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# Assessment of the Incubation Period for Invasive Listeriosis

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## Abstract

We characterized incubation periods among outbreak-associated listeriosis cases, using a simulation model to account for patients with multiple exposure dates. The median was 11 days; 90% of cases occurred within 28 days, and incubation periods varied by clinical manifestation.

### Keywords

*Listeria*; incubation period; listeriosis

*Listeria monocytogenes* is a gram-positive bacterium that causes the food-borne disease listeriosis [1]. The disease is rare, with an estimated 1600 illnesses annually in the United States [2], but severe, with a case-fatality rate of approximately 20% [3]. Groups at higher risk include older adults, persons with immunocompromising conditions (eg, cancer and diabetes), and pregnant women [4]. Invasive *L. monocytogenes* infections include bacteremia, central nervous system (CNS) infection (eg, meningitis), and, less commonly, focal infections, including septic arthritis, endophthalmitis, and endocarditis [1,5].

The listeriosis incubation period is defined as the time interval from eating a contaminated food to symptom onset. It is commonly cited as 3–70 days (median, 3 weeks), largely based on data from a 1985 listeriosis outbreak in California linked to pasteurized Mexican-style cheese (median incubation period, 31 days), and case reports of sporadic infections [6, 7]. A 2013 study by Goulet et al [8] examining incubation periods for 37 cases, predominantly from Europe in 1980–2012 with single reported exposure dates, found an 8-day median incubation period (range, 1–67 d), nearly one-third the previous estimate.

Given the discordant median incubation period estimates published to date, we assessed the incubation periods of cases recorded during US outbreak investigations, using a multiple exposure simulation model [9] that allowed us to include not only cases with a single reported exposure date, which might bias the findings to foods consumed infrequently, but also cases with multiple exposure dates.

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## METHODS

We reviewed all outbreak-associated invasive *L. monocytogenes* cases reported to the Centers for Disease Control and Prevention from 1985 to 2015 with exposure date information available. Incubation periods were calculated using consumption dates and illness onset. If a single consumption date was reported, an incubation period was designated as "single." An incubation period was designated as "possible" if a food was consumed multiple times, there was illness onset date uncertainty, or purchase date was used as a consumption date proxy. All possible exposure dates were included in a multiple exposure date simulation model producing a uniform frequency distribution of each possible incubation period [9]. For example, if a patient's exposure occurred 5–10 days before illness onset, the integers 5–10 were randomly selected for 10 000 model iterations. We excluded cases with only a minimum (eg, patient reported consuming the implicated food at least 2 weeks before illness onset) or maximum (eg, patient reported consuming the food sometime in the 2 weeks before illness onset) possible incubation period available.

Clinical manifestations and the specimen source were used to classify cases into 4 clinical manifestation categories: (1) CNS cases (*L. monocytogenes* isolated from cerebrospinal fluid or from blood with clinical findings of CNS involvement), (2) bacteremia cases (*L. monocytogenes* isolated from the blood without CNS involvement), (3) pregnancy-associated cases (*L. monocytogenes* isolated from a pregnant woman, newborn, or products of conception), and (4) other listeriosis cases. Mother-infant pairs, which typically reflect transplacental infection, were counted as single cases. We classified foods implicated in outbreaks as produce, dairy, or meat/seafood.

Analyses were performed for single reported incubation periods alone and for single and possible incubation periods using US data alone and with European data from Goulet et al [8]. We calculated the median incubation period and the first and third quartiles for each clinical manifestation. Quantile regression was used to estimate the median incubation period, adjusting for clinical manifestation and food category.

## RESULTS

### US Cases

Data were available for 56 US cases. Eight cases were excluded because only a minimum or maximum possible incubation period was reported. Of the remaining 48 cases, 20 (42%) had single incubation periods and 28 (58%) had possible incubation periods (Table 1). Twenty cases (47%) were associated with bacteremia, 13 (30%) were CNS cases, 7 (16%) were pregnancy-associated, 3 (7%) were classified as other listeriosis (ie, cases with focal infection), and 5 could not be classified by clinical manifestation, owing to insufficient information.

### Single Incubation Period

Of 20 US cases with a single incubation period, the median was 9 days (range, 1–70 days). By clinical manifestation, the median incubation period was 19 days (range, 7–23 days) for 3 pregnancy-associated cases (18%), 7 days (1–29 days) for 10 bacteremia cases (53%), and

9.5 days (3–16 days) for 4 CNS cases (23%). There were no significant differences in median incubation periods between clinical manifestation categories.

### Combined (Single and Possible) Incubation Period

Among all 48 US cases, the median incubation period was 11 days (range, 0–70 days). An estimated 90% of cases occurred within 28 days of exposure. Again, there were no significant differences in median incubation periods between clinical manifestation categories.

### Incubation Period for Combined US and European Cases

The median incubation period was 10 days (range, 0–70 days) when we combined 48 US and 37 European cases (34 single and 3 possible incubation periods). Of 54 cases with single incubation periods, 8 (15%) had incubation periods >28 days; 6 were pregnancy-associated (31, 33, 36, 37, 42, and 67 days), 1 was associated with bacteremia (29 days), and for 1 the clinical manifestations were unknown (70 days). In a quantile regression model, the median incubation period for pregnancy-associated cases (21 days) was 16 days longer (95% confidence interval [CI], 9.09–22.91) than for bacteremia cases (5 days) and 11 days longer (2.87–19.13) than for CNS cases (10 days). Ninety percent of cases occurred within 28 days of exposure. In non-pregnancy-associated cases, the incubation period was ≤2 weeks in >75% of cases and ≤3 weeks in 85%; in pregnancy-associated cases, it was ≤5 weeks in >75% and ≤6 weeks in 90%.

### Food Category Analysis

Of 85 cases, 39 (46%) were linked to dairy products, 35 (41%) to produce, and 11 (13%) to meat or seafood. Compared with cases linked to produce, a larger percentage of those linked to dairy were pregnancy-associated (11 cases [28%] for dairy vs 3 [9%] for produce). In a quantile regression model controlling for clinical manifestation, the incubation period for cases linked to produce was 1 day longer than for the other food categories at the 25th percentile (95% CI, −1.64 to 3.64), 3 days longer at the median (−.18 to 6.18), and 6 days longer at the 75th percentile (.39–11.61).

## DISCUSSION

This examination of US incubation period data for listeriosis, the largest to date, found a median incubation period of 11 days among cases with single and multiple possible incubation periods. The inclusion of cases with multiple possible exposure dates allowed for a large sample size and inclusion of cases linked to foods consumed on more than one occasion.

The median incubation period in this study is similar to that reported by Goulet et al [8] (8 vs 11 days), but different from the typically reported 3 weeks. However, the incubation periods for clinical manifestation categories differed between this study’s combined analysis and that of Goulet et al for bacteremia cases (9 vs 2 days, respectively), CNS cases (13 vs 9 days), and pregnancy-associated cases (11 vs 27.5 days).

The incubation period differences observed between US and European analyses, however, must be interpreted with caution given the relatively few cases in each category, particularly among pregnant women, and other host and external factors that may influence incubation period. These factors include the implicated food, the *L. monocytogenes* dose ingested, host susceptibility and response, and the virulence of the *L. monocytogenes* strain. In a healthcare-associated listeriosis outbreak in Norway caused by highly contaminated Camembert cheese, the median incubation period was approximately 3–4 days (range, 1–24) [10]. The short median incubation period may reflect the high number of bacteria (estimated $1 \times 10^8$ organisms) and the fact that most patients had an immunocompromising condition. Conversely, a French outbreak linked to Brie cheese included a large number of pregnancy-associated cases (55%) with prolonged incubation periods (median, 32 days; range, 17–67), suggesting that host response and susceptibility or strain virulence played a role [11].

Although there was no significant difference between produce and other food commodities at the 50th percentile (P = .06), cases linked to produce had a significantly longer incubation period (6 days) at the 75th percentile with adjustment for clinical manifestation. Produce seems to be an increasingly common source of listeriosis outbreaks in the United States [12], and more enumeration testing after outbreaks would help determine whether produce items are usually associated with lower or higher *L. monocytogenes* doses than meat or dairy products. Produce is often eaten raw, so there is less opportunity for pathogens to be killed and items could vary dramatically in level of contamination, making generalizations difficult.

After a food recall or listeriosis outbreak public notices, person are often concerned if they have eaten the food involved. Our finding that incubation periods were ≤2 weeks in >75% and ≤3 weeks in 85% of non-pregnancy-associated cases (≤5 weeks in >75% and ≤6 weeks in 90% of pregnancy-associated cases), may help influence treatment and monitoring decisions. These data may also improve the food histories collected during outbreak investigations. Given that the exposure window of highest concern may be 5–6 weeks before illness onset for patients with pregnancy-associated illness and 3 weeks for others, food histories may be taken in this time frame. However, other factors, such as comparability with historic interview data and ease of questionnaire administration, should also be considered.

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## References

1. Vazquez-Boland JA, Kuhn M, Berche P. *Listeria* pathogenesis and molecular virulence determinants. Clin Micobiol Rev. 2001; 14:584–640.
2. Scallan E, Hoekstra RM, Angulo FJ, et al. Foodborne illness acquired in the United States—major pathogens. Emerg Infect Dis. 2011; 17:7–15. [PubMed: 21192848]
3. Centers for Disease Control and Prevention. Vital signs: *Listeria* illnesses, deaths, and outbreaks—United States, 2009–2011. Morb Mort Week Rep. 2013; 62:448–52.

4. Swaminathan B, Gerner-Smidt P. The epidemiology of human listeriosis. Microbes Infect. 2007; 9:1236–43. [PubMed: 17720602]
5. Silk BJ, Date KA, Jackson KA, et al. Invasive listeriosis in the foodborne diseases active surveillance network (FoodNet), 2004–2009: further targeted prevention needed for higher-risk groups. Clin Inf Dis. 2012; 54(suppl5):S396–404.
6. Linnan MJ, Mascola L, Lou XD, et al. Epidemic listeriosis associated with Mexican-style cheese. N Engl J Med. 1998; 319:823–8.
7. Mandell, GL., Bennett, JE., Dolin, R. Principles and practice of infectious diseases. 7th. Philadelphia, PA: Churchill Livingstone Elsevier; 2010. p. 2707-14.
8. Goulet V, King LA, Vaillant V, et al. What is the incubation period for listeriosis? BMC Inf Dis. 2013; 13:11.
9. Meltzer M. Multiple contact dates and SARS incubation periods. Emerg Inf Dis. 2004; 10:207–9.
10. Johnson BO, Lingaas E, Torfoss D, et al. A large outbreak of *Listeria monocytogenes* infections with short incubation period in a tertiary care hospital. J Infect. 2010; 61:465–70. [PubMed: 20813130]
11. Goulet V, Jacquet C, Vaillant V, et al. Listeriosis from consumption of raw-milk cheese. Lancet. 1995; 345:1581–2.
12. McCollum JT, Cronquist AB, Silk BJ, et al. Multistate outbreak of listeriosis associated with cantaloupe. N Engl J Med. 2013; 369:944–53. [PubMed: 24004121]

## Table 1

Listeriosis Incubation Periods by Clinical Manifestation

| | US Cases by Type of Incubation Period | | | |
|---|---|---|---|---|
| **Clinical Manifestation** | **Single (n = 20)[a]** | **Possible (n = 28)[b]** | **Combined (n = 48)[c]** | **European and US Combined (n = 85)[c]** |
| Cases with known clinical manifestation, No. | 17 | 26 | 43 | 81 |
| CNS | 4 | 9 | 13 | 23 |
| Bacteremia | 9 | 11 | 20 | 28 |
| Pregnancy-associated | 3 | 4 | 7 | 17 |
| Other | 1 | 2 | 3 | 3 |
| Incubation period, median (range), d | 9 (1–70) | 12 (0–31) | 11 (0–70) | 10 (0–70) |
| CNS | 9.5 (3–16) | 13 (0–22) | 13 (1–21) | 10 (0–21) |
| Bacteremia | 7 (1–29) | 7 (0–28) | 9 (0–29) | 5 (0–29) |
| Pregnancy-associated | 19 (7–23) | 7.5 (0–30) | 11 (1–30) | 23 (0–67) |
| Other | 9 (NA) | 17 (8–23) | 9.5 (9–23) | 10 (8–23) |

Abbreviations: CNS, central nervous system; NA, not applicable.

[a] Incubation period during which a single date of consumption was reported.

[b] Incubation period during which a food was consumed multiple times, or for which there was uncertainty about the consumption date or illness onset date or the purchase date was used as a proxy for consumption date to calculate the incubation period.

[c] Including all single and possible incubation periods.