brucella bacteria (76-78). However according to some expert's idea, immune responses that are due to this kind of vaccine are not more powerful than protein vaccine's responses (30). Of course some of these researches showed that injection of plasmid DNA carrying the BLS gene (PCDNA-BLS) as a immunogenic to BalB/C mouse could make humoral and cellular immune responses, which are more effectiveness than responses due to recombinant protein against *B. abortus* (79). DNA vaccine that codes for super oxide dismutase (SOD) can cause Th1 immune cellular response and protection against *B. abortus* 2308 strain (78). Yu et al. showed that combined DNA vaccine which is consisted of the genes encoding L7/L12, SOD and Bcsp31 antigens can make superior protection than live vaccine strains like RB51 and S19 (80) so this is one of the important advantages of DNA vaccines, it means usage of several antigens simultaneously are possible in them. One of the problems for consumption of DNA vaccine is the required amount of DNA to get the desired response (68).

Conclusion

According to the significance of brucellosis as a serious problem for public health, necessity of this disease control must be in the premiership. However available livestock's vaccines for this disease control had effective function until now, but had also some side-effects, so, because of this reason, for eradication of this disease some vaccines with more effectiveness protection mid fewer side-effects are more useful.

Ethical issues

We have no ethical issues to declare

Conflict of interests

We declare that we have no conflict of interests.

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