



Mortality risk factors for listeriosis – A 10 year review of non-pregnancy associated cases in England 2006–2015

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SUMMARY

Listeriosis: is a foodborne illness that can result in septicaemia, Central Nervous System (CNS) disease, foetal loss and death in high risk patients.

Objectives: To analyse the demographic trends, clinical features and treatment of non-perinatal listeriosis cases over a ten year period and identify mortality-associated risk factors.

Methods: Reported laboratory-confirmed non-pregnancy associated cases of listeriosis between 2006 and 2015 in England were included and retrospectively analysed. Multivariate logistic regression analysis was performed to determine independent risk factors for mortality.

Results: 1357/1683 reported cases met the inclusion criteria. Overall all-cause mortality was 28.7%; however, mortality rates declined from 42.1% to 20.2%. Septicaemia was the most common presentation 69.5%, followed by CNS involvement 22.4%. CNS presentations were significantly associated with age < 50 years, and septicaemia with older age. Age > 80 years (OR 3.32 95% CI 1.92–5.74), solid-organ malignancy (OR 3.42 95% CI 2.29–5.11), cardiovascular disease (OR 3.30 95% CI 1.64–6.63), liver disease (OR 4.61 95% CI 2.47–8.61), immunosuppression (OR 2.12 95% CI 1.40–3.21) and septicaemia (OR 1.60 95% CI 1.17–2.20) were identified as independent mortality risk factors.

Conclusions: High risk groups identified in this study should be the priority focus of future public health strategies aimed at reducing listeriosis incidence and mortality.

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Introduction

Listeria monocytogenes is a foodborne pathogen that is ubiquitous within the environment. Frequently reported vehicles of infection include dairy products, delicatessen meats, seafood and pre-prepared foods requiring no further cooking. Its ability to survive refrigeration temperatures and wide pH ranges makes it particularly problematic for the food industry. Infection with this bacterium results in a spectrum of clinical presentations ranging from asymptomatic infection or a mild self-limiting gastroenteritis to more severe disease including septicaemia and central nervous system (CNS) infections which can be fatal; it can also cause septic abortion or stillbirth in pregnant women. Listeriosis is typically associated with certain risk groups that have weakened immune

systems such as pregnancy, extreme ages of life (particularly neonates and elderly individuals), immunosuppressed patients and patients with underlying co-morbidities including liver or renal disease and diabetes mellitus.^{1,2}

In 2010, the incidence of listeriosis was estimated to be 0.337 per 100 000 persons with a death rate of 0.080 per 100 000 persons globally.³ Although infection is rare, it is a significant contributor to deaths caused by foodborne infections with reported cases-fatality rates ranging from 20% to 44%.^{1,2,4–10}

A review of listeriosis cases in England and Wales between 1990 and 2009 identified certain malignant neoplasms (such as intrathoracic cancers), alcoholism, cardiovascular disease, increasing age, and treatment to reduce gastric acid secretion as factors positively associated with mortality.¹ Recent international reviews have, however, reported other risk factors such as corticosteroids, renal failure,² chronic lymphocytic leukaemia (CLL)(7), non-haematological cancers (liver, oesophagus, lung and pancreatic),⁷ liver disease,¹¹ delayed appropriate

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antibiotic therapy,^{5,6,12} multi-organ failure, monocytopenia,¹³ bacteraemia,⁵ meropenem¹⁴ and gentamicin use.⁴ UK has an ageing population with those aged over 65 years reported to be 18% in 2016 and further rises predicted until 2030.¹⁵ Since the previous review, there has been increasing use of novel immunomodulatory therapies for certain medical conditions, some of which have been directly associated with an increased risk of listeriosis.^{16,17} Reports of more unusual manifestations of infection with *Listeria* spp. including vascular graft and prosthetic joint infections have also emerged recently.¹⁸ This study was undertaken to ascertain whether any changes in the clinical presentation and outcomes of listeriosis in England had occurred in association with these host factor changes.

Objectives

In this study we reviewed all reported non-pregnancy associated listeriosis cases in England to identify whether any significant changes had occurred, over a ten year period (2006–2015), in the clinical spectrum of illness, treatment received, demographic trends and risk factors associated with mortality.

Methods

Surveillance of listeriosis in England

Public Health England (PHE), formerly the Health Protection Agency, coordinates national surveillance of listeriosis in England. Reporting of cases of listeriosis to PHE by diagnostic laboratories is mandatory under the Health Protection (Notification) Regulations 2010 in England. Listeriosis cases are ascertained through the electronic reporting of laboratory-confirmed cases from frontline diagnostic laboratories and/or the voluntary referral of cultures to PHE, Gastrointestinal Bacterial Reference Unit (GBRU) for typing.

For the purposes of surveillance, cases of listeriosis are defined by the isolation of *L. monocytogenes* from a usually sterile site e.g. blood or cerebrospinal fluid (CSF) in combination with a compatible clinical illness. Cases are classified further as pregnancy associated (all maternal–foetal patients and neonatal patients, with a mother–baby pair considered a single case-patient) and non-pregnancy-associated cases (illness in patients > 28 days of age). For each case, clinical data are sought, using standardised Clinical Questionnaires (CQ), from the responsible Consultant Medical Microbiologist at the local diagnostic laboratory. This questionnaire collects data on symptoms, co-morbidities, antibiotic treatment and outcome within the 30 days prior to illness onset. In addition, epidemiological data, including food history, are routinely collected by direct interview with the case or a proxy by local health protection teams using a separate Enhanced Surveillance Questionnaire (ESQ) within the 30 days prior to onset of illness.

Data from both questionnaires are entered into a Microsoft Access database. Case mortality data collected on both ESQs and CQs, are augmented routinely with mortality data from the Office of National Statistics data (where listeriosis was recorded on the death certificate) and with Health Protection Team case management reports (HPZone). Where isolates are referred to GBRU for testing, data from final laboratory reporting which includes isolate serogroup are reconciled with cases' data based on patient identifiable information.

Data handling

All pregnancy-associated (defined as pregnant mothers or infants less than 28 days of age) were excluded from the analysis; this was because recording of mother–baby pairs as a single case where clinical information and outcome could correspond to either

the mother or infant. Where data was available from both CQs and ESQs, information was combined. For any discrepancies between ESQs and CQs, ESQ data was used in preference as this was obtained directly from the case. Corresponding serotype and antibiotic susceptibility data were extracted from an electronic laboratory database and combined with the clinical data for analysis.

Patients were divided in groups according to age (under 15, 16–49, 50–59, 60–69, 70–79 and over 80 years), gender and year of infection. Patients' clinical data were reviewed and were coded as immunosuppressed if they had one or more underlying condition causing immunosuppression e.g. malignancy, systemic or autoimmune diseases, chronic renal failure, chronic liver disease, primary or secondary immunodeficiency, transplant recipients or were taking immunosuppressive therapy (including prolonged corticosteroids, cytotoxic agents and immunomodulatory treatments), alcoholism and malnutrition. Time to presentation was calculated from the onset of symptoms to presentation or admission to a healthcare facility.

Additional variables analysed as potential risk factors for mortality included clinical presentation, underlying co-morbidities and *L. monocytogenes* serotype. Clinical presentation was categorised as CNS involvement with or without meningitis (defined by *L. monocytogenes* isolated from CSF or brain tissue or clinical evidence of CNS infection), septicaemia (characterised by *L. monocytogenes* isolated from blood with features of systemic sepsis in the absence of CNS involvement), febrile gastroenteritis or 'Other' (for example, peritonitis). Co-morbidities were categorised into groups consisting of cardiovascular, renal disease, liver disease, auto-immune disorders, alcoholism, Lymphoid, haematopoietic and related malignancies, solid-organ malignancies and other co-morbidities (including those with multiple co-morbidities). Malignancies were categorised according to ICD10 criteria. Death was the outcome of interest, where data on death was missing, patients were assumed to be alive.

Laboratory methods

All *L. monocytogenes* isolates referred to the reference laboratory were serogrouped using the multiplex PCR assay of Doumith et al. as described previously.^{19,20} Antimicrobial susceptibility testing was performed on 63 isolates received from the referring laboratories. Minimum Inhibitory Concentrations (MICs) were determined by agar dilution and a combination of British Society for Antimicrobial Chemotherapy (BSAC) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used for interpretation. All isolates were tested for ampicillin susceptibility, additional antimicrobials were tested at the request of the referring laboratory including: chloramphenicol, ciprofloxacin, co-trimoxazole, daptomycin, erythromycin, gentamicin, linezolid, meropenem, moxifloxacin, rifampicin, teicoplanin, tetracycline and vancomycin.

Statistical methods

Data analyses were conducted using Microsoft Excel and Stata version 13.0 (Stata Corporation USA). Death was the outcome of interest and risk factors assessed included age, gender, year of infection, serotype, clinical presentation and underlying co-morbidities. Baseline groups were selected based on size and generalisability which consisted of those aged 15–49 years, male sex and Serotype 1/2a. Presence of a clinical feature or co-morbidity was compared to absence of that feature.

Logistic regression model fitting was conducted in a semi-structured way. First, age categorisation was assessed in terms of group breadth. Likelihood ratio (LR) tests indicated that further

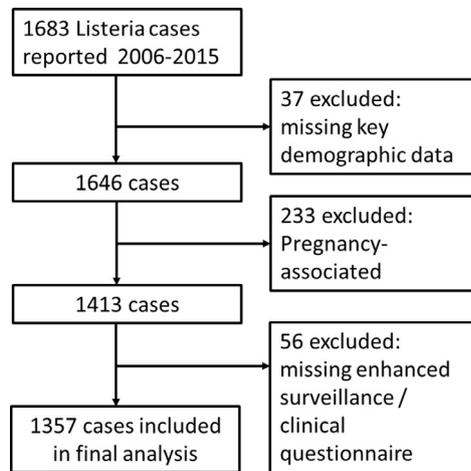


Fig. 1. Flow chart showing patient selection for analysis.

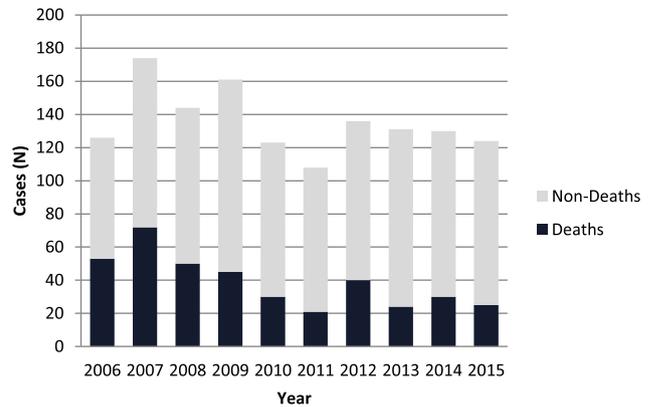


Fig. 2. Number of *L. monocytogenes* cases reported per year and associated deaths.

collapsing of age groups was not warranted. Gender and calendar time were then added to the model, and the structure of the time component (individual year effects vs. a linear trend) over time was investigated, including potential age-time interactions. Having identified a suitable structure for age, gender and time variables, each of the risk factors were considered in turn while adjusting for age, gender and year; at this stage, collapsing of categories to smaller groups was considered, such as the malignancy categories. Finally, a multivariate model was fitted to include all relevant risk factors, and examine whether any risk factors, in particular age and time, were altered by adjustment for other variables. Model comparison was via LR tests. Chi squared tests were performed to examine the relationship between clinical presentation with serotype, age and gender. A sensitivity analysis was performed excluding those with missing mortality data to assess the impact of this assumption.

Results

Cases of listeriosis 2006–2015

Demographics

Between 1st January 2006 to 31st December 2015, 1683 cases of listeriosis were reported in England. Following exclusion of cases with missing demographic data, pregnancy-associated cases, and cases lacking both an ESQ and CQ, 1357 (80.6%) cases were included in the analysis as shown in Fig. 1. A total of 761/1357 (56.1%) of cases were male. The most represented age group was 70–79 years 375/1357 (27.6%). The number of reported cases ranged from 123–174 per year (Fig. 2).

Clinical features and co-morbidities

Of all cases, 1096 (80.7%) had data available for both symptom onset and presentation to hospital. The range of time from symptom onset to presentation was –89 to 30 days, which accounted for cases that were admitted to hospital prior to their presentation of listeriosis. After exclusion of these 69 cases, the mean time from symptom onset to presentation was 2.8 days. Septicaemia was the most common clinical presentation 943/1357 (69.5%), followed by CNS involvement 304/1357 (22.4%), ‘other’ presentations 203/1357 (15.0%) and finally febrile gastroenteritis 156/1357 (11.5%). CNS involvement with septicaemia was present in 162 (11.9%) of cases, 103 (7.5%) had a combination of febrile gastroenteritis and septicaemia, 72 (5.3%) had a combination of septicaemia with another clinical syndrome. A combination of septi-

caemia, CNS involvement and febrile gastroenteritis was reported in six (0.4%) cases. Fever was the most frequently reported clinical feature 832/1357 (61.3%), followed by confusion 517/1357 (38.1%), diarrhoea 475/1357 (35.0%), headache 434/1357 (32.0%) and abdominal pain 368/1357 (27.1%).

The effect of age and gender on clinical presentation was also assessed; there was a trend towards gastroenteritis and female sex, however, this was not significant (50.6% vs. 43.1%, $p=0.072$). There was no association between gender and other types of clinical presentation. CNS presentations were more commonly seen in younger age groups (children and adults under 50 years) $p < 0.001$, and presentation with septicaemia was significantly associated with older age $p=0.005$. There was no association demonstrated between age and other clinical presentations.

Information on underlying co-morbidities was recorded for 1250 (92.1%) cases. An underlying co-morbidity was reported for 1008/1250 cases (80.6%), the most common being malignancy 381/1250 (30.5%) followed by multiple co-morbidities 232/1250 (18.6%) and auto-immune diseases 114/1250 (9.1%). The number of underlying conditions ranged from one to seven. Of 873 (64.3%) cases recorded as immunosuppressed, 422/876 (48.2%) were due to an underlying medical condition, and 451 (51.4%) due to immunosuppressive therapy. The majority of cases (695/1008, 68.9%) had at least one reported underlying condition followed by 192 (19.0%) who had two.

Microbiological results

The most common source of positive culture was blood 1139/1357 (78.6%) or blood in combination with a specimen from another site 1139/1357 (83.9%) – usually CSF, followed by CSF alone 150/1413 (10.6%) Other sources included ascitic fluid, tissue samples and swabs.

Serotype 4b was the most common infecting serogroup of strains where serotyping was performed (622/1184, 52.5%) as shown in Fig. 3.

Management of cases and antimicrobial resistance

Information on antibiotic therapy was collected; however, dosage and duration of treatment were not recorded. For 1064 cases (78.4%) some treatment information was provided. Of these, 1030 were reported to have received at least one antibiotic, 650 ≥ 2 antibiotics, 157 ≥ 3 antibiotics, and 35 received at least 4 different antibiotics during their illness. Amoxicillin or ampicillin were the most commonly used therapies (760/1064, 71.4%), followed by gentamicin (468/1064, 44.0%), meropenem (127/1064, 11.9%), piperacillin-tazobactam (111/1064, 10.4%) and

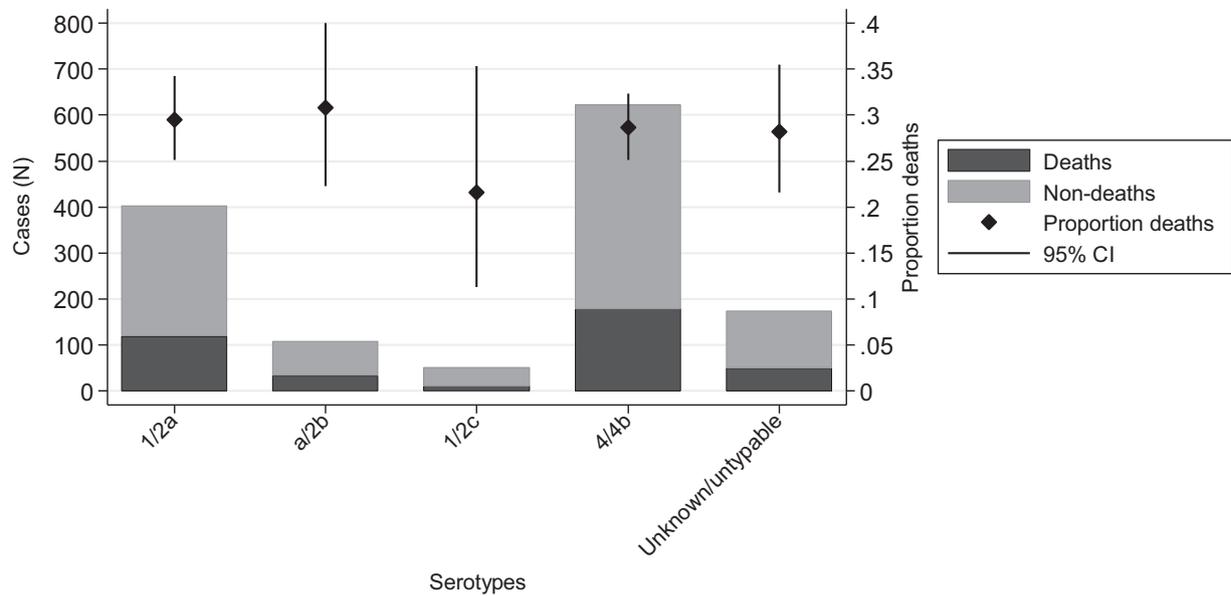


Fig. 3. Serotype distribution of *L. monocytogenes* strains isolated from cases by mortality status ($n=1357$). Proportions of deaths, and 95% confidence intervals, are displayed under a secondary y-axis.

Table 1
Antimicrobial susceptibility results of referred *L. monocytogenes* isolates ($N=63$).

Antibiotic	Total number of isolates tested	Susceptible (%)	Intermediate (%)	Resistant (%)
Ampicillin	63	63 (100)	–	–
Chloramphenicol	7	7 (100)	–	–
Ciprofloxacin	17	1 (6)	5 (29)	11 (65)
Co-trimoxazole	2	2 (100)	–	–
Erythromycin	9	9 (100)	–	–
Daptomycin	1	–	–	1 (100)
Gentamicin	17	17 (100)	–	–
Linezolid	16	14 (88)	2 (12)	–
Meropenem	4	4 (100)	–	–
Moxifloxacin	15	8 (53)	7 (47)	–
Rifampicin	0	9 (100)	–	–
Teicoplanin	16	16 (100)	–	–
Tetracycline	15	4 (27)	7 (47)	1 (6)
Vancomycin	17	17 (100)	–	–

co-trimoxazole (111/1064, 10.4%). A combination of amoxicillin and gentamicin were used for 385 (36.1%) cases. Antibiotic susceptibility testing was performed on 63 case isolates as shown in Table 1.

Serotype-related clinical outcomes

There was no association between serotype and risk of death. Serotype 4b was the most common serotype in those presenting with neuroinfection (56.9%) with an OR of 2.0 (95% CI 1.5–2.7, $p < 0.001$), whilst serotype 1/2b was significantly associated with ‘other’ presentations of illness (OR 1.9, 95% CI 1.1–3.3, $p = 0.019$). There was no association between serotype and septicaemia or gastroenteritis.

Risk factors for mortality

Mortality status was missing for 147 (10.8%) patients who were assumed to be alive, and 390 patients were therefore estimated to have died resulting in an overall case fatality rate of 28.7%; with rates ranging from 19.4–41.3% per year.

The odds of deaths appeared to decline over the ten year period and, despite a small spike in 2012, there was an overall linear trend with an estimated decrease of 10% each year (Fig. 4). The

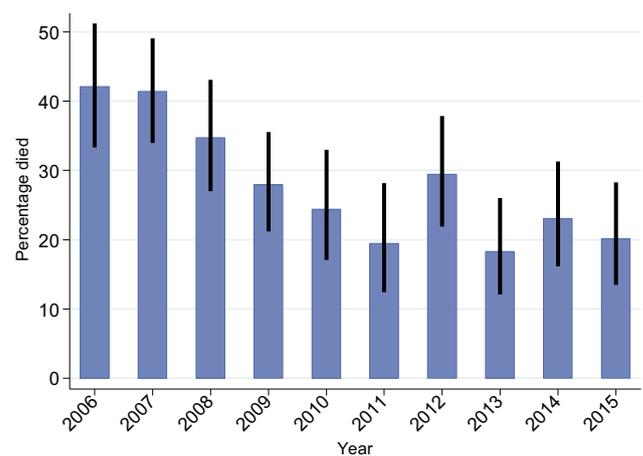


Fig. 4. Percentage of deaths by year with binomial 95% confidence intervals.

risk of death increased with increasing age (Table 2); mortality was highest for patients aged over 80 years with an adjusted OR of 3.32 (95% CI 1.92–5.74) $p < 0.001$. There was no significant effect of gender on mortality risk. Cases presenting with septicaemia had an increased risk (adjusted OR = 1.60, 95% CI 1.17–2.20) of death,

Table 2

Univariable and multivariable logistic regression for factors predicting death amongst listeriosis cases. Adjusted Odds Ratios (OR) were determined following adjustments for age, gender, time trend, serotype, underlying conditions and co-morbidities.

Variable	Died/N (%)	Unadjusted		Adjusted	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age category					
<15	1/15 (6.7)	0.44 (0.06–3.54)	0.442	0.50 (0.06–4.34)	0.530
15–49	21/151 (13.9)	1 (ref)		1 (ref)	
50–59	38/180 (21.1)	1.66 (0.92–2.97)	0.090	1.18 (0.64–2.18)	0.598
60–69	97/323 (30.0)	2.66 (1.58–4.46)	<0.001	1.97 (1.14–3.41)	0.015
70–79	114/357 (31.9)	2.90 (1.74–4.85)	<0.001	2.53 (1.47–4.33)	0.001
80+	119/331 (36.0)	3.47 (2.08–5.80)	<0.001	3.32 (1.92–5.74)	<0.001
Gender					
Males	216/761 (28.4)	1 (ref)		1 (ref)	
Females	174/596 (29.2)	1.04 (0.82–1.32)	0.743	1.06 (0.82–1.37)	0.659
Temporal trend					
Change per year increase	N/A	0.88 (0.84–0.92)	<0.001	0.90 (0.86–0.94)	<0.001
Serotype					
1/2a	119/403 (29.5)	1 (ref)		1 (ref)	
1/2b	33/107 (30.8)	1.06 (0.67–1.69)	0.792	1.14 (0.69–1.86)	0.611
1/2c	11/51 (21.6)	0.66 (0.33–1.32)	0.239	0.65 (0.31–1.36)	0.253
4/4b	178/622 (28.6)	0.96 (0.73–1.26)	0.753	1.03 (0.77–1.39)	0.845
Unknown/Non-typeable	49/174 (28.2)	0.94 (0.63–1.39)	0.740	1.03 (0.68–1.58)	0.878
Meningitis/CNS					
No	309/1053 (29.3)	1 (ref)		1 (ref)	
Yes	81/304 (26.6)	0.87 (0.66–1.17)	0.360	1.15 (0.82–1.60)	0.419
Septicaemia					
No	91/414 (22.0)	1 (ref)		1 (ref)	
Yes	299/943 (31.7)	1.65 (1.26–2.16)	<0.001	1.60 (1.17–2.20)	0.004
Gastroenteritis					
No	351/1201 (29.2)	1 (ref)		1 (ref)	
Yes	39/156 (25.0)	0.81 (0.55–1.18)	0.273	0.80 (0.53–1.20)	0.278
Other principal illness					
No	325/1154 (28.2)	1 (ref)		1 (ref)	
Yes	65/203 (32.0)	1.20 (0.87–1.66)	0.263	1.33 (0.91–1.94)	0.140
Comorbidity					
None/not underlying	59/359 (16.4)	1 (ref)		1 (ref)	
Cardiovascular	20/42 (47.6)	4.62 (2.37–9.00)	<0.001	3.30 (1.64–6.63)	0.001
Renal	12/45 (26.7)	1.85 (0.90–3.79)	0.093	1.60 (0.76–3.34)	0.216
Liver	28/62 (45.2)	4.19 (2.36–7.43)	<0.001	4.61 (2.47–8.61)	<0.001
Alcohol	4/18 (22.2)	1.45 (0.46–4.57)	0.523	1.44 (0.44–4.71)	0.549
Auto-immune	18/114 (15.8)	0.95 (0.54–1.70)	0.871	0.88 (0.48–1.60)	0.671
Lymphoid, haematopoietic	51/172 (29.7)	2.14 (1.39–3.29)	0.001	1.80 (1.14–2.85)	0.012
Solid organ malignancy	108/240 (45.0)	4.16 (2.85–6.07)	<0.001	3.42 (2.29–5.11)	<0.001
Other Immunosuppression	68/222 (30.6)	2.25 (1.51–3.35)	<0.001	2.12 (1.40–3.21)	<0.001
Any other	22/83 (26.5)	1.83 (1.05–3.22)	0.034	1.44 (0.81–2.58)	0.215

however, no effect was seen in patients presenting with another form of clinical presentation (Table 1). A number of co-morbidities were associated with an increased risk of death including cardiovascular disease - adjusted OR 3.30 (95% CI 1.64–6.63) $P=0.001$, liver disease - adjusted OR 4.61 (95% CI 2.47–8.61) $p<0.001$, lymphoid and haematopoietic malignancy - adjusted OR 1.80 (95% CI 1.14–2.85) $p=0.012$ and Immunosuppression (for reasons other than malignancy) - adjusted OR 2.12 (95% CI 1.40–3.21), $p<0.001$. A sensitivity analysis excluding those with missing mortality data was performed and did not demonstrate an appreciable impact except for a minor weakening of the effect estimates for some of the comorbidities.

Discussion

In this study, we tried to determine the direct effects of suspected mortality risk factors for listeriosis using a multivariate model to minimise confounding factors. We found an overall decreasing trend in mortality rates over the ten year study period in keeping with findings from previous UK and international reviews^{1,2,11}; a 10% annual reduction in mortality rate was identified which was similar to the US reported figure of 4.26%.¹¹ The total number of annual cases has remained stable and is similar to previous reports from England and Wales, despite an ageing population.²¹ This finding does contradict a US study which reported

a reduction in case numbers in addition to mortality over time,²² however, a more recent US study examining listeriosis cases during 2009–11 proposed that the annual incidence of listeriosis may not have actually decreased.²³ Reassuringly, mortality rates appear to be decreasing which may reflect improvements in case detection, empirical therapy, clinical management and healthcare systems over the ten year period.

We identified increasing age as a risk factor for mortality particularly in the over 80 year cohort which is consistent with findings from other studies.^{1,2,4,7} Age was also significantly associated with disease presentation; CNS involvement was associated with younger cases while presentation with septicaemia was associated with older age. Elderly patients are at an increased risk of death from listeria infection, although many guidelines and public health awareness campaigns in England are targeted at specific risk groups such as pregnant women. This review highlights the need to focus more efforts on prevention of listeriosis in the elderly.

Haematological malignancy was identified as a significant risk factor for mortality; however, solid organ malignancies were associated with an even greater risk of death which is consistent with findings from two US Studies.^{2,11} A French study reported a significantly increased risk in the acquisition of listeria amongst chronic lymphocytic leukaemia patients (> 1000 fold) versus other haematological malignancies and solid-organ malignancies (100–1000 fold) although the effect of these conditions on mortality

was not analysed.⁷ Other underlying conditions associated with increased mortality risk in our study were cardiovascular and liver disease both of which have been previously reported.^{1,11,24} In contrast to the conclusions from a Spanish study, we did not identify renal failure as a significant risk factor for mortality⁴; this finding might also be supported by a Belgian case series of patients with neurolisteriosis who found renal disease to actually be protective.²⁴ Goulet et al. reported any underlying condition being associated with increased risk of death except in patients with diabetes and valvular disease.⁷

Our study showed that septicaemia was associated with a significantly increased risk of mortality, however, no significant difference was seen for patients presenting with neurolisteriosis or other disease presentations. Many previous studies have reported similar findings with bacteraemia or sepsis being associated with the highest mortality.^{2,5,13} The evidence to date on the risk of neurological infection appears to be mixed with some reports of increased mortality^{7–9} and other studies reporting lower mortality rates.^{2,13} Our study found no significant effect on mortality in patients presenting with meningitis or other forms of neurolisteriosis.

Whilst there was an association seen between serotype and presentation with CNS involvement with serotype 4b being the most commonly identified serotype in neurolisteriosis cases, we found no association between serotype and risk of death, unlike a Danish cohort study which found an increased mortality risk in patients infected with serotype 4b.⁸

The strains that underwent antimicrobial testing displayed susceptibility to all first line agents used for the treatment of invasive infection, namely ampicillin, chloramphenicol, meropenem, gentamicin, glycopeptides and co-trimoxazole. This was reassuring given the increasing rates of drug resistance reported in food isolates.²⁵ Aminopenicillins were the most commonly used antibiotic (71.4%), followed by gentamicin and meropenem. Due to the lack of consistent reporting of antibiotic therapy for cases, we were unable to analyse the effects of particular antibiotic regimens on mortality. Standard listeria therapy in England consists of a combination of amoxicillin or ampicillin and gentamicin; however, there is little clinical evidence to date to support this practice of combination treatment with an aminoglycoside. A few studies have reported no improvement in prognosis when aminoglycosides were used in patients with CNS infection^{5,26} and one Spanish study identified gentamicin use as a risk factor for early mortality in all types of listeriosis.⁴ A Belgian case series found antibiotic monotherapy to be protective in patients with neurolisteriosis,²⁴ whilst a recent French study reported improved survival in patients given a beta-lactam, co-trimoxazole or aminoglycoside.¹³ One could argue that the benefit of adjunctive aminoglycoside in the treatment of neurolisteriosis is questionable given the difficulties of this drug in crossing the blood-brain barrier; however, further studies addressing this question are needed before final conclusions can be drawn. Treatment delay or inappropriate empirical therapy have been widely reported as risk factors for mortality,^{5,6,12} however, this information was also not routinely recorded in the surveillance questionnaires, therefore, we were not able to review this in our study.

Strengths and limitations

Although notification of isolation of the organism is mandatory in England, notification of the clinical syndrome of listeriosis in the absence of a positive culture is not; therefore, our case number may still be an underestimation of the true burden of disease. Milder cases of listeriosis in low risk individuals, such as those with febrile gastroenteritis, are unlikely to present to health-care facilities or have cultures taken which may have affected our case

numbers and therefore inflated mortality rates. The mortality rates we report here are, nevertheless, comparable to those reported from previous studies which also ascertain cases of listeriosis on the severe end of the clinical spectrum.

Much of our data relied on information collected from the enhanced surveillance or clinical questionnaires and occasionally there were inconsistencies between them. Data from the ESQs were prioritised; however, this may have resulted in reporting bias as much of this information was obtained directly from the patient in some cases sometime after the episode. Categorisation of clinical presentation by syndromes (such as CNS or septicaemia) was performed by the reporting laboratory and not defined by precise parameters, therefore, may have led to inaccurate recording. The clinical questionnaires may also have been affected by recording bias as hospital clinicians may have been more likely to return questionnaires for the more severe cases.

Mortality data was not captured at a defined time point following infection but at the time of data entry following receipt of completed questionnaires. If a patient subsequently died without listeriosis being recorded on the death certificate, this information would not have been captured in our system, however, given the variety of sources used for mortality data acquisition, we believe the mortality figures are reasonably accurate.

Conclusions

Increasing age, malignancy, cardiovascular disease, liver disease and immunosuppression and presentation with septicaemia were identified as independent risk factors for mortality. No association between mortality and listeria serotype was identified in this study. Septicaemia was the most common clinical presentation, followed by CNS involvement, 'other' presentations and febrile gastroenteritis. Whilst there has been no significant change in listeriosis case numbers in England between 2006 and 2015, there has been a reduction in mortality rates; advances in diagnostic modalities and clinical management may be contributory factors. Further studies should focus on collecting standardised clinical syndromic information along with details of risk factors for example, solid organ malignancy type and immune-modulating agents used. More focus on food safety interventions and raising awareness in these high risk groups is needed to reduce the incidence of listeriosis in the future.

Ethics

The data presented in this study was collected as a part of routine national surveillance for food borne pathogens by Public Health England and therefore ethical approval was not necessary.

Declarations and conflicts of interest

We declare no competing interests.

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