

Ongoing High Incidence and Case-Fatality Rates for Invasive Listeriosis, Germany, 2010–2019

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We used 10 years of surveillance data to describe listeriosis frequency in Germany. Altogether, 5,576 cases were reported, 91% not pregnancy associated; case counts increased over time. Case-fatality rate was 13% in non-pregnancy-associated cases, most in adults ≥ 65 years of age. Detecting, investigating, and ending outbreaks might have the greatest effect on incidence.

Listeria monocytogenes infections are primarily food-borne and cause gastrointestinal disease or invasive syndromes among infected persons (1). Because *L. monocytogenes* is an intracellular pathogen and because invasive listeriosis is the primary manifestation in diagnosed listeriosis, persons with deficient cell-mediated immunity are at increased risk for its symptoms, including sepsis and meningitis. In addition, infection during pregnancy can lead to chorioamnionitis and fetal infection that can result in miscarriage and stillbirth even 2 months after the mother is exposed. One study found that 44% of patients with non-pregnancy-associated (NPA) listeriosis in Germany had received immunosuppressive therapy ≤ 3 months before illness onset and another 28% had a coexistent immunocompromising illness, such as diabetes (2). Testing for bacteria in blood cultures or cerebrospinal fluid (CSF) is recommended for diagnosis.

Listeria is ubiquitous in the environment and can produce biofilms in the food production environment and thus contaminate ready-to-eat (RTE) products, which are typically consumed raw or without further processing. *Listeria* species grow during shelf life, even at low temperatures, and multiply to concentration levels that make invasive listeriosis and outbreaks more

likely. For these reasons, it is suspected that *L. monocytogenes* exposure is very common but the disease rare. However, in recent years several large outbreaks have been reported in Germany (3–7).

The Study

We analyzed mandatory notification data about invasive listeriosis cases in Germany during 2010–2019 to describe time trends, case-fatality rates, demographic distribution, clinical and diagnostic characteristics, and geographic trends (Appendix, <https://wwwnc.cdc.gov/EID/article/27/9/21-0068-App1.pdf>). In total, 5,576 listeriosis cases were reported during the 10-year study period; 5,064 (91%) of those were NPA and 486 (9%) were pregnancy associated, 241 in mothers and 245 in newborns. Information on disease manifestation was not transmitted for 26 cases. The lowest annual incidence was in 2011 (0.41/100,000 residents) and the highest in 2017 (0.93/100,000 residents); the average for 2010–2019 was 0.69/100,000 residents. We observed a steady increase in cases during 2011–2017, but incidence in 2019 was lower than in previous years. Exceptionally high numbers were reported in the third quarters of 2016, 2017, and 2018 (Figure 1).

Among the 5,064 NPA listeriosis case-patients, 2,032 (40%) were female and 3,855 (76%) were ≥ 65 years of age (Table 1). Listeriosis among adolescents and children other than newborns is rare (37 cases). Incidence in adults 18–44 years of age is $< 0.1/100,000$ residents, in contrast with incidence among adults ≥ 85 years of age: 3.99/100,000 residents for men and 2.08/100,000 residents for women. Annual median age of case-patients increased steadily from 72 years of age in 2010 to 77 years of age in 2019.

Sources for testing samples included CSF (657, 13%), blood (4,097, 81%), and material from other usually sterile sites (274, 5%) (Table 2). A significantly higher proportion of *L. monocytogenes* was detected in CSF among adults 18–64 years of age (24%) than among those ≥ 65 years of age (9%) ($p < 0.01$); for most

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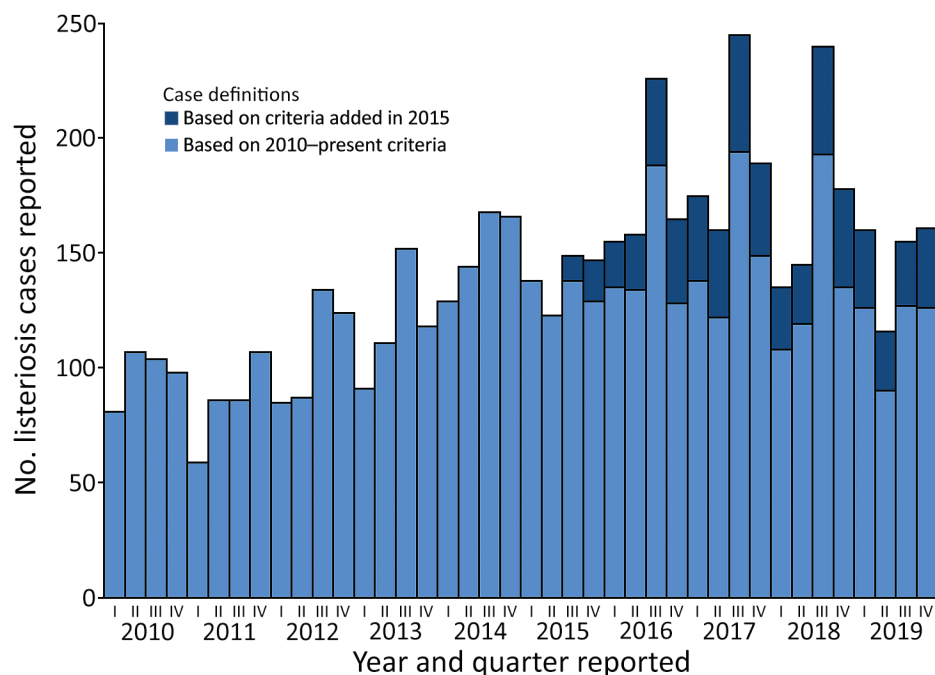


Figure 1. Distribution of pregnancy-associated and non-pregnancy-associated listeriosis cases, by year and quarter, Germany, 2010–2019 (n = 5,576). In the x-axis labels, I corresponds to January–March, II to April–June, III to July–September, and IV to October–December. Before the third quarter of 2015, two groups of patients were not included in the reference definition: those with unknown or unfulfilled clinical criteria and those with nucleic acid detection only. Data from these groups are displayed separately to make the changes in trends over time more apparent.

case-patients ≥ 65 years of age, the isolate was detected from blood. Most NPA case-patients (95%) were hospitalized; we found no differences among age groups ($p = 0.689$). Altogether, 658 NPA case-patients have been reported deceased. The case-fatality rate for NPA cases was 13%, significantly higher among patients ≥ 65 years of age (14%) than among those 18–64 years of age (10%; $p < 0.001$). Listeriosis was the main cause of death for 324 (49%) of NPA case-patients and a contributing factor for 280 (43%). NPA case-fatality rates increased over the 10-year study period, but mainly because of an increase in listeriosis case-patients who died from causes other than listeriosis (Figure 2). For 54 (8%) deceased case-patients, cause-of-death information was missing. Of 301 pregnancy-associated cases, 50% were confirmed from blood

cultures and 54% from samples of newborn, stillborn, or maternal tissues (in some cases, both). A total of 32 fetal losses and 26 neonatal deaths resulted in a case-fatality rate of 19% for pregnancy-associated cases.

Conclusions

The aging of the population of Germany as a result of demographic shifts that will continue in the coming years may partially explain the increase in listeriosis cases and the median age of patients. In addition, factors related to the foodborne nature of the disease and an increase in exposure to *Listeria* must be presumed; it is possible that people eat more RTE food or that RTE food is more likely to become contaminated, although only single-case findings of *L. monocytogenes* > 100 CFU/g have been detected in RTE foods in recent years (8).

Table 1. Average annual incidence of notified cases of non-pregnancy-associated listeriosis, by age and gender, Germany, 2010–2019*

Patient age, y	No. male case-patients	Incidence among male case-patients	No. female case-patients	Incidence among female case-patients	Overall no. cases	Overall incidence
Total	3,029	0.74	2,032	0.48	5,061	0.61
≤ 17	15	0.02	22	0.03	37	0.03
18–44	84	0.06	87	0.07	171	0.06
45–49	56	0.21	37	0.14	93	0.18
50–54	120	0.35	68	0.20	188	0.28
55–59	195	0.58	100	0.30	295	0.44
60–64	280	1.01	145	0.51	425	0.75
65–69	389	1.68	207	0.81	596	1.23
70–74	509	2.96	295	1.51	804	2.19
75–79	612	3.53	371	1.73	983	2.54
80–84	452	3.30	369	1.92	821	2.49
≥ 85	317	3.99	331	2.08	648	2.71

*Incidence is given as no. cases/100,000 residents.

Table 2. Clinical characteristics of notified cases of invasive listeriosis, Germany, 2010–2019*

Characteristic	Pregnancy-associated, no. (%) cases	Non-pregnancy-associated, no. (%) cases			Total
		Children/adolescents <18 y	Adults 18–64 y	Adults ≥65 y	
Total	301 (100)	37 (100)	1,172 (100)	3,855 (100)	5,064 (100)
Sex					
F	301 (100)	22 (59)	437 (37)	1,573 (41)	2,032 (40)
M	0				
Isolate source†					
Cerebrospinal fluid	6 (2)	21 (57)	277 (24)	359 (9)	657 (13)
Blood	152 (50)	15 (41)	800 (68)	3,282 (85)	4,097 (81)
Other sterile site	NA	1 (3)	87 (7)	186 (5)	274 (5)
Birth setting‡	162 (54)	NA	NA	NA	NA
Severity					
Hospitalization§	253 (84)	36 (97)	1,064 (95)	3,535 (95)	4,635 (92)
Death or fetal loss¶	58 (19)	0# (0)	113# (10)	545# (14)	658# (13)

*NA, not applicable

†When *Listeria monocytogenes* is isolated from multiple anatomic sites, only a single site is reported (priority order: cerebral spinal fluid, blood, other sterile site, and birth setting).

‡Either from a newborn, fetus, stillborn or from maternal tissue (placental tissue, uterus, cervix).

§Hospitalizations among singleton neonates for 224 pregnancy-associated cases.

¶26 neonatal deaths, 32 fetal losses. Among all pregnancy-associated cases 161 premature births were recorded.

#Information available for 4,989/5,064 (99%) of notified cases.

The additional case numbers in some quarters of the year (Figure 1) were all associated with large-scale outbreaks (3,6). Successfully identifying and controlling large outbreaks, especially after whole-genome sequencing-based surveillance was introduced, possibly explains why the trend in increases ended after 2017 (9). Overall listeriosis incidence in Germany is higher than in all neighboring countries except Denmark (10). In Europe, incidence is generally higher in countries in Scandinavia and the Baltic region and lower in the United Kingdom and Ireland (10).

As is the case for other pathogens, listeriosis surveillance results in underascertainment, although it is difficult to quantify by how much. *Listeria* sepsis cannot be clinically distinguished from other bacterial sepsis, and isolating *Listeria* or detecting DNA from blood samples is often impossible because bacteremia is absent or intermittent. In addition, laboratory diagnostic testing is often not performed after abortions or stillbirths or for persons who are found dead.

Listeriosis has one of the highest case-fatality rates among notifiable infectious diseases. The case-fatality rate for Germany in this study is surprisingly lower than that for Europe overall, 15.6% (10), and for the United States, 21% (11). A cohort study in France reported a 3-month death rate of 45% for bacteremia from *Listeria* infection and 30% for neuroinvasive cases (12). Lower rates may be partially explained by well-equipped intensive care units, but it is more likely that many deaths occurring long after original disease notifications were not reported to public health departments.

Of interest, surveillance data from the United States indicate more listeriosis among women and higher proportions of pregnancy-associated cases (11,13) than in our study. One explanation might be that, in Germany, meat products, more often eaten by men, constitute prominent outbreak vehicles (3,4,6,7), whereas in the United States several outbreaks were caused by nonanimal products or cheese (11).

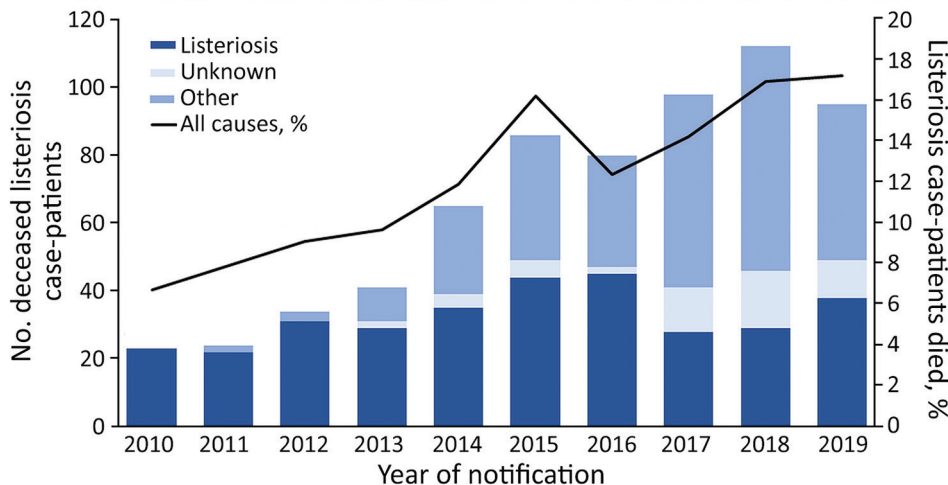


Figure 2. Distribution of non-pregnancy-associated listeriosis cases (n = 5,061) in which the patients died (n = 658) and case-fatalities by year and cause of death, Germany, 2010–2019. Black line indicates percentage of infected persons who died.

Systematic whole-genome sequence typing of *Listeria* isolates from patients would aid in detecting and investigating outbreaks. These molecular data should be integrated into surveillance data from cases notifications and isolates found in food. Combining data from molecular surveillance with epidemiologic investigations would help systematically identify and eliminate contaminated sources, which might have the greatest effect on reducing the overall burden of listeriosis and thus flattening its high incidence curve. Two factors interact to have the greatest influence on personal risk profiles. Listeriosis is highly associated with age, which is affirmed in our study, and strongly associated with documented immunosuppressive conditions (2). Persons with these risk profiles should be targeted in information campaigns about how to safely consume RTE foods and avoid certain types of cheeses, meat products, and smoked or gravled (cured) fish products. All food producers, and especially those providing food for immunocompromised patients in healthcare facilities, should take steps to minimize *L. monocytogenes* hazards when producing, selecting, and preparing food.

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Appendix

Description of listeriosis surveillance in humans in Germany

According to the German Protection against Infection Act, laboratory confirmation of *Listeria monocytogenes* isolation or detection of nucleic acids from blood, cerebrospinal fluid (CSF), or other usually sterile sites is notifiable to local health authorities. These agencies complete and verify clinical information by adding data derived from interviewing patients or their physicians. In neonates, the isolation or detection of nucleic acids of *L. monocytogenes* is notifiable and fulfills the listeriosis case definition independent of clinical signs and symptoms of the newborn and mother. Data on patients fulfilling criteria for the reference definition are electronically transmitted to the federal state health authorities and from there to the Robert Koch Institute (RKI) (1). The reference definition for listeriosis (2) includes clinical criteria (fever, influenza-like symptoms, sepsis, meningitis, meningoencephalitis, or local infections) and laboratory criteria (isolation of *L. monocytogenes* or detection of nucleic acid from *L. monocytogenes* in blood, CSF, or another normally sterile site). Before the third quarter of 2015, two groups of patients were not included in the reference definition: those with unknown or unfulfilled clinical criteria and those with nucleic acid detection only. Data from these groups are displayed separately in Figure 1 in the main article (dark blue part of bars) to make changes in trends over time more apparent. The German surveillance system counts mother and child as 2 separate cases on the basis of time and place of infection. In contrast, for the analyses of clinical characteristics and isolate sources mother-child pairs are counted as 1 pregnancy-associated case. This led to discrepancies in total numbers between the figures and tables.

When patients in notified cases die, local health authorities specify the circumstances of death, including whether the patient died directly or indirectly from listeriosis. The information on the death certificate could then be used to assess the circumstances of death.

Unless listeriosis was mentioned as part of the causal chain leading to death, “other cause” would be selected as cause of death.

The consultant laboratory for *Listeria* at RKI collects and performs whole genome sequencing (WGS) on clinical *L. monocytogenes* isolates from human infections in Germany. Unlike in the reportable disease notification system, submission of clinical *L. monocytogenes* isolates from primary laboratories to the RKI consultant laboratory is voluntary but is encouraged by public health authorities. Genome sequence information from isolates in individual cases in *L. monocytogenes* clusters or outbreaks can thus be linked with notified listeriosis cases throughout Germany. In case of outbreak detection by WGS, mandatory notification data from listeriosis cases and typing data for the *L. monocytogenes* isolates that were sent to the RKI can be merged for investigation.

Subtyping of *L. monocytogenes* isolates from food samples was performed at the National Reference Laboratory for *Listeria monocytogenes* at the German Federal Institute for Risk Assessment (BfR) in Berlin. The consultant laboratory and the BfR regularly compare *L. monocytogenes* strain identities from clinical and food isolates.

The information on outbreaks is submitted to the federal state and local public health departments. After detection, cross-regional listeriosis outbreaks are jointly investigated by the public health services as well as food safety agencies of the districts, cities, federal states, and at the national level. Listeriosis surveillance in Germany is limited in the sense that food consumption histories are only collected after detection of outbreaks. Patients or their relatives who consent are interviewed using a standard comprehensive exploratory questionnaire. If a certain food is already indicated as the probable vehicle, a shorter, more focused questionnaire is used for the interview. Furthermore, several listeriosis outbreak investigations require international collaboration, including with the European Center for Disease Prevention and Control (ECDC) and its Epidemic Intelligence Systems. In parallel, food safety agencies (e.g., European Food Safety Authority) play important roles on all levels of the federal system to safeguard necessary investigations and interventions. The OneHealth approach has been incorporated by stakeholders for foodborne disease surveillance and control in Germany. Data on the occurrence of zoonotic pathogens and related antimicrobial resistance in food has been collected by food safety authorities of the federal states since 2009 as part of official food and veterinary surveillance guidelines. Information is evaluated and published annually (3).

Description of listeriosis outbreaks relevant for Germany

In recent years, several protracted and geographically widespread listeriosis outbreaks have been identified in Germany through the systematic application of bacterial typing identified by WGS in the context of disease surveillance. An outbreak with 79 cases occurring during 2012–2016 (4), predominantly in south Germany, could be successfully traced back to meat products from a specific company by systematic typing of *L. monocytogenes* isolates (5). Another listeriosis outbreak with 83 cases during 2013–2017 was associated with meatballs (6), a source pinpointed by patient interviews and confirmed by WGS. In the course of this outbreak investigation, 2 distinct genotypes turned out to be involved. One of the largest European outbreaks included 112 notified listeriosis cases throughout Germany and happened during 2018–2019. A case-control study followed by targeted household food sampling of listeriosis patients identified blood sausage from 1 supermarket chain as a possible vehicle. The association between the outbreak cases and the blood sausage was confirmed by WGS (7). In 2019, there was a nationwide outbreak with 39 cases primarily in healthcare facilities. Epidemiologic and food tracing investigations in healthcare facilities enabled the detection of contaminated meat products from a manufacturer that provided catering for hospitals (8). The detection of this company as the source led to a large-scale product recall and was accompanied by extremely broad media coverage.

In 2021, BfR and RKI published a report on 22 listeriosis outbreaks in Germany in recent years that focused on the role of salmon or salmon products (9). There were a total of 218 cases reported. Forty-four case-patients died, 17 from listeriosis; 4 cases were pregnancy-associated. The clinical isolates from the 22 outbreaks identified by WGS are not genetically related to each other but each outbreak closely related to isolates from different salmon products (9).

Federal states in eastern Germany show higher incidence compared with those in western Germany (Appendix Figure). The lowest average annual incidence was seen in Saarland (0.48/100,000) and the highest in Saxony (1.28/100,000). The geographical pattern of listeriosis distribution in Germany remains largely unexplained. Recently identified listeriosis outbreaks had regional patterns most likely determined by retail supply organization but outbreak areas were not concordant with high-incidence areas.

Even though these prominent outbreaks highlight meat and salmon products as vehicles for listeriosis outbreaks, it should be kept in mind that other food items, particularly cheeses, sliced fruits, and prepared salads, might cause outbreaks or sporadic cases.

International outbreak investigations provide evidence for fruits (10,11), sprouts (12), ice cream (13), and pasteurized dairy products (14,15), but also raw dairy products (16,17), fish (18–20) and frozen products (21) as sources, showing the wide range of possible listeriosis outbreak vehicles. The largest known listeriosis outbreak in world history took place in South Africa in 2017–2018 and was caused by the processed RTE meat product polony, a smoked sausage typically made of pork and beef (22). Of the 937 laboratory-confirmed cases, 465 (50%) were pregnancy-associated (22).

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Appendix Figure. Spatial distribution of average annual incidence of pregnancy-associated and non-pregnancy associated listeriosis in federal states, Germany, 2010–2019 (n = 5,575)