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The duration of fecal *Salmonella* shedding following clinical disease among dairy cattle in the northeastern USA

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Abstract

The objectives of this study were to determine the duration of fecal *Salmonella* shedding among dairy cattle in the northeastern United States following laboratory-confirmed clinical disease and to evaluate whether age group or serotype was associated with either shedding period or mortality. Study farms included 22 dairy herds that had at least two previous salmonellosis cases confirmed by fecal culture. Veterinarians continued to submit culture samples from clinical suspects following herd enrollment, and fecal samples from positive cattle were collected monthly until three sequential negative results were obtained or until loss to follow-up. There were 357 culture-positive clinical cases that each involved a single serotype during the shedding period. The Kaplan-Meier median duration of fecal *Salmonella* shedding was 50 days, and the maximum was 391 days. *S.* Newport was the predominant serotype, accounting for 51% of the cases. Age group and serotype were not significant predictors of *Salmonella* shedding duration in a Cox proportional hazards model, when stratifying by herd. However, the proportion of adult cows shedding for at least two consecutive monthly samples was significantly greater than the proportion of female calves shedding for this duration (Fisher's exact test p-value < 0.01). Age group was also associated with mortality in this study; calves with salmonellosis were more likely to die than cows as estimated by a logistic regression model which controlled for herd as a random effect (p-value = 0.04).

Keywords

Salmonella; Dairy cattle; Fecal shedding

1. Introduction

Salmonella is a zoonotic enteric pathogen with significant public health implications, resulting in approximately 1.4 million illnesses, 16,000 hospitalizations, and between 400 – 600 deaths annually in the U.S. alone (Mead, et al., 1999; Voetsch, et al., 2004). Though primarily a cause of self-limiting acute enteritis (diarrhea, abdominal pain, and fever, with a typical duration of four to seven days), *Salmonella* can produce invasive infections that lead to sepsis and death. People generally acquire salmonellosis through foodborne exposure, although direct contact with infected animals is another possible route (Mead, et al., 1999; L Plym and Wierup, 2006). Preliminary CDC FoodNet data from 2007 show that *Salmonella* accounted for 38% of

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all laboratory-confirmed cases of foodborne infections, based on surveillance in 10 states (Centers for Disease Control and Prevention (CDC), 2008). Dairy cattle are considered an important source of *Salmonella* serotypes that are a threat to human health. Fecal contamination of beef carcasses at the time of slaughter is thought to represent the predominant route of transmission. According to the 1996 USDA National Animal Health Monitoring System (NAHMS) report, 15% of culled dairy cows were shedding *Salmonella* at livestock markets, and 66% of markets had at least one cow shedding *Salmonella* (Wells, et al., 2001). Contamination of crops by manure used as fertilizer, as well as water contamination by manure run-off, are additional sources of transmission (Islam, et al., 2004; Sivapalasingam, et al., 2004). Those who work or otherwise interact with livestock are also at risk of infection via direct exposure when cattle are shedding *Salmonella*.

Introduction of *Salmonella* onto a dairy farm can occur through a variety of routes, including purchased cattle, contaminated feed or water, wild animals such as rodents and birds, and human traffic (Bender, 1994; Evans and Davies, 1996; Sanchez, et al., 2002; Nielsen, et al., 2007). Thus, the presence of *Salmonella* on a farm is not an unexpected finding. In fact, one study involving 110 dairy farms in four states found that over 90% of the farms had at least one *Salmonella*-positive culture obtained (fecal and/or environmental) during the course of five sampling visits over a one year period (Fossler, et al., 2004). The NAHMS Dairy 2002 study, based on a single sampling visit to five herds in each of 21 states, found that 31% of herds yielded at least one *Salmonella*-positive fecal culture (Blau, et al., 2005). Considering these high herd-level prevalence values, it would seem logical that fecal shedders within a herd represent a potential point of intervention to mitigate public health risk.

Clinical signs of salmonellosis in cattle may include diarrhea, fever lasting one to seven days, anorexia, dehydration, decreased milk production, abortion, and evidence of endotoxemia (Divers and Peek, 2008). Infected cattle can shed the organism while ill and following clinical recovery, and asymptomatic shedders never show signs at all. Once a cow has become infected, the duration and magnitude of fecal shedding are important determinants of public health risk. Widespread environmental contamination can result from *Salmonella* shedding, and the organism can survive for prolonged periods in suitable conditions outside a host (Wray and Wray, 2000; You, et al., 2006). Fecal shedding also increases the risk of within-herd transmission, potentially serving as a source of infection for other animals in the herd. Finally, the shedding of *Salmonella* on one farm increases the probability of inadvertent transmission to other herds, perpetuating the cycle of infection. All of the above lead to an increased risk of zoonotic transmission. In addition to its public health consequences, salmonellosis can be a costly disease for dairy producers on account of mortality, treatment expenses, reduced milk yield, and weight loss within the herd (Peters, 1985; Huston, et al., 2002).

The objectives of this study were to determine the duration of fecal *Salmonella* shedding among dairy cattle in the northeastern United States following laboratory-confirmed clinical disease and to ascertain whether age group or serotype was predictive of either shedding period or mortality.

2. Materials and Methods

2.1. Study design

This study was based on data collected prospectively as part of a larger project to estimate the incidence of salmonellosis among dairy cattle from 831 herds in the northeastern USA (Cummings, et al., In Press). In that project, *Salmonella* culture was performed on fecal samples obtained from dairy cattle with compatible clinical signs (including diarrhea with blood, mucus, or a foul odor, fever of at least 103°F, depression, and decreased appetite) between February, 2004 and September, 2005. The current study included 22 herds that had at least two laboratory-

confirmed *Salmonella* cases during that time span; these herds all had on-farm individual cow milk production records as well. Herds were enrolled as they became eligible at the time of the second positive *Salmonella* culture, with dates ranging from June, 2004 to March, 2005. Following herd enrollment, veterinarians continued to submit culture samples from suspected salmonellosis cases, using the same clinical case guidelines. If an animal had a positive fecal *Salmonella* culture on initial testing, subsequent fecal samples were then collected by project personnel at approximately monthly intervals until three sequential negative results were obtained or until the animal was lost to follow-up due to death, sale, or lost animal identification. All animals were classified as pre-weaned female calves, pre-weaned male calves, heifers (from weaning to calving age), or adult cows based on their age at the time of laboratory-confirmed clinical salmonellosis.

2.2. Sample collection and processing

Fecal samples were collected via rectal retrieval, with a new glove being used to collect each sample. Approximately 10 g of fecal matter was placed into a Para-Pak bottle (Meridian Bioscience Inc., Cincinnati, OH) and sealed. All samples were shipped to the Animal Health Diagnostic Center (AHDC) at Cornell University for bacteriologic culture. Standard culture methods were used to isolate *Salmonella* from feces. Individual fecal swabs from sample bottles were enriched in 10 ml of Tetrathionate broth (Difco, Detroit, MI) containing 0.2 ml of iodine solution; the mixture was incubated at 42°C for 18–24 hours. After incubation, the sample-broth mixture was streaked onto Brilliant Green agar with novobiocin (BGN; Becton Dickinson and Company, Franklin Lakes, NJ) and Xylose Lysine Tergitol 4 (XLT-4) selective media, and both plates were incubated at 37°C for 18–24 hours. Red colonies (lactose non-fermenting bacteria) on BGN and black colonies (H_2S-producing bacteria) on XLT-4 were inoculated into Kligler Iron Agar (KIA) slants and then incubated at 37°C for 18–24 hours. XLT-4 plates without suspected colonies were re-incubated at 37°C for an additional 18–24 hours before checking again for characteristic black colonies. Colonies on KIA slants which exhibited the biochemical properties of *Salmonella* were then serogrouped by slide agglutination using standard protocols. Those colonies that were positive by slide agglutination were then identified as *Salmonella* using the Sensititre Automated Microbiology System's A80 panel (TREK Diagnostic Systems Inc., Cleveland, OH). Confirmed *Salmonella* isolates were sent to the USDA, APHIS National Veterinary Services Laboratories (NVSL) in Ames, Iowa for serotyping using established procedures for cell wall (O) and flagellar (H) antigen identification (Edwards and Ewing, 1972).

2.3. Data analysis

For each clinical case, the duration of shedding was defined as the interval between the sampling date of the first laboratory-confirmed *Salmonella* positive and the sampling date of the last laboratory-confirmed positive before three consecutive negative samples were obtained, with the addition of 15 days to account for shedding during half the sampling interval. Animals lost to follow-up before three consecutive negative samples were right-censored. Estimates of shedding duration were determined by age group and by serotype. Survival analysis techniques, including the Kaplan-Meier method and Cox proportional hazards model, were used to test the association between age group, serotype, and the dependent variable, duration of *Salmonella* shedding in days. The proportional hazards model was stratified by herd in order to control for any herd-level confounding factors. Model fit was assessed by plotting the martingale and deviance residuals. A sensitivity analysis was performed to test the effect of our assumption that censoring times were independent of the duration of fecal *Salmonella* shedding among cattle in this study. Thus, we repeated the model under two extreme scenarios: that all censored cattle reached the endpoint of *Salmonella* shedding at the time of censoring, and alternatively that censored cattle remained censored but had a censoring time equal to the longest period of *Salmonella* shedding in the study. We then compared the

parameter estimates and hazard ratios from our original model with those of the two hypothetical models. In addition to our survival analysis methods, Fisher's exact test was used to compare age groups by proportion shedding *Salmonella* for at least two consecutive monthly samples.

Bivariable analysis using the chi-squared test was utilized to determine whether age group or serotype was significantly associated with mortality. A logistic regression model was used to further investigate associations with mortality while controlling for herd as a random effect, with vital status serving as the dichotomous outcome variable. The generalized estimating equations (GEE) method was employed, and a backward stepwise approach was used to identify a final model. All data analysis was performed in SAS (version 9.1; SAS Institute Inc., Cary, NC), and p-values < 0.05 were considered significant.

3. Results

3.1. Descriptive statistics

Median herd size was 553 adult cattle (range: 245–1516). The median number of culture-positive clinical cases per herd was eight (range: 2–121). There were 357 clinical cases that each involved a single serotype during the period of shedding. Only eight clinical cases were culture-positive for multiple serotypes during the shedding period, and these were excluded from the statistical analysis. Of the cattle that yielded at least two positive samples, 92% (86/94) had the same serotype isolated from all of them. Overall, the Kaplan-Meier median duration of fecal *Salmonella* shedding was 50 days, and the maximum was 391 days. A total of 183 animals (51%) were lost to follow-up before three sequential negative results were obtained, of which 179 were either adult cows (135) or female calves (44); all of these cases were therefore right-censored. Among the censored adults, 59 (44%) were lost to follow-up due to death, 69 (51%) due to sale, and the remaining 7 (5%) due to unknown reasons. Among the censored female calves, however, 33 (75%) were lost to follow-up due to death, while sale and unknown reasons only accounted for one (2%) and 10 (23%), respectively.

Of the 357 culture-positive clinical cases, 77% were adult cows and 21% were female calves, with the rest being either heifers, male calves, or of unknown age group. The Kaplan-Meier median duration of shedding among adult cows was 51 days, while the maximum was 391 days. In contrast, the Kaplan-Meier median duration of shedding among female calves was 45 days, with a maximum of only 72 days.

The predominant serotype was Newport, accounting for 51% of the cases, followed by Infantis, 4,5,12:i:-, Typhimurium, and Kentucky; these five serotypes comprised 83% of the total (Table 1). Ten other serotypes made up the remainder and were treated as one serotype category ("Other") in the analysis. The Kaplan-Meier median duration of shedding was highest among those cattle infected with the Kentucky serotype (105 days), while the maximum was seen in a cow infected with Newport (391 days).

3.2. Risk factor analysis

Examination of the residual plots revealed adequate fit of the Cox proportional hazards model. The two hypothetical models for our sensitivity analysis assumed (1) that censored cattle reached the endpoint of *Salmonella* shedding at the time of censoring and (2) that censored cattle had a censoring time of 391 days. The parameter estimates and hazard ratios from these models and our true model were all comparable (the hazard ratios from hypothetical model 1, hypothetical model 2, and our true model, respectively, were as follows: Cow [0.7, 1.3, 0.8], 4,5,12:i:- [1.4, 3.0, 2.4], Infantis [1.5, 0.9, 1.7], Kentucky [1.2, 1.1, 0.8], Newport [0.7, 1.8, 1.0], and Typhimurium [1.1, 1.9, 1.2]). Age group and serotype were not significant predictors

of *Salmonella* shedding duration in our model, when stratifying by herd (Table 2). However, the proportion of adult cows shedding for at least two consecutive monthly samples was significantly greater than the proportion of female calves shedding for this duration (Fisher's exact test p-value < 0.01). Only 8% of calves had an observed duration of *Salmonella* shedding greater than 30 days, and none reached a shedding time of three months. In contrast, 22% of cows had an observed shedding duration greater than 30 days, and 7% of cows had an observed duration in excess of three months. Figure 1 is a Kaplan-Meier graph of survivorship function which illustrates the difference in shedding duration between these age groups after about 30 days.

Chi-squared testing revealed that mortality was significantly higher (p-value < 0.01) among female calves (45%, 33/73) than among adult cows (22%, 59/269). Calves with salmonellosis were also more likely to be die than cows in a logistic regression model which controlled for herd as a random effect (p-value = 0.04, Table 3). The serotype of the *Salmonella* isolate was not significantly associated with mortality in this study.

4. Discussion

A number of studies have described the prevalence and/or risk factors for fecal *Salmonella* shedding among dairy cattle (Kabagambe, et al., 2000; Warnick, et al., 2001; Huston, et al., 2002; Fossler, et al., 2004), but few have examined the duration of shedding in either subclinical or clinical cases. This study had the particular advantage of involving a large number of clinically affected animals from multiple herds. Over 350 cattle with laboratory-confirmed salmonellosis were tested via fecal culture at approximately monthly intervals until three sequential negative results were obtained or until loss to follow-up.

Although we obtained data on a large number of cattle, the relatively small number of enrolled herds (22) may have introduced a degree of selection bias into this study. These herds were all located in either New York (15) or Vermont (7) and may not be representative of all dairy operations in the northeastern USA. These herds were also quite homogeneous with respect to a number of important covariates of interest in this study, thus precluding analysis; for example, all 22 herds utilized free-stall housing, and only one used a flush water system to remove manure from alleys. It is possible that additional selection bias may have arisen from our requirement that study herds had to have had at least two previous laboratory-confirmed *Salmonella* cases in order to be eligible. Perhaps the pattern of *Salmonella* shedding is different among those herds with sporadic cases of disease in individual animals, although we found no significant correlation between the number of cases per herd and the maximum duration of fecal *Salmonella* shedding within that herd. Finally, the issue of informative censoring must be addressed, particularly in light of the high percentage of censored cases in this study. It is conceivable that those cattle that were right-censored due to death or sale would have had an extended duration of fecal *Salmonella* shedding on account of disease severity. However, our sensitivity analysis led us to decide that even if our assumption of independent censoring was not met, we would have reached the same conclusions. Furthermore, loss of an animal due to death or culling is, in practical terms, a means of bringing an end to that animal's shedding of *Salmonella* into the dairy farm environment. One could argue that these outcomes be considered as legitimate endpoints of fecal *Salmonella* shedding duration on the dairy farm.

In this study, fecal *Salmonella* shedding exceeded one year in two animals, with the maximum duration (391 days) being seen in an adult cow infected with the Newport serotype. This is more than twice the maximum shedding time (190 days) reported in a study involving two dairy herds that had experienced clinical outbreaks of *Salmonella* Newport (Cobbold, et al., 2006). Prolonged periods of shedding could lead to extensive environmental contamination and an increased risk of within-herd transmission and spread to other herds. As evidenced in

this study, shedding often persists well beyond the typical duration of clinical signs in cattle with salmonellosis. Furthermore, extended survival of the organism in the environment is possible; one study found that *S*. Newport could survive in manure for at least six months over the course of winter (Clegg, et al., 1983). Despite the fact that multiple *Salmonella* serotypes are common in the dairy farm environment (Wells, et al., 2001; Edrington, et al., 2004), over 91% of the cattle with multiple positive samples in this study had the same serotype isolated from all of them. This is consistent with true bacterial colonization rather than organisms simply passing through the gastrointestinal tract. However, we cannot rule out either re-infection from the environment or a pass-through effect as contributing to repeated positive samples in some cattle.

Adult cows tended to shed *Salmonella* in their feces longer than calves did, in part because affected calves often died early in the course of their disease. In fact, the odds of mortality were significantly higher among calves in a logistic regression model controlling for herd as a random effect. Of the 34 calves lost to follow-up for known reasons, death was the cause in 33 of them. Dairy herd outbreaks that involve calves represent an important concern for producers because of high case fatality. On the other hand, infected cows are more likely to have an extended duration of shedding, which can result in significant public health consequences in addition to potential transmission to other cattle.

Serotype was not a significant predictor of *Salmonella* shedding duration in this study, according to a Cox proportional hazards model. It may be that host (immune status) and environmental factors (herd management and hygiene practices) play a more prominent role in determining the length of shedding. Alternatively, other pathogen factors such as dose of inoculum may have a significant effect on shedding duration. One study found that periparturient cows and cows designated as sick by farm personnel were more likely than other cattle to be shedding *Salmonella* in their feces (Fossler, et al., 2005). According to another study, cows in early lactation (≤ 60 DIM) were more likely to be shedding *Salmonella* than cows in late lactation (Fitzgerald, et al., 2003). Therefore, it seems logical that physiologic stress and concurrent illness could predispose to prolonged fecal shedding among dairy cattle. A number of studies have reported large herd size as a risk factor for fecal *Salmonella* shedding in dairy herds (Kabagambe, et al., 2000; Huston, et al., 2002; Blau, et al., 2005; Fossler, et al., 2005). Large herds tend to be housed in free-stalls, which present considerable challenges when combating manure-transmitted pathogens, and they may have a greater likelihood of purchasing cattle from outside sources. It is conceivable that these factors could lead to increased duration of fecal *Salmonella* shedding among individual cattle as well. Manure management could also play a role in shedding; one study found that farms where manure was removed from alleys via a flush water system were more likely to have *Salmonella* shedders than farms that employed a different system (Kabagambe, et al., 2000). Again, it is possible that a similar mechanism could also lead to prolonged shedding among individual animals.

Newport was clearly the major serotype in this study, accounting for over half the cases. This is particularly noteworthy since Newport is also an increasingly important human pathogen and has generally been multidrug-resistant among cattle in recent years (Cummings, et al., In Press). According to CDC FoodNet data from 2006, the annual incidence of foodborne *S*. Newport infections in the U.S. had increased by 42% over the average annual incidence for 1996–1998 (Centers for Disease Control and Prevention (CDC), 2007). Multidrug resistance is also on the rise; the prevalence of the most common MDR *S*. Newport phenotype increased from 1% of human Newport isolates tested by the National Antimicrobial Resistance Monitoring System (NARMS) in 1998 to 21% of isolates tested in 2003. This phenotype, Newport-MDRAmpC, is characterized by resistance to at least nine antimicrobial agents (ampicillin, amoxicillin-clavulanic acid, cefoxitin, ceftiofur, cephalothin, chloramphenicol, streptomycin, sulfamethoxazole/sulfisoxazole, and tetracycline). It also displays decreased

susceptibility to ceftriaxone, a crucial drug used for treating invasive *Salmonella* infections in children. This serotype undoubtedly represents an important threat to public health. Reported risk factors for Newport-MDRAmpC infection in people include direct exposure to a dairy farm (Gupta, et al., 2003), consumption of uncooked ground beef (Varma, et al., 2006), and consumption of unpasteurized dairy products (Centers for Disease Control and Prevention (CDC), 2008); these examples illustrate the key role that dairy cattle play as a source of MDR *Salmonella* Newport.

5. Conclusion

In this study, adult cattle with clinical salmonellosis tended to shed the organism in their feces longer than calves did, partly because calves often died early in the course of disease. Newport was the predominant serotype observed, accounting for over half the cases. The duration of fecal *Salmonella* shedding may exceed one year in some animals, and shedding frequently persists well beyond the typical length of clinical signs in cattle with salmonellosis. Additional work is needed to determine whether various herd-level covariates, such as housing type and manure management system, are significantly associated with the duration of fecal *Salmonella* shedding among cattle. A large sample of herds with diverse production methods would be required for such a study. It would also be valuable to examine other animal-level factors, including stage of lactation and concurrent disease, as potential predictors of *Salmonella* shedding duration.

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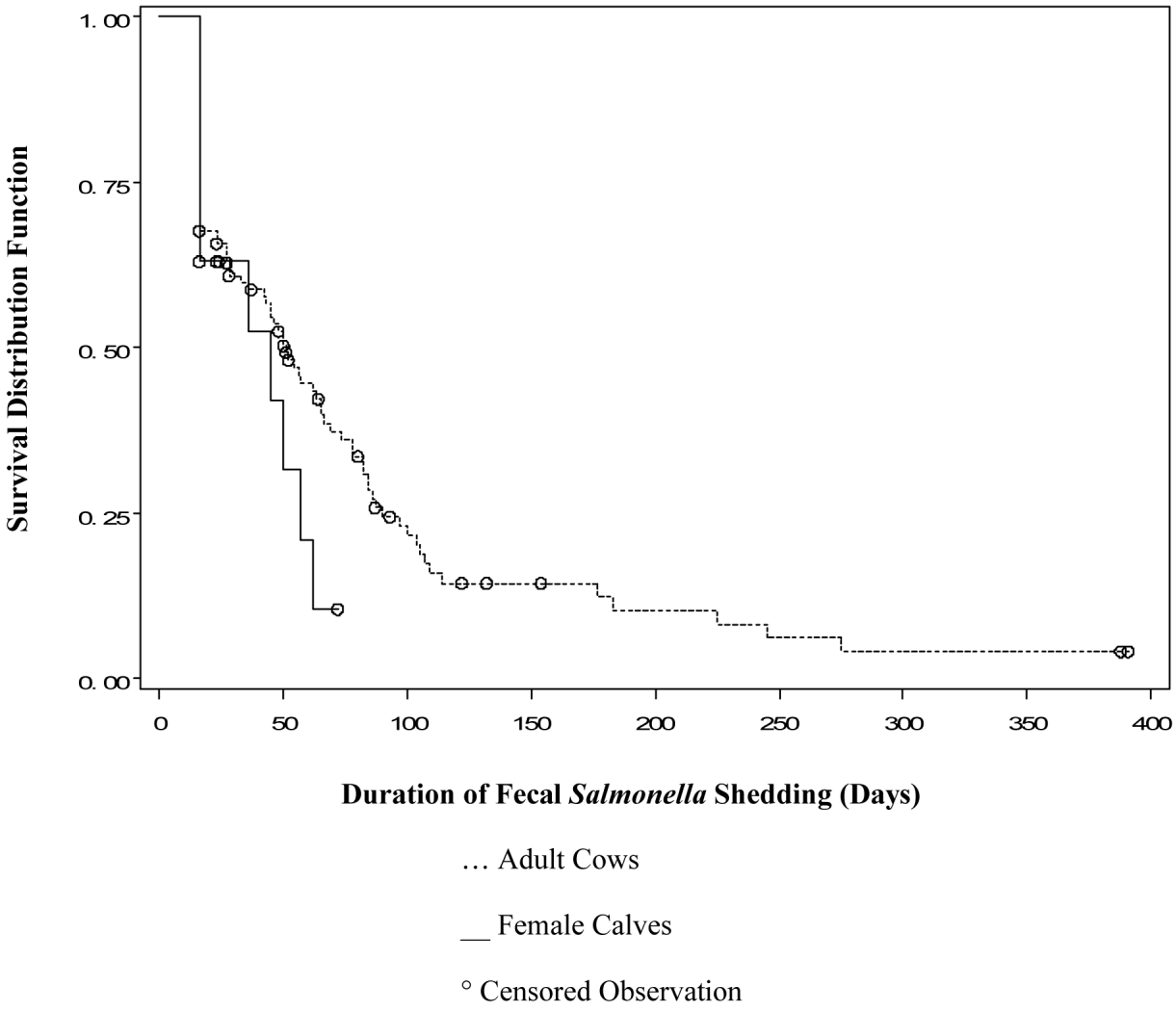

Figure 1.
Kaplan-Meier survival curves for duration of fecal *Salmonella* shedding among adult cows and female calves from 22 dairy herds in the northeastern USA

Table 1

Duration of fecal *Salmonella* shedding by serotype among 357 culture-positive clinical cases from 22 dairy herds in the northeastern USA

Serotype	% (N)	Kaplan-Meier Median Duration of Shedding (days)	Max Observed Duration of Shedding (days)
4,5,12:i:-	9% (32)	16	183
Infantis	10% (37)	16	84
Kentucky	5% (17)	105	245
Newport	51% (182)	50	391
Typhimurium	8% (30)	66	66
Other*	17% (59)	69	388

*Agona (4), Anatum (9), Bardo (3), Cerro (2), Mbandaka (10), Montevideo (1), Muenchen (3), Muenster (15), Ohio (10), Oranienburg (2)

Table 2

Association between fecal *Salmonella* shedding duration and age group/serotype among dairy cattle in the northeastern USA, when stratifying by herd in a Cox proportional hazards model

Variable	Hazard Ratio	95% Confidence Interval
• *Age Group*		
Cow	0.8	(0.5, 1.2)
Calf	1.0	---
• *Serotype*		
4,5,12:i:-	2.4	(0.3, 17.2)
Infantis	1.7	(0.2, 12.6)
Kentucky	0.8	(0.1, 7.0)
Newport	1.0	(0.4, 2.7)
Typhimurium	1.2	(0.3, 4.8)
Other	1.0	---

Likelihood Ratio Chi-square = 8.3 (df = 6)

Table 3

Association between mortality and age group among dairy cattle with salmonellosis in the northeastern USA, when controlling for herd as a random effect in a logistic regression model

Variable	Odds Ratio	95% Confidence Interval	p-value
• *Age Group*			
Calf	2.9	(1.04, 8.4)	0.04
Cow	1.0	---	---

Deviance = 384 (df = 340)