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REVIEW ARTICLE

Vaccination against Hemorrhagic Septicemia of Bovines: A Review

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ABSTRACT

Hemorrhagic septicemia is an important disease of cattle and buffaloes in Asia, particularly the South and Southeast Asia. Since outbreaks lead to numerous deaths and severe economic loss, control by vaccination is extremely important. However, the current use of broth vaccine for quick coverage in outbreak area followed by the oil adjuvant vaccine in the surrounding areas has failed to control the disease. The recommended annual vaccination using oil adjuvant vaccine prior to the monsoon season has not been effectively implemented leading to vaccination failure. Furthermore, the required vaccination coverage of 70% animal population has not been fulfilled, exposing the unvaccinated animals to disease outbreaks. Thus, a modified vaccination regime to improve vaccination coverage is suggested. This involves two major aspects; the use of OIE disease zoning concept to reduce area size and population number for vaccination, and the use of live attenuated vaccine to enhance vaccination coverage. The zoning concept that identifies the hotspots to be vaccinated with the oil adjuvant vaccine is most suitable to be adopted in the South Asia where animals are kept intensively with close human contact. On the other hand, the use of live attenuated vaccine might be suitable in Southeast Asia where animals are kept under extensive system with minimal human contact. Nevertheless, the respective veterinary authority should guaranty vaccination coverage of at least 70% of the susceptible animal population to effectively control disease outbreaks.

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INTRODUCTION

Hemorrhagic septicemia in cattle and buffaloes is one of the important diseases not only in Malaysia but also in many parts of the world, particularly Asia. It is caused by *Pasteurella multocida* B:2 leading to pathological changes in the respiratory tract (Khin *et al.*, 2010; Hussain *et al.*, 2014; Annas *et al.*, 2015a), septicemia (Annas *et al.*, 2015b) and disease outbreaks in cattle and buffaloes (Rafidah *et al.*, 2010; Khan *et al.*, 2011; Gajendragad and Uma, 2012; Otomaru *et al.*, 2015). In Malaysia alone, outbreaks of this disease lead to an estimated annual loss of USD500,000.00 (Joseph, 1989) while parts of India report loss of USD130,000.00 due to hemorrhagic septicemia between 2007 and 2011 (Singh *et al.*, 2014).

While stressful conditions contribute significantly to the outbreak of hemorrhagic septicemia in cattle and buffaloes, control of this disease through the control of stresses proved difficult (Benkirane and De Alwis, 2002; Moustafa *et al.*, 2015). Thus, vaccination appears to be the most common and cheap mean of controlling outbreaks of hemorrhagic septicemia. Vaccination against hemorrhagic septicemia was practiced as early as 1928. It is now widely practiced and has been adopted in most of the countries experiencing the disease (Ahmad *et al.*, 2014).

Since hemorrhagic septicemia typically leads to acute death, control of the disease by means of treatment using antibiotics and serum therapy has been in vain (De Alwis, 1999). Thus, most research activities on hemorrhagic septicemia are being focused on the control of the disease through vaccine development and vaccination. Research on control of hemorrhagic septicemia was carried out since 1960s (Thomas, 1968). Eventually, an effective hemorrhagic septicemia oil-adjuvant vaccine was produced in 1978 (Chandrasekaran and Yeap, 1978; Ahmad *et al.*, 2014). Although an effective vaccine has been developed (Gowrakkal *et al.*, 2014), the disease could not be effectively contained in countries where hemorrhagic septicemia is endemic. This is evidenced when approximately 3,089 deaths were recorded from outbreaks of this disease between 1994 and 2009, leading to a loss of approximately USD3.9 million (Kamarudin, 2005; Rafidah *et al.,* 2010). A study in Pakistan revealed a total loss of USD20 million (Farooq *et al.,* 2007) and USD784 million in India (Singh *et al.,* 2014). The main reason was the low vaccination coverage (Saharee and Salim, 1991) due to several factors including the difficulties in injecting the oil adjuvant vaccine since there are many types of cattle management practiced in many countries (Benkirane and De Alwis, 2002). Thus, a different approach should be studied and adapted to effectively increase the vaccination coverage of cattle against hemorrhagic septicemia (OIE, 2012). This paper discusses some issues that lead to vaccination failure and suggests vaccination modification to enhance the effect of vaccination against hemorrhagic septicemia.

Issue in the control of hemorrhagic septicemia: Most buffaloes in the world are located in Asia and buffalo remains as high economic importance for many smallholding farmers in developing countries, particularly in Asia (Cruz, 2010). Southeast Asia keeps mostly swamp buffaloes for meat, where they are allowed to graze in the harvested paddy fields, along roadsides and on the edges of cultivated plots with minimal human contact (Yindee, 2011). South Asia keeps river buffaloes for milk and they are kept mainly within the village, usually within the house compound close to humans (Cruz, 2007).

Even though vaccination against hemorrhagic septicemia has been carried out in cattle and buffaloes of most affected developing countries, the effectiveness remains uncertain. Although many factors are found to influence the potency of hemorrhagic septicemia vaccine (Sarwar *et al.,* 2015), the main reasons for the failure, among others are the ineffective vaccination regime and the poor vaccination coverage.

Vaccination Regime: The popular oil adjuvant vaccine is able to provide protection against experimental hemorrhagic septicemia in young buffalo calves beyond 250 days (Shah *et al*., 1997). It has been shown that protective immunity induced by the oil adjuvant vaccine was increased by 10^5 folds for lethal challenge, while secondary vaccination induced a further 10-fold increase in resistance to lethal challenge. The protection lasted for at least 20 weeks after a primary oil adjuvant vaccination (Dawkins *et al*., 1991) and lasted 12 months following booster dose (Sarwar *et al.,* 2015). With a much superior immune response and longer lasting protection provided by the oil adjuvant vaccine, it is only natural that many countries with endemic problem of hemorrhagic septicemia tend to shift to the oil adjuvant vaccine for control of the disease (De Alwis, 1993; Ahmad *et al*., 2014). The vaccination regime adopted for the oil adjuvant vaccine is yearly intramuscular vaccination that gives both a higher degree and a longer duration of immunity up to 1 year (Shah *et al*., 1997; Muniandy *et al*., 1998). For a maximum effect, vaccination should be given one month prior to the monsoon or rainy season (Bain *et al*., 1982; Yoe and Moktar, 1993). Therefore, Vietnam recommended vaccination in February-March (Kral *et al.,* 1993), Malaysia in September (Jamaludin, 1993) and Sri Lanka between June and August (De Alwis, 1999) while vaccination coverage should be at least 70% (Neramitmansook, 1993). In spite of the recommended vaccination regime, most endemic countries practice vaccination once there is an outbreak.

Once there is an outbreak, vaccination is quickly done using broth bacterin vaccine to provide quick but low level coverage in the affected area (Chandrasekaran *et al*., 1994). This is followed by ring vaccination in the surrounding areas using the oil adjuvant vaccine to provide a solid coverage that lasted for a year (De Alwis, 1993). Then the recommended yearly vaccination regime covering 70% of the animal population was quickly forgotten until another outbreak. This stopgap measure in controlling hemorrhagic septicemia provides short-term solution but allows later outbreaks of hemorrhagic septicemia since frequency and timing of vaccination are important in controlling the disease. Failure of the veterinary authority to implement the recommended vaccination regime and ensure solid protection of cattle and buffaloes remains a major contributing factor to the frequent outbreaks of the disease in many Asian countries.

Vaccination Coverage: While the oil adjuvant vaccine provides higher degree and longer duration of protection, the thick viscosity of the oil adjuvant vaccine is of major concern. It is difficult to be drawn into syringes and difficult to be administered in the field while local swelling, sterile abscesses, and post-vaccination shock were reported in some animals following vaccination with the oil adjuvant vaccine (Joseph, 1979; Bain *et al*., 1982; Neeramitmansook, 1993). Therefore, injectable oil adjuvant vaccine is less popular in the field although it has been shown to stimulate prominent and prolonged immunity (Muniandy *et al*., 1998). Furthermore, livestock production system in many developing countries, particularly the Southeast Asian countries uses either extensive or semi-extensive type of management with little animal handling. This leads to difficulties in gathering animals for vaccine injection resulting in low vaccination coverage of approximately 17% two decades ago (Saharee and Salim, 1991) that reduced further to 7% recently (Rafidah *et al.,* 2010). This issue has been reported in Malaysia, the Philippine, Vietnam, Thailand and Indonesia (Syamsudin, 1993; Yeo and Mokhtar, 1993). Thus, disease outbreaks are often reported in the unvaccinated animals (Rafidah *et al*., 2010).

Vaccination coverage of less than 80% may lead to the recurrence of disease outbreaks (Bain *et al*., 1982; Syamsudin, 1993). Extensive nature of animal keeping, poor accessibility to animals, poor facilities and the reluctance of owners to vaccinate routinely in the absence of disease contribute to disease outbreaks (Mosier, 1993). A pilot hemorrhagic septicemia eradication program, based on mass vaccination over a period of 3 years, was conducted in an Indonesian island in which 89%, 94%, 82%, 93% and 80% of cattle, buffalo, goat, sheep and pig population, respectively, were vaccinated. The incidence of hemorrhagic septicemia was re-evaluated after a year and was found to reduce the incidence to 53 cases with 5 carrier animals. Thus, another mass vaccination was carried out for another year that eventually revealed no cases of hemorrhagic septicemia (Syamsudin, 1993). It was concluded that vaccination coverage of 70% leads to sporadic occurrence of hemorrhagic septicemia while coverage of more than 80% is able to significantly reduce the incidence of the disease.

Modification in the concept of vaccination regime

Concept of zoning: The Office International des Epizooties (OIE) recommended that hemorrhagic septicemia free zone could be established when there has not been report of the disease for at least 3 years (OIE, 2015b). This standard has taken into consideration the carrier status of animals following an outbreak. Thus, in developing control strategy against hemorrhagic septicemia, two zones need to be established; the infected zones that reported outbreaks of hemorrhagic septicemia in the last 3 years and the free zones that were free of hemorrhagic septicemia in the last 3 years. When the concept of free and infected zones was applied to Peninsular Malaysia for example, it can be cornered into only two out of 11 states. This reduces the number of animals to be vaccinated from a total of 737,659 head in Peninsular Malaysia to a total of 169,795 animals in these two states (DVS, 2015), a 77% reduction in number of animals to be vaccinated. Furthermore, the zone concept can be further applied to identify the infected and free districts within the infected states. This zoning exercise eventually reduces the area size for vaccination and the number of animals to be vaccinated. Therefore, adopting the earlier regime of annual vaccination prior to the monsoon season within the infected zones may enhance the vaccination coverage to reach the minimum target of 70% vaccinated population (Kamarudin, 2005). This zoning method is deemed most suitable for the South Asian countries where animals are kept intensively with close human contact.

The concept of zoning and vaccination require efforts to protect the free zone from incursion of infected animals and to ensure outbreaks in the infected zone are eliminated within the zone. Implementing strict measures on animal movements especially from infected zones can protect the free zone. Thus, importation of animals into the free zone can only be allowed from other free zones. When importing from infected zones, the imported animals must not show clinical sign, were kept in quarantine station for a month and negative of the causative organism in the naso-pharynx during quarantine, and were vaccinated not less than 30 days prior to shipment. This measure requires establishment of inter-state quarantine facilities and regular monitoring of the animals in quarantine. Thus, it requires investment in infrastructure and additional manpower to manage the facility (Kamarudin, 2005).

Increasing the vaccination coverage: Injectable vaccines such as the oil adjuvant vaccine have been shown to stimulate prominent and prolonged immunity. However, livestock production system in many developing countries uses either extensive or semi-extensive type of management with little animal handling. This leads to difficulties in gathering animals for vaccine injection, thus vaccination coverage is low (Saharee and Salim, 1991). Disease outbreaks are often reported in the unvaccinated extensive animals. Therefore, the use of intranasal live attenuated vaccine that allows self-vaccination and increases vaccination coverage among animal population might be the answer (Rafidah *et al.*, 2011; Saleem *et al.*, 2014). Intranasal administrations not only stimulate the mucosal immunity of the exposed host but also transmit the organism to the in-contact hosts and eventually stimulate their mucosal immunity. All (100%) non-vaccinated animals that were kept together with the intranasally exposed animals showed similar stimulation leading to 100% protection of the in-contact animals against challenge (Rafidah *et al.*, 2012). This is an interesting finding since there is a possibility of intranasal vaccination with live vaccine leads to self-vaccination of the in-contact animals and should be considered to be used in the annual vaccination regime for Southeast Asian countries where most animals are kept semi-intensive or extensively with minimal human contact.

Recently, *Pasteurella multocida* mutants that are capable of providing heterologous protection against infection caused by virulent *P. multocida* has been patented (Garcia *et al.*, 2011). The said mutants are defective in *fur ompH* and *fur ompH galE* genes and are prepared as live vaccine to provide protection against infection by *Pasteurella multocida* including hemorrhagic septicemia.

Earlier, a *P. multocida* B:3,4 isolated from a fallow deer was used as a live vaccine was shown to provide partial protection in cattle and buffalo calves when given either subcutaneously or intradermally, the live vaccine was further improved by delivery via intranasal aerosol (Myint *et al*., 1987). The safety, efficacy and cross-protectivity of the live intranasal aerosol hemorrhagic septicemia vaccine were tested in young cattle and buffaloes in Myanmar, where more than 1.5 million animals were vaccinated between 1989 and 1999 at a recommended dose of 2×10^7 viable organisms (Myint *et al*., 1987). Intranasal administration of 100 times the recommended dose to 50 cattle and 39 buffalo calves proved innocuous. Three of three (100%) vaccinated buffaloes were protected at 7 months after vaccination while three of four (75%) buffaloes were protected against a subcutaneous challenge with serotype B:2 after 12 months. Similarly in cattle, eight of eight (100%) cattle survived a serotype B:2 challenge at 12 months after vaccination. The protection seemed to come from serum antibodies, which was detectable by the passive mouse protection test. The serum antibodies remained high in cattle at 10 days and five weeks after they were vaccinated. Furthermore, the serum of vaccinated cattle provides passive cross-protection in mice against infection with *P. multocida* serotypes E:2, F:3,4 and A:3,4 (Carter *et al.*, 1991; Myint *et al.*, 2005). However, the vaccine has occasionally been associated with sporadic outbreaks of the disease (Jones and Husseini, 1982; Rimler and Wilson, 1994; OIE, 2015a) and occasional virulence to young animals (Myint and Carter, 1989), making it unacceptable (Benkirane and De Alwis, 2002). The empirically derived, live, attenuated vaccines can protect against heterologous serotypes, but because the basis for attenuation is undefined, reversion to virulence is not uncommon (Adler *et al*., 1999).

Previously, an attenuated live vaccine derived from a virulent *P. multocida* B:2 isolate (strain 85020) was developed by deletion of the *aroA* gene (Hodgson *et al.*, 2005). It was thought to be a suitable live vaccine candidate that recognised the 37kDa protein as the major immunogen, producing a high degree of protection against *P. multocida* B:2 infection in mouse and calf models (Tabatabaei *et al.*, 2002, 2007; Ataei *et al.*, 2009). However, upon experimental testing in cattle calves via the intramuscular and intranasal routes, it was observed that only the intramuscular vaccination route was able to provide protection against *P. multocida* B:2 infection. On the other hand, the intranasally vaccinated cattle calves were not protected (Hodgson *et al.*, 2005). Thus, it was concluded that the *aroA* mutant strain is an effective live-attenuated vaccine only if given via the intramuscular route. Therefore, this does not effectively contribute in improving the vaccination coverage problem in hemorrhagic septicemia.

Coordinated Vaccination Program: Most cattle and buffaloes in Asia belong to smallholders (Cruz, 2007), who are unaware of the vaccination program and the importance of controlling hemorrhagic septicemia (Kral *et al.,* 1993). Therefore, they rely on the coordinated efforts by the veterinary authority for proper implementation of vaccination program that enables the control of hemorrhagic septicemia. On the other hand, veterinary authorities are facing with the lack of cooperation from the smallholder farmers in implementing the vaccination program. Only during an outbreak will the farmers cooperate in massive vaccination program (Kral *et al.*, 1993). Awareness of control measure that should achieve 70% vaccination coverage by the smallholder and more importantly by the veterinary authority is important in trying to control the disease. Veterinarians, veterinary authority and animal health field officers as well as the smallholder farmers should be trained to enhance awareness and improvement of the quality of the veterinary extension service (Benkirane and De Alwis, 2002) toward achieving the 70% vaccination coverage.

Although most literatures suggest annual vaccination prior to the monsoon season, it is advisable for the veterinary authority to analyze the outbreak pattern in their country to understand the epidemiological pattern that is important in developing a vaccination regime.

Conclusions: Among the reasons for failure of vaccination against hemorrhagic septicemia is the inability to vaccinate more than 70% of the animal population. This is due to the large number of animals to be vaccinated and the inability to restrain enough animals for vaccination. Therefore, the concept of zoning could focus on the susceptible population for vaccination while the use of live vaccine might enhance self-vaccination toward increasing the number of vaccinated animal population.

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