Updates in managing *Salmonella* Dublin

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Abstract

Salmonella Dublin, a host-adapted *Salmonella* serotype in cattle, has become substantially more prevalent in dairy and calf-rearing facilities in the U.S. and Canada since 2012. *S*. Dublin bacteria isolated from U.S. and Canadian farms commonly exhibit multidrug-resistant characteristics. This multidrug resistance substantially complicates the treatment and control of salmonellosis due to *S*. Dublin infection. Because it is a zoonotic disease, S. Dublin infection in cattle also presents a potential risk to human health. In cattle, *S*. Dublin infection results in high morbidity and mortality rates in young calves and decreases the performance of mature animals. Clinical signs usually include pneumonia, respiratory distress and hyperthermia. Diagnosis is based on bacterial identification via culture or PCR assay, or serological testing. Treatment involves correcting dehydration and electrolyte imbalances and decreasing inflammation; the use of antimicrobials is controversial. Prevention and control are via enhanced biosecurity practices.

Key words: salmonellosis, calf health, zoonosis, latent carrier

Introduction

Salmonella enterica subspecies *enterica* serovar Dublin (*S*. Dublin) is a Gram-negative bacterium commonly affecting dairy cattle. *Salmonella* Dublin is host-adapted to cattle, where it can cause severe disease and compromise the welfare of young and mature bovine, and the economic return of the producer.[1-4] Moreover, *S*. Dublin is a zoonosis that can cause severe disease in humans.[5,6] Some countries like Denmark initiated a surveillance and control program since 2002, and as a result, the prevalence of *S*. Dublin was reduced from 25 to 7% from 2002 to 2015.[7] In countries without a control program, however, the prevalence of infections is high.[8] Also, *S*. Dublin has been the most frequently identified serotype among bovine *Salmonella* isolates from clinical samples submitted to veterinary diagnostic laboratories in the U.S. and U.K.[9-12]

In the U.S., *S*. Dublin has become one of cattle's most important multi-drug resistant (MDR) bacteria.[5,13] The MDR has complicated the treatment of clinically sick animals and has become a threat to human medicine.[14] In addition, *S*. Dublin may be difficult to control and eradicate from positive herds, as infection may persist in latent carriers and intermittently be shed to the environment.[2]

Importance of *Salmonella* Dublin

Prevalence in dairy farms

Salmonella Dublin is present worldwide, but estimates of the proportion of *S*. Dublin-infected herds vary greatly by country (Table 1). Some European countries have established an *S*. Dublin control and eradication that includes routine testing of all farms.[15-17] Although no country is free from salmonellosis, nine E.U. countries report only sporadic cases. Some countries, namely Finland, Norway and Sweden, have additional restrictions for cattle trade in place.[18] Conversely, more limited information regarding the prevalence of *S*. Dublin is available in countries without control programs. However, *S*. Dublin has been identified as one of the most common isolates of *Salmonella* spp. in dairy farms in the U.S., Germany and the U.K.[9-12, 19]

In 2014, the USDA's National Animal Health Monitoring System (NAHMS) conducted a cross-sectional study including 234 farms nationwide. *Salmonella* Dublin was present in 0.7%, 6.7% and 1.8% of the operations, milk samples and milk filters, respectively.[20] Additionally, the University of Minnesota Veterinary Diagnostic Laboratory (VDL) determined that *S*. Dublin was the most prevalent serotype isolated from bovine samples between 2005 and 2014, representing 31.8% of all isolates examined from 880 dairy farms from the upper Midwest.[9] Likewise, *S*. Dublin was the most prevalent serotype in bovine samples in the University of Wisconsin VDL, accounting for 23% of all isolates from 2006 to 2015.[10] Similarly, *S*. Dublin has been the most common *Salmonella* serovar isolated from bovine samples at the Michigan State University VDL between 2018 and 2022, representing 10-20% of all bovine *Salmonella* isolations (Table 2). In Germany and Italy, however, *S*. Typhimurium was the most frequently isolated serovar in cattle samples collected as part of official outbreak investigations, followed by serovar Dublin accounting for 30-40% of samples.[19,21]

Human health hazard

Salmonella Dublin is a zoonotic bacterium that can cause rare but severe illness in humans, and it is characterized by acute gastroenteritis and bacteremia.[5] The case fatality for *S*. Dublin has been reported as the highest compared to other *Salmonella enterica* serotypes and has been described as six times greater than *Salmonella* Typhimurium.[22] The consumption of raw milk or raw dairy products has been associated with outbreaks of human salmonellosis caused by serovar Dublin.[23-26] However, farm personnel, veterinarians and any person in direct contact with cattle are at risk of infection by accidentally ingesting animal feces or fluids.[27]

The U.S. Foodborne Disease Active Surveillance Network determined an increase in the incidence of human *S*. Dublin by 7.6 times from 1968 to 2013.[5] The same study determined an increase in hospitalization from 68 to 78% and an increase in mortality from 2.7 to 4.2% when comparing 1996-2004 with 2005-2013.[5] As discussed in the following section, *S*. Dublin has been characterized as a multidrug-resistant bacterium to common antibiotics used to treat bacterial infections in humans and animals. Therefore, *S*. Dublin is a pathogen that can affect human health severely and compromise medical treatment. Therefore, it is fundamental to prevent and reduce the risk of infection from cattle to farm workers, animal caretakers, and from animal-derived food to humans.

Table 1: Estimation of *S.* Dublin prevalence across different countries.

Country (region)[1]	National control plan	Apparent prevalence	Method for prevalence estimation	Reference
Canada (Alberta)	No	15.6%	Antibody testing in bulk tank milk in all farms in Alberta.	[57]
Canada (British Columbia)	No	30%	Antibody testing in bulk tank milk in all farms in British Columbia.	[58]
Canada (Ontario)	No	25%	Antibody testing on bulk tank milk and serum of 20 heifers in 100 herds.	[59]
Canada (Ontario)	No	5.1%	Antibody testing on bulk tank milk in all dairy farms in Ontario.	[60]
Denmark	Yes	9%	Bulk tank milk antibody testing every 3 months as part of national control program.	[16]
Germany	No	0.7%	Isolation in samples of cecal contents on slaughterhouse (n=283).	[61]
Great Britain	No	38%	Quarterly bulk tank milk antibody testing in 401 herds.	[62]
Sweden	Yes	1%	Bulk tank antibody milk testing in 4,683 herds.	[63]
The Netherlands	Yes	9%	Bulk tank milk antibody testing every 4 months as part of national control program.	[64]
United States	No	0.7%	Bulk tank milk PCR in 234 herds.	[20]
United States (New York State)	No	0.9%	Bulk tank milk antibody testing in 4,896 herds.	[65]

1 When no region is specified, the study aimed to represent the whole country.

Table 2: Prevalence and antimicrobial susceptibility patterns of *Salmonella* Dublin in bovine isolates at the Michigan State University Veterinary Diagnostic Laboratory from 2018 to 2022.[8]

	Year				
	2018	**2019**	**2020**	**2021**	**2022**
Number of *Salmonella* spp. isolations in bovine samples	206	202	223	186	131
Number (%) of *S.* Dublin isolations	26 (12.6%)	36 (17.8%)	36 (16.1%)	22 (11.8%)	25 (19.1%)
Antimicrobial susceptibility of *S.* Dublin isolates[1]					
Ampicillin	0%	0%	0%	0%	0%
Ceftiofur	4%	6%	8%	18%	12%
Clindamycin	0%	0%	0%	0%	0%
Danofloxacin	85%	80%	91%	90%	88%
Enrofloxacin	65%	83%	91%	90%	88%
Florfenicol	3%	0%	2%	9%	4%
Neomycin	0%	0%	0%	0%	0%
Penicillin	0%	0%	0%	0%	0%
Sulfadimethoxine	4%	0%	0%	4%	0%
Trimethoprim/Sulfamethoxazole	85%	100%	100%	95%	96%
Tetracycline	0%	0%	0%	4%	0%
Tulathromycin	62%	88%	66%	50%	68%

1 Expressed as the percentage of susceptible isolates.

Antimicrobial resistance

The prevalence of MDR *S.* Dublin is associated with geographical location. While *S.* Dublin is considered one of the most common MDR serotypes in the U.S.,[13] MDR is not common in the European *S.* Dublin isolates.[28] However, *S.* Dublin MDR can reduce the success of treatments, delay recovery and increase mortality and costs in humans and cattle.[14]

In North America, *S.* Dublin has a 43% higher MDR prevalence than other *Salmonella* isolates.[5] The National Antimicrobial Resistance Monitoring System (NARMS) reported that among *S.* Dublin isolates, 84% were resistant to five or more classes of antimicrobial drugs, and 57% were resistant to seven or more.[5] Furthermore, a 29 to 79% increase was observed in the proportion of isolates resistant to one or more antimicrobial classes when comparing 1996-2004 with 2005-2013.[5]

U.S. isolates of *S.* Dublin are generally susceptible to gentamicin, amikacin, cefoxitin, cephalothin, enrofloxacin, meropenem and azithromycin.[6,13] Even though this pathogen is susceptible to enrofloxacin, this drug is only allowed to treat bovine respiratory disease pathogens (specifically *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis*) in non-lactating cows and dairy replacements younger than 20 months. Hence, enrofloxacin is not labeled as a treatment for *S.* Dublin infections, and the extra-label use of this drug is prohibited for food animals in the U.S. Although most producers and veterinarians would treat respiratory disease without a pathogen isolation diagnosis, current U.S. regulations imply that enrofloxacin cannot be used when S. Dublin is suspected or confirmed. This complicates the proper treatment of sick calves and potentially might increase the use of drugs that *S.* Dublin has a reduced susceptibility to. The antimicrobial susceptibility pattern of *S.* Dublin isolated has largely remained unchanged in recent years (Table 2), with *S.* Dublin being generally susceptible to only four antimicrobials. Among those four, only trimethoprim/sulfamethoxazole has been labeled for treating *Salmonella* infections.

Pathogenesis and clinical signs of *Salmonella* Dublin infection in cattle

Salmonella Dublin infection in cattle can cause respiratory disease and septicemia. The disease is transmitted by two major routes: oral and vertical (Figure 1). In the oral route, susceptible cattle ingest the bacteria through contact with materials contaminated by feces or other bodily fluids (e.g., milk, saliva, nasal secretions) from infected animals. In the vertical route, infected pregnant cows transmit the disease to their offspring in utero. This can result in abortion in the last trimester of gestation or the birth of congenitally infected calves. Aerosolized transmission is also possible, especially among calves housed in tight, confined spaces.

Once an animal is infected, *S.* Dublin colonizes the digestive tract and moves to the mesenteric lymph nodes. From there, it can disseminate and cause systemic disease. Adaptation of *S.* Dublin to cattle is attributed to the selective survival of strains capable of evading the host's immune response. In these instances, the inflammatory response to infection in the intestine is ineffective in preventing systemic dissemination of infection. Because of the more invasive capacity of *S.* Dublin, clinical signs of infection with this serotype are more severe than they are with salmonellosis from other, less pathogenic, bovine-adapted *Salmonella* serotypes, such as Cerro.

The clinical signs of *S.* Dublin infection depend on the affected patient's age and the pathogen's endemicity in the herd. Although *S.* Dublin infection can affect cattle of all ages, it is most common in calves aged 2-12 weeks. In naive herds, the pathogen is rapidly transmitted, and an outbreak ensues. Although most *Salmonella* infections present as GI disease, *S.* Dublin infection is often a respiratory illness. Typical clinical signs of *S.* Dublin infection in calves include:

- Hyperthermia (fever)
- Obtundation (listlessness)
- Anorexia
- Pneumonia
- Respiratory Distress (e.g., elevated respiratory rate, coughing)
- Dehydration
- Septicemia

Arthritis (swollen joints) and meningoencephalitis can also occur in calves after bloodborne transmission of the bacteria. Bloody diarrhea is also possible but not very common. A peracute presentation may occur in calves, and sudden death in 1-2 days may result from endotoxic shock. Calves 6-8 weeks old that survive acute infection can develop chronic infection characterized by poor growth rate, ill thrift, lameness due to arthritis, and loose stool. Morbidity, mortality and case fatality rates for *S.* Dublin infection outbreaks in dairy calves are 10.5-34.8%, 2.3-18.2%, and 26.4%, respectively.[3,29]

In adult cattle, typical clinical signs of *S.* Dublin infection include:

- Slight fever
- Mild diarrhea
- Sudden decrease in milk production

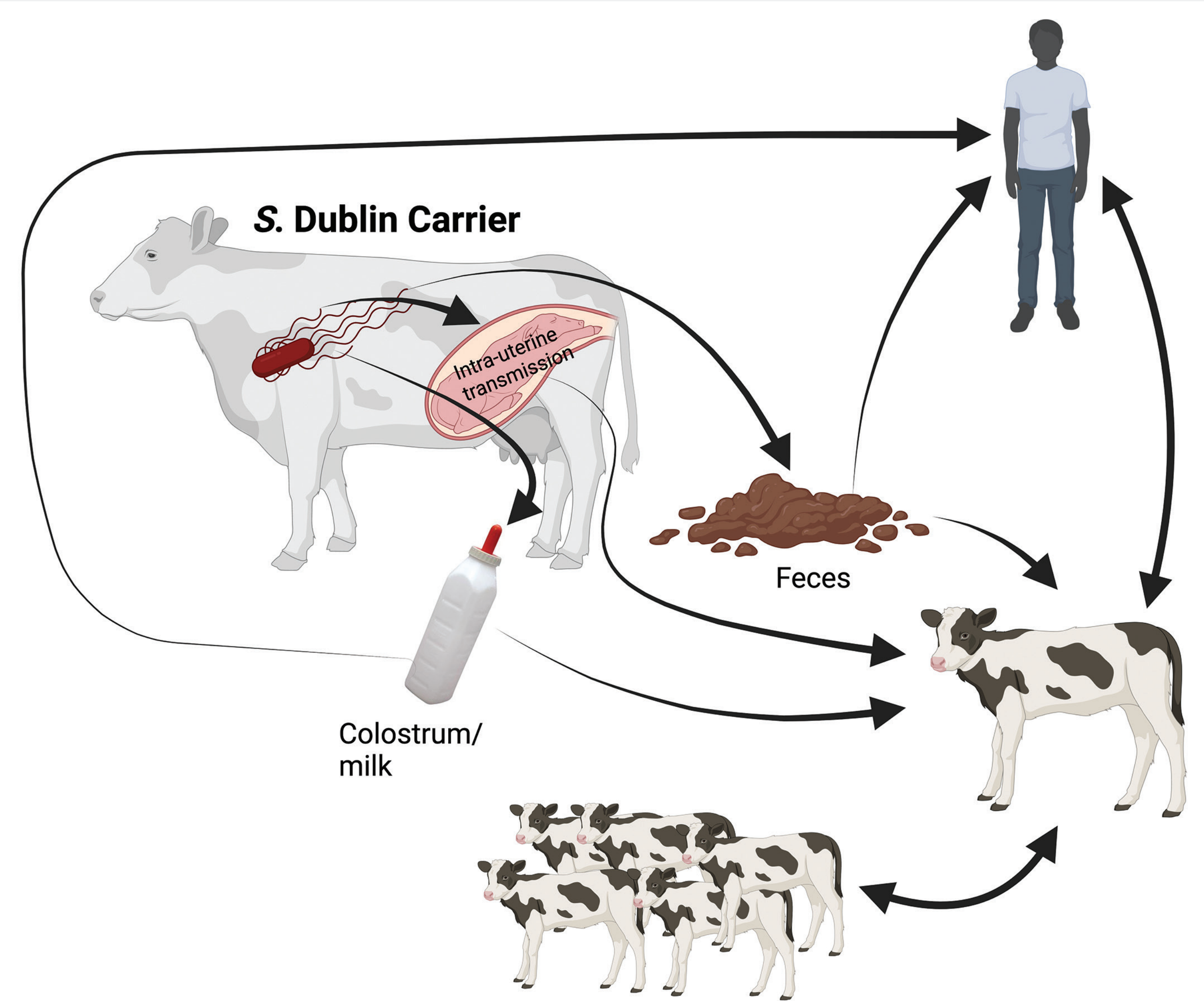
Less typically, *S.* Dublin infection in adults can cause bloody diarrhea and, in rare instances, death. Pregnant cattle may abort as a result of bacteremia. *S.* Dublin infection in adult cattle can generate persistent infections without clinical signs. These latent carriers can periodically shed the pathogen in feces or fluids during times of stress or when immunocompromised, contributing to disease transmission in affected herds.

Diagnosis

Bacterial identification

Bacteriological culture has been useful for isolating and identifying *S.* Dublin to trace infections and active shedders.[2,30] Bacteriological culture can be performed utilizing a variety of samples, including feces and fluids from live animals, organs from necropsies, aborted fetuses, or environmental samples. This method aims to isolate live bacteria.[2] Thus, the procedure involves pre-enrichment and selective enrichment to allow bacterial growth, followed by plating and confirmation.[2] This method has been described as more relevant in acute infections and clinically ill animals, as the correct isolation will depend on the number of bacteria in the sample.[2,3,30] For that reason, the sensitivity of this assay has been described as low,[32] and it has a limitation that latent carriers might be undetected due to the intermittent fecal shedding of *S.* Dublin. Bacteriological culture using samples from dung pits, drinking water, milk filters and feces of clinically ill animals was associated with a sensitivity of 45, 5, 7 and 38% for detecting *S.* Dublin, respectively.[33]

Figure 1: Illustration of the transmission routes for *Salmonella* Dublin. Symptomatic infected animals and latent carriers shed the bacterium to the environment under stress conditions, primarily in the peripartum. Once *S.* Dublin is shed in feces and secretions (saliva, colostrum, and milk) it can survive in the environment. The newborn calf may uptake the bacterium via fecal-oral route at calving or by consumption of raw colostrum or milk from infected cows. Moreover, the infected calf will shed the bacterium to the environment, where susceptible calves will ingest *S.* Dublin through direct contact or fomite (contaminated surfaces or objects). In addition, the intrauterine infection of the fetus in the last trimester of gestation may occur, resulting in abortion or the birth of an infected calf. Finally, the zoonotic route will occur mainly in caretakers working with symptomatic animals and latent carriers at calving. The human will uptake *S.* Dublin from feces and secretions during calving assistance, cleaning equipment or facilities, manipulating raw colostrum and milk, or close contact with sick animals. Created with **BioRender.com**



In post-mortem examination of clinically ill animals, the collection of tissues from the lungs, spleen, liver, intestine loops, gallbladder, intestinal content and lymph nodes increases the probability of bacteria isolation.[3,34] A potentially more sensitive and faster method for the detection of genetic material of *Salmonella* is the polymerase chain reaction test (PCR) or real-time PCR.[35] Persson, et al.[36] described an *S.* Dublin-specific real-time PCR. The procedure for this method requires a pre-enrichment of the sample from lysates or extracted DNA.[35] To increase sensitivity, a DNA extraction is recommended.[35] However, the specificity of the assay in comparison to the numerous other *Salmonella* serotypes is yet to be determined.

Serology

The detection of immunoglobulins against *S.* Dublin is performed through an enzyme-linked immunosorbent assay (ELISA). This method has a lower cost than bacteriological culture, and it can be used as a monitoring strategy in the herd to identify latent carriers during control and eradication programs.[37-38] *Salmonella* Dublin is part of the D-serogroup of *Salmonella* and has the antigenic factors O1, O9 and O12; therefore, cross-reaction between serovars sharing O antigens may occur.[39] The ELISA is based on detecting immunoglobulins directed to the LPS O- antigen from serum, milk and bulk tank milk (BTM) samples.[40,41] The kit is commercially available in several diagnostic laboratories across the U.S. to monitor *Salmonella* infections in cattle herds. The results provided in this ELISA are semi-quantitative for antibody concentration as they are expressed in ODC% (optical density coefficient). The interpretation of the result is based on an estimated cut-off point to determine positive animals depending on the sample. The ODC% cut-off for serum, milk from an individual, or BTM is 35 ODC%. A positive correlation exists between the ODC% and antibody concentration in a sample. In BTM, the greater the ODC%, the higher the spread of infection in the herd.[42] Sequential samples should be obtained from individual animals using milk or serum samples to identify latent carriers of *S.* Dublin due to their intermittent and low-intensity shedding. The limitations of this assay include that the sensitivity and specificity are age-dependent, as it performs better as a diagnostic test in animals older than 100 days.[32] Additionally, milk samples have the limitation that only lactating cows can be tested.[2,33]

Necropsy

There are no pathognomonic lesions in internal organs for infections with *S.* Dublin. However, while considering the age of the animal and the clinical signs, a necropsy may be helpful to guide diagnosis or for sample collection. In calves with clinical presentation, the gross pathologic findings in the lungs include pulmonary congestion, suppurative pneumonia, and chronic bronchopneumonia, depending on the severity of the clinical case.[13,34] The intestinal lesions may include diffuse catarrhal hemorrhagic enteritis, ileitis and mesenteric lymphadenitis.[3,34] The intestinal content is watery, malodorous and may contain mucous, blood, or fibrin clots.[3, 34] Moreover, the liver is enlarged with rounded edges, hemorrhagic areas on the capsular surface, and gelatinous gallbladder edema.[3] In some cases, swollen joints may be a finding.[13]

Treatment

There is no targeted treatment for *S.* Dublin infection beyond the general recommendations for any *S. enterica* infection, which are to correct dehydration and electrolyte imbalances and to decrease inflammation. Calves with systemic infection should be administered NSAIDs (e.g., flunixin meglumine, 1 mg/lb [2.2 mg/kg], IV, every 24 hours; or meloxicam, 0.23 mg/lb [0.5 mg/kg], IV or SC, every 24 hours for up to 5 days) to manage inflammation.

The administration of antimicrobials for treating *S.* Dublin infection is controversial for several reasons. First, appropriate antimicrobial selection is challenging because most *S.* Dublin strains are multidrug-resistant. U.S. strains are frequently not susceptible to antimicrobials labeled for use in calves with septicemia. Thus, in most cases, treatment with antimicrobials would require extra-label administration of these drugs and determination of withholding periods for meat under the direction of a licensed veterinarian.

Second, using an antimicrobial deemed potentially effective, based on the susceptibility of *S.* Dublin to the drug, is usually not permitted to treat *S.* Dublin infection. For example, U.S. isolates of *S.* Dublin are usually susceptible to enrofloxacin; however, the use of enrofloxacin to treat *S.* Dublin infection is extra-label drug use, which is prohibited for fluoroquinolones in food-producing animals in the U.S.

Finally, there is a risk of enhancing pathogen resistance to antimicrobials with continuous administration, and cattle treated with antimicrobials are more likely to become latent carriers of *S.* Dublin that contribute to further transmission of infection.

Prevention and control strategies

Prevention and control goals for *S.* Dublin infection in cattle are to 1) minimize pathogen exposure and 2) maximize pathogen resistance. Sanitation and biosecurity are critically important for achieving these goals.

Farm management practices

The following farm management practices can help minimize transmission of *S.* Dublin infection among cattle:[8]

- Providing clean, dry calving pens and avoiding large group-calving areas.
- Removing calves from contact with their dams' feces as soon as possible after birth.
- Placing calves in a clean environment, where they have no contact with other calves or adult cattle.
- Maintaining strict control of colostrum management.
- Feeding pasteurized, rather than raw, milk to calves.
- Identifying and isolating newly sick cattle immediately, and ensuring that farm personnel handle sick cattle separately.
- Sanitizing and disinfecting all equipment used between animals.
- Ensuring that personnel wash hands, boots and any common equipment used between groups of animals.

Sanitation

Research has demonstrated that practices associated with the cleaning and disinfection of the environment are key elements in the prevention and control of *S.* Dublin.[38,43,44] Thus, when cattle become infected with *S.* Dublin, it is essential to thoroughly clean and disinfect the environment. All organic material (e.g., bedding, contaminated feed, feces) must be removed, and all surfaces must be completely washed down with water plus a detergent cleaner to remove any organic residues. A disinfectant should then be applied to ensure proper contact time.

Disinfectants used to combat *Salmonella* spp. include halogens (e.g., dilute chlorine bleach), phenols, quaternary ammonium compounds, and oxidizing agents (e.g., potassium peroxymonosulfate). Pressure washers should be avoided because they can transmit aerosolized bacteria to both calves and personnel operating the washers.

Biosecurity

The purchase of cattle, particularly from multiple sources, is a major risk factor for introducing *S.* Dublin into a herd.[38,45-47] Given the intermittent shedding of carriers, quarantine screening using fecal testing has a low sensitivity. Clinically ill cattle should be isolated from the herd and not returned too quickly to the main herd after clinical signs abate.

Because the bacterium can also be transmitted via inanimate objects (e.g., boots, clothes and equipment), strict biosecurity practices should be implemented for visitors to the farm. *S.* Dublin can infect rodents; therefore, rodent control and protection of feed stores are important biosecurity measures.

Vaccination

Commercial and autologous vaccines have been used to control *S.* Dublin in herds. However, published studies have not evaluated autologous vaccines for their efficacy in preventing and reducing the clinical signs or the shedding of *S.* Dublin in dairy animals. A commercially available modified-live vaccine (EnterVene-D, Boehringer Ingelheim) is recommended for animals older than two weeks with a booster after 12 to 16 days. The benefits of an attenuated-live *S.* Dublin vaccine are associated with a robust response at the mucosal level due to its action on lymphoid tissue in the gut and a robust cell-mediated immune response due to intracellular proliferation.[48,49] Recent research also suggests that siderophore receptor vaccines might be immunogenic in newborn calves.[50]

The age for the first dose can be too late as calves may get infected with *S.* Dublin at birth or in the first hours of life. Moreover, limited research addresses the dam vaccination as an approach for producing antibodies that can be delivered to the newborn calf through colostrum.[51] The evidence suggests that specific antibodies for *S.* Dublin are in a higher concentration in the colostrum of cows vaccinated 30 days before dry-off than in non-vaccinated cows.[51] However, it remains unknown if those antibodies have a protective effect on the newborn calf. A recent study also explored the effect of vaccinating *S.* Dublin latent carriers with the commercial attenuated-live vaccine on vertical transmission. In this study, latent carriers vaccinated at dry-off with a live culture *Salmonella* Dublin commercial vaccine were five times less likely to give birth to a seropositive calf.[52]

Alternative routes of vaccine administration have also been explored. Research evaluating intranasal and oral vaccination of four-day-old calves suggests these are safe routes.[53,54] Using these extra-label routes of administration reduced the disease severity as calves administered the vaccine had a reduced mortality rate compared to unvaccinated calves.[54] However, the incidence of pneumonia, abnormal fecal scores and the fecal shedding of *S.* Dublin were not reduced.[53,54] Furthermore, no differences were observed in the average daily gain or antibody concentration at 10 weeks and 10 months of life compared to control calves.[54] Importantly, earlier studies noted that oral vaccination required a larger dose to induce a measurable immune response and was not protective against challenge.[55] Thus, existing evidence does not support the use of this alternative route of administration.

Additionally, few studies assessed the cross-protection between *Salmonella enterica* with modified-live vaccines. Mohler, et al.[34] found that calves younger than two weeks of life orally vaccinated with modified-live *S.* Typhimurium had less severe clinical signs, improved appetite and reduced fecal shedding when challenged with *S.* Dublin compared to control calves. However, calves in that study were challenged with a dose of *S.* Dublin to induce disease and minimize mortality, and respiratory clinical signs were not assessed. Similar results were found using an attenuated-live *S.* Typhimurium on diarrhea and shedding of *S.* Newport and *S.* Cerro.[48] Moreover, there is a study assessing the vaccination of the dry cow with an S. Newport bacterin to provide cross-protection in an *S.* Typhimurium challenge in calves fed colostrum from vaccinated dams. Despite higher serological titers, no difference in mortality, clinical signs, hematology and fecal cultures were observed in calves fed colostrum from vaccinated cows and the control group.[56] Based on this research, the cross-protection between *Salmonella* spp. and potential protection against *S.* Dublin in dairy herds is still in development.

Conclusions

S. Dublin severely affects cattle and human health. Recent reports indicate its prevalence has increased in several countries in the last several years, making it an emergent pathogen. Information on pathogenicity, antimicrobial resistance, risk factors and preventive management practices is available. However, more research is still needed on the effectiveness of strategies that could be implemented in dairy facilities to prevent and control *S.* Dublin.

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