

# Listeriosis: a resurgent foodborne infection

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## Abstract

*Listeria monocytogenes* is the causative agent of human listeriosis, a potentially fatal foodborne infection. Clinical manifestations range from febrile gastroenteritis to more severe invasive forms, including sepsis, meningitis, rhombencephalitis, perinatal infections, and abortions. In recent years, an increasing rate of listeriosis has been reported in several European countries. These increases primarily reflect a higher rate of bacteraemic listeriosis in those  $\geq 65$  years of age, and are not otherwise correlated with geography, gender, ethnicity, socioeconomic factors or infectious serotypes. In the late 1980s, an upsurge in listeriosis rates was due to the contamination of a small number of food products. However, a restricted range of strains was responsible for most of the additional cases at that time, and no evidence exists for such a pattern since 2001. From a clinical perspective, the importance of isolating the pathogen as a prerequisite for an accurate epidemiological investigation and ultimately stopping transmission cannot be overemphasized.

**Keywords:** Foodborne, incidence, lethality, *Listeria monocytogenes*, listeriosis, review

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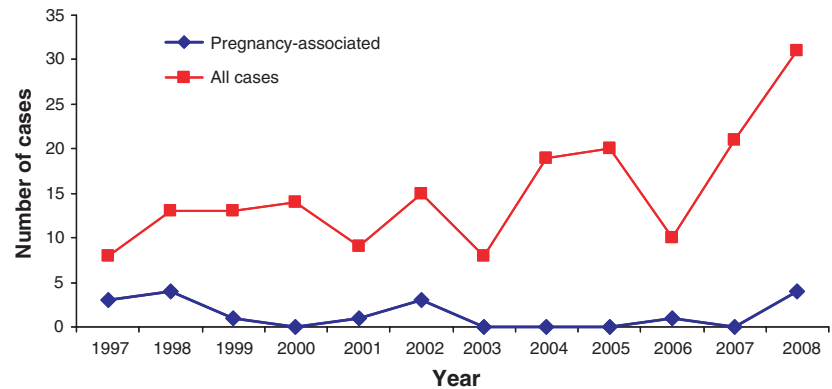
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## Introduction

Listeriosis is a rare but potentially serious infection caused by *Listeria monocytogenes*. This organism can be found throughout the environment in soil, vegetation and animals. The main route of transmission is believed to be through consumption of contaminated food. However, infection can also be transmitted, albeit very rarely, directly from infected animals to humans, as well as between humans [1]. In neonatal infections, *L. monocytogenes* can be transmitted from mother to child *in utero* or during passage through the infected birth canal. There are also rare reports of nosocomial transmission attributed to contaminated material or patient-to-patient transmission via healthcare workers [1]. The bacterium is particularly successful in causing foodborne disease, because it survives food-processing technologies that rely on acidic or salty conditions [2], and, unlike many pathogens, can continue to multiply slowly at low

temperatures, allowing for growth even in properly refrigerated foods.

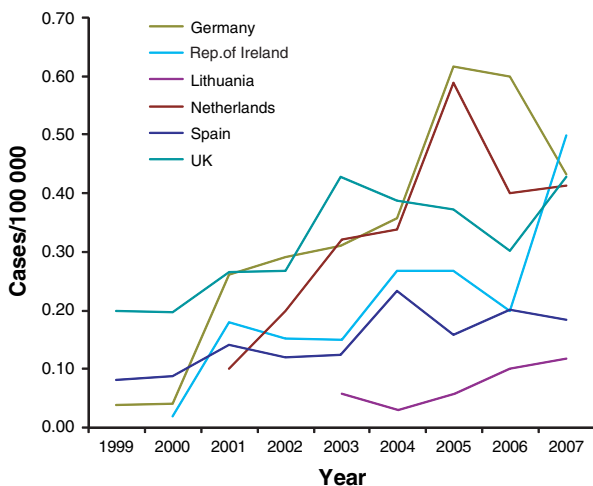
In recent years, an increasing rate of listeriosis has been reported in several European countries [3–10]. These increases primarily reflect a higher rate of bacteraemic listeriosis in those  $\geq 65$  years of age, and are not otherwise correlated with geography, gender, ethnicity, socioeconomic factors or infectious serotypes [6,7]. The Annual Epidemiological Report on Communicable Diseases in Europe 2008 states: “There appears to have been a significant increasing trend in the listeriosis notification rate in the EU from 2003 to 2006” [11]. Half (53.8%) of the EU member states with confirmed cases also reported an increasing trend during the 2-year period 2006–2007 [12]. The cause of this increasing incidence, which, as shown in Fig. 1, was still ongoing in 2008, in Austria at least, is unknown. A total of 1554 confirmed cases of listeriosis were reported from 26 EU member states in 2007. The EU notification rate was 0.3 per 100 000 population [12]. Incidences for six EU countries are given in Fig. 2 [13].



**FIG. 1.** Absolute number of cases of invasive listeriosis, Austria 1997–2008 ( $n = 181$ ).

## Clinical Manifestations

*L. monocytogenes* causes two forms of listeriosis: non-invasive gastrointestinal listeriosis and invasive listeriosis. In immunocompetent individuals, non-invasive listeriosis develops as a typical febrile gastroenteritis. In immunocompromised adults, such as the elderly and patients receiving immunosuppressive agents, listeriosis can manifest as septicaemia or meningoen- cephalitis. Invasive listeriosis can also be acquired by the fetus from its infected mother via the placenta [13]. Perinatal listeriosis can lead to abortion, birth of a stillborn fetus or a baby with generalized infection (*granulomatosis infantiseptica*), and sepsis or meningitis in the neonate. Neonatal listeriosis is subdivided into two clinical forms: early-onset (usually defined as occurring within the first week of life) and late-onset. The late-onset type may occur from one to several weeks after birth.



**FIG. 2.** Listeriosis incidence in six EU countries, 1999–2007 (modified from *Eurosurveillance*, with permission).

Listeriosis during pregnancy is a serious threat to the unborn child. One-third of culture-confirmed cases of maternal–fetal infections result in abortion or stillbirth. However, the prognosis for live-born babies is good, even in those severely ill [10]. Pregnancy-associated cases refer to listeriosis in pregnant women or in the neonates (up to 28 days of life), and the non-pregnancy-associated cases to older babies (>28 days) [1]. Most maternal infections occur during the third trimester of pregnancy, when T-cell immunity is most impaired. Infected women typically develop non-specific flu-like symptoms but may remain asymptomatic. Listeriosis has rarely been observed during the first trimester [14].

In non-pregnancy-associated cases, listeriosis mainly manifests as meningoen- cephalitis or septicaemia. The median incubation period is estimated to be 3 weeks. Outbreak cases have occurred 3–70 days following a single exposure to an implicated product. The onset of meningoen- cephalitis, which is rare in pregnant women, can be sudden, with fever, intense headache, nausea, vomiting and signs of meningeal irritation, or may be subacute, particularly in an immunocom- promised or elderly host. Rhombencephalitis involving the brainstem is an unusual form of listeriosis. *L. monocytogenes* can also produce a wide variety of focal infections; cases of conjunctivitis, skin infection, lymphadenitis, hepatic abscess, brain abscess, cholecystitis, peritonitis, splenic abscess, pleuropulmonary infection, joint infection, osteomyelitis, pericarditis, myocarditis, arteritis, necrotizing fasciitis and endophthalmitis have been described [1,15–18]. In Europe, approximately 10–20% of clinical cases are pregnancy-associated (including neonates within the first 4 weeks of birth), but the majority of cases occur in non-pregnant immuno- compromised individuals, especially the elderly. Approximately 10% of patients have no known risk factor or underlying disease predisposing them to infection with *Listeria* [6]. In Austria in 1997–2007, patients without known risk factors ranged in age from 1 to 64 years (average, 45.2 years; median, 46.6 years). The overall mean age of the

Austrian non-pregnancy-associated listeriosis patient in that period was 64.3 years (median, 66.2 years; range, 0.8–93.5 years), i.e. significantly greater than the age of patients with underlying diseases [6].

## Epidemiology and Transmission

### Outbreak cases

Clusters, suspected or confirmed to represent community outbreaks, have contributed to the recent increased incidence in some countries. In 2005, ten cases of listeriosis in a small area of Switzerland were due to locally made and distributed soft cheese [19]. In 2006, the Czech Republic experienced one large outbreak, involving 78 patients, of whom 13 died; here also, soft cheese was identified as the source [3]. During the period 2006–2007, Germany recorded an outbreak of 16 cases caused by presliced ready-to-eat (RTE) delicatessen meat (sausage salad) (International Meeting on Emerging Diseases and Surveillance, 2009, Abstract 10.098). In 2008, Austria experienced an outbreak of febrile gastroenteritis, including three cases of invasive listeriosis associated with jellied pork contaminated with *L. monocytogenes* [20]. However, the overall proportion of cases related to clusters remained stable and low; therefore, these clusters did not account for the increased incidence in Austria.

### Sporadic cases

Whereas much has now been learned about epidemic listeriosis, little is known about sporadic listeriosis, which, in fact, represents the majority of cases [5]. Dietary risk factors for sporadic listeriosis have been assessed through case–control studies. In a study conducted during the period 1986–1987 in the USA, case patients were significantly more likely than controls to have eaten uncooked or non-reheated hot dogs (frankfurters) or undercooked chicken. An estimated 20% of the overall risk of listeriosis was thought to be attributable to consumption of these foods [21]. Another study performed in the USA from 1988 to 1990 found that case patients were significantly more likely than controls to have eaten soft cheeses or delicatessen foods [22]. Other exposures associated with an increased risk of sporadic disease included recent use of antacids, laxatives or H<sub>2</sub>-receptor antagonists [22]. Dietary risk factors for sporadic listeriosis were also examined in a study in Denmark; drinking unpasteurized milk or eating pâté were the only risk factors identified [23].

Although listeriosis is said to be 100–1000 times more common in patients with AIDS than in the age-matched general population, it is somewhat surprising that it is not seen more commonly, given the ubiquity of the organism. Among

181 cases of invasive listeriosis documented in Austria from 1997 until 2008, only one patient was human immunodeficiency virus-positive [6] (unpublished data, F.A.). A partial explanation may lie in the experimental observation that resistance to listeriosis appears to be mediated by lymphocytes that do not carry CD4 or CD8 markers [24]. In addition, it is likely that many cases are prevented by routine *Pneumocystis jirovecii* prophylaxis with trimethoprim–sulphamethoxazole.

## Diagnosis of Listeriosis

Listeriosis is diagnosed by a positive culture from a normally sterile site. *L. monocytogenes* can be readily cultured from clinical specimens such as blood, cerebrospinal fluid (CSF), amniotic fluid, placenta, meconium, lochia, gastric washings or ear swabs from newborns, by directly plating the material onto blood agar plates and incubating overnight at 35°C in an ambient atmosphere. Stool specimens (other than meconium) should be selectively enriched for *Listeria* before being plated on selective agar media. Classic cold enrichment over months is no longer necessary. PCR is the only test utilized for rapid detection of *L. monocytogenes* in clinical specimens. The PCR assay is particularly useful when prior administration of antimicrobial agents is likely to compromise culture.

Various test protocols were evaluated for CSF samples and tissue samples (fresh or in paraffin blocks). Gram staining and microscopic examination of CSF or meconium permit only a presumptive diagnosis. For clinical specimens, the importance of isolating the pathogen as a prerequisite for an epidemiological investigation and appropriate infection control cannot be overstressed [25].

Because listeriosis during pregnancy is serious and difficult to diagnose, blood cultures should be considered for any pregnant woman presenting with fever, especially if accompanied by flu-like or gastrointestinal symptoms [26]. Vaginal or stool cultures are not helpful in diagnosis, because some women are asymptomatic carriers [26]. Indeed, faecal carriage of *L. monocytogenes* occurs in 1–15% of the population [27]; the incidence of women carrying *L. monocytogenes* in the vagina is lower [26].

Listerial rhombencephalitis is a rare manifestation of listeriosis. In contrast to other listerial infections of the central nervous system (CNS), the majority of listerial rhombencephalitis cases occur in previously healthy adults; no cases have been reported in infants [28]. Blood cultures may or may not reveal growth of the organism in these cases. Serological responses to commercially available whole cell antigens (Gruber–Widal reaction using *L. monocytogenes*

suspensions O and H) are not diagnostic, because of antigenic cross-reactivity between *L. monocytogenes* and other Gram-positive bacteria such as staphylococci, enterococci and *Bacillus* species [29]. Furthermore, patients with culture-confirmed listeriosis have been known to have undetectable antibody levels. Positive serological findings must be treated with caution and, in cases other than rhombencephalitis, exact diagnosis should be based on detection of the pathogen. Serological responses to listeriolysin O (LLO) are supposed to be more reliable [30]. An ELISA for the detection of anti-LLO IgG in human serum and plasma is commercially available (DIATHEVA, Fano, Italy). LLO, a polypeptide protein secreted by *L. monocytogenes*, is a major virulence factor produced by all pathogenic *L. monocytogenes* strains but released in the culture medium only at low levels. For this reason, the LLO protein, used in the DIATHEVA assay as test antigen, is expressed in *Escherichia coli*.

## Treatment of Listeriosis Patients

*In vitro*, *L. monocytogenes* is susceptible to a wide range of antibiotics, with the exception of fosfomicin, first-generation quinolones and third-generation cephalosporins, although a few exceptional strains exist. Susceptibility testing is usually performed using Mueller–Hinton agar, with or without blood (5% horse blood or 5% sheep blood) [31]. For trimethoprim–sulphamethoxazole, the blood is lysed. Antimicrobial *in vitro* susceptibilities of *Listeria* have not changed markedly over the past 35 years [31,32]. Although optimal therapy has not been verified by randomized clinical studies, penicillin or ampicillin alone, or in combination with gentamicin, are considered to be the drugs of choice. The clinically effective antibiotics penicillin and ampicillin are only bacteriostatically effective against *L. monocytogenes*, thus emphasizing the importance of the body's own cellular defence mechanisms [33].

Addition of gentamicin has not been proven to be clinically advantageous, as synergy has only been demonstrated *in vitro* [34]. Moreover, in animal models, gentamicin does not reliably show a synergistic effect [35]. A gentamicin-supplemented protocol should not be prescribed for pregnant women, because of possible teratogenic effects [2,33]. As *Listeria* does not produce  $\beta$ -lactamase, the addition of  $\beta$ -lactamase inhibitors in the treatment of listeriosis is ineffective. There is no relevant difference between the MIC values of ampicillin alone and ampicillin combined with sulbactam for the treatment of infection due to *L. monocytogenes* [32].

For patients with  $\beta$ -lactam allergy, trimethoprim–sulphamethoxazole or erythromycin may be considered. Steps

should be taken to establish and document true penicillin allergy prior to starting treatment with these second-line agents. Transplacental passage of erythromycin has been shown to provide subtherapeutic concentrations in both the amniotic fluid and fetal serum [36]. Therefore, many experts recommend using an alternative. Vancomycin has also been used in cases of bacteraemic listerial infection [37]. However, the results obtained from a model of rhombencephalitis in gerbils strongly suggest that intravenous vancomycin is unlikely to be effective in patients with CNS infection [35]. Linezolid is another agent that has been used successfully to treat listerial infections [38]. Other antibiotics used in cases of listeriosis include meropenem and rifampicin [39]. It has been speculated that, at least in the immunocompromised host, the addition of rifampicin, which is effective against intracellular *L. monocytogenes* and will penetrate the CSF, could help to eradicate residual bacteria [32]. Resistance has been reported with rifampicin monotherapy [33]. Kayser *et al.* [40] reported, as early as 1989, good *in vitro* activity of meropenem. Another study with this antibiotic showed good activity in experimental meningitis in guinea pigs [41].

*L. monocytogenes* reproduces in the reticuloendothelial system and survives intracellularly after uptake by macrophages [33]. The bone marrow might be a unique niche for *L. monocytogenes* [42]. This means that the organism cannot be reached by certain antibiotics; this might contribute to the differences between *in vitro* and *in vivo* results. Macrolides and quinolones accumulate within host cells and may attack the intracellular *Listeria* organisms. Moxifloxacin may be a promising candidate; however, no clinical trials have provided firm evidence [43]. *L. monocytogenes* is intrinsically resistant to nalidixic acid (MIC >128 mg/L) and shows decreased susceptibility to therapeutically important fluoroquinolones, such as ciprofloxacin (MIC 0.5 – 2 mg/L) [44]. In an animal model, ciprofloxacin was only weakly active in the spleen, liver and CNS [35]. However, the newer derivatives of the quinolones (e.g. levofloxacin and moxifloxacin) exhibit strong bactericidal activity against *L. monocytogenes* [45,46].

Antimicrobial drugs that are of questionable value in animal experiments or for the treatment of human listeriosis include clindamycin and aminoglycosides when administered individually [33]. Cephalosporins have hardly any *in vitro* effect against *L. monocytogenes*. The reason is the minimal or non-existent affinity of listerial penicillin-binding proteins 3 and 5 for cephalosporins [47]. Despite good *in vitro* activity, even cephalothin had no effect on experimental listeriosis in mice [33]. In addition, cephalothin lacks satisfactory CSF penetration. Reports of therapeutic failures prove that cephalosporins are not indicated for the treatment of listeriosis [48].

Fosfomycin was previously considered to be ineffective in treating listeriosis, as revealed by *in vitro* laboratory data [33]. Therefore, despite achieving theoretically excellent concentrations in brain and other tissues, fosfomycin has not been used in the management of listeriosis. However, in 1979, a report demonstrated that fosfomycin might have a positive effect on *L. monocytogenes* infections in mice [49]. Recent research has demonstrated that the effect of fosfomycin on *L. monocytogenes* is dependent on the expression of the Hpt protein encoded by the *hpt* gene, which is under the control of the central virulence regulator protein PrfA. Hpt, an organophosphate–inorganic phosphate anti-reporter, enables *L. monocytogenes* to use hexose phosphates from the host cell cytosol as an energy source, enabling intracellular movement. As the virulence regulator gene *prfA* is switched off extracellularly, Hpt becomes downregulated and *L. monocytogenes* is resistant to fosfomycin in *in vitro* susceptibility tests. However, upon upregulation of the virulence regulator during infection, *L. monocytogenes* becomes susceptible to fosfomycin. BALB/C mice, as used in *in vivo* tests, survived a challenge of  $10^8$  CFUs per mouse, whereas the LD<sub>50</sub> in controls was  $1.77 \times 10^4$  CFUs of *L. monocytogenes* [50].

It is generally recommended that patients should be treated for at least 14 days [33]. Even if a host appears to be clinically improved, the intracellular concentration resulting from short-course antibiotic treatment may not be sufficient for complete sterilization. Indeed, in immunosuppressed patients, relapses have been reported after 2 weeks of penicillin therapy [51]. In pregnancy, there are additional considerations, such as adequate treatment of the placenta, and potential ongoing infection of the fetus or placenta. There has been concern that placental infection may not be clinically apparent, but could progress once antibiotic therapy has been withdrawn. For this reason, some experts have suggested at least 3–4 weeks of treatment during pregnancy [37]. Patients with rhombencephalitis should be treated with antibiotics for at least 6 weeks [28].

Although there are no data concerning the efficacy of antimicrobials in listerial gastroenteritis, it could be argued that, in both symptomatic and asymptomatic persons known to have ingested a food implicated in an outbreak, and who have a high risk of invasive disease because of underlying illness, pregnancy or age (elderly), it might be prudent to administer oral amoxicillin or trimethoprim–sulphamethoxazole for 7 days [20]. Recently developed protocols employing gerbils and genetically engineered mice now allow the effect of antibiotics to be studied in animal models relevant to humans [52].

The CLSI has not yet provided specific guidelines for *in vitro* susceptibility testing of *Listeria*. Apart from penicillin,

ampicillin and trimethoprim–sulphamethoxazole, for which clinical CLSI breakpoints for *Listeria* susceptibility testing are defined, the usual CLSI criteria for staphylococci are applied [53,54].

## Immunization/Chemoprophylaxis

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At present, there is no immunization available for listeriosis. Engineered live-attenuated *L. monocytogenes*, which elicits strong cellular immune responses, is currently being evaluated in clinical trials as an anticancer vaccine [55]. The utility, or even the feasibility, of eradicating gastrointestinal colonization to prevent invasive listeriosis is unexplored. However, asymptomatic individuals at high-risk of listeriosis, who are known to have ingested a food implicated in an outbreak, could reasonably be given 7 days of oral ampicillin or trimethoprim–sulphamethoxazole treatment [20,56].

## Discussion

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Listeriosis is essentially a foodborne disease, and this is no longer questioned. The upsurge in listeriosis rates in the late 1980s was due to contamination of a variety of food products, including coleslaw, unpasteurized milk and Mexican-style soft cheese [1]. A restricted range of strains was responsible for most of the additional cases at that time, and most human cases are still associated with *L. monocytogenes* serovars 1/2a, 1/2b and 4b. Whereas the number of reported cases was quite stable during the period 1996–2002, an increase was observed again during the period 2003–2007. Currently, it appears that the numbers of cases of listeriosis are stable in some countries, or, as in Germany, have returned to those recorded previously.

The reasons for the changing incidence of listeriosis remain unclear. No evidence exists for a causative role of gradual demographic or behavioural changes. Cairns and Payne [7] postulated that this phenomenon might be a consequence of changes in government policy regarding business practices that have had widespread effects on food processing, distribution and preparation. Goulet *et al.* [5] hypothesized that the recently reduced salt content in RTE products may contribute to the growth of the organism, if present as a contaminant, and increase the likelihood of infection when these products are consumed by susceptible individuals. The food industry reduced the salt content of selected products, such as RTE meat products, in response to recommendations in 2002 from food safety agencies, asking for a 20% reduction in average salt intake, spread over

5 years, in order to prevent disease attributable to hypertension-related conditions. Wagner *et al.* [57] studied samples of RTE foodstuffs in Vienna, Austria. They found 4.8% of 946 samples collected from 103 supermarkets to be positive for *L. monocytogenes*, with five smoked fish samples exceeding the tolerated limit of 100 CFUs per gram of food. Products showing the highest contamination rate were fish and seafood (19.4%), followed by raw meat sausages (6.3%), soft cheese (5.5%) and cooked meat products/pâtés (4.5%). The overall contamination rate of 640 RTE foodstuffs collected at the household level was 1.7%. Importantly, most high-risk foods were collected from households of elderly individuals. Pulsed-field gel electrophoresis typing of the collected *L. monocytogenes* isolates revealed a high degree of diversity among the isolates collected at the household level. Moreover, evidence from EU-wide routine food safety investigations indicates that a substantial proportion of RTE products may be contaminated by *L. monocytogenes* [12]. *L. monocytogenes* was detected in 1.8% of RTE meat products and meat preparations of beef tested in 2007 (in 0.7% with >100 CFUs/g), in 2.5% of RTE products and meat preparations of pork (in 0.6% with >100 CFUs/g), in 2.6% of RTE products and meat preparations of poultry (in 0.7% with >100 CFUs/g), in 1% of soft and semi-soft cheeses made from raw or low-heat-treated milk (in 0.3% with >100 CFUs/g), and in 18.3% of RTE fish products (2.4% with >100 CFUs/g) [12]. It is therefore essential to control foods that permit *L. monocytogenes* to grow to numbers exceeding the arbitrarily defined minimal infectious dose of  $10^5$  CFUs per gram or millilitre of foodstuff. However, the dose-response relationship remains unclear [58]. Strain-specific differences in virulence seem to be of the utmost importance. Newer risk assessment modelling suggests a  $10^{-9}$  to  $10^{-13}$  probability of infection with a dose of 100 organisms, and a  $10^{-6}$  to  $10^{-9}$  probability of infection at 1 000 000 organisms [58].

Although exposure to *L. monocytogenes* cannot be avoided completely, proper food preparation and storage can decrease the risk. Pregnant women and immunocompromised individuals should be advised to avoid consumption of raw milk, unpasteurized soft cheeses, delicatessen meats, hot dogs that are not adequately heated, refrigerated pâtés, and smoked seafood, because they can be contaminated at a high level [2]. Avoiding cross-contamination is also an important protective strategy; all utensils and surfaces should be washed well after preparation of meat or cutting of prepared foods [2]. No clear evidence exists for the specific inclusion of listeriosis in pre-conception care [59]. In addition to individual advice to consumers, control of listeriosis requires action from public health agencies and from the food industry.

Important control strategies from public health agencies include developing and maintaining timely and effective disease surveillance programmes, as well as promptly investigating clusters of listeriosis cases. Routine characterization of human, food and environmental isolates, and utilization of large-scale subtype databases, will hopefully facilitate Europe-wide outbreak detection and control in the near future [60].

## Conclusions

*L. monocytogenes* has been recognized as a human pathogen for more than 80 years. The demographic shift and the widespread use of immunosuppressive medications, to treat malignancy and manage organ transplantation, have increased the immunocompromised population at increased risk of listeriosis. Moreover, consumer lifestyles have changed, such that less time is available for food preparation and more RTE and takeaway foods are consumed. Changes in food production and technology have led to the production of foods with longer shelf-lives that are typical 'Listeria-risk foods', because the bacteria have time to multiply, and the food does not undergo a listericidal process, such as cooking, before consumption. Unlike infection with other common foodborne pathogens, listeriosis is associated with a high case-fatality rate of approximately 20–30% [61]. Epidemiological investigations during the past 30 years have shown that epidemic listeriosis and sporadic listeriosis are mainly caused by consumption of contaminated food. Nevertheless, despite the high rates of contamination of certain foods with *L. monocytogenes*, listeriosis is a relatively rare disease as compared with other common foodborne illnesses, such as campylobacteriosis or salmonellosis. However, because of its high case-fatality rate, listeriosis is, after salmonellosis, the second most frequent cause of foodborne infection-related deaths in Europe.

## Transparency Declaration

The authors declare that they have no conflict of interest.

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