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Haemorrhagic septicemia: A persistent nuisance in Indian livestock review

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Abstract
Hemorrhagic Septicemia (HS) caused by *Pasteurella multocida* (serotypes B:2 and E:2), is an acute, fatal septicemic disease. India being an endemic country faces higher mortalities among the affected animals persistently. Appropriate use of potent vaccines, *viz*., live attenuated vaccine, recombinant vaccine; subunit vaccine, DNA vaccine etc. help extensively in prevention of HS. As HS causes huge production losses and imparts the maximum mortalities, it is alarming in disguise to emphasize on prevention and control strategies compulsorily, prioritizing the regular surveillance, monitoring, and administration of the most potent vaccines given to all the concerned animals in the field. Thus, the current review paper concentrates on a number of aspects in Asian nations (India), which shows to be the most effective weapon in winning a control war against pasteurellosis.

Keywords: Hemorrhagic septicemia (HS), Immunotherapies, *Pasteurella multocida*, vaccines

1. Introduction
Haemorrhagic Septicemia (HS) is a lethal form of pasteurellosis and one of the most economical contagious bacterial diseases of tropical Asian animals, mainly cattle and water buffaloes. It is caused by defined serotypes (B2 and E2) of *Pasteurella multocida* and came under OIE List B disease. Morphologically, it is gram negative coccobacilli residing as a commensal organism in the nasopharynx of cattle, water buffalo, bison, infrequently in pig, sheep and goat. However, water buffaloes are more prone to HS than cattle (Cuevas *et al*., 2020) [17]. It has been also reported in horses, donkeys, camels, yaks, elephants, various species of deer and other wild ruminants, producing a fatal form of pasteurellosis (OIE 2019) [107]. The first account of acute pasteurellosis was reported in species of cattle, swine and deer (Cuevas *et al*., 2020) [17].
In 1880, Louis Pasteur used *Pasteurella multocida* for development of an attenuated vaccine. This adaptable pathogen remains one of the most fascinating organisms, with numerous secrets buried deep within its DNA (Harper *et al*., 2006) [59]. Despite the fact that various vaccine formulations are commercially available against HS as outbreak occurs in India every year. Immunization measures at the start of an outbreak are ineffective in preventing high mortality rates, therefore identifying HS endemic areas and prioritizing obligatory vaccination throughout the state is critical to preventing outbreaks. The present review focus general characteristics, etiology, transmission, incidences in India, gross lesions, diagnosis and recent advancements in vaccines with prophylactic measures for HS.

1.1 Sources and transmission
The bacteria are opportunistic in nature, meaning it prefers to infect people who are immuno-compromised or have recently experienced stress. *Pasteurella multocida* is spread through ingestion or inhalation, either directly or indirectly through fomites such as contaminated feed and water (Abubakar and Zamri-Saad, 2011) [2]. Hemorrhagic septicemia is considered to spread mostly by respiratory secretions, although they have also been found in other secretions and excretions, such as faeces and urine (OIE 2019) [107]. Usually, infected animals become carriers retaining these organisms in lymphatic tissues accompanying with the upper respiratory tract and intermittently shedding in nasal discharges. Stress is main factor to shed these pathogens.

Nucleic acids were also discovered in the lung, reticulum, ileum, and ureter of experimentally infected buffalo calves in 6 weeks after inoculation, despite the fact that corticosteroids did not cause shedding from these sites after 15-17 days (Shivachandra *et al*., 2011; OIE 2019) [134, 107]. Carriage of P. multocida in cattle and water buffalo appears to be highest shortly after an outbreak, with up to 20% of surviving animals becoming carriers for a time, but then it is drop by 5% or less soon after 6 months (OIE 2019) [107]. *P. multocida* can survive for hours in the environment and not viable for long periods, and live-in days in damp soil or water (Shivachandra *et al*., 2011) [134]. Transmission is aided by rainy weather and high humidity. Biting arthropods do not appear to play a role in the disease's epidemiology.

1.2 Biochemical and structural characteristics

Scientist Louis Pasteur carried out the isolation of Pasteurella in 1880 as the etiological agent of fowl cholera; since then, several inductions had made in its categorization and designation (De Alwis, 1999; Peng *et al*., 2019) [38, 113]. In 1929, based on various biochemical and structural characteristics, the related organisms were grouped together (Dabo *et al*., 2007; Harper & Boyce, 2017) [36, 58]. Lipopolysaccharide and the capsular structure are the factors considered for classification of *Pasteurella* into various serotypes and serovars. The *Pasteurella multocida* was classified into 5 capsular sero-groups, *viz*., A (hyaluronic acid), B (arabinose, mannose and galactose), D (heparin), E (uncharacterized) and F (chondroitin) and 16 somatic serotypes on the basis of passive hemagglutination and gel diffusion precipitation tests. The nomenclature of the isolates consists of capsular serogroup letter followed by a somatic serovar number (Rosner 1992; Boyce 2000; Harper 2012) [124, 21, 60]. Besides, the isolates of *Pasteurella multocida* associated with the causation of HS were found to be member of type B of Carter (1955), Type 6 and Type 2 of Heddleston (Heddleston and Rebers, 1972) [65] classification systems.

1.3 Microscopic identification and Isolation

Detection and diagnosis of pasteurellosis, the conventional methods are given the upmost priority, which relied upon microscopic identification of the organism and/or bacterial isolation on selective media (Christensen 2010) [30]. *P. multocida* reveals rod shaped in bipolar staining with Leishman's, Methylene blue or Giemsa stains. The isolation can be made on 5% sheep's blood agar (preferable media), Chocolate agar, Mueller Hinton agar and BHI agar at 37 ºC (OIE 2012; Panna *et al*., 2015) [108, 111]. On the other hand, the phenotypic characterization based on morphology, carbohydrate fermentation patterns and serology are a bit challenging, though, the biochemical strips can be used despite of its limited accuracy leaving difficulty in species differentiation (Hunt 2000; Wilson & Ho, 2013) [71, 156].

1.4 Clinical Signs and symptoms

Most of the cases of HS are found to be peracute followed by death within 24 hours (Shivachandra *et al*., 2011) [134]. Affected animals showed fever, respiratory distress, nasal discharge and excessive salivation, however these signs are unnoticed due to short period of disease (Odugbo *et al*., 2005) [106]. Acute cases are characterized by a fever that can last up to three days. It is characterized by fever, lacrimation, hyper salivation, recumbent sometime, anxiety, mucopurulent nasal discharge, and loss of appetite (Kawasaki *et al*., 2015; Moustafa *et al*., 2017) [77, 98]. Along with-it, oedematous swelling also seen in pharyngeal region which extend upto brisket, difficulty in respiration, cyanosis and diarrhea.

1.5 Characteristics gross findings

Grossly, severe sepsis usually seen and characterized by extensive hemorrhages along with hyperemia and edema. Occasionally, ecchymotic hemorrhages are seen, mostly on heart. In peracute cases, there are only few lesions and sometimes no lesions are observed. Some location such as mandibular region or neck or brisket or legs, subcutaneous edema may be occurred. Petechial hemorrhages are found on all over internal organs, mainly to the serosal surfaces. The lungs are edematous and congested, and hemorrhages may be present. Though it is feasible, extensive pneumonia is unusual. In some animals, digestive tracts are hyperemic and congested, and petechiae and ecchymoses can appear in the abomasum and intestinal mucosa. Lymph nodes (mostly pharyngeal and cervical) are swollen and congested. Hemorrhagic gastroenteritis is common in calves. Prior to death, neither group of animals was observed to exhibit any evident neurological indications (OIE 2019) [107].

1.6 Diagnosis

Further with the advancements of technology and disease diagnostics, molecular detection of virulent genes decodes the confirm identification of the organism's existence. In fact, Polymerase Chain Reaction, sequence-based phenotyping analysis etc. using primers for specific genes like 16S rRNA gene have replaced the phenotypic methods for identification, characterization and differentiation of *P. multocida* from the other members of *Pasteurellaceae* family (Hunt 2000; Townsend, 2001; Christensen 2010; Taylor 2010) [71, 30, 146, 145]. For example, genes encode for virulence in *P. multocida* strain 36950 genome contains the ICE segment carrying 88 genes in which 12 genes are responsible for antimicrobial resistance (Michael, 2012). Evidences are there which link the association of various respiratory diseases in dairy calves to *P. multocida*. Techniques involving lung tissue culture (Hirose 2003) [69], nasopharyngeal swabs (Catry 2006) [25] and transtracheal washes (Singer 1998; Virtala 2000) [135, 152] enable their link up. Studies focusing on respiratory tract of the animals inferred the evidences of the organism in tonsils, nasopharynx and other parts of the upper respiratory tract, from which shedding of the organism occurs during stressed conditions. In addition, some studies recently have stated the involvement and the role of Gastro-intestinal tract and urinary tract in the infection-spread (Shafarin, 2007; Annas *et al*., 2014) [129, 10].

2. Reports of HS in and around India

HS is considered as one of the economically important disease in Southeast Asia, prominent in countries like India, Indonesia, Philippines, Thailand, Malaysia (Verma and Jaiswal, 1998) [149]. The mortality rate reported from India and surrounding nation's *viz*., Bangladesh, Cambodia, Pakistan and Sri Lanka to be in the range of 20.4-54.2% (De Alwis and Vipulassiri, 1981; Saini 1991; Khan 2011; Mondal and Yamage 2014; Kawasaki 2015) [38, 126, 79, 95, 77]. Moreover, the disease is reported to be endemic in India, Bhutan, Myanmar, Sri Lanka, Malaysia, China, Indonesia, Mongolia and Philippines and are hence categorized into Category 'A' (Benkirane 2002) [14]. One of the evidences of endemic nature of Indian subcontinent is the work done by Kumar *et al*.

(2004) [82] considering 418 samples from different animal (cattle, buffalo, sheep, goat, pig, rabbit, leopard, deer) and avian (chicken, duck, quail, turkey, geese) populations across 17 states of the country revealing the nation-wide existence of *P. multocida* organism (Fig.1).

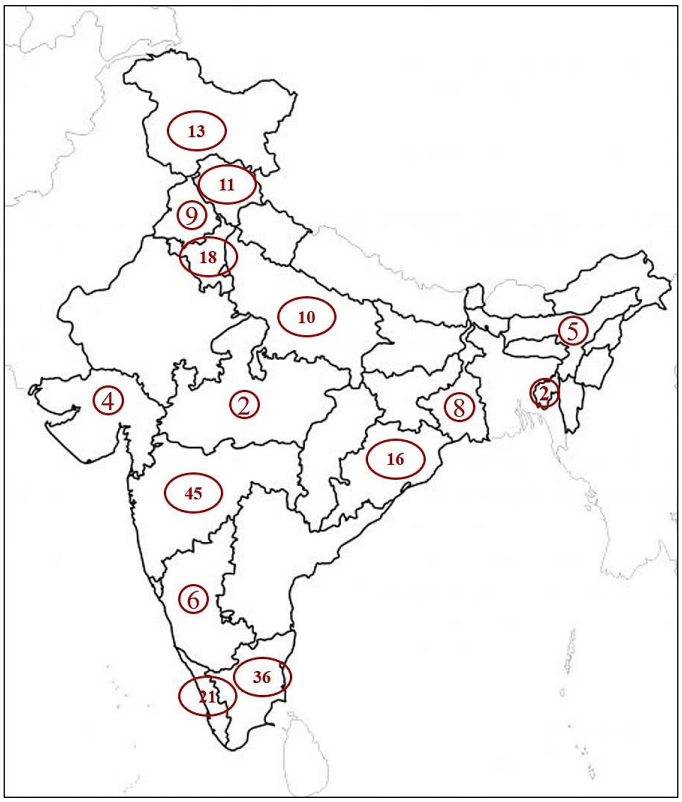


Fig 1: Isolates of *P. multocida* obtained in the study of Kumar *et al*. (2004) across various geographical regions of India indicating endemicity of HS in the country

Consequently, various studies highlighted the persistency of the disease time-to-time. Recently in 2020, a study conducted by Prajapati *et al*. (2020) [116] found 32% positivity of *P. multocida* from 345 clinical samples obtained from apparently healthy, pneumonic and septicemic animals (cattle. buffalo, sheep, goat, pig and rabbit) from Karnataka, Uttar Pradesh, Mizoram and Assam states of India with the presence of 8 different virulent genes in all the positive cases. Likewise, below is listed (Table 1) various studies conducted in several parts of the country in different time periods showing the consistency of the effect of *P. multocida* in Indian landmass.

Table 1: List of numerous works done in various parts of India by various researchers

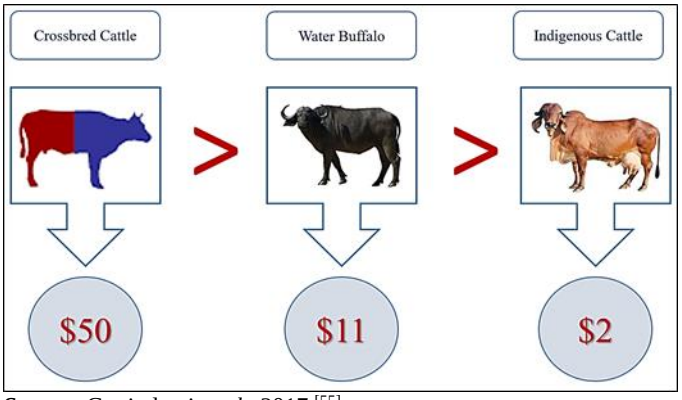
State	Region	Time period	Animal	Reports	Reference
Karnataka	Chitradurga and Hassan districts	2011-13	Indigenous cattle, cross bred cattle, buffaloes	Higher mortality in <1-year aged indigenous cattle whereas more in >1-year aged cross bred cattle, buffaloes.	Govindaraj *et al*., 2017 [55]
Karnataka	Bangalore, Bangalore Urban and Rural, Kolar, Chikkaballapur districts	2015-16	Sheep	7.4% *P. multocida* and 7.2% *M. haemolytica* with h igher multidrug resistance of *M. haemolytica* (25.9%) than *P. multocida* (7.1%).	Sahay *et al*., 2020 [125]
Karnataka	South Karnataka	2014	Buffalo	Isolation of *P. multocida* 2213 and 3213 strains.	Abrahante *et al*., 2014 [1]
Assam	Baska, Golaghat and Kamrup districts	2016	Indigenous and cross bred cattle	Higher seropositivity in indigenous cattle (33.5%) than cross bred (18.5%) cattle with more (35.7%) herd prevalence in rural farms.	Shome *et al*., 2019 [120]
Assam	Guwahati		Pig (*P. multocida* isolates)	Positive for capsular types A (66.66%) and B (33.33%) and outer membrane genes, iron acquisition genes, dermo necrotoxin encoding gene and filamentous haemagglutinin encoding gene.	Devi *et al*., 2018 [44]
West Bengal	Murshidabad district	2013	Cattle, buffalo	Among 2.16% positive animals, 85.71% were buffaloes and 14.28% cattle and 33.76% animals (86.53% buffalo, 13.46% cattle) died before onset of treatment.	Mitra *et al*., 2013 [92]
Uttar Pradesh	Akbarpur village	2002	Buffalo	Five isolates obtained were subjected for phenotypic and genotypic characterization and hence applicability of molecular methods found superior than conventional methods for rapid epidemiological investigations.	Kumar *et al*., 2004 [82]
Uttar Pradesh	Izatnagar	Over a	Small ruminant	On virulence gene profiling, 100% isolates showed positive	Sarangi

		Period of 10 years		for 8 virulent genes, 95.45% for *pfhA* gene, >90% for *ptfA* and *hsf-2* genes, also for *toxA* gene with 17.04% isolated to be multidrug resistant.	*et al*., 2015 [127]
Maharashtra	Nagpur	2006	Indigenous pig (dead)	Isolation of nine strains with six were CAPA and three showed CAPD capsular types and all were resistant to sulfadiazine and cloxacillin.	Kalorey *et al*., 2008 [75]
Himachal Pradesh	Palampur	Over a period of 1 year	Cattle	Among the 23 isolates of *P. multocida* obtained, 19 were of capsular type B and 4 of type A with 5 virulent genes were common in both except for *sodC* was in 50% of type A.	Verma *et al*., 2013 [150]

3. Economic losses

HS was the second most reported disease in India during the decades of 1990-2000 and 2000-2010 and was responsible for the maximum number of deaths among large ruminants as reported by NADRES (Otte *et al.*, 2012) [53]. In fact, it was instituted to be the primary cause of mortality and the second most cause of morbidity during 1974-1986, heading of other diseases like Foot and Mouth Disease, Black Quarter, Rinderpest (Dutta 1990) [48]. An average annual loss of INR 287.81 lakh was reported due to number of cases and deaths reported during the period of 1991-2005 (Singh and Prasad, 2008) [136]; though considered to be an underestimation of the actual losses (Ahuja 2008) [7]. According to Verma *et al*. (2004) [151], an estimated annual economic loss in the Indian state of Haryana was around INR 58 million. Whereas, in the tropical countries of Indonesia and Malaysia, the estimation of economic loss annually, accounted in the past was US $4000-6000 and US $1 million respectively in which buffaloes were found to be more prone comparatively (FAO 1991) [51].

Mostly the disease noticed to be occurred in in-milk animals imparting a huge economic loss to the entire dairy industry including the livestock-farmers. However, the outbreak frequencies were detected more in 2002 and peaking in 2005 but due to vaccination drive, a decrease in the outcomes had been noticed thereafter. In a study, Govindaraj *et al*. (2017) [55], estimated the milk loss and the associated economic consequences. They inferred that the mean milk loss was the highest in crossbred cattle ($50/animal/outbreak) followed by water buffaloes ($11/animal/outbreak) and indigenous cattle ($2/animal/outbreak) which is also presented pictorially in the Fig. 1 below.



***Source*:** Govindaraj *et al*., 2017 [55]

Fig 2: Mean milk loss in different milch animals of India

Sample surveys were used as the method of collection of data on HS in states of Maharashtra, UP, MP and Himachal Pradesh during the period of 2009-2012 (Sharma 2012; Singh 2012) [132, 140]. According to the data reported by Government of India, the case fatality rates were 28.08% and 42.87% in cattle and buffalo respectively, which on the other hand in the survey studies were 57.38% and 56.63% respectively. In buffaloes, the mortality and morbidity losses were 77.03% and 22.97% while in cattle these were 76.52% and 23.48% respectively (Singh 2014) [137]. Among the different components accounting for the morbidity losses the factor responsible for the highest loss was reduction in growth which accounted for 11.72% followed by milk loss for 4.96% which was then by other losses like opportunities cost (2.87%), treatment cost (2.30%) and reduction in work capacity (1.19%), depicted in the Figure 2 below.

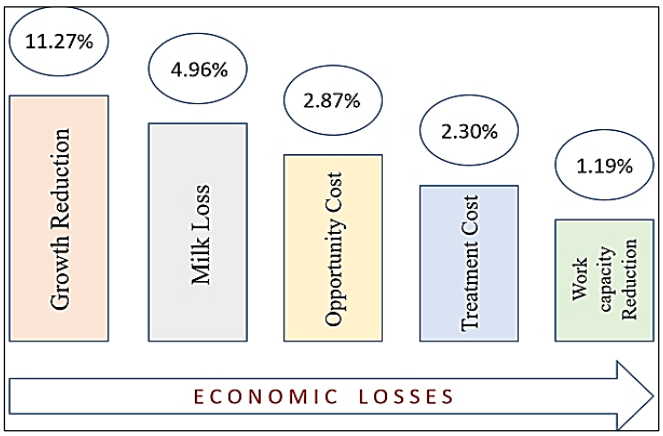


Fig 3: Factors contributing economic losses

4. Prevention and Control

The foremost step of prevention is the adoption of proper hygienic husbandry practices including sanitation, herd immunization etc. Overcrowding of animals should be avoided especially during the monsoons as it raises the stress conditions. The field veterinarians and animal owners should do immediate reporting of the disease occurrences to the higher authorities (especially in endemic areas). Antibiotic treatment should be started as early as possible and antimicrobial susceptibility testing (AST) should be practiced for concrete solution of the problem (OIE 2019) [107]. The policies of quarantine, control of animal-movement, tracing of contacts and disinfection be compulsorily followed at the farm premises. The removal of persistent carriers from the herd is another important measure towards reduction of shedding and circulation of the pathogens among the other herd-mates. Besides, regular surveillance and monitoring help in early detection of the disease and are the need of the hour in order to save the livestock and the industry as a whole from the devastating effects of the pathogens. Importantly, routinely practice of vaccination help controlling of the disease in the endemic areas as vaccination usually protects an animal for a period of 6 months. The places where the practice of vaccination is difficult to conduct, the strategy of ring vaccination can be employed. Thus, immunization can be a potent game-changer and it should be emphasized unanimously for prevention and control of the disease.

4.1 Immunization

The control methods cannot sufficiently manage to limit the infection until the protection strategies are carried out (Carter 2003) [24]. Thus, immunotherapies possess an extreme impact against the infectious diseases (Baba 1984) [12]. Below are mentioned the various immunotherapy trials.

4.2 Passive immunization

Passive immunization is the administration of antibodies to the patient's bodies. Passive immunization can be either naturally acquired from maternal antibodies and can be artificially induced by hyper-immune sera inoculation. This is generally achieved by hyper immune sera administration to have immediate response to both the animals affected and suspected animals which are devoid of active immunity (Ahmad *et al*., 2011) [5]. Several studies had been carried out since very long in order to establish a valid immunization element to protect the animals against *Pasteurella* organisms. The studies conducted between 1975 and 1990 successfully raised antisera against Clemson University avirulent *P. multocida* vaccine (CU vaccine), potassium thiocyanate extract of *Pasteurella*, and the heat killed bacterium and this conferred immunity to baby turkeys, rabbits and mice respectively (Bierer and Derieux 1975b; Lu *et al*., 1987) [16, 88].

Again, studies performed in 1991 proved that the monoclonal antibodies (mAbs) raised against outer membrane proteins (OMP) of *P. multocida* were effective in providing immunity to rabbits and mice (Lu *et al*., 1991a; Lu *et al*., 1991b; Lu *et al*., 1991c) [85, 86, 87]. Later, the studies conducted after 1997 till 2007 showed that ammonium sulphate perceptible protein fractions (PSAP) of *P. multocida*, outer membrane protein H (OmpH), Omp87, and mixture of OMPs of *P. multocida* proved to be effective against homologous infection in mice, rabbits and bovine (VasfiMarandi *et al*., 1997; Adler *et al*., 1999; Dabo *et al*., 2007) [148, 3, 36].

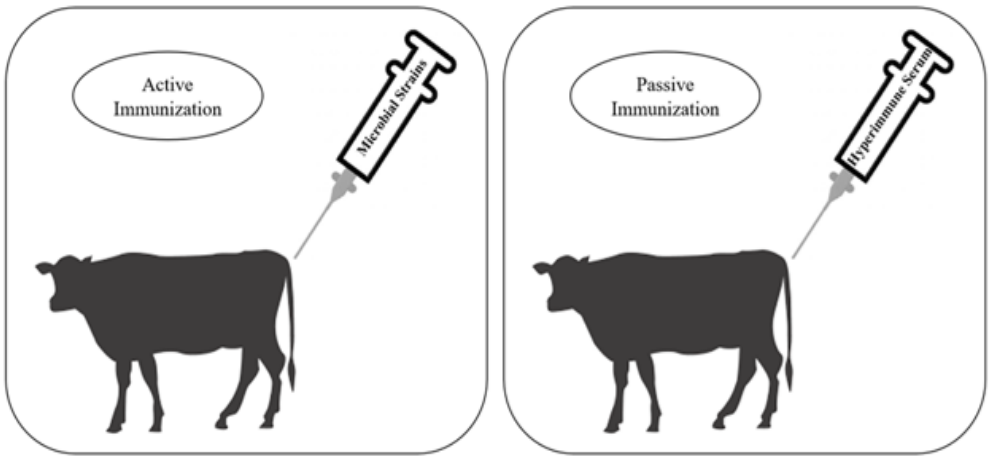


Fig 4: Show the different of active and passive immunization

4.3 Active immunization

The most effective and economic method to confer protection to animals against Pasteurellosis is vaccination (Fischer *et al*., 2007) [52]. There are different types of vaccines available which is depicted below.

The inactivated vaccines (bacterias) were prepared from *Pasteurella* killed by various ways using heat, drying, formalin, phenol, or sodium azide (Heddleston *et al*., 1958) [62]. Hence, there can be a number of types of vaccines based on such preparations. The immunization of chickens using formalin-killed *P. multocida* showed high homologous potency (Heddleston *et al*., 1968) [63]. The bacterin induced high cross-immunity against the bacterial challenge, but the immunity tends to be host specific, half of which conferred by the standard bacterium (Heddleston *et al*., 1974; Rebers and Heddleston, 1972) [64, 65]. Though later, the establishment of lung exposure to formalin-killed *P. multocida* vaccine induced protective immunity in calves against homologous challenge cannot be made (Dowling *et al*., 2004) [45]. The formalin-killed oil-adjuvanted *Pasteurella* vaccine proved to provide low immune response (Rahman *et al*., 2016) [119] and resulted in local tissue irritation and lesions in mice. The heat killed oil-adjuvanted vaccines (OAV) showed reduced local reaction in poultry, and conferred 60% cross-protection to mice against homologous challenge. Subsequently, the advantageous role of adjuvants was studied. OAV formulated with saponin was seen to provide strong humoral and cellular immune response against hemorrhagic septicemia in mice and calves (Kumar *et al*., 2011) [83]. The multiple emulsion vaccine (MEV), prepared by re-emulsifying of OAV with Tween 80, helped to protect buffaloes against hemorrhagic septicemia over 6 months and extended for one-year in rabbits and calves (Chandrasekaran *et al*., 1994) [27]. The animals vaccinated by OAV and double emulsion vaccines had gained a long-lasting protection that reached 12 months against hemorrhagic septicemia (Chandrasekaran *et al*.,1994; Shah and de Graaf 1997; Tabatabaei *et al*., 2002) [27, 130, 144]. Multivalent vaccines preparation is another approach for improving Pasteurella killed bacterin (Borkowska-Opacka *et al*., 1996) [20]. There are many disadvantages associated with vaccination with bacterias like it lacks the ability to raise cross serotype protection, provides ineffective and short immunity, and immunized animals continue to suffer disease outbreak (Gyles *et al*., 2004; Nassar *et al*., 2012) [56, 105]. Furthermore, bacterin results in inflammation at the site of injection (Ahmed *et al*., 1974) [6].

4.4 Live attenuated vaccine

Avirulent strains of *P. multocida* are used to formulate live attenuated vaccines, which provide high protection to cattle for 13 months but lacked the maternal potency (Verma *et al*., 1998; Myint and Carter 1989; Myint *et al*., 2005) [149, 101, 102]. The induction of homologous and heterologous protection to mice and chicks was seen by the capsular serotype of *P. multocida* (Bierer and Deriuex 1975a; Wong and Kucera 1982; Chung *et al*., 2005) [15, 158, 32]. Besides, a promising

strategy to produce potent attenuated vaccines was by induction of mutations by mutagenic substances such as N-methyl-N-nitro-N-nitrosoguanidine. The use of the streptomycin antibiotics was another way to induce attenuation. It provided complete protection for rabbits against homologous infection and protected turkeys against fowl cholera (Wei and Carter 1978; Mosier *et al*., 1998) [154, 96]. It was seen that streptomycin-dependent live *P. multocida* type A3 and B vaccine provided immunity to cattle without any adverse effects (Alwis and Carter, 1996; Catt *et al*., 1985) [9, 26].

If gene encoding the *P. multocida* toxins are deleted it results in the production of an effective live attenuated vaccine against atrophic rhinitis in mice (Petersen *et al*., 1991) [114]. A safe preparation of live aroA deleted derivative of *P. multocida* serotype B:2 used in calves and mice was seen to induce protection against homologous challenge (Adler *et al*., 1996; Tabatabaei *et al*., 2002; Hodgson *et al*., 2005; Ataei *et al*., 2009) [4, 144, 70, 11]. Live temperature-sensitive *P. multocida* mutant induced a humoral response against homologous infection in pigs (Muller *et al*., 2000) [100]. The mutant that expresses the N-terminal truncated fragment of *P. multocida* toxin (N-PMT) had the capability to be used as potent vaccine against wild-type challenge in pigs (Seo *et al*., 2010) [128]. Due to high potency of an attenuated derivative that only expresses N-PMT was used to prevent atrophic rhinitis in mice (Kim *et al*., 2012) [81]. The main advantage of live attenuated vaccines is the induction of cross-serotype protection and cellular immunity that is better than inactivated vaccines but they may cause systemic infections **(**Gyles *et al*., 2004; Haesebrouck *et al*., 2004) [56, 57].

4.5 Subunit vaccines

Subunit vaccines consist of immunogens derived from a pathogen such as its proteins and polysaccharides that when injected in a host can elicit immunity. These are referred to as 'second generation vaccine'. *P. multocida* capsular antigens have been used as vaccine candidates in the past. Scientists have injected cattle with high dose of capsular antigens of *P. multocida* and found the animals to be immunized against HS for about 14 months (Nagy and Penn, 1976; Brown *et al*., 1980; Maslog, 1998) [103, 22, 90]. The outer membrane proteins (OMPs) derived from *P. multocida* are other important virulence factors that can be used for immunization of animals. Identification of such OMPs and their manipulation as vaccine can prove beneficial. The use of OMPs for vaccination started well in 1991 with vaccination of *P. multocida* OMP against homologous challenge. The results showed decreased severity of pneumonia and enhanced phagocytosis in cattle (Pati *et al*., 1996; Confer *et al*., 1996) [112, 34], but no such effects in other animals like mice (Gatto *et al*., 2002) [54] unless an adjuvant was used along with the OMP (Basagoudanavar *et al*., 2006; Kharb *et al*., 2011) [13, 80]. The iron-regulated OMP (IROMP) when used as vaccine has conferred protection to calves (Borkowska-Opacka and Kedrak, 2003; Kedrak and Borkowska-Opacka, 2003; Prado *et al*., 2005) [19, 78, 115].

Bacterial adhesins are another interesting target. Poultry and other animals have been successfully vaccinated against Gram-negative bacteria by using purified siderophore receptor proteins produced by *Pasteurella* strains (Emery *et al*., 2000) [49]. Another potential target is the bacterial peptidoglycan-associated lipoprotein (PAL) for the development of subunit vaccine. A study was conducted in which Omp16 lipoprotein which encodes for mature Omp16 of *P. multocida* B:2 strain P52, was cloned and overexpressed as fusion protein in *E. coli*. Results demonstrated that mice immunized with purified recombinant non-lipidated Omp16 fusion protein, elicited significant antigen-specific serum antibody titres and more pronounced increase in Th2 response (IgG1) (Shivachandra *et al*., 2017) [133]. Side-by-side. *Pasteurella* lipoprotein E (PlpE) has been also used to immunize against *P. multocida* without any adverse effects (Chomnawang *et al*., 2009; Chang *et al*., 2011; Hatfaludi *et al*., 2012) [29, 28, 61]. *P. multocida* lipoprotein B (PlpB) is another subunit vaccine candidate as mice immunized with 200 g of purified *P. multocida* lipoprotein B (rPlpB) were protected against challenge infection with *P. multocida* strain LZ-PM (Wei *et al*., 2017) [155].

4.6 Recombinant vaccines

Recombinant vaccines constitute the third generation of vaccines and the first attempt for developing a recombinant vaccine was done for vaccinating pigs against atrophic rhinitis caused by *Pasteurella multocida* in 1994 by using a non-toxic recombinant derivative of the *P. multocida* toxin (rPMT) (Bording *et al*., 1994) [18]. Since then, a number of successful attempts have been made in using recombinant vaccines against *Pasteurella* caused diseases in chicken, pigs etc. The various recombinant proteins that can be used as vaccine candidates are adhesive protein (rCp39), P6-like protein, OmpH, OmpA, filamentous hemagglutinin peptides (rFHAB2), *P. multocida* lipoprotein E (PlpE), OmpH, and lipoprotein E (PlpE) genes fusion (PlpEC-OmpH), recombinant clone ABA-392, and sub- clone CSI57 J (Mostaan *et al*., 2020) [97]. A study was conducted where recombinant PlpE or OmpH and lipoprotein E (PlpE) gene fusion (PlpEC-OmpH) was successfully used as vaccine for shipping fever caused by *P. multocida* in cattle (Okay *et al*., 2012) [109]. Another study focused on using recombinant clone ABA392 derived from *P. multocida* serotype B and the results showed that it provided 83% immunity against HS in mice (Hussaini *et al*., 2011) [73]. They also used expressed sub-clone CSI57 J of *P. multocida* serotype B successfully against HS in mice (Hussaini *et al*., 2012) [72].

An inactivated recombinant vaccine that encodes for a fimbrial protein of *P. multocida* B:2 has been used against HS in goats and provided protection against high dose challenge as well as stimulated the local and systemic immune response (Mohd Yasin *et al*., 2011) [94]. An intranasal recombinant OmpH-based vaccine has been successfully developed to protect dairy cattle from HS. The results when compared to buffaloes that received commercial HS bacterin vaccine, the recombinant OmpH vaccine was seen to elicit protective ability as well as induce antibody and cell-mediated immune response against virulent *P. multocida* strains (Muenthaisong *et al*., 2020) [99]. Another recombinant vaccine ABA392/pET30a elicits both cellular and humoral immunity and intranasal administration provokes mucosal immunity as well. In addition to this, the vaccine shows no hepatotoxicity and nephrotoxicity (Kang *et al*., 2019) [76].

4.7 DNA vaccines

DNA vaccines constitute the fourth generation of vaccines. DNA vaccines provide various advantages like no risk of infection, ease of development and production, antigen presentation by MHC class I as well as by MHC class II, polarization of T-cell response toward type 1 or type 2, stability and cost-effectiveness, long-term persistence of

immunogen etc. (Mostaan *et al*., 2020) [97]. The first DNA vaccine against *Pasteurella* was derived from *P. multocida* Toxin (PMT) gene, which gave a protective response in mice and swine (Register *et al*., 2007) [122]. A group of researchers in India developed and investigated the immune response developed in response to a DNA vaccine expressing transferrin binding protein of *P. multocida* and their results showed that the DNA vaccine provided superior immune response and protection against hemorrhagic septicemia in cattle and buffaloes (Singh *et al*., 2011) [139].

A DNA vaccine prepared by amplifying the OmpH gene obtained from *P. multocida* was injected in rats and increased serum antibody levels were observed and the protective efficacy was found to be greater than that provided by the live attenuated vaccine (Yassein *et al*., 2021) [159]. A new DNA vaccine named as pVAX1-ABA392, having gene ABA392 sub-cloned into a pVAX1 expression vector, has been injected in rats and the immunized rats have shown a high titre of protective antibodies (Shamini *et al*., 2020) [131].

5. Conclusion

Haemorrhagic septicemia (HS) is well-recognized infectious disease caused by bacteria and of economic importance in most of the part of India. Because of the bacterium's specificity, HS can be prevented with vaccination to reduce losses in dairy production. HS has been detected more frequently in unvaccinated animals during HS epidemics and vaccination is critical for preventing HS. New technology for the generation of effective vaccine is now challenge to prevent threat of HS. Both ineffective preventive measures and inadequate incidences may contribute to severe impact on livestock sector. The consistent and systemic surveillance at herd level should be carried out to minimize risk of herd health. Therefore, extension work is need at rural level and encourage the farmers to accomplishment recent and hygienic animal practices by giving government subsidies.

6. References

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