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MINI-REVIEW

Strategies for control and eradication of Brucellosis from endemic regions and infected herds

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Abstract

Brucellosis is an important zoonotic disease affecting large number of dairy herds and other animal species having impact on livestock farming, economy and public health in several regions of the world. The control of Brucellosis still remains a major challenge in veterinary practice owing to different levels of farming practices and perceptions among producers, lack of herd health policy, absence of screening of animals for prevalence of Brucellosis, lack of vaccination, movement of animals, occupational risks, chronicity and latency in animals, endemicity of the disease in the region/herds, increased demand and consumption of milk and other dairy products (raw and unpasteurized), etc. These factors not only hinder the control programmes but become critical in the long run to control or eliminate brucellosis among the herds or region. Several countries have achieved success in control and eradication of brucellosis through test and slaughter, vaccination and routine screening for brucellosis. As of now in the absence of test and slaughter as a matter of policy in our country in order to reduce the prevalence or to eradicate the brucellosis from the infected herds of the regions, vaccination coupled with routine screening for the disease seems to be the best and viable alternative. Therefore there is an urgent need of long-term control policy to facilitate control measures at regional and local levels. In this review some of the options suitable for control of disease such as vaccination (adult and calf hood vaccination), tracking of affected and vaccinated animals and public health education etc have been discussed for control of the brucellosis from the region.

Key words: Brucellosis, constraints, control, eradication, surveillance, vaccination.

Introduction

Brucellosis is caused by different species of bacteria of the Genus *Brucella,* which infect a specific animal species. It affects cattle, swine, sheep and goats, camels, equines and dogs. It may also infect other ruminants, some marine mammals and humans. The disease in animals is characterized mainly by abortions or reproductive failure. The animals (which) typically recover, and will be able to have live offspring following the initial abortion, may continue to shed the organisms in their secretions/excretions. Brucellosis in cattle (*B. abortus*) in sheep and goats (*B. melitensis*) and in swine (*B. suis*) are diseases listed in the World Organization for Animal Health (OIE) *Terrestrial Animal Health Code* and must be reported to the OIE (*Terrestrial Animal Health Code*-2012) on its status/occurrence. The highest incidence of brucellosis in animals is observed in the Middle East, the Mediterranean region, sub-Saharan Africa, China, India, Peru, and Mexico.

Brucellosis typically spreads when the animal aborts or gives birth. High levels of bacteria are found in the birth fluids of an infected animal. The bacteria can survive outside the animal in the environment for several months, particularly in cool moist conditions. They remain infectious to other animals which become infected by ingesting the bacteria, present in the contaminated feed and water. The bacteria also colonize the udder and contaminate the milk. The disease can also infect animals and humans through cuts in the skin, or through mucous membranes. Brucellosis is an occupational Zoonoses and a potential risk to veterinarians and farmers who handle infected animals and aborted fetuses or placentas. Brucellosis is one of the most easily acquired laboratory infections, and calls for strict safety precautions in laboratory when handling cultures and heavily infected samples.

Brucellosis is readily transmissible to humans, causing acute febrile illness – undulant fever – which may progress to a more chronic form and can also produce serious complications affecting the musculo–skeletal, cardiovascular, and central nervous systems. Movement and mixing of herds and species are probably the main risks for transmission of brucellosis, among animals. The sale of animals along the trade route and contact with local herds can contribute to the spread of infection. Humans acquire infection by consuming the contaminated milk and milk products and contact with the infected animals.

Constraints in the control of Brucellosis and need for effective control programme

The tropical region farming environments, coupled with lack of proper herd health practices create favorable conditions for the spread and transmission of brucellosis in the animal herds. The risks associated with lack of scientific practices make it difficult to control the problems of brucellosis and also lack of alternatives and simple and/or affordable solutions further favours the continuation of the problem, in animal populations.

Disease confirmation in animals leads to distress sale by farmers and spread of infection to other animals/place. Migration of infected herds with frequent contacts with other herds at common feeding grounds and near water sources favours the spread of the brucellosis. Increased trade movements of animals and regional and trans-border migration might pose an even greater risk, in particular, movement of cattle from uncontrolled areas. Animals are often moved from areas with low market value to areas of higher prices for trade and slaughter purposes. These movements often include older and weaker animals that may have an increased risk for being infected with brucellosis (Caporale *et al.,* 2009). Lack of cost effective treatment to animals, and lack of public awareness on the economic importance of the disease, etc all of which together act as risk factors for the occurrence of brucellosis may need to be considered when developing control programmes.

Control Strategies/ Options:

Control measures for animal brucellosis are based on the elimination of infected animals and/or the vaccination of susceptible domestic animal species. However, further actions, such as control of animal movements and epidemiological investigations, are needed to achieve the strategic objectives. Following are some of the main strategies as advised by OIE:

1. Elimination of infected animals: So that the source of infection for other animals and for humans may be eliminated. Though effective, through test and slaughter not practically feasible in our country.
2. Vaccination of young animals: Vaccination of the young animals helps to eliminate the infected animals, minimize the abortions, increases the herd immunity and reduces the incidence of infections.
3. Mass vaccination (young and adult animals): In highly endemic areas mass vaccination of animals of all age groups, is advocated. This will lower the economic cost, and the herd immunity is quickly established.
4. Heat treatment of milk or pasteurization/UHT are of quite effective in ensuring the safety of the milk as most of the pathogenic microbes are killed including *Brucella* and help in reducing the incidence of brucellosis among consumers of milk and milk products.
5. Hygiene and sanitation of infected premises and herds: Premises in and around the animal shed should be cleaned with disinfectants and all the debris should be disposed properly.

Vaccination

Mass vaccination is the primary way of brucellosis control in livestock. This should be combined with other measures such as methods that limit the spread of the pathogen, allow identification of animals and herds, and increase community participation in the control programme.

Brucella abortus strain 19 vaccines

The most widely used vaccine for the prevention of brucellosis in cattle is the *Brucella abortus* S19 vaccine, which remains the reference vaccine to which any other vaccines are compared. It is used as a live avirulent/attenuated vaccine and is normally given to female calves aged between 3 and 6 months or (4-8 months) as a single subcutaneous dose of 5–8 × 10^{10} viable organisms. A reduced dose of vaccine that contains 3 × 10^8 to 3 × 10^9 organisms can be administered subcutaneously to adult cattle, but some animals will develop persistent antibody titres and may abort and excrete the vaccine strain in the milk (Stevens *et al.,* 1995). Alternatively, it can be administered to cattle of any age as either one or two doses of 5 × 10^9 viable organisms, by the conjunctival route. This gives protection without the development of persistent antibody response and reduces the risks of abortion and excretion of organism in milk when adult cattle are vaccinated. However, in general, calves under 75 days of age are immunologically immature in response to S19 vaccine, and hence vaccination with this strain is not advised.

Vaccination with S19 vaccine has several advantages such as; the organism behaves as an attenuated strain when given to sexually immature cattle. In rare cases, it may produce localized infection in the genital tract. Antibody responses persist for 6 months or longer, and are likely to occur in a substantial proportion of cattle that have been vaccinated subcutaneously with the standard dose. The vaccine is safe for most animals if administered to calves between 3 and 6 months or (4-8 months) of age. It may also be used in adult animals at a reduced dose. The vaccine strain is stable and reversion to virulence is extremely rare.

Occupational risk: Vaccinators, if not properly protected with PPE (Personal Protective Equipments), run the risk of contracting infection. Hence, they are advised to take precautionary measures/care.

Brucella abortus strain RB51 vaccine

Since 1996, *B. abortus* strain RB51 has become the official vaccine for prevention of brucellosis in cattle in several countries (Schurig *et al.,* 2002). However, there is disagreement with regards to the protection of herd by strain RB51 as compared to the protection induced by S19 in cattle (Morgan *et al.,* 1969; Stevens *et al.,* 1994 and Uzal *et al.,* 2000). For adult cattle, the recommended dose is $1\text{-}3 \times 10^9$ viable strain RB51 organisms. In USA, calves are vaccinated subcutaneously between the ages of 4 and 12 months with $1–3.4\times 10^{10}$ viable strain of RB51 organisms (Olsen *et al*., 2000). In other countries, it is recommended to vaccinate calves (4–12 months of age) with a $1–3.4 \times 10^{10}$ dose, with revaccination from 12 months of age onwards with a similar dose to elicit a booster effect and increase immunity.

The full doses of RB51 vaccine when administered intravenously to cattle resulted in severe placentitis and placental infection in most of the vaccinated cattle, and excretion of RB51 strain in milk in number of vaccinated animals. It can induce abortion in some cases if pregnant cattle are vaccinated. Reduction in the dose of the vaccine is able to eliminate the source of side effects. However, this reduced dose does not protect against *B. abortus* when used as a calf hood vaccine, but does protect when used as an adult vaccine. Revaccination of cattle with a reduced dose of RB51 in endemic zones does not cause abortions and protects 94% of animals against field infection.

It should be emphasized that RB51, as well as S19, can infect humans and cause undulant fever if not treated after accidental exposure during vaccination programmes (WHO, 2004).

Brucella melitensis strain Rev. 1 vaccine

The most widely used vaccine for the prevention of brucellosis in sheep and goats are the *Brucella melitensis* Rev.1 vaccine and remain the reference vaccine with which other vaccines are compared (Cloeckaert *et al.,* 2002). The RB51 vaccine is not effective in sheep against *B. melitensis* infection. The Rev.1 vaccine is a freeze-dried suspension of live *B. melitensis* biovar 1. Rev.1 strain for the immunization of sheep and goats. It is normally given to lambs and kids aged between 3 and 6 months as a single subcutaneous or conjunctival inoculation. The standard dose is between 0.5×10^9 and 2.0×10^9 viable organisms. The subcutaneous vaccination induces strong interferences in serological tests but recommended in combined eradication programmes of cattle, sheep and goats (Cloeckaert *et al.,* 2001; Ewalt and Bricker, 2000). However, when this vaccine is administered conjunctivally, it produces a similar protection without inducing a persistent antibody response. Care must be taken when using Rev.1 vaccine to avoid the risk of contaminating the environment or causing human infection. In developing countries and endemic areas, vaccination of the whole population has to be considered as the best option for the control of the disease (Bosseray *et al.,* 1992). However, in spite of them Rev.1 vaccine is known to cause abortion and excretion of organism in milk when animals are vaccinated during pregnancy, either with a full or reduced dose. These side-effects are considerably reduced when adult animals are vaccinated conjunctivally (full dose) before mating or during the last month of pregnancy. Therefore, when mass vaccination is the only means of controlling the disease, a vaccination campaign should be recommended using the standard dose of Rev.1 administered by the conjunctival route when the animals are not pregnant or during the late lambing and prebreeding season.

The subcutaneous vaccination of young animals and the vaccination of adult animals, even at reduced doses, may lead to long-term persistence of vaccinal antibodies in a significant proportion of vaccinated animals that creates serious interferences in the serological diagnosis of brucellosis. As indicated above, conjunctival vaccination minimizes these problems and thus it is helpful in eradication programmes. Therefore, the serological diagnosis of brucellosis should take into account the vaccinal state of the herd and the overall frequency distribution of antibody titers detected in the group of animals tested (Raghunatha *et al.,* 2013).

Frequency of Vaccination

Vaccination should be carried out regularly during a period long enough to produce a fall in prevalence of the disease in population of animals, but complete elimination of the disease by testing, segregation and slaughter is far more complex and necessitates greater commitment and more financial investment. As a general rule, a control strategy based on mass vaccination is considered to be effective at low to medium (5% to 10%) animal or herd prevalence rates. Depending on the species and breeding system, 6 to 12 years of regular annual or biannual vaccination are required. Vaccination should be carefully planned with respect to periods of migration, and follow-up vaccinations may need to be planned for unvaccinated females that were pregnant at the time of vaccination.

The timing of vaccination of young stock is equally important. They should be vaccinated before sexual maturity in order to reduce the length of the period that they are unprotected and susceptible to infection. Biannual vaccination of young stock may be required especially in cases of year-round breeding programmes are planned. At lower prevalence rates, or when a significant portion of the livestock population has been vaccinated and protected, introduction of test and slaughter is recommended, either alone or combined with continued vaccination of young replacement animals, depending on disease prevalence. A rapidly effective vaccination strategy for brucellosis control in areas with high prevalence has not been identified, although a test-and-slaughter strategy, as used for resolving isolated foci of brucellosis or herds with high disease prevalence, has been recommended. Financially, this option is unattractive and unlikely to be feasible in resource-poor countries, like India. Moreover, uninfected and vaccinated replacement animals may not be available.

A key question that remains unanswered is when vaccination can be phased out, or stopped? No definite answer can be given as this depends on vaccination coverage, the presence and effectiveness of other complementary measures, and most importantly, the presence of an effective post-vaccination plan, to locate any sign indicating reappearance of the infection. Premature termination of vaccination has been a common cause of vaccination failure in brucellosis control programmes and can result in a rapid re-emergence of the disease.

New *Brucella* Vaccines: Recombinant strains versus S19 and Rev.1 vaccines

New mutant vaccines for brucellosis are being developed to overcome the disadvantage of conventional vaccines. In recent study, which evaluated recombinants made from strain 19, found that vaccination with strain M1-luc, induced similar protection against experimental challenge as vaccination with that of strain19 (Fiorentino *et al.*, 2008). *Brucella melitensis* recombinant strains in which outer membrane protein 25 (*omp25*), *asp24*, *cydA* and *virB2* genes have been deleted have been evaluated in goats (Schelling *et al.*, 2007; Smits *et al.*, 2013). Vaccination with the omp25 mutant gave similar protection against abortion as equivalent to that of Rev.1. Overall data suggested that Rev.1 vaccination was more effective at preventing infection than the recombinant strains. New technologies, such as DNA vaccines and nanoparticles, may be capable of delivering *Brucella* antigens in a way that induces protective immunity in domestic livestock or wildlife reservoirs of brucellosis (Blasco, 1997; Ward *et al.*, 2012). As such, all these are still in experimental stages and may become the vaccine for future.

Control programmes on herd basis

Epidemics of brucellosis in Cattle herds with enhanced abortions, test and disposal of reactors may be unsatisfactory in order to control the outbreak. Because spread occurs faster during epidemics than eradication measures employed. Vaccination of non-reactors with S19 vaccine is recommended, although it may cause abortion in small percentage of animals. In heavily infected herds with less abortion occurrence, all calves should be vaccinated with S19 immediately and positive reactors must be culled as soon as possible. Periodic Milk Ring Test (at 2-3 month interval), CFT, ELISA and culture tests are to be conducted. In herds with low degree of infection/occurrence, calves should be vaccinated and positive reactors have to be culled.

Calf hood Vaccination

Vaccinated animals have a high degree of protection against abortion and 65-75% are resistant to most kinds of exposure. The remaining 25-35% of vaccinated animals may become infected but usually do not abort. Calf hood vaccination has several advantages such as; it is effective method of control of abortion in the herd, and there will be reduction in the reactor losses in herds and also less number of tests to eliminate brucellosis from infected herds. It has several disadvantages such as, serum residual vaccine titres may be there, and show persistent positive MRT for long time, also show persistent S19 infection in a small percentage of adult vaccinates.

Adult Vaccination

Vaccinating adult cattle with S19 reduces number of infected cows in large dairy. Complete eradication can be done by test and slaughter policy. In *Brucella* free herds where heifers are vaccinated, positive titers may persists for up to 18 months. In most control programmes, vaccination is usually permitted up to 12 months of age, but the proportion of persistent post vaccinal serum and whey reactions increases with increasing age of vaccinates. Vaccination of bulls is of no value in protecting them against infection and has resulted in development of orchitis and presence of *B. abortus* strain 19 in the semen.

Systemic reactions to S19 vaccine occur rarely in both calves and adults and may be more severe in Jersey calves than in other breeds. Symptoms like local swelling, particularly in adult cattle and high fever lasting for 2-3 days, anorexia, listlessness and temperature drop in milk yield may be noticed. Vaccination with S19 vaccine does not have a deleterious effect on the subsequent conception rate. RB51 vaccine is as efficacious as S19 vaccine but much less abortigenic in cattle. The organism is cleared from the blood stream within 3 days and is not present in nasal secretions, saliva or urine.

Adult vaccination, even with a low dose should not be used in uninfected herds because of the persistent titers, which may also lost for more than 12 months in up to 15% of vaccinated animals and because of the potential for abortion.

Supplementary Measures

1. **MOSS (Monitoring and Surveillance)**: An up-to-date livestock census and an effective surveillance system are crucial for the control of brucellosis, as the disease may quickly re-emerge from remaining foci of infection. Although test and slaughter may be an option for the management of remaining or re-emerging foci of infection, such a strategy is frequently not an option because of the cost and culture/tradition. The surveillance system determines baseline prevalence, monitors the progress and effectiveness of the control programme, and is crucial for disease monitoring after the cessation of vaccination. Mass vaccination should minimize further spread of disease, but small foci may persist and post vaccination surveillance is essential for their early detection.
2. **Tracking of vaccinated and infected animals:** It is essential for determining population coverage and identifying non-vaccinated herds or non-vaccinated animals in vaccinated herds. Although a simple identification method such as an ear punch might be sufficient for vaccinates it does not allow identification of individual animals, which is preferable when tracing sources of infection, or controlling trade and livestock movement.
3. **Hygienic measures**: These include isolation or disposal of infected animals, disposal of aborted fetuses, placentas and uterine discharges and disinfection of contaminated areas. All cattle, horses and sheep and goats should be tested for brucellosis as a matter of routine herd health programme.
4. **Public Health Education**: Calf hood vaccination programme can be considered for eradication in an area when the level of infection is below 4% of the cattle population. Infected herds are quarantined and tested at intervals until negative. It gives protection and it facilitates control and eradication of Brucellosis from the region.

In this regard, in our country a National Control Programme on Brucellosis has been taken up by Project Directorate on Animal Disease Monitoring and Surveillance (PD-ADMAS), ICAR, Hebbal, Bangalore, which aims at reducing the impact of a disease on human health and to reduce the economic losses, by adapting biannual village level screening of pooled milk samples and biannual *B. abortus* S19 vaccination for female calves of 4 to 8 months age.

Conclusion

Brucellosis is important Zoonoses affecting both animal health/production and human health. It is also important an important occupational Zoonoses. As of now, the control of brucellosis in domestic/wild animals mainly depends on the prompt and regular vaccination (S19), MOSS, hygiene and sanitation in animal herds, source traceability of the disease and people’s participation and co-operation. It should be remembered that vaccination to the animals is the only best available option and vaccinators should take utmost care while vaccinating the animals to avoid the contract of infection. Effective treatments are available for human infection and should be treated properly if diagnosed for brucellosis.

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