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Contribution of Endemic Listeriosis to Spontaneous Abortion and Stillbirth in a Large Outdoor-housed Colony of Rhesus Macaques (*Macaca mulatta*)

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***Listeria monocytogenes* is an endemic agent in the primate population at the California National Primate Research Center and has been associated with both sporadic cases and a general outbreak of pregnancy failures. The primary objective of this study was to verify the incidence of *L. monocytogenes*-associated abortion and fetal deaths in the Center's outdoor breeding colony. In addition, we sought to compare the group of female macaques that presented with *Listeria*-associated abortion with both those with nonlisteria-associated abortion and animals with successful pregnancy outcome. We calculated the incidence of *L. monocytogenes*-associated abortion and stillbirth by dividing the number of positive *L. monocytogenes* cultures from aborted fetuses by the number of pregnant female macaques from 1989 through 2009. To compare the pregnancy outcome of female macaques that have presented *L. monocytogenes*-associated abortion and stillbirth, we created 2 control groups: female macaques with successful pregnancy outcomes during the 1999 breeding season and animals with nonlisteria-associated pregnancy failure. These macaques were followed for 2 subsequent breeding seasons. The results showed a range in the incidence of *L. monocytogenes*-associated abortion and stillbirth from 0% to 8.39% throughout the 1989 to 2009 breeding seasons. In addition, the *Listeria*-associated abortion group did not present statistically significant differences in fertility and abortion rates when compared with the control groups. We conclude that although *L. monocytogenes* is an endemic agent at the Center's outdoor breeding colony, the agent's incidence varied in significance. Furthermore, an episode of *L. monocytogenes*-associated abortion did not affect subsequent pregnancies.**

Listeriosis is a foodborne infection caused by *Listeria monocytogenes*, a motile, nonspore-forming, gram-positive bacillus that exhibits aerobic and facultative anaerobic characteristics.[1,22,26] Outbreaks of listeriosis have been reported among colonies of captive animals of various species, including guinea pigs and rabbits, and have been attributed to coprophagia or contamination of feed.[23] In humans, this infection is reported most frequently in developed countries[29] as a cause of zoonosis[1,18,24]. Immunocompromised and pregnant subjects represent vulnerable populations who are most susceptible to *L. monocytogenes* because of their suppressed T-cell–mediated immunity.[4,5,22,26,27] Listerial infection during pregnancy can results in placentitis, spontaneous abortion, and fetal or neonatal deaths in numerous species.[6,7,9-19,24] As in humans, the consequences of the infection in pregnant rhesus monkeys generally results in abortion during the last third of the pregnancy (that is, between days 110 and 155) and has been described as a generalized infection characterized by pyogranulomatous microabcesses in the placenta and fetal body.[15,27]

Because identifying cases of spontaneous abortion and subsequent pregnancy loses of unknown etiology is both an economic and colony-health concern at the California National Primate Research Center, this study aimed to verify the contribution of *Listeria monocytogenes*-associated abortion to the total spontaneous abortion and stillbirth rates in the Center's breeding colony. Listerial infection in NHP has received increasing attention, and the Center's animal population represents a valuable research model for *Listeria*-associated abortion. Given its resemblance to human listeriosis,[16] listerial infection in NHP may represent a valuable tool for the understanding of the epidemiologic and pathophysiologic aspects of listerial infection in human populations. In addition, findings from the current study will improve our understanding of the biology of *Listeria* spp. in outdoor breeding colonies and possible confounding factors in biomedical research.

Materials and Methods

Study design. The rhesus macaques in this study were housed outdoors in a seminatural environment. The total number of breeding female macaques (age, 3 to 19 y) and the numbers of conceptions and pregnancy losses were abstracted from the Center's database. The incidence of *L. monocytogenes*-associated abortion was calculated by dividing the number of positive *L. monocytogenes* samples cultured from the respective aborted fetuses in the given year by the number of pregnant female macaques. Sterile cotton swabs were used to take samples from the placental tissues and from the brain, lungs, and peritoneum of all fetuses that were necropsied. Swabs were cultured by

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using selective media for *Listeria* spp. (lithium chloride–phenylethanol–moxalactam media, Hardy Diagnostics, Santa Maria, CA). Plates were incubated at room temperature for 24 to 48 h.[13] Suspect colonies were identified by using a commercial kit (API *Listeria*, BioMérieux, Marcy l'Etoile, France). This test was designed to distinguish the genus, species, and subspecies of *Listeria*.[2] According to the Center's clinical laboratory database, the sensitivity of the test is 99.5%, and its specificity is reported to be 97. 7%.[13]

The population of female macaques housed in the outdoor breeding colony that conceived between the 1989 and 2009 breeding seasons was defined as the population at risk of *L. monocytogenes*-associated abortion. Pregnancy in these female macaques was detected through abdominal palpation, and ketamine was used for sedation (100 mg/mL; 0.1 mL/kg); a macaque was considered to be pregnant when the fetal head circumference was detected after the day 50 of pregnancy.

Subsequent female macaques that presented with suspected *L. monocytogenes*-associated abortion were evaluated for *L. monocytogenes* by culture also. Tables 1 and 2 compare the pregnancy outcomes of the various groups. These data were collected over 2 consecutive breeding seasons (1999–2000 and 2000–2001).

The reproductive history of the animals before and after the 1998–1999 breeding season was retrieved and summarized in Table 3.

Study groups. *L. monocytogenes* was isolated from the placenta or fetal tissues of 44 macaques housed outdoors during 1998–1999 breeding season. The macaques were 3 to 18 y old and had no previous history of listeriosis. Of the 44 animals, 20 were excluded from the study group because they were moved to indoor housing or died during the 2-y study period.

Control group 1. For comparison with the study group, we used data from 24 female macaques that were randomly selected from 381 outdoor-housed rhesus macaques with successful pregnancies during the 1998–1999 breeding season and no previous history of listeriosis.

Control group 2. For control group 2, we randomly selected 24 female macaques with no previous history of listeriosis from the group of 120 rhesus macaques with spontaneous abortions or stillbirths during the 1998–1999 breeding season that were not associated with *L. monocytogenes* infection.

Statistical analysis. We used two-way ANOVA followed by Bonferroni posthoc testing (with significance defined as a P value of less than 0. 05) to compare the data among the study group and control groups 1 and 2 (Prism version 5.0, GraphPad Software, La Jolla, CA).

Results

Incidence of *L. monocytogenes*-associated abortion and stillbirth. The incidence of *L. monocytogenes*-associated abortion varied from 0 cases (1991, 1992, 1994, and 2000) to 44 cases (8.39% in 1999; Figure 1).

Rates of *L. monocytogenes*-associated abortion and stillbirth. The annual rates of abortions and stillbirths associated with *L. monocytogenes* per total annual spontaneous abortions were calculated from 1989 to 2009. The calculated rate was the highest in 1999 followed by 2003 (Figure 2).

Late-term fetuses that were culture-positive for *L. monocytogenes* had varying postmortem decomposition. Mild to moderate subcutaneous amber to pink gelatinous edema was present. In addition, varying amounts of amber to pink fluid were present in the peritoneal (ascites) and pleural (hydrothorax) cavities. The primary and secondary placental discs had multifocal to coalescing gray to tan areas (Figure 3), which microscopically corresponded to necrosis and a mixed inflammatory cell infiltrate that consisted mainly of neutrophils and histiocytes (Figure 4). Microscopically, the lung, conducting airways, and alveolar lumens contained varying mixtures of neutrophils, histiocytes, and aspirated amniotic squames. Disseminated fetal infection was present occasionally, but tissue lesions might have been obscured by postmortem decomposition.

Discussion

Our data demonstrate that the incidence of abortion and stillbirth due to *L. monocytogenes* from 1989 to 2009 varied from 0% (no cases; 1991, 1992, 1994, and 2000) to 8.5% (44 cases, 1999). Although the number of *L. monocytogenes*-associated cases may be underestimated in early pregnancy due to the inaccuracy of abdominal palpation and subclinical early embryonic mortality, this difference in rates reveals the apparent paradox between the broad dissemination of the agent in the environment and the sporadic occurrence of the disease in the form of outbreaks in the Center's outdoor breeding colony, as seen during the 1995–1996, 1998–1999, 2002–2003, and 2004–2005 breeding seasons.

These findings might be attributed to the weather or even to the saprophytic characteristic of the agent. *L. monocytogenes* is prevalent during cooler months with increased precipitation,[23] given that the agent can grow at cold temperatures when other organisms cannot, thus giving *L. monocytogenes* a competitive advantage that increases the number of organisms in the soil and the risk of infection.

The measures currently used at the Center to reduce the propagation of *L. monocytogenes* include appropriate drainage by crowning and the removal of puddled water. In addition, feces and excess chow are removed daily. Last, the feeders and the concrete pads beneath the trays are steam-cleaned biweekly.

Data collected from manifestations of the disease in humans support a saprozoonotic characteristic of this agent. For instance, a listeriosis outbreak in humans that occurred from early August 1998 through January 1999 was caused by the strain serotype 4b of *L. monocytogenes* and led to at least 101 cases of illness and 21 deaths reported by 11 states across the country.[3] Similarly, an outbreak reported in 2011 across the United States occurred when an increased incidence of *L. monocytogenes*-associated abortion was observed in the outdoor NHP breeding colonies. These data may provide circumstantial evidence of the epidemiologic effect of the disease shared by humans and NHP. In the current study, however, we did not identify a significant correlation (Pearson's product-moment correlation coefficient) between the *L. monocytogenes*-associated abortion and local climate data, such as average precipitation, average minimal temperature, and average maximal temperature (data not shown).

The manifestation of clinical signs during an outbreak of *L. monocytogenes* appears to be associated with the extent of exposure and the immunologic status of the animals. In an experimental infection, some NHP treated with 10^3 to 10^6 cfu of *L. monocytogenes* presented normal births, whereas others experienced stillbirth.[28] Furthermore, a strong antibody response in the initial infection, followed by a decrease of these titers after 55 d, has been associated with stillbirth.[28] Such findings support the possibility that a cellular immune response may confer protection against future infections in naturally infected NHP.

Although the number of pregnancy losses caused by *L. monocytogenes* in the first third of the pregnancy is difficult to determine, the greatest proportion (91.5%) of pregnancy losses in the Center's breeding colony were late-term (about 110 to 165 d)

Table 1. Pregnancy outcomes in study group and control groups 1 and 2

	Study group			Control group 1			Control group 2		
Animal	Age (y)	1999–2000	2000–2001	Age (y)	1999–2000	2000–2001	Age (y)	1999–2000	2000–2001
1	4	L	L	4	L	L	4	L	L
2	5	L	N	5	L	L	5	L	L
3	5	L	L	5	L	L	5	L	L
4	5	S	L	5	N	L	5	L	L
5	5	L	S	5	L	S	5	L	S
6	6	L	L	6	L	S	6	L	L
7	6	S	L	6	L	L	6	L	S
8	6	N	L	6	L	L	6	S	S
9	6	L	L	6	L	L	6	L	L
10	7	L	L	7	L	L	7	L	L
11	7	L	L	7	L	L	7	L	L
12	7	L	S	7	L	L	7	L	L
13	7	L	L	7	L	L	7	L	L
14	7	L	S	7	L	L	8	L	L
15	9	L	L	9	L	L	9	S	L
16	9	L	L	9	L	L	9	L	S
17	11	L	L	11	L	L	11	L	S
18	11	L	L	11	L	L	11	L	L
19	11	S	L	11	L	L	11	L	N
20	13	S	L	13	L	L	13	N	S
21	14	L	N	14	L	L	14	N	L
22	14	L	L	14	L	S	14	L	L
23	16	L	L	16	L	L	16	L	L
24	16	L	L	16	L	L	16	S	S
Total									
N		1	2		1	0		2	1
L		19	19		23	21		19	16
S		4	3		0	3		3	7

L, live birth; N, no conception; S, abortion or stillbirth
The study group comprised rhesus macaques with *Listeria*-associated abortion or stillbirth during the 1998–1999 breeding season.
Control group 1 comprised rhesus macaques with a successful pregnancy outcome during the 1998–1999 breeding season.
Control group 2 comprised rhesus macaques that experienced pregnancy failure (non*Listeria* etiology) during the 1998–1999 breeding season.

abortion. This result is similar to findings in experimental infection of NHP[27,28] and other domestic animals. This fact may be attributed to the increased levels of progesterone, which can lead to a decline in immunologic responses[25] and thus allow *L. monocytogenes* to invade extraintestinal sites. In addition, the last trimester of pregnancy in this colony typically coincides with the coolest months of the year, during which the prevalence of *L. monocytogenes* in the soil may be increased. Given that abortions with unknown etiology also occurred frequently during the coolest months (February and March), additional research is warranted.

The reproductive history of the macaques revealed single episodes of *L. monocytogenes*-associated abortion, suggesting long-term resistance against the pathogen, as previously reported regarding the proliferation of antibodies and antigen-specific lymphocytes against *L. monocytogenes* in experimentally infected monkeys.[27,28] Additional studies of the antigenic specificity and determinants of persistent IgG antibody responses are needed to better understand the resistance to this organisms.

No cases of *L. monocytogenes*-associated abortion occurred in the Center's indoor breeding colony. This finding confirms the reports from primate research centers elsewhere that monkeys housed indoors experience less *L. monocytogenes* exposure than do those housed outdoors.[27]

Table 2. Reproductive outcome: June 1999–September 2001

	Total no. of conceptions	Total no. of abortions
Study group	45 (93.75%)	7 (15.6%)
Control group 1	47 (97.91%)	3 (6.4%)
Control group 2	46 (95.83%)	10 (21.7%)

The study group (n = 24) comprised rhesus macaques with *Listeria*-associated abortion or stillbirth during the 1998–1999 breeding season.
Control group 1 (n = 24) comprised rhesus macaques with a successful pregnancy outcome during the 1998–1999 breeding season.
Control group 2 (n = 24) comprised rhesus macaques that experienced pregnancy failure (non*Listeria* etiology) during the 1998–1999 breeding season.

The cases of abortion and stillbirth for which an etiology could not be determined suggest various possibilities, including (a) chemical or physical variables at sample collection, (b) other potentially infectious agents, and (c) metabolic, anatomic, or traumatic complications that caused collateral damage to otherwise healthy cells or tissues and possibly death of the fetus.

Natural or experimental exposure to infectious agents such as simian parvovirus has caused pregnancy failure in various NHP populations.[8,20,21] In addition, Ljungan virus, a member of Picornavirus family, has recently been associated with repeated

Table 3. Reproductive history of the female macaques from the study group and control groups 1 and 2 before and after the 1998–1999 breeding season

	Study group				Control group 1				Control group 2			
	Before		After		Before		After		Before		After	
Case	C	A	C	A	C	A	C	A	C	A	C	A
1	0	0	6	2	0	0	11	1	0	0	7	0
2	0	0	4	2	0	0	9	0	1	1	14	5
3	0	0	13	0	0	0	13	2	1	1	14	5
4	1	1	5	1	1	1	3	1	1	0	9	1
5	1	0	9	1	1	1	3	2	1	0	2	1
6	2	0	9	1	1	0	2	1	1	0	14	0
7	3	0	10	1	2	2	6	1	2	1	5	1
8	2	0	8	5	2	0	9	0	3	3	2	2
9	1	0	6	0	1	0	1	0	2	0	6	0
10	2	0	6	0	2	1	6	1	3	0	8	0
11	3	0	7	2	2	0	10	1	2	0	7	3
12	3	0	7	2	2	1	6	1	2	0	12	0
13	2	0	12	1	1	3	10	1	3	0	12	1
14	4	1	2	1	3	0	2	0	3	1	8	1
15	4	0	2	0	4	1	12	0	4	0	10	4
16	5	0	5	0	6	1	11	3	5	0	3	1
17	7	0	5	0	6	2	2	0	6	0	6	3
18	6	0	3	0	6	0	6	0	7	1	5	1
19	6	1	4	2	9	1	4	1	5	0	2	1
20	10	0	6	1	8	6	5	2	0	2	11	2
21	10	1	2	0	9	1	9	0	0	0	4	0
22	10	0	3	0	11	3	7	5	12	3	4	0
23	11	0	3	0	9	1	4	1	5	1	7	2
24	12	0	4	2	10	1	2	2	12	1	2	2

A, number of abortions; C, number of conceptions.

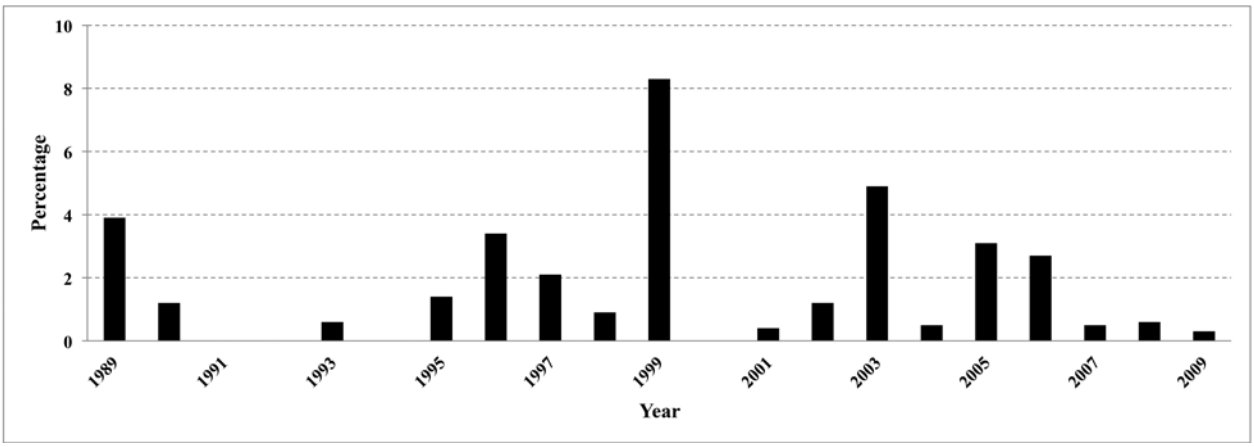

Figure 1. Incidence of *L. monocytogenes*-associated abortion and stillbirth at the CNPRC. The incidence varies ranging from 0 cases (1991, 1992, 1994, and 2000) to 44 cases (8.39%) in 1999.

pregnancy losses in rodents and humans.[16] Limited serologic investigation of simian parvovirus and parechovirus in female NHP breeders that presented with spontaneous abortion at the Center did not reveal any trends (data not shown).

In summary, even though *L. monocytogenes* is recognized as a potent fetocidal agent in primate populations, it may not be the main cause of pregnancy loses at the California National Primate Research Center. In addition, it appears unlikely that *L. monocytogenes* causes permanent damage in the female reproductive system. The study group of macaques did not differ from control groups 1 and 2, but the poor obstetric outcomes in the animals in the study group and control group 2 compared with control group 1 may reveal the opportunistic character of *L. monocytogenes* within subjects predisposed to pregnancy failures.

The single episodes of *L. monocytogenes* infection among the female macaques that presented with subsequent spontaneous abortion or stillbirth remain an important issue to be considered. In a previous study performed at the Center, swabs were collected from the genital tract, and bacteriologic culture was performed after *L. monocytogenes*-associated abortion during the 1999 breeding season. None of these subsequent samples

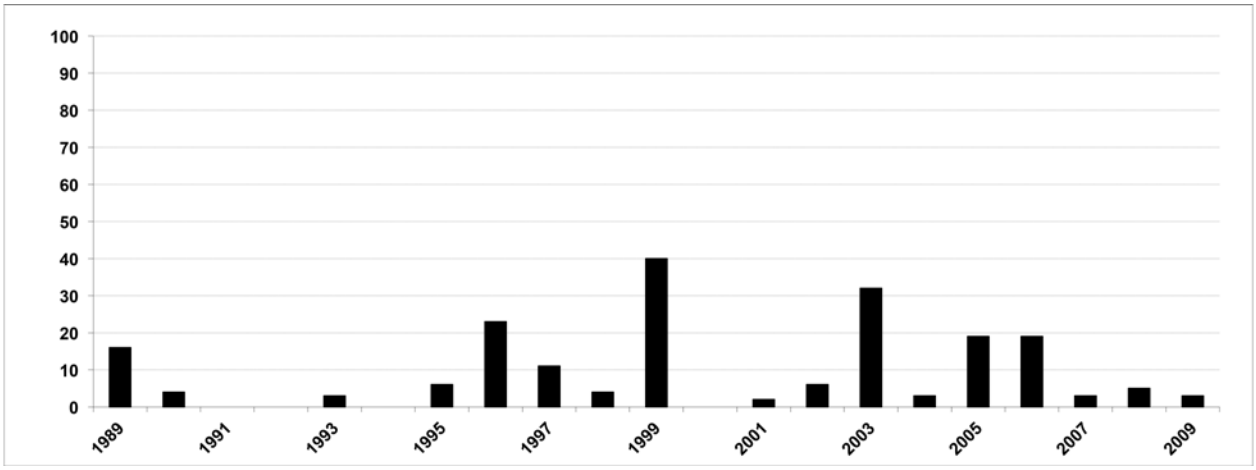

Figure 2. Rate of *L. monocytogenes*-associated abortion and stillbirth in the CNPRC per spontaneous abortion cases at the CNPRC. The annual rates of the abortion and stillbirths associated with L.monocytogens per total annual spontaneous abortions from 1989 to 2009. The rates varied from zero (1992,1994,2000) to the highest rate (40%) in 1999 followed by 2003(32%) .

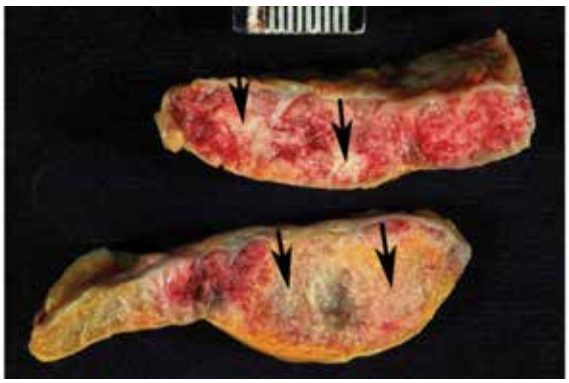

Figure 3. Placenta infected with *Listeria monocytogenes*. The arrows indicate diffuse, well-demarcated areas.

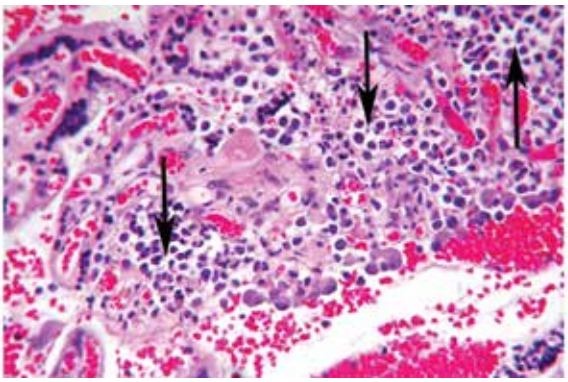

Figure 4. Placentitis caused by *Listeria monocytoges*. The arrows indicate a mixed inflammatory infiltrate composed mainly of neutrophils and hystiocytes. Hematoxylin and eosin stain; magnification, 40×.

yielded bacterial growth, indicating that *L. monocytogenes* does not survive in the genital tract after infection (data not shown). In addition, given that *L. monocytogenes* has been identified as an important cause of zoonosis, outbreaks in NHP may be an epidemiologic concern with ongoing repercussions among humans.

Microbiologic cultures undoubtedly provide an invaluable diagnostic tool, but potential pitfalls must be considered. More consistent techniques such as protein-based (immunohistochemistry) and DNA-based (in situ hybridization, PCR analysis) methods show potential for future studies.

At this point, the Center's Pathology Unit has been investigating various specific causes of pregnancy failure in the breeding colony. From a wider perspective, these NHP may be used as biologic models to study human *L. monocytogenes*-associated abortion as well as pregnancy failures of other etiologies.

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