



REVIEW ARTICLE

BACTERIAL CAUSES OF NEONATAL MORTALITY IN SHEEP: A REVIEW

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Citation: Osunkoya, D., Jemilehin, F. O., Adetoyan, E. J., Ajala, O. O., 2026: Bacterial causes of neonatal mortality in sheep: A review. *Folia Veterinaria*, 70, 1, 19–32.

Received: August 12, 2025

Accepted: January 9, 2026

Published: March 15, 2026

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Ethical considerations: When reporting experiments on animals Observation of the ARRIVE guidelines 2.0: Updated guidelines for reporting animal research, published on July 14, 2020 (DOI: 10.1371/journal.pbio.3000410), is applied. The authors ensure that all procedures were performed in compliance with the guidelines for animal care of their institutions or with national/international guidelines.

ABSTRACT

Sheep farming plays a significant role in global livestock production, contributing to the output of meat, wool, and milk, and providing income for millions of livestock farmers, especially in developing countries. In this review, the role of bacteria in the aetiology and pathology of neonatal lamb mortality, including management and prevention strategies, is discussed. Several bacteria are known to cause neonatal mortality in sheep, with *Escherichia coli* consistently identified as the most common pathogen, responsible for 15–20% of neonatal deaths worldwide. Other important bacterial pathogens include *Salmonella* spp., *Pasteurella multocida*, and *Mannheimia haemolytica*. Additionally, *Brucella melitensis* and *Campylobacter fetus* subsp. *fetus*, among others, have also been recognised as bacterial causes of neonatal mortality in lambs. This review demonstrates that bacterial infections cause lamb losses in sheep during the first two weeks of life. Effective management and preventative strategies—such as prompt vaccination, adequate colostrum intake, good sanitation, responsible antibiotic use, and supportive care—can significantly reduce bacterial infections in newborn lambs. This reduction will lower neonatal mortality rates, support sustainable sheep production, and contribute to global food security.

Keywords: bacteria; neonate; mortality; sheep production

INTRODUCTION

Sheep farming plays a significant, albeit variable, role in global livestock production, contributing to the produc-

tion of meat, wool, and milk, and providing income for many farmers, especially in developing countries [1].

Early mortality in lambs is a significant constraint to sustainable sheep production, with multifactorial factors

attributed to both infectious and non-infectious causes [2]. Lamb mortality before weaning reduces sheep fertility and profitability for sheep farmers. In certain regions, this condition can also develop into significant income losses [3].

Neonatal mortality in sheep is defined as lamb deaths within the first week of life, with the highest risk in the initial 48 hours [4]. Lamb mortality rates vary, ranging from 10 to 25% between pregnancy diagnosis and sale, depending on the production system used [4], with early neonatal mortality (within 48 hours) accounting for 62.1% of neonatal deaths in some studies [4]. Neonatal lambs are most susceptible to infectious diseases on the day they are born, with up to 50% of all pre-weaning mortality occurring during this period [3].

Predisposing factors include insufficient colostrum intake, inadequate monitoring during lambing, hypothermia, and poor feeding practices [5]. Low birth weight, young or primiparous ewes, and low dam weight at lambing also increase mortality risk [6]. Respiratory disorders, diarrhoea, starvation, and trauma caused by bacterial infections are considered major causes of neonatal mortality in lambs [6, 7, 8, 9, 10].

The sheep placenta is epitheliochorial and does not allow the humoral transfer of immune components from the ewe to the lamb. Newborn lambs are thus born markedly hypogammaglobulinaemic and depend entirely on passive transfer of colostral immunoglobulins, acquired by suckling, for immunological protection after lambing.

Passive immunity must be acquired within the first 24 hours in newborn lambs, as gut closure to immunoglobulin absorption occurs between 24 and 36 hours after birth [11]. When adequate passive transfer of immunity does not happen, lambs are said to suffer from 'failure of transfer of passive immunity', which puts neonatal lambs at increased risk of morbidity and mortality [11].

Lamb mortality is associated with low immunoglobulin status 24 hours after birth [11], demonstrating the importance of ensuring good colostrum intake in newborn lambs. Adequate colostrum intake relies on two complementary factors: the ability of the lamb to ingest sufficient amounts (through vigorous sucking behaviour) and the concentration and quantities of colostral immunoglobulins available from the ewe [11].

Bacterial infections are a major cause of neonatal death, accounting for 36% of early neonatal deaths in one study [12]. *Escherichia coli* is consistently identified as

the most prevalent pathogen, responsible for 14–30.8% of neonatal deaths [12]. Other common bacterial causes include *Pasteurella multocida*, *Clostridium perfringens*, and *Staphylococcus aureus* [4]. *Listeria monocytogenes* and *Campylobacter fetus* have also been implicated [13].

Besides infections, traumatic lesions and congenital malformations also contribute to neonatal mortality [12]. *Escherichia coli* is frequently isolated from lambs that die in the first two weeks of life and is often associated with diarrhoea and septicaemia [12, 13]. *Pasteurella* spp. are commonly found in respiratory infections and are significant contributors to neonatal mortality [13]. *Salmonella* spp. can cause enteritis and septicaemia in lambs [13].

Most bacterial-related deaths occur within the first few days of life. For example, in one study, the highest mortality rate was observed in lambs under 15 days old [12]. Septicaemia and pneumonia are frequently identified as causes of death, with *E. coli* being a common agent in septicaemic cases [12].

This paper aims to review the role of bacteria in the aetiology and pathology of neonatal lamb mortality and also suggest management and prevention strategies.

Economic Impact of Bacterial-Caused Neonatal Mortality on Sheep Farming

Bacterial-caused neonatal mortality in sheep has significant economic implications, directly affecting farmers' income and sustainable livestock production. Lamb mortality rates, often reaching 15–20% globally, represent a significant loss of potential income from meat, wool, and breeding stock [14].

Each lamb lost equates to a direct financial loss, with studies estimating the value of a single lamb at approximately \$28.5 to \$90, depending on the production system and market conditions [14].

Diarrhoea and pneumonia are the major clinical signs associated with infectious diseases leading to pre-weaning mortality [15, 16]. Diarrhoea is the most devastating clinical sign in newborn lambs under 21 days of age, which is accompanied by enteritis, abdominal pain, and an increase in faecal fluidity [17].

Indirect costs further compound the economic burden [15, 16]. These include expenses related to veterinary services, medications (e.g., antibiotics for bacterial infections like *E. coli*), and labour for boarding sick lambs [15]. Additionally, farms with high neonatal mortality experience

reduced productivity due to fewer surviving lambs reaching marketable age or affecting replacement stock [17, 18].

Preventable bacterial infections also lead to increased reliance on antibiotics, raising concerns about global antimicrobial resistance and regulatory pressures [19]. The cost-effectiveness of preventive measures, such as vaccination and improved hygiene practices, is evident in reducing mortality rates and associated losses [15].

Beyond finances, neonatal mortality imposes emotional stress on farmers, leading to frustration and emotional trauma over preventable deaths [16]. This mental toll can affect decision-making and farm management practices [16].

Common Bacterial Pathogens in Neonatal Mortality in Sheep

- ***Escherichia coli* (*E. coli*):** This bacterium is frequently identified as a major cause of neonatal lamb mortality [11, 12]. It is often associated with septicaemia and gastrointestinal infections and is isolated in a significant proportion of cases, such as 65% of septicaemic cases and 30.8% of bacterial infections overall [11, 12].
- ***Pasteurella* spp.:** These bacteria are commonly linked to respiratory infections and are significant contributors to neonatal mortality in sheep. *Pasteurella multocida* is specifically noted in some studies [12].
- ***Salmonella* spp.:** These pathogens can cause enteritis and septicaemia in lambs, contributing to neonatal mortality [18].

Common Infections and Conditions

- **Septicaemia:** Often caused by *E. coli*, this condition is a leading cause of neonatal lamb mortality [11].
- **Pneumonia:** Respiratory infections, including those caused by *Pasteurella* spp., are common in neonatal lambs [11, 12].
- **Gastrointestinal Infections:** Diarrhoea and enteritis are frequently associated with bacterial pathogens like *E. coli* and *Salmonella* spp. [12].

Escherichia coli

Pathogenesis of *Escherichia coli* in Neonatal Lamb Mortality

Escherichia coli contributes to neonatal lamb mortality primarily through septicaemia and endotoxaemia, of-

ten following intestinal colonisation and is reported to be the most harmful organism in the first two weeks of birth. Since the immune system of the lambs has not been fully developed. [11, 20]. Lambs typically acquire pathogenic *E. coli* via faecal-oral transmission in contaminated environments or vertical exposure during parturition [11]. After ingestion, non-enterotoxigenic strains colonise the gut mucosa, triggering catarrhal gastroenteritis and compromising intestinal barrier integrity [20]. This allows bacterial translocation into the bloodstream, leading to systemic infection – a process implicated in 65% of septicaemia neonatal lamb deaths [11].

Key pathogenic mechanisms include:

- **Endotoxin release:** Lipopolysaccharides (LPS) from *E. coli* cell walls induce systemic inflammation, causing elevated serum endotoxin levels linked to poor prognosis [20, 21].
- **Organ invasion:** Post-bacteraemia, the bacteria cause interstitial pneumonia, hepatitis, and nephritis through hematogenous spread [11, 20].
- **Microbiome dysbiosis:** Antibiotic treatment exacerbates endotoxaemia by altering gut microbiota, enabling secondary pathogens like *Proteus mirabilis* to proliferate [19].

Pathological findings show distinct patterns: untreated lambs develop generalised inflammatory lesions (meningoencephalitis, interstitial nephritis), while antibiotic-treated cases exhibit enterotoxemic damage with intestinal ischemia [19]. Virulent strains like O78: NM demonstrate nasal mucosal tropism, suggesting alternative entry routes beyond the gastrointestinal tract [20].

Susceptibility is influenced by delayed colostrum intake, impairing passive immunity, high bacterial load exposure in contaminated lambing areas, and gut microbiota composition, where resistant lambs maintain lower jejunal bacterial counts [11, 20, 22]. Approximately 14% of neonatal deaths are directly attributed to *E. coli* infections, with mortality peaking within 48 hours post-parturition [11, 20].

Clinical Manifestations of *Escherichia coli* in Neonatal Lamb Mortality

Bacterial pathogens are responsible for high rates of mortality in lambs, with *E. coli* being considered an important cause of diarrhoea in lambs [10].

The clinical manifestations of *Escherichia coli* infections in neonatal lambs include signs of septicaemia, enteritis, and respiratory distress [11, 13]. Lambs affected by septicaemia *E. coli* often exhibit weakness, lethargy, loss of appetite, and rapid progression to recumbency or sudden death [13]. Neurological symptoms such as ataxia, seizures, or muscle spasticity may also occur before death [11].

Enteric infections caused by *E. coli* lead to diarrhoea, dehydration, and electrolyte imbalances, which can further compromise the lamb's condition [13, 19]. Respiratory involvement may manifest as laboured breathing or nasal discharge, especially in cases of mixed bacterial infections [13].

Post-mortem findings frequently reveal systemic inflammation, including interstitial pneumonia, gastrointestinal lesions, and evidence of bacteraemia [11]. Infected lambs may also show pulmonary oedema and pericardial effusion [11].

Mode of Transmission of *Escherichia coli* in Neonatal Lamb Mortality

Escherichia coli transmission in neonatal lamb mortality primarily occurs through vertical transmission during parturition and environmental exposure [23, 24]. Lambs can ingest the bacteria from contaminated vaginal secretions during parturition, particularly if the ewe is colonised [24]. Post-parturition, faecal-oral transmission is common in unsanitary environments, with poor hygiene in lambing areas facilitating bacterial spread [24, 25]. Contaminated colostrum or milk, especially when bottle-fed under unhygienic conditions, also introduces pathogens [23, 24]. In severe cases, *E. coli* enters the bloodstream, causing septicaemia linked to 14% of neonatal deaths [11]. Risk factors include delayed colostrum intake, overcrowding, and unhygienic obstetric manipulations during dystocia and wet conditions that promote bacterial survival [23, 24]. Early-life infections often arise within 24–48 hours, emphasising the critical perinatal exposure window [11, 25].

***Streptococcus* spp.**

Pathogenesis of *Streptococcus* spp. in Neonatal Mortality in Sheep

Streptococcus agalactiae (Group B *Streptococcus*, GBS) is a leading cause of neonatal infections, including sepsis, meningitis, and pneumonia [26, 27]. Group

B *Streptococcus* colonises the maternal genital tract and can be transmitted to lambs during parturition [28]. The pathogenesis involves several virulence factors that enable bacterial adherence, invasion, and immune evasion. Key virulence factors include the haemolytic pigment, hyaluronidase, pili, adhesins, and the sialic acid-rich capsular polysaccharide [26, 27]. These factors facilitate colonisation of epithelial surfaces, invasion of host barriers, and evasion of immune clearance [28]. The completion of GBS genome sequencing has provided insights into the organism's metabolism and gene regulation, offering potential targets for novel preventive strategies [29]. Current prevention methods include maternal screening and antibiotic prophylaxis, while vaccine development remains an active area of research [27].

Respiratory syncytial virus (RSV) and *Streptococcus pneumoniae* co-infections can lead to severe respiratory disease, particularly in neonates. In a lamb model, RSV–*S. pneumoniae* co-infection resulted in increased lung pathology, neutrophil infiltration, and cytokine dysregulation, despite lower bacterial loads [30]. Respiratory syncytial virus infection enhances *S. pneumoniae* virulence through direct binding of RSV G protein to pneumococcal penicillin-binding protein 1a, leading to increased bacterial adherence and upregulation of virulence genes [31]. In pre-term lambs, RSV infection induced a heightened pro-inflammatory response, characterised by increased cytokine production and neutrophil recruitment, but with reduced neutrophil activation [32]. Respiratory syncytial virus infection in neonatal lambs also caused lung inflammation, architectural remodelling of lung-draining lymph nodes, and activation of caspase-mediated cell death pathways [32]. These findings highlight the complex interactions between RSV and *S. pneumoniae* in exacerbating respiratory disease severity.

Clinical Manifestation of *Streptococcus* spp. in Neonatal Mortality in Sheep

Group B *Streptococcus* (GBS) is a significant cause of neonatal infections, presenting as early-onset disease (EOD) within the first week of life or late-onset disease (LOD) between 7–89 days [33]. EOD typically manifests within 24 hours of parturition, with symptoms including sepsis, pneumonia, and meningitis [34, 35]. Common clinical presentations include fever, poor activity, respiratory distress, and irritability [35]. EOD has a higher incidence

of pneumonia and mortality compared to LOD, while meningitis is more prevalent in LOD cases [35].

Group B *Streptococcus* infections can lead to severe complications, including neurodevelopmental injuries and long-term disabilities [33]. Globally, GBS infections affect over 300,000 neonates annually, resulting in 90,000 deaths [33]. Prevention strategies, such as intrapartum antibiotic prophylaxis, are crucial in reducing the incidence of GBS infections in neonates [36].

Mode of Transmission of *Streptococcus* spp. in Neonatal Mortality in Sheep

The transmission of *Streptococcus* spp. in neonatal lamb mortality occurs through vertical, horizontal, and environmental routes. **Vertical transmission** primarily involves exposure to maternal vaginal or faecal secretions during parturition, where *Streptococcus agalactiae* (Group B *Streptococcus*) colonises mucosal surfaces of lambs [37]. **Horizontal transmission** arises postnatally via contaminated environments, such as bedding, equipment, or milk, particularly in settings with poor hygiene [37, 38]. The **navel** serves as a critical entry point for pathogens like *Streptococcus dysgalactiae*, especially if not properly disinfected after parturition [38]. Additionally, wounds from management practices (e.g., tail docking, castration) create portals for bacterial invasion [38]. Co-infections with viruses like respiratory syncytial virus (RSV) may exacerbate respiratory transmission of *Streptococcus pneumoniae* through aerosolised droplets [30]. Maternal colonisation and environmental persistence of *Streptococcus* spp. in lambing areas further amplify infection risks, particularly in overcrowded or unsanitary conditions [38]. Prophylactic measures, including navel disinfection and improved biosecurity, are essential to mitigate transmission [38].

Clostridium perfringens

Pathogenesis of *Clostridium perfringens* in Neonatal Mortality in Sheep

In lambs, the infection often begins with the ingestion of *C. perfringens* spores or vegetative cells from contaminated environments or maternal faeces. Once in the intestine, the bacteria multiply rapidly and colonise epithelial cells, releasing toxins. This toxin disrupts cell membranes by hydrolysing phospholipids, leading to necrosis, vascu-

lar damage, and systemic absorption of toxins [39]. The systemic effects include haemolysis, jaundice (icterus), and haemoglobinuria due to the destruction of red blood cells [39].

Severe cases result in sudden death due to shock and multi-organ failure. Post-mortem findings include centrilobular hepatic necrosis, acute tubular injury in the kidneys, splenic congestion, and pulmonary oedema [39]. Factors such as inadequate colostrum intake and stress increase susceptibility. Diagnosis is challenging due to the widespread presence of *C. perfringens* in healthy animals; quantitative toxin detection methods are needed for confirmation [39]. Preventive measures include vaccination against clostridial toxins and improved hygiene during lambing.

Clinical Manifestation of *Clostridium perfringens* in Neonatal Mortality in Sheep

Clostridium perfringens causes severe enteric diseases in sheep, particularly affecting neonatal lambs. Type B and C infections typically result in lamb diarrhoea, characterised by sudden death or acute symptoms like cessation of nursing, listlessness, and bloody diarrhoea [40]. Type D enterotoxaemia often presents with neurological signs and sudden death in well-conditioned lambs [41]. Diagnosis relies on clinical signs, post-mortem findings, and laboratory confirmation, with toxin detection in intestinal contents being crucial [40]. Histopathological examination of the brain is particularly useful for type D diagnosis [40]. *C. perfringens* infections can cause rapid, severe illness with high mortality rates, as observed in neonatal foals [42]. The first reported case of *C. perfringens* type B in New Zealand highlights the potential for geographical spread and emphasises the importance of vaccination in prevention [43].

Gross findings include generalised icterus, red urine in the bladder, and organ congestion [39]. Post-mortem findings often reveal haemorrhagic enteritis with mucosal ulceration and systemic lesions such as pulmonary oedema and splenic congestion [39].

Mode of Transmission of *Clostridium perfringens* in Neonatal Mortality in Sheep

Clostridium perfringens is a common pathogen in livestock, causing enteritis and mortality, particularly in neonates [44]. The bacteria are ubiquitous in environments

such as soil, water, and animal intestines [45]. Transmission occurs through ingestion of spores or vegetative cells from contaminated sources, including colostrum and feed [45]. Predisposing factors include environmental contamination, intestinal pH, imbalance of gut microflora, and nutrition [45]. In lambs, *C. perfringens* types A, B, and D are prevalent, with higher infection rates observed in cold periods [44]. Neonatal lambs are particularly susceptible due to underdeveloped immune defences [42].

Listeria monocytogenes

Pathogenesis of *Listeria monocytogenes* in Neonatal Mortality in Sheep

Listeria monocytogenes is a Gram-positive, facultative intracellular pathogen that causes severe infections in humans and animals [46].

Lambs that develop septicemic disease may acquire infection from contamination on the ewe's teat or from the ingestion of milk containing the organism from ewes with subclinical bacteremia, through the navel from the environment, and also as a congenital infection [47, 48].

The bacterium invades host cells using proteins like internalin (InlA/InlB), which interact with cellular receptors to trigger internalization [48]. It also uses Act-A, a protein that is important in intracellular movement by acting on polymerisation and is also thought to play a role in cell tropism (adhesion) and invasion.

Once inside, *L. monocytogenes* escapes the phagosome using listeriolysin O and replicates in the cytoplasm [49]. The pathogen then spreads cell-to-cell by exploiting host actin polymerisation machinery through its ActA protein [50]. This intracellular lifecycle allows *L. monocytogenes* to evade host immune responses and establish systemic infections [47]. The bacteria can cross the intestinal barrier, leading to infection of the liver, brain, and placenta [47]. Despite antibiotic treatment, listeriosis has a high mortality rate of 25–30%, primarily due to severe meningoen- cephalitis [47].

Clinical Manifestation of *Listeria monocytogenes* in Neonatal Mortality in Sheep

Listeria monocytogenes is a pathogenic bacterium that can cause severe infections, particularly in neonates. Clinical manifestations primarily include septicaemia and meningoen- cephalitis [51, 52]. Neonatal listeriosis often

presents with nonspecific symptoms such as fever, depression, and respiratory distress [53, 54]. The infection can be transmitted from dam to foetus, with maternal symptoms including fever and diarrhoea [54]. Preterm neonates may exhibit more severe symptoms compared to full-term infants [54]. Diagnosis is confirmed through positive blood cultures, and treatment typically involves intravenous administration of ampicillin or penicillin for 1–2 weeks [54]. Cephalosporins are ineffective against *L. monocytogenes* [54]. Despite treatment, mortality rates remain high due to the combination of immunocompromised hosts and often delayed diagnosis [52].

Mode of Transmission of *Listeria monocytogenes* in Neonatal Mortality in Sheep

Listeria monocytogenes can cause severe neonatal infections through both vertical and horizontal transmission. Vertical transmission occurs transplacentally or during parturition, leading to early-onset listeriosis [52, 55]. Horizontal transmission can happen postnatally through ingestion or contact with contaminated sources [56]. Neonates are particularly susceptible due to their immature immune systems and gut microbiota [56]. Nosocomial infections have been reported, with cross-contamination occurring through shared equipment or personnel [57]. The placenta plays a crucial role in protecting the foetus, but *L. monocytogenes* can evade this barrier using virulence factors like internalin proteins [55]. Various animal models have been used to study *L. monocytogenes* transmission to investigate their pathogenesis [55]. Proper disinfection of medical equipment is essential to prevent nosocomial spread [57].

Pasteurella multocida

Pathogenesis of *Pasteurella multocida* in Neonatal Mortality in Sheep

Pasteurella multocida is a significant bacterial pathogen causing respiratory diseases in various animals, including neonatal lambs. The bacterium typically resides in the upper respiratory tract of healthy animals but can become pathogenic under stress conditions [58]. Key virulence factors include the capsule, lipopolysaccharide, and *Pasteurella multocida* toxin, which aid in evading host immunity and promote bacterial survival [58, 59]. *P. multocida* often acts as a secondary pathogen following prima-

ry viral infections that compromise respiratory defences [60]. Stressful conditions, such as transport, heat stress, and overcrowding, impair the animal's immune response, allowing *P. multocida* to proliferate and invade lung tissue, leading to bronchopneumonia [59, 60]. The disease progresses rapidly, with clinical signs ranging from mild respiratory distress to acute death, characterised by severe fibrinous or fibrinopurulent bronchopneumonia and fibrinous pleurisy [60].

Clinical Manifestation of *Pasteurella multocida* in Neonatal Mortality in Sheep

Pasteurella multocida infections in neonatal lambs can cause severe respiratory distress and systemic illness, often leading to acute death without prior clinical signs [11].

Clinical manifestations include depression, lethargy, inappetence, coughing, and nasal discharge [61]. Post-mortem findings typically reveal lung consolidation and pleuropneumonia [62]. *P. multocida* is a significant cause of neonatal mortality in sheep, with infections often resulting in septicæmia or pneumonia [11]. The prevalence of lung lesions can be high in lambs, with severe lesions significantly reducing growth performance [62]. Risk factors for neonatal pasteurellosis include animal exposure, vertical transmission, low birth weight, and early onset of symptoms [63]. Prevention and control strategies should focus on appropriate antimicrobial selection, reliable diagnosis, and development of vaccines targeting relevant serotypes [61].

Mode of Transmission of *Pasteurella multocida* in Neonatal Mortality in Sheep

Pasteurella multocida is a significant cause of neonatal infections, with transmission occurring through various routes. While animal exposure, particularly to cats and dogs, is a major risk factor [63], vertical transmission from ewe to lamb during parturition has been documented [64]. Horizontal human-to-animal transmission, though rare, has also been reported [65]. Neonatal pasteurellosis often presents as bacteraemia with or without meningitis, with onset after 72 hours of age significantly associated with meningitis [63]. Treatment typically involves β -lactam antibiotics, sometimes combined with aminoglycosides or chloramphenicol [63]. In a broader context of neonatal infections in lambs, *P. multocida* is one of several bacterial species implicated in both early (hebdomadal) and later

(post-hebdomadal) neonatal deaths, with infections often resulting from umbilical contamination at parturition or ingestion [66].

Other Bacterial Infections

Staphylococcus aureus

Staphylococcus aureus is a commensal bacterium that can become an opportunistic pathogen, causing various infections, including skin lesions, pneumonia, and bloodstream infections [67, 68]. The bacterium employs several virulence factors, notably Panton-Valentine leukocidin (PVL) and alpha-toxin (Hla), which are associated with necrotic skin infections and severe pneumonia [69]. During the transition from colonisation to invasion, *S. aureus* upregulates genes involved in adhesion, toxin production, and nutrient acquisition [67]. In bloodstream infections, *S. aureus* secretes coagulases and displays agglutinins, leading to abscess formation [68]. The pathogen also recruits and destroys immune cells, facilitating its spread to new sites or hosts [68].

Methicillin-resistant *Staphylococcus aureus* (MRSA) poses significant challenges in livestock settings due to its resistance to multiple antibiotics [70]. MRSA can cause various infections, ranging from skin and soft tissue infections to severe systemic conditions [70]. In livestock, MRSA is associated with suppurative skin conditions, wound infections, and mastitis [71]. The emergence of livestock-associated MRSA, particularly ST-398, has raised concerns about zoonotic transmission to farmers, veterinarians, and abattoir workers [71]. MRSA has been detected in retail meat and raw milk, indicating potential foodborne transmission risks [72]. Preventive measures include maintaining hygiene during animal handling and processing, reducing antibiotic use in livestock, and screening animals and their products for MRSA [71]. Combining herbal extracts with antibiotics shows promise in combating MRSA and reducing antibiotic resistance [73].

***Salmonella* spp.**

Salmonella enterica is a significant zoonotic pathogen affecting both humans and animals, capable of causing gastroenteritis and systemic infections [74]. In neonatal

lambs, *S. enterica* subsp. *diarizonae* can lead to diarrhoea and histopathological changes in the abomasum and small intestine [75]. The pathogen's ability to invade the intestinal epithelium is crucial for infection, with invasion occurring as early as 15 minutes post-infection in calves [76]. However, the magnitude of intestinal invasion does not necessarily correlate with host specificity in sheep [77]. The host response to *Salmonella* infection involves upregulation of chemokines and cytokines, leading to neutrophilic inflammation [76]. While some *Salmonella* serovars have broad host ranges, others are host-adapted, influencing their ability to persist in systemic sites and cause disease [74, 77].

***Mycoplasma* spp.**

Mycoplasma ovipneumoniae plays a significant role in respiratory diseases of sheep, particularly in lambs. It is commonly isolated from pneumonic lungs and associated with various pathological findings, including suppurative bronchopneumonia and interstitial pneumonia [78]. *M. ovipneumoniae* contributes to lamb mortality, often in conjunction with other pathogens like *Mannheimia* spp. and *Pasteurella multocida* [79]. The bacteria colonise the respiratory tract, causing ciliostasis and eliciting an exudate that allows secondary bacterial infections [80]. Chronic non-progressive pneumonia (CNP) in lambs is frequently associated with *M. ovipneumoniae*, with multiple strains often present in affected lungs [80]. Transmission occurs through direct contact or inhalation of aerosols, with ewes potentially serving as persistent carriers [79]. While *M. ovipneumoniae* is a primary agent in ovine respiratory diseases, other mycoplasmas like *M. arginini* appear to play a less significant role [78].

Some Less Frequently Isolated Bacteria

Corynebacterium pseudotuberculosis and *Mannheimia haemolytica* [12].

Pathophysiology of Bacterial Infections in Neonatal Lambs

Neonatal lambs have an immature immune system that makes them susceptible to most bacterial infections. This immunological immaturity is characterised by low leukocyte counts, reduced neutrophil phagocytic activity, and diminished cytokine responses to pathogen-associated

molecular patterns [81]. Neonatal lambs exhibit a distinct innate immune system biased towards TH2-/TH17-polarizing and anti-inflammatory cytokine production, with impaired TH1-polarising cytokine production [82]. This leaves them particularly susceptible to intracellular pathogens. They also have deficient expression of complement and antimicrobial proteins and peptides, contributing to their vulnerability to pyogenic bacteria [82]. The immature immune system, combined with the need for invasive veterinary procedures, makes neonatal lambs highly susceptible to common pathogens [83]. This vulnerability is exacerbated in compromised newborn lambs, such as those requiring intensive care [84]. This immunologic immaturity creates a vulnerable window during the first postnatal week, allowing pathogens like *Escherichia coli*, *Streptococcus* spp., and *Clostridium perfringens* to invade and colonise mucosal surfaces [81].

Infectious Routes and Colonisation

The gastrointestinal tract of newborn lambs is rapidly colonised by microbes after parturition, with the initial microbiome significantly influenced by early neonatal events and feeding modes [85]. Suckling lambs acquire microbes primarily from the dam's teats and ambient air, while artificially bottle-fed lambs receive bacteria mainly from the dam's vagina, air, and pen floor [86]. Bottle feeding can increase potential microbes like *Escherichia/Shigella* and delay anaerobic microbe establishment [86].

Bacterial Virulence and Toxins

Bacterial pathogens produce various toxins and virulence factors that play crucial roles in disease progression. *Escherichia coli* strains possess multiple virulence factors, including adhesion proteins, secretion systems, and toxins such as heat-labile enterotoxins and Shiga toxins [87]. *Clostridium perfringens* produces enzymes like alpha toxin (phospholipase C) and kappa toxin (collagenase), which disrupt membrane integrity, as well as toxins affecting vascular endothelium and haemolysins [88]. *Staphylococcus aureus* synthesises alpha-toxin and toxic shock syndrome toxin, while other bacterial toxins include botulinum and tetanus neurotoxins [89]. These toxins employ diverse mechanisms to affect eukaryotic cells, contributing to pathogenicity. These toxins exacerbate systemic inflammation, triggering cytokine storms and multi-organ failure.

Immune Evasion and Outcomes

Streptococcus species employ various mechanisms to evade host immune responses. *Streptococcus pyogenes* utilises streptolysin O to induce rapid macrophage apoptosis, hindering immune clearance and enhancing virulence [90]. Both *S. pyogenes* and *S. pneumoniae* secrete complement evasion factors that interfere with opsonisation and terminal pathway lysis [91]. *S. pneumoniae*'s polysaccharide capsule protects against complement-mediated opsonophagocytic killing, while its surface-associated glycosidases modulate host defence proteins by removing glycans, affecting their stability and function [92]. These glycosidases also contribute to biofilm formation, enhancing bacterial resilience against antimicrobials and immune attacks. Additionally, they facilitate bacterial adherence and nutrient acquisition by hydrolysing host glycans [92].

Clostridium perfringens, particularly types B and D, poses significant threats to neonatal lambs, causing sudden death through enterotoxaemia and systemic vascular damage [43]. *C. perfringens* type B, newly reported in New Zealand, produces both beta and epsilon toxins, leading to haemorrhagic enteritis and vascular damage [43]. The epsilon toxin of type D causes cerebral endothelial damage, resulting in vasogenic oedema and focal necrosis [43].

Clostridial infections are part of a broader spectrum of neonatal infections in lambs, which account for approximately 7.5% of lamb mortalities [66]. These infections often result from umbilical contamination or ingestion [66]. Fortunately, effective control of clostridial diseases can be achieved through toxoid vaccines, with protection transferred to neonatal lambs via colostrum [93].

Escherichia coli infections pose a significant threat to neonatal lambs, causing high mortality rates and economic losses in sheep farms [4, 94]. *E. coli* was identified as the primary bacterial cause of neonatal mortality in lambs, representing 63.4% of isolates [4]. Vaccination of pregnant ewes with *E. coli* surface proteins or formalin-inactivated bacterins can provide passive immunity to newborn lambs, significantly reducing morbidity and mortality rates [95, 96]. Lambs born to vaccinated ewes demonstrate increased resistance to both homologous and heterologous *E. coli* challenge exposures [95]. Risk factors associated with neonatal mortality include lack of vaccination, not separating neonates from adults, and starvation-mothering exposure [4]. While antibiotics were used to treat infections, probiotics were found to be more effective in controlling new infection rates [94].

Management and Prevention Strategies

The management and prevention of bacterial infections in neonatal lambs are critical to reducing neonatal mortality and ensuring the overall health of lambs, particularly during their first few days of life. Effective strategies include vaccination, promotion of colostrum intake, maintaining sanitation and biosecurity, implementing antibiotic therapy, and providing supportive care.

Vaccination programs play a significant role in the prevention of infections such as *E. coli* and Clostridia, which are common causes of neonatal distress. Studies show the importance of vaccines in providing immunity against specific pathogens, which can significantly reduce the incidence of disease outbreaks in lambing seasons. Furthermore, the timing of vaccine administration aligns with lamb rearing practices to ensure optimal protection, especially against diseases like pneumonia triggered by pathogens such as *Mannheimia haemolytica* [11].

The intake of colostrum, the first milk produced by ewes, is vital to lamb survival and health. Research indicates that an adequate amount of colostrum can substantially lower the chances of infections, as it provides essential antibodies and promotes the development of the gut microbiota, enhancing the neonate's immune response [97]. For instance, studies show that high immunoglobulin G levels in lambs correlate with better outcomes post-colostrum intake, thus supporting their physiological capabilities against bacterial infections [98]. This passive immunity can diminish the necessity for prophylactic antibiotics and decrease mortality rates associated with bacterial diseases like watery mouth caused by *E. coli* [97].

Sanitation and biosecurity are foundational aspects of managing bacterial infections. Good farm management practices, such as daily cleaning of lambing pens, can mitigate the build-up of pathogenic microorganisms in the environment, lowering flock mortality rates [11]. Regular disinfection of the pen of pregnant ewes waiting for parturition, cleaning of teats and equipment, feeding sufficient colostrum, and timely change of bedding are among the measures that can reduce infection in neonatal lambs.

Specifically, the improper handling of lambs during critical neonatal procedures like castration and tail docking without adequate sanitation has been associated with the prevalence of infections such as joint ill [38]. Instituting rigorous biosecurity protocols can minimise the risk of contagious infections, supporting both individual and herd health.

Antibiotic therapy is another key strategy, particularly in treating established infections. However, judicious use remains essential to avert antimicrobial resistance. For instance, while antibiotics like gamithromycin have shown effectiveness against *Mycoplasma* infections, caution is recommended due to the increasing resistance seen in various pathogens [99]. In managing infections, supportive care, which encompasses hydration and nutritional support, remains crucial alongside antibiotic treatment to bolster the recovery of affected lambs [30].

CONCLUSION

This review discussed the role of bacteria in the aetiology and pathology of neonatal lamb mortality, including management and prevention strategies. Several bacteria were reported to cause neonatal mortality in sheep, most especially in the first two weeks of life, with *Escherichia coli* consistently identified as the most prevalent pathogen globally. Other significant bacterial pathogens include *Salmonella* spp., *Pasteurella multocida*, and *Mannheimia haemolytica*. Additionally, *Brucella melitensis* and *Campylobacter fetus* subsp. *fetus*, among others, were also identified as bacterial causes of neonatal mortality in lambs. Overall, the integration of vaccination strategies, robust sanitation practices, promotion of colostrum intake, appropriate use of antibiotics, and provision of supportive care forms a comprehensive approach to managing bacterial infections in neonatal lambs. This multi-faceted strategy will not only reduce neonatal mortality but also foster sustainable livestock productivity, especially in developing countries.

Generative AI Statement

The authors declare that no generative AI and AI-assisted technologies were used in writing this manuscript.

Authors' Contributions

All the Authors contributed to the design, writing, editing and proof reading of this manuscript. All the authors read and approved the final manuscript.

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