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Redefining the population at risk of listeriosis in England and Wales

by

Piers Andrew Nicholas Mook

Submitted for consideration for the degree of

Doctor of Philosophy by published work – Health Sciences

Warwick Medical School

University of Warwick

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Index of published work for consideration

Statement of ethical considerations

There are no ethical considerations as this body of work was carried out within the context of primary disease surveillance.

Submission declaration

I declare that the submitted material as a whole is not substantially the same as published or unpublished material that I have previously submitted, or am currently submitting, for a degree, diploma, or similar qualification at any university or similar institution. No parts of the works submitted have been submitted previously for any aforementioned qualification.

Statement of candidate's contribution to the published work

Contribution of candidate	**Co-authors in agreement***
Paper 1. Disease presentation in relation to infection foci for non-pregnancy-associated human listeriosis in England and Wales, 2001 to 2007 Piers Mook validated the employed coding scheme and provided comments on this manuscript prior to submission.	Gillespie IA, McLauchlin J, Little C, Penman C, O'Brien S J
Paper 2. Concurrent Conditions and Human Listeriosis, England and Wales, 1999 – 2009 Piers Mook took a lead role in the study design, coding scheme and statistical method. He managed and coded the study data, performed the statistical analysis, took a lead in writing the manuscript in liaison with co-authors and responded to reviewers as corresponding author.	Gillespie IA, O'Brien SJ
Paper 3. Mortality risk factors among human cases of listeriosis in England and Wales, 1990 to 2009 Piers Mook took a lead role in the study design, coding scheme and statistical method. He managed and coded the study data, performed the statistical analysis, took a lead role in drafting the paper in liaison with co-authors and responded to reviewers as corresponding author.	Patel B, Gillespie IA
Paper 4. Existing medications amongst listeriosis patients in England, 2007 - 09 Piers Mook took a lead role in the study design, coding scheme and statistical method. He managed and coded the study data, performed the statistical analysis, took the lead role in drafting the paper in liaison with co-authors and responded to reviewers as corresponding author.	Jenkins JM, O'Brien SJ, Gillespie IA
Paper 5. Human listeriosis in England, 2001-2007: association with neighbourhood deprivation Piers Mook validated the employed coding scheme and provided comments on this manuscript prior to submission.	Gillespie IA, Little CL, Grant KA, McLauchlin J
Paper 6. Listeria monocytogenes Infection in the Over-60s in England Between 2005 and 2008: A Retrospective Case-Control Study Utilizing Market Research Panel Data	Gillespie IA, Little CL, Grant K, Adak GK

Piers Mook was partially responsible for initiating this study, in that he suggested that it would be interesting to look at the findings from the deprivation study in the context of supermarket distribution. He discussed the methodology with the lead author throughout the development of this study and reviewed the analysis and manuscript prior to submission.	
Paper 7. Emergence of pregnancy-related listeriosis amongst ethnic minorities in England and Wales Piers Mook took a lead role in the study design, coding scheme and statistical method. He managed and coded the study data, performed the statistical analysis, took a lead role in writing the manuscript in liaison with co-authors and responded to reviewers as corresponding author.	Grant KA, Little CL, Kafatos G, Gillespie IA

*An exhaustive list of co-authors. Attested statements of contribution and circumstance under which the work was carried out can be found in Appendix 2.

Word Count

Summary: 641

Background: 1,121

Aims and objectives: 275

Materials and methods: 852

Summary of the published work: 2,065

Discussion: 3,833

Conclusion: 255

Total: 9,042

Abbreviations

ACMSF	Advisory Committee on the Microbiological Safety of Food
BNF	British National Formulary
CI	Confidence interval
CNS	Central nervous system
FSA	Food Standards Agency
HES	Hospital Episode Statistics
HPA	Health Protection Agency
ICD-10	International Classification of Diseases - version 10
LGP	Laboratory of Gastrointestinal Pathogens
NHS	National Health Service
ONS	Office for National Statistics
OR	Odds ratio
PCR	Polymerase chain reaction
RR	Relative risk
UK	United Kingdom

Summary

Listeriosis is a rare but severe food-borne disease caused by the opportunistic, bacterial pathogen *Listeria monocytogenes*. The elderly, those who are immunocompromised and pregnant women and their unborn or newborn infants are disproportionately affected. Listeriosis has a high case fatality ratio (up to 44%) and is the commonest cause of death ascribed to a food-borne pathogen in the United Kingdom (UK).

The number of cases of listeriosis in England and Wales reported to the Health Protection Agency (HPA) - the arms length governmental body mandated with protecting the health of the population - increased from an average of 110 cases per year between 1990 and 2000 to an average of 192 cases per year between 2001 and 2009. The epidemiology of listeriosis appeared to change with the observed increase almost exclusively among non-pregnancy related cases, aged ≥60 years presenting with bacteraemia in the absence of central nervous system infection (CNS). Given the potential severity of listeriosis and that, as a predominantly food-borne disease, these infections are largely avoidable, there was a public health imperative to investigate the observed increase.

Disease presentation, concurrent conditions, medications, deprivation, diet and mortality risk factors amongst non-pregnancy related listeriosis cases and ethnicity amongst pregnancy related cases were investigated using national surveillance data. The increased incidence of bacteraemic cases occurred in those with cancer, particularly digestive organ malignancies (Odds ratio (OR) [95% confidence interval

(CI)]: 16.7 [3.8 – 73]) and, to a lesser degree, those with conditions that necessitate treatment with stomach acid inhibiting medication (3.2 [1.5 – 6.6]).

Ethnicity and/or deprivation were found to be important drivers for infection. Compared to the most affluent areas, disease incidence was 38% (95% CI: 16 to 65) higher in the most deprived areas of the country. Cases were more likely than the general population to purchase foods from convenience stores (OR [95% CI]: 5.37 [3.53 – 8.17]) or from local services - bakers (3.40 [2.39 – 4.86]), butchers (1.62 [1.11 – 2.34]), fishmongers (5.05 [3.19 – 7.99]) and greengrocers (1.92 [1.32 – 2.78]) - and their risk profile changed with increasing deprivation. The proportion of pregnancy related cases classed as ethnic increased significantly from 2001 to 2008 (chi-square test for trend; p=0.002). The increase in the proportion of pregnancy related cases that were ethnic was most marked in 2006, 2007 and 2008, when the incidence was higher than expected given the underlying population (Relative risk (RR) [95% CI]: 2.38 [1.07 – 5.29], 3.82 [1.82 – 8.03] and 4.33 [1.74 – 10.77], respectively).

A wide range of underlying conditions appeared to increase the risk of infection, most notably diseases of the liver (RR [95% CI]: 22.4 [17.7 – 28.4]), systemic connective tissue disorders (18.3 [12.6 – 26.6]), neoplasms of the lymphoid, hematopioetic, and related tissues (17.6 [15.1 – 20.6]), psychoactive substance (alcohol related in 96% of reports; 12.3 [9.4 – 16.1]) and renal failure (12.2 [9.8 – 15.1]). Associated medications, including cytotoxic drugs (RR [95% CI]: 320.9 [228.5 – 450.7]), drugs affecting the immune response (18.5 [11.6 – 29.5]) and corticosteroids (11.1 [8.5 – 14.6]), and food groups, most notably smoked salmon

(OR [95% CI]: 4.82 [2.99 – 7.76]), other cold cooked fish (22.32 [15.85 – 31.44]), camembert (4.80 [2.32 – 9.90]), hard cheese other than cheddar (2.37 [1.69 – 3.30]), blue cheese (2.24 [1.47 – 3.43]), also appeared to be associated with increased risk of infection.

Underlying conditions, particularly malignancies of the breast (OR [95% CI]: 3.2 [1.7 – 6.2]) and respiratory and intrathoracic organs (3.9 [2.2 – 7.1]), alcoholism (2.7 [1.6 – 4.3]), cardiovascular diseases (1.4 [1.01 – 1.9]), treatment to reduce stomach acid secretion (1.6 [1.1 – 2.3])and increasing age (cases ≥80 years versus less than 60 years; 3.1 [2.3 – 4.2]) increased the risk of death amongst cases.

This cohesive body of work redefines the population at risk of listeriosis and indicates that there is added value in actively targeting appropriate food safety advice at a range of vulnerable groups other than pregnant women, to whom information has previously been routinely and preferentially disseminated.

1. Background

1.1 Introduction

Listeriosis is a rare but severe food-borne disease caused by the opportunistic, bacterial pathogen *Listeria monocytogenes*. Infections might manifest clinically as bacteraemia, meningitis, encephalitis, rhombencephalitis, meningoencephalitis, febrile gastroenteritis, miscarriage, spontaneous abortion or still birth. Three main groups of people are disproportionately affected: the elderly, those whose cell-mediated immune function is compromised, and pregnant women and their unborn or newborn infants. The incubation period for invasive listeriosis is generally considered to be between three and 70 days with an estimated median of three weeks but there have been reports of cases occurring up to 90 days after a single exposure[1]. Importantly, listeriosis has a high case fatality ratio - estimates among non-pregnancy related cases ranging from 19-44%[2-7] - and has been identified as the commonest cause of deaths ascribed to a food-borne pathogen in the UK[8].

Pregnant women can transmit infection to their foetus, for which the result can be fatal, but may not experience overt symptoms of infection themselves. Pregnant women rarely experience infections with CNS involvement[6], which are considered to be those that clinically manifest as meningitis, encephalitis, rhombencephalitis or meningoencephalitis. In addition, granulomatosis infantiseptica is a potential sequalae among neonates that survive infection. Healthy individuals might also have asymptomatic infection or exhibit mild symptoms of a non-invasive infection (gastrointestinitis) only[9]. Furthermore, while rare, a characteristically self limiting

non-invasive infection may be transmitted by direct contact with infected animals or animal material causing local, cutaneous popular lesions only. This form of disease is, however, generally limited to those in the veterinarian and farming professions[10;11].

Empirical treatment for invasive *L. monocytogenes* infection is commonly penicillin or ampicillin alone or in combination with gentamicin, which has anti-β-lactamase activity, for non-pregnancy related cases (pregnancy is a contraindication for gentamicin). The added benefit versus hazard risk of this combination therapy remains debated as a consequence of the associated nephrotoxicity of this aminoglycoside and its inability to cross the blood-brain barrier[12-15]. For those with a β-lactam allergy, erythromycin or trimethorpim-sulphamethoxazole might be considered.

There are two main approaches for disease control at the population level: provide adequate dietary advice on the avoidance of high-risk foods to those at increased risk of infection or reduce the contamination of food products.

1.2 The organism

L. monocytogenes is the only important human pathogen of the six species in the genus *Listeria – Listeria ivanovii* is an animal pathogen and has caused human disease rarely[16;17]. It is a gram positive, facultative anaerobe capable of proliferation between temperatures of 0.4°C and 50°C[18], thus allowing growth – all be it slow – in foods kept at normally adequate refrigeration temperatures. While killed by thorough cooking or pasteurisation, it is able to survive acid or salt based food-

processing. Consequently, foods most likely to be contaminated with *L. monocytogenes* are those which are not pasteurised, uncooked or only part-cooked, including: dairy products (particularly soft cheeses), cold cuts of meat, pâtés, smoked fish, ready meals which have been pre-cooked and then chilled for some time before consumption, or vegetables. This organism is widely distributed in the environment and can colonise animal intestines without causing infection, including those of healthy humans[19]. Consequently, it may readily enter the food-chain and persist in commercial food production environments via a variety of routes, which makes prevention challenging.

1.3 History

While others might have grown this bacterium without a clear classification, *L. monocytogenes* was first isolated and described in 1926 by E.G.D Murray. It could not be assigned to any existing bacterial genus and was initially referred to as *Bacterium monocytogenes* on account of a characteristic monocytosis found in infected rabbits and guinea pigs[20]. The current nomenclature has been employed as scientific vernacular since 1940[21].

Human cases were first reported in 1929 but were considered to be the consequence of zoonotic infection[22]. It was indicated as a food-borne pathogen in 1979 after an outbreak investigation in a Boston hospital[23], which may have involved raw vegetables. However, this mode of transmission was only widely accepted in 1981 after an outbreak associated with coleslaw in Canada[19], which was also the first to highlight *L. monocytogenes* as a serious public health problem. The implicated coleslaw contained cabbage grown in fields fertilised with compost and

raw manure from a flock of sheep known to have had listeriosis. Reported outbreaks linked by microbiological evidence to dairy products in the USA (milk[24] and soft cheese[1]) and Switzerland (soft cheese[25]) during the 1980s provided supporting evidence of this transmission mode and the public health importance of this pathogen.

Approximately 95% of human infections are caused by serotypes 1/2a, 1/2b and 4b[26] and large outbreaks are generally caused by strains of serotype 4 - 80% of reported cases that belonged to an identified outbreak or cluster in England and Wales between 2001 and 2009 (HPA unpublished data) - which may be indicative of an increased pathogenicity in this subtype. The potentially protracted incubation period makes the identification of specific food vehicles problematic in terms of identifying clusters in time due to increased issues of recall. This has likely resulted in under-reporting of outbreaks and, in more general terms, hampered the elucidation of the epidemiology of listeriosis. However, the majority of cases are not from common source outbreaks or suspected clusters but are sporadic - 96% in England and Wales between 2001 and 2009 (HPA unpublished data).

1.4 Incidence and trends in England and Wales

The annual incidence of listeriosis in England, Wales and Northern Ireland nearly doubled between 1985 and 1989 before rapidly declining in 1990 to baseline levels[27]. This increase was largely attributed to pâté consumption from a single manufacturer and disproportionately affected pregnant women[28]. This outbreak prompted targeting of health communication materials on listeriosis avoidance to

pregnant women[29] and these messages have been preferentially disseminated to this group since[30].

Between 1990 and 2000, the number of cases of listeriosis in England and Wales reported to the HPA national listeriosis surveillance system was relatively stable at a mean of 110 cases per year (2.14 cases per 1,000,000 population; Figure 1). However, between 2001 and 2009 there was a substantial increase in the number of cases reported, with a mean of 192 cases per year (3.58 cases per 1,000,000 population; RR [versus 2001-2009]: 1.68, 95% CI: 1.56 – 1.81). It appeared that the epidemiology of listeriosis changed with this observed increase almost exclusively among non-pregnancy related cases (Figure 1) and particularly those aged ≥60 years presenting with bacteraemia in the absence of CNS infection (Figure 2). The reason for this change was not fully understood, but appeared not to be the consequence of surveillance artefacts or explained by demographic, clinical or microbiological factors[2] nor the result of changes in population structure (Figure 3). Similar patterns with no definitive reasoning have since been reported in other European countries[31;32].

Figure 1: Trends in listeriosis cases by patient type in England and Wales, 1990 to 2009

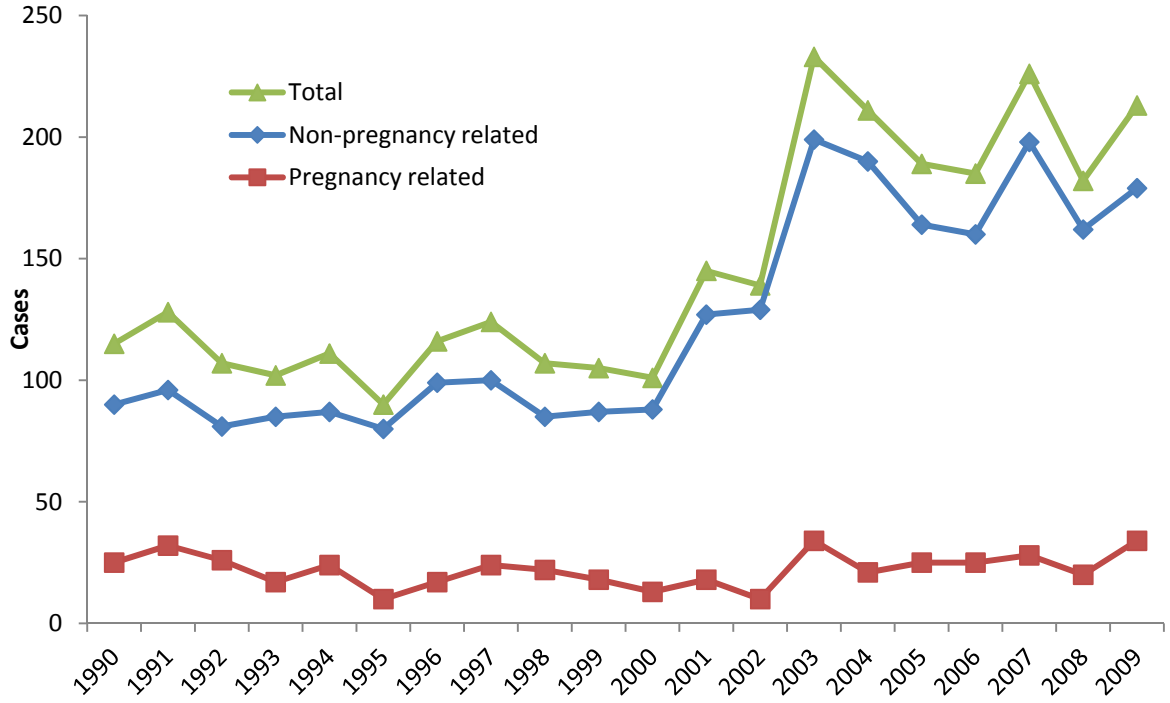


Figure 2: Trends in non-pregnancy related listeriosis cases by age and clinical presentation in England and Wales, 1990 to 2009

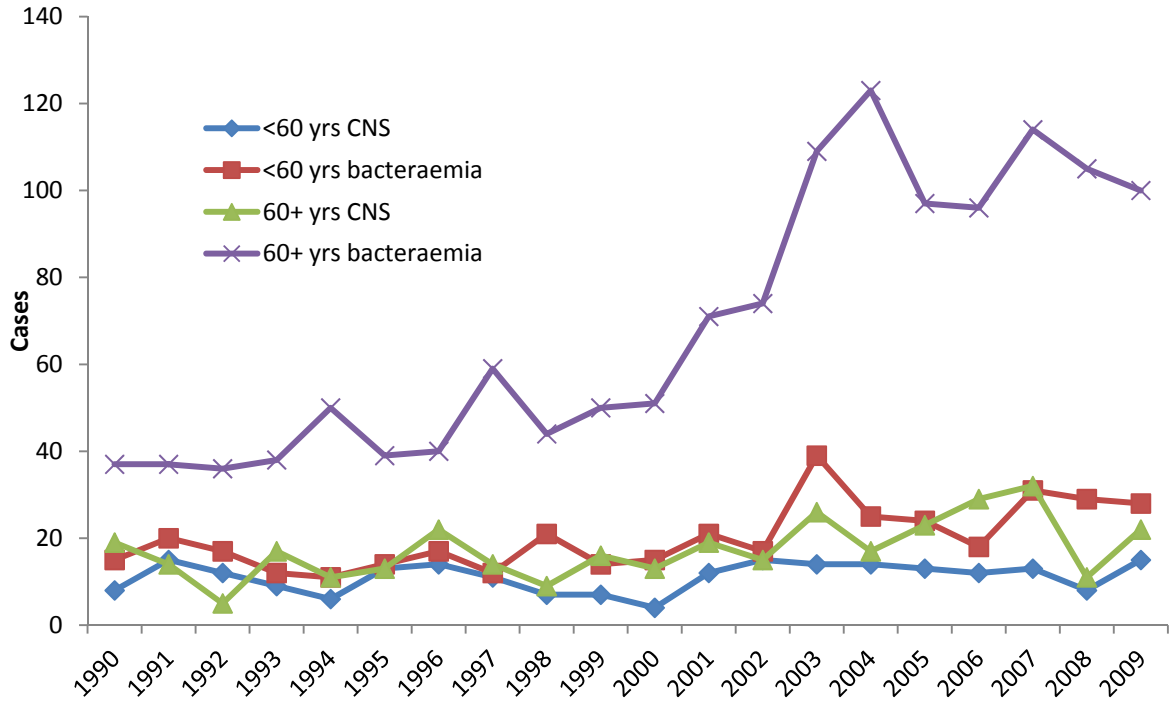
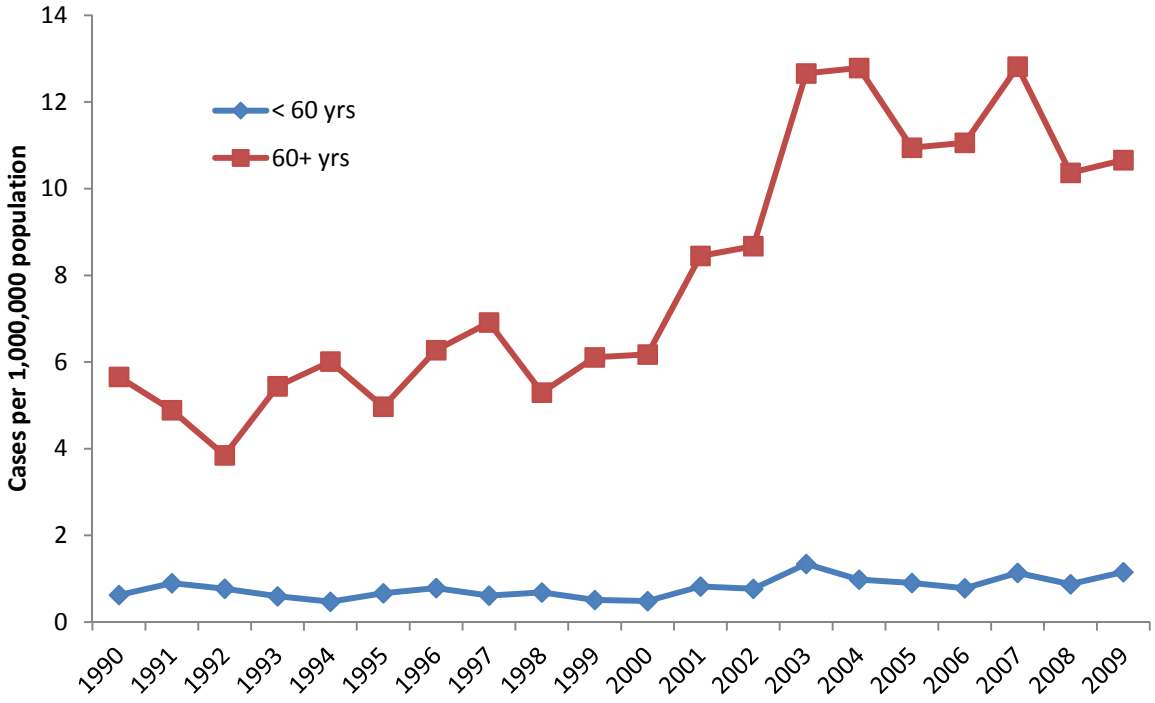


Figure 3: Trends in rate of non-pregnancy related listeriosis by age in England and Wales, 1990 to 2009



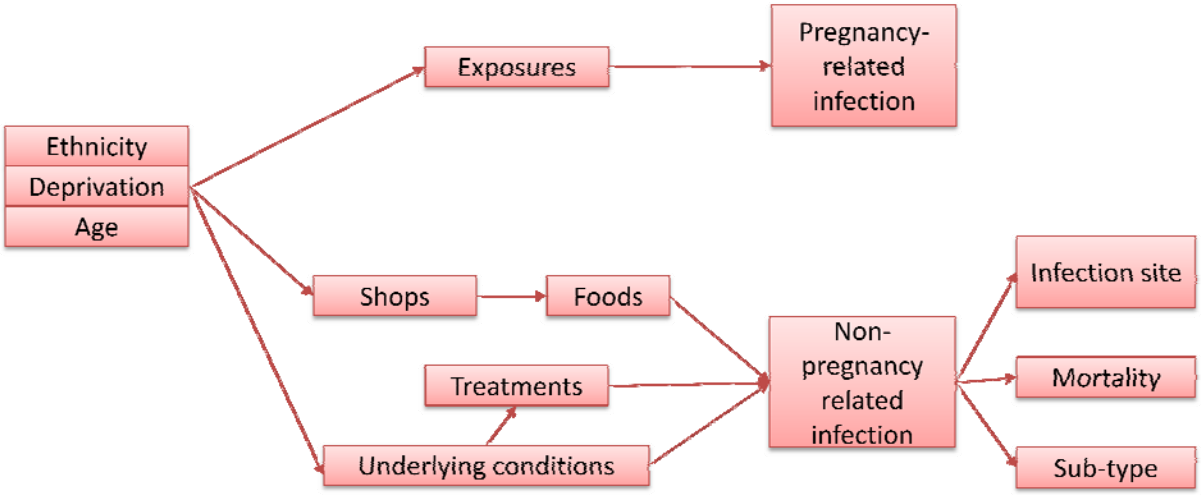
2. Aims and objectives

Given the potential severity of listeriosis and that, as a predominantly food-borne transmitted organism, infections with *L. monocytogenes* are largely avoidable, there was a public health imperative to investigate the observed increase in England and Wales.

This investigation had two strategic research aims set in the context of the observed increase and altered disease presentation since 2000: to more accurately characterize the population at increased risk of listeriosis and identify factors that influence outcome. These aims were to be achieved by interrogating standardised epidemiological, clinical and microbiological data captured by the national surveillance system for listeriosis in England and Wales.

At the outset of this research, no single hypothesis was developed as to the putative cause of the increased incidence. Instead, a systematic, strategic approach to investigating the increase was devised. In August 2008, a hypothesised causal model for listeriosis was mapped out (Figure 4) and used as a framework within which a co-ordinated, objective-based research plan was developed. Potential distal and proximal prognostic factors[33] to infection, as well as infection outcomes were identified for investigation.

Figure 4: Hypothesized causal pathway for listeriosis



In an effort to address the research aims, the following objectives were identified:

- Investigate differences between non-pregnancy related cases presenting with bacteraemia and CNS infections
- Inform on the relative role of co-morbidities on the risk of listeriosis
- Identify prognostic factors for mortality amongst listeriosis cases
- Inform on the relative role of existing medications on the risk of listeriosis
- Investigate health inequalities which might exist in relation to listeriosis
- Identify high risk food exposures for *L. monocytogenes* infection
- Investigate the role of ethnicity amongst pregnancy related cases of listeriosis

3. Materials and methods

3.1 National surveillance of listeriosis in England and Wales

The HPA, Colindale, London has co-ordinated the national surveillance of listeriosis in England and Wales since 1990. National surveillance was conceived and established following the increase in cases associated with the pâté-linked outbreak, when the need for a more robust scheme to monitor cases in England and Wales was identified.

Case ascertainment is multifaceted: voluntary referral of cultures or isolates to the national reference laboratory – Laboratory of Gastrointestinal Pathogens (LGP), HPA, Colindale - from local microbiology laboratories for identification and/or confirmation and subtyping (approximately 80% of cases); voluntary electronic reporting of laboratory-diagnosed infections from these same laboratories (approximately 80% of cases); or by both mechanisms (approximately 60% of cases). Epidemiological and microbiological data collected by these mechanisms are combined, checked for duplication, and stored in a Microsoft Access (Microsoft Corporation, Redmond, WA, USA) database.

As per food and environmental isolates, clinical isolates referred to LGP from local microbiology laboratories are confirmed phenotypically[34] (until 2003) or by real-time polymerase chain reaction (PCR)[35]. They are further characterised by serotyping (using a gel-based multiplex PCR since 2005)[36;37], phage typing[38] (until 2003), pulsed-field gel electrophoresis[39] (on a subset of isolates between 2003 and 2007), amplified fragment length polymorphism analysis[40] (between 2004 and

2010) and fluorescent amplified length polymorphism analysis[41] (since 2008 on clinical isolates and all isolates since 2010).

A case of listeriosis is defined as an individual from whom *L. monocytogenes* is isolated from a normally sterile site, most often cerebrospinal fluid or blood, and who presents with a clinically compatible illness. Cases are further classified as pregnancy related (all maternal-foetal or maternal-neonatal cases; these pairs are considered as a single case for surveillance purposes) or non-pregnancy related (those aged more than 1 month). Pregnancy related cases involving a neonate can be further stratified into late and early onset. Early onset cases are neonates symptomatic at birth or within 48 hours and infection is ascribed to *in utero* transmission from the mother. Late onset cases are those where symptoms develop more than 48 hours after birth and are predominantly thought to be the result of infection during passage through the birth canal. Rarely, late onset cases can be a consequence of nosocomial transmission via indirect contact with early onset cases, for example through common birthing staff or equipment[42;43]. Only laboratory confirmed cases are captured by the national surveillance system and are likely to be at the severe end of the clinical spectrum for listeriosis, having necessitated hospitalisation in most instances. Consequently, less severe invasive and non-invasive infections are likely to be under-reported using this case-capture mechanism.

This passive surveillance scheme is enhanced by requesting referral of isolates or cultures that had not yet been received by LGP but had been reported electronically. Furthermore, clinical data are augmented with that collected from

the consultant medical microbiologist responsible for each case using a standard clinical questionnaire since 1990, including clinical outcome, onset date, date of hospital admission, principal listeriosis illness, symptom data (since 2005) and antibiotics and other prescribed and non-prescribed medications (Appendix 3.1). Additional exposure data – foods consumed, food retailers visited and travel in the 30 days prior to symptom onset, collected since 2005 - and demographic data are sought from local health protection teams, who use a standardised trawling questionnaire (Appendix 3.2) to interview cases or a close relative, as available, directly or in liaison with environmental health officers.

Using quintiles of established indices of multiple deprivation, socio-economic status estimates are derived from case postcode data. Furthermore, cases are classified as 'ethnic' (belonging to an ethnic minority) or 'non-ethnic' (not belonging to an ethnic minority) on the basis of their surname and first name, as available. Case defined ethnicity data are captured for cases for whom a trawling questionnaire is completed. The subjective name-based classification scheme has been validated using case defined ethnicity data as an appropriate means of identifying individuals who describe their own ethnicity as something other than white British[44].

3.2 Datasets used for comparative analyses with surveillance data

To fully realise the potential of surveillance data, comparisons between these data and a number of other population based datasets were conducted:

- Hospital Episode Statistics (HES) finished consultant episode data, aggregated by the International Classification of Diseases (ICD-10) coding

system. These data were obtained from the Health and Social Care Information Centre and quantify episodes of continuous admitted patient care under a single consultant in National Health Service (NHS) hospitals in England, according to the primary diagnosis.

- NHS prescription data for England aggregated by British National Formulary (BNF) chemical summary level and year. These data were supplied by NHS Prescription Services.

- Commercial purchasing behaviour data from the Worldpanel Purchase database, supplied by Taylor Nelson Sofres, London. This is the largest continuous consumer panel dataset in Great Britain and captures data on 48,000 individuals from 25,000 households. This is a representative sample of the British population with regard to age, social class and regional distribution.

- Data on live births to mothers, stratified by location of birth of the mother, were supplied by the Office for National Statistics (ONS).

4. Summary of the published work

4.1 Differences between non-pregnancy related cases with different sites of presentation - bacteraemia versus CNS infections (Paper 1)

To understand the altered disease presentation - predominantly those aged over 60 years who presented with bacteraemia in the absence of CNS infection - and identify factors that might explain the observed increase, demographic, clinical and microbiological factors among 571 bacteraemic cases of *L. monocytogenes* infection occurring in 2001 to 2003 and 2005 to 2007 were compared with those for 207 cases with CNS infections for the same time period.

Bacteraemic cases were more likely to have gastrointestinal symptoms or underlying medical conditions than CNS cases. The latter was most marked in those with malignancies and digestive organ malignancies in particular (OR [95% CI]: 16.7 [3.8 – 73.0]). Treatment to reduce stomach acid secretion modified the effect of non-malignant underlying conditions on presentation, i.e. cases with a non-malignant underlying condition not taking acid-suppressing medication were no more likely to have a bacteraemia or CNS infection (1.5 [0.8 – 2.7]) where as those taking acid-suppressing medication were more likely to have a baceteraemia (3.2 [1.5 – 6.6]). However these therapies did not modify the effect of malignancies on having a bacteraemia or CNS infection.

4.2 Concurrent conditions experienced by non-pregnancy related cases (Paper 2)

Pathological or iatrogenic immunosuppression can increase an individual's susceptibility to *L. monocytogenes* infection. This predisposition is thought to be a function of suppressed T-cell mediated immunity induced by the condition antecedent to the *L. monocytogenes* infection. Those with cancer, diabetes, AIDS and liver or kidney disease are considered to be predisposed to severe infection and consequent mortality.

To inform on the relative role of co-morbidities with regard to risk of listeriosis, the concurrent conditions of 1,413 non-pregnancy related cases of *L. monocytogenes* infection in England for the fiscal years 1999 to 2008 were coded according to ICD-10 and compared with HES finished consultant episode data. Rates of concurrent conditions among listeriosis cases per million HES finished consultant episodes and relative risks (with the rate of all other condition groups other than the one in question as the comparison group) were calculated for each ICD-10 chapter and sub-group. These relative risks highlighted those concurrent conditions among listeriosis cases for which the frequency was increased relative to other reported conditions, having accounted for the size of the underlying hospitalised population with these conditions.

The majority of these cases had at least one concurrent condition (82%). A wide variety of conditions were associated with an increased risk of infection. Malignancies accounted for over a third of conditions described and the associated rate was increased five-fold compared to other conditions (RR [95% CI]: 4.9 [4.4 –

5.5]) and almost 18 times increased for cancers of the blood (17.6 [15.1 – 20.6]). Other high risk conditions included diseases of the liver (22.4 [17.7 – 28.4]), systemic connective tissue disorders (18.3 [12.6 – 26.6]), psychoactive substance (alcohol related in 96% of reports; 12.3 [9.4 – 16.1]), renal failure (12.2 [9.8 – 15.1]), diabetes mellitus (11.4 [9.0 – 14.5]), hypertensive diseases (8.0 [5.2 – 12.2]), and non-infective enteritis/colitis (4.3 [3.3 – 5.6]). For most high risk conditions the risk of infection was significantly higher in older patients (4.6 [4.1 – 5.3]).

4.3 Predictors of mortality amongst non-pregnancy related cases (Paper 3)

Although non-pregnancy related listeriosis is a rare disease compared to other gastro-intestinal pathogens, it is one of the UK Food Standards Agency's (FSA) priority pathogens as a result of the increase in case numbers during the 2000s and its high case fatality rate. However, there had been no assessment of whether this changing epidemiology had altered disease severity and what factors were prognostic for death amongst those with disease.

To inform on the role of a number of demographic, microbiological and clinical factors on the risk of death amongst non-pregnancy related cases of listeriosis, a cohort of 1864 cases reported between 1990 and 2009 were interrogated using univariable techniques and subsequent multivariable logistic regression. In these analyses, death status was the outcome of interest and demographic, microbiological and clinical factors were considered to be exposures. Given that most cases in this cohort (81%) had at least one known concurrent condition and we were interested in identifying the most important concurrent conditions in terms of mortality, the comparison group for each underlying condition variable in

the univariable analyses was all other underlying condition than the one in question. In the multivariable analysis, we built a categorical variable of those with underlying conditions shown to be significant in the univariable analysis based on increasing prevalence among the cohort; each case could only be assigned a single underlying condition. In addition, a subset of cases with available data (n=694; 2005-2009) was interrogated to investigate the use of antibiotic therapy on outcome.

The absence of any underlying condition had a protective effect on outcome among these cases (OR [95% CI]: 0.4 [0.3 – 0.6]). Malignancies of the breast (3.2 [1.7 – 6.2]) and respiratory and intrathoracic organs (3.9 [2.2 – 7.1]), alcoholism (2.7 [1.6 – 4.3]), cardiovascular diseases (1.4 [1.01 – 1.9]), increasing age (≥80 years versus less than 60 years; 3.1 [2.3 – 4.2]), and treatment to reduce stomach acid secretion (1.6 [1.1 – 2.3]) were positively associated with mortality. Furthermore, the five year subset analysis identified any antibiotic therapy as a protective factor for mortality, including that with anti-listerial activity only (0.1 [0.03 – 0.3]) which had the strongest evidence of a protective association. Illness in winter or spring was associated with an increased risk of death in this subset analysis (1.6 [1.1 – 2.3]).

4.4 Prescribed medication amongst non-pregnancy related cases (Paper 4)

In addition to the direct effect of concurrent conditions, treatments for these conditions might also result in an individual becoming immunocompromised and more susceptible to *L. monocytogenes* infection.

In order to investigate the relative role of existing medication on the risk of listeriosis, medications reported by 512 non-pregnancy related cases reported between 2007 and 2009 were coded according to the BNF and compared with NHS prescription services data. Medication rates among listeriosis cases per million prescriptions in England and relative risks (with the rate of all other medication groups other than the one in question as the comparison group) were calculated for each BNF chapter and section where 10 or more medications were reported. These relative risks highlighted those medications reported among listeriosis cases for which the frequency was increased relative to other reported medications, having accounted for the number of prescriptions for these medications in England.

The medication rate for the malignant disease and immunosuppression BNF chapter was most increased relative to other chapters (RR [95% CI]: 18.5 [14.0 – 24.4]).The rates for cytotoxic drugs (320.9 [228.5 – 450.7]), drugs affecting the immune response (18.5 [11.6 – 29.5]) and corticosteroids (11.1 [8.5 – 14.6]) were particularly high compared to other sections.

4.5 Socio-economics of non-pregnancy related cases (Paper 5)

Although a potentially severe disease with regard to patient outcome, putative socio-economic determinants had not been investigated in detail. Consequently, health inequalities that might exist for listeriosis, and could be used by policy makers to target specific interventions, were not apparent.

To investigate health inequalities that might exist in relation to listeriosis, 1,179 cases with postcodes reported in England from 2001 to 2007 (stratified into all

non-pregnancy related, non-pregnancy related aged ≥60 years and pregnancy related groups) were linked to ONS lower super output areas (based on their postcode) and assigned a socio-economic status score using 2007 indices of deprivation. Incidence calculations by quintile for the indices of deprivation were then performed using the relevant population data for each group (all, non-pregnancy related, non-pregnancy related aged ≥60 years and pregnancy related cases). Incidence in each quintile relative to the lowest quintile (least deprived) was calculated.

For non-pregnancy related cases with appropriate exposure data between 2005 and 2007 (n=1710), food purchasing patterns were interrogated and comparison made with the general population (commercial food purchasing denominator data).To further quantify risk, food purchasing, storage and consumption case data were stratified by quintiles of increasing neighbourhood deprivation and trends across quintiles examined.

Compared to the most affluent areas, disease incidence was higher in the most deprived areas of the country (RR [95% CI]: 1.38 [1.16 – 1.65]). This effect was observed in all non-pregnancy related patients (1.27 [1.05 – 1.53]), those aged ≥60 years (1.36 [1.09 – 1.71]) and was more marked for pregnancy related cases (2.20 [1.18 – 4.08]). Cases were more likely than the general population to purchase foods from convenience stores (OR [95% CI]: 5.37 [3.53 – 8.17]) or local services - bakers (3.40 [2.39 – 4.86]), butchers (1.62 [1.11 – 2.34]), fishmongers (5.05 [3.19 – 7.99]) or greengrocers (1.92 [1.32 – 2.78]).

In addition, the risk profile of cases changed with increasing deprivation. Cases from more deprived areas were more likely to: report their own ethnicity as something other than white British (chi-square test for trend; p=0.01); avoid soft blue cheese (p=0.04) or pâté (p=0.01); eat liver sausage (p=0.04), cold roast turkey (p=0.045) or prepacked cold turkey (p=0.048); or shop in two national supermarket chains (p<0.05), a national discount supermarket (p=0.004), local bakers (p=0.02), fishmongers (p=0.03) or greengrocers (p<0.001). Cases from more deprived areas were no more likely to have acute or long standing medical conditions (p=0.22).

4.6 Diet of non-pregnancy related cases aged ≥60 years (Paper 6)

Recommendations on the avoidance of high risk food exposures for listeriosis are largely based on epidemiological and/or microbiological evidence from outbreaks, microbiological surveys of foods and exposure data from sporadic cases captured by national surveillance. Standardised epidemiological exposure information has been sought on cases of listeriosis since 2005. However, the added value of these accrued data on informing on high risk exposures for disease is limited without some perception of the prevalence of these same exposures in the population at risk of listeriosis.

To attend to this information gap, the exposures of 159 cases aged ≥60 years reported in England from 2005-2008 were compared to those of market research panel members (representative of the general population in terms of age and gender) of the same age group and for the same time period and geography. Exposures were grouped to facilitate comparison and odds ratios calculated.

Cases were more likely than panel members to report the consumption of cooked beef (OR [95% CI]: 1.8 [1.32 – 2.51]), processed pork (2.00 [1.46 – 2.74]), smoked salmon (4.82 [2.99 – 7.76]), other cold cooked fish (22.32 [15.85 – 31.44]), prawns (1.50 [1.01 – 2.24]), milk (7.51 [3.96 – 14.26]), butter (1.78 [1.29 – 2.46]), hard cheese other than cheddar (2.37 [1.69 – 3.30]), blue cheese (2.24 [1.47 – 3.43]), camembert (4.80 [2.32 – 9.90]), other cheese (1.65 [1.19 – 2.28]) and mixed salads (1.72 [1.20 – 2.47]). They were less likely to report the consumption of other pork (0.18 [0.08 – 0.41]), other seafood (0.35 [0.21 – 0.57]), dairy spread (0.26 [0.19 – 0.36]), other dairy products (0.21 [0.15 – 0.30]), sandwiches (0.08 [0.06 – 0.11]) or fresh vegetables (0.03 [0.02 – 0.05]).

4.7 Ethnicity amongst pregnancy related cases (Paper 7)

While the annual rate of pregnancy related listeriosis remained static in contrast to that for non-pregnancy related listeriosis for the period 2001 to 2008, two coincident yet unconnected cases of pregnancy related listeriosis in 2008 in Eastern European women reported to the national listeriosis surveillance system for England and Wales prompted a review of the role of ethnicity in pregnancy related listeriosis for this period.

Pregnancy related cases identified in England and Wales between 2001 and 2008 were classed as “ethnic” (belonging to an ethnic minority; n=66) or “non-ethnic” (n=114) based on their name. The numbers of live births to mothers who were born inside and outside of the UK during this period were used as denominators for the calculation of rates of non-ethnic and ethnic pregnancy-related listeriosis, respectively. Relative risks were calculated to assess disparity in risk between ethnic

minorities and non-ethnic minorities and trends over the study period examined. Demographic, clinical and exposure data were compared between ethnic and non-ethnic cases.

The proportion of pregnancy related cases classed as ethnic increased significantly from 2001 to 2008 (chi-square test for trend; p=0.002) whereas this trend was not observed for non-pregnancy related cases. The incidence among the ethnic population was higher than that among the non-ethnic population in 2006, 2007 and 2008 (RR [95% CI]: 2.38 [1.07 – 5.29], 3.82 [1.82 – 8.03] and 4.33 [1.74 – 10.77], respectively). Pregnancy related cases classed as ethnic were more likely to consume pâté (Fisher's exact test; p=0.02), cabbage (p=0.005) or dill (p=0.016) and shop in either of two supermarket chains (p<0.05) or local bakeries (chi-square test; p=0.046) than those that were classed as non-ethnic.

5. Discussion

The increase in listeriosis cases between 2001 and 2009 compared to the previous 11 year period suggested that the existing public health risk communication strategy for listeriosis was not adequate to reach all those at increased risk of infection. Considerable work was undertaken by the HPA to define more accurately the population at risk of listeriosis and to inform on the observed increase and altered disease presentation.

The research presented here demonstrates how the aims and objectives of this research have been met. This series of co-ordinated epidemiological studies investigated altered disease presentation, concurrent conditions, medications, deprivation, diet and mortality risk factors amongst non-pregnancy related listeriosis cases in England or England and Wales (as data allowed) and ethnicity amongst pregnancy related cases in England and Wales. This cohesive body of work redefines the population at risk of listeriosis and should be considered by policy makers targeting future food safety advice beyond pregnant women, to whom information has previously been routinely and preferentially disseminated.

The first paper in this portfolio highlighted previously unrecognised differences between the clinical presentation of *L. monocytogenes* infection (CNS vs. bacteraemia) in England and Wales during the period of observed increase. It indicates that the increase in incidence of bacteraemic cases during the period of increase occurred in those with cancer (particularly of the digestive organs) and, to a lesser degree, those with other underlying conditions that necessitate treatment

with stomach acid inhibiting medication. This class of medication has previously been shown to increase the risk of developing other gastrointestinal infections[45-47] by facilitating passage through and subsequent colonisation of the digestive tract. It might be reasonable to assume that the absence of an effective stomach acid barrier may also have a role to play in predisposing individuals to developing listeriosis, and this is supported by evidence from animal models[48].

The important role of cancers in non-pregnancy related listeriosis is supported by the findings of Paper 2, which employed a novel denominator to systematically assess the rates of reported conditions concomitant to listeriosis, in the context of hospital consultations, among a cohort of cases larger than that previously considered. Cancers were the largest group of reported conditions and the associated rate was increased five-fold compared to other conditions and particularly increased for cancers of the blood. Other conditions were also found to have increased rates and largely reflected a population that, either as a result of the condition or treatment for the condition, were immunocompromised (most notably systemic connective tissue disorders and diseases of the liver).

The validity of these findings was reinforced by a review of medications received by listeriosis cases in the two weeks prior to infection in the context of national prescriptions (Paper 4) – a method not previously employed to investigate the role of medications in listeriosis. The rates for cytotoxic drugs (predominantly used for the treatment of cancers), drugs that affect the immune response and corticosteroids, which can also be used as immunosuppressants, were significantly and substantially higher than other medications. The rates of acid suppressing

drugs could not be fully assessed due to the level of resolution employed, however. Available data didn't enable an examination of underlying conditions whilst controlling for medications and vice versa and so the findings of both analyses are likely to be affected by uncontrolled confounding. However, the fact that both analyses indicate the same conditions is encouraging.

Paper 3, which is the largest study of its kind amongst a cohort of listeriosis cases, shows that underlying conditions, increasing age and treatment to reduce gastric acid secretion are independently associated with mortality amongst non-pregnancy related cases of listeriosis. It also demonstrates that while the number of deaths has increased during the period of increased incidence of disease, the case-fatality ratio has actually decreased, which is likely to be a function of the altered clinical presentation. Compared with all other underlying conditions, malignancies of the breast and respiratory organs, alcoholism and cardiovascular disease were the most important with regard to effect on fatal outcome but that is not to say that others were not associated with mortality compared to individuals with no underlying conditions. These highlighted underlying conditions are among those identified by the review of underlying conditions most common among listeriosis cases.

The observed parity between the conditions and medications that would appear to predispose individuals to infection and those that result in the most severe outcome re-enforces the need to better inform these identified high risk groups with regard to food safety messages on the avoidance of listeriosis. Not only are certain groups at risk of infection but some are more at risk of dying as a consequence of infection. In addition, the clinician's index of suspicion for *L.*

monocytogenes infection and subsequent treatment decisions should be informed by a history of high risk conditions (especially those with a high measure of effect for mortality) and use of certain medications, including gastric acid suppressants.

Paper 6 was considered to be the first application of market research data to infectious disease epidemiology using a case-control method to identify high risk food. A wide variety of foods were associated with increased risk of infection in those aged over 60 years, the age group which carries the greatest burden of listeriosis and in which the increase in cases since 2001 was observed. The burden of disease is likely to be compounded in this age group because not only is immune function modulated by age, and so predisposing to infection, but this group carries a greater burden of chronic disease and as a result will likely be further immunocompromised. Consequently, the public health impact of listeriosis is likely to increase as the population in England and Wales ages. Previously there has been no strategy in place to communicate food safety messages on the avoidance of high risk food to those aged over 60 years or even the subset of this population who are at further risk due to underlying conditions and subsequent treatment. The wide variety of high-risk food groups identified here might reflect this or, alternatively, the ubiquity of the microorganism in the environment.

UK food safety advice on the avoidance of foods that give rise to listeriosis is currently delivered to pregnant women only. This group are at increased risk due to modulation in immune function that occurs during pregnancy. However, Paper 7 illustrates how pregnant women are not comprehensively reached with these messages or do not adhere to food safety advice on the avoidance of high risk

foods. While the incidence of pregnancy related listeriosis has remained stable during the period of increased incidence of non-pregnancy related listeriosis, the proportion of pregnancy related cases from ethnic minorities has increased, even in the context of a dynamic population. Clearly, information on how to avoid contracting listeriosis and/or the potential consequence of infection on pregnancy outcome is not being appropriately delivered to pregnant women from ethnic minorities and this should be addressed. Ethnic minorities among pregnant women are already targeted in the USA[49] and Australia[50] and such a model should be followed in England and Wales.

Furthermore, people belonging to ethnic minorities are more likely to be from more deprived areas, which have been shown to be associated with increased risk of listeriosis (Paper 5). We have presented the most in-depth analysis so far on the impact of ethnicity and deprivation on listeriosis; ethnicity and/or deprivation appear to be important drivers for infection but further work is required to investigate the independent effect of these factors and examine existing barriers and exposures.

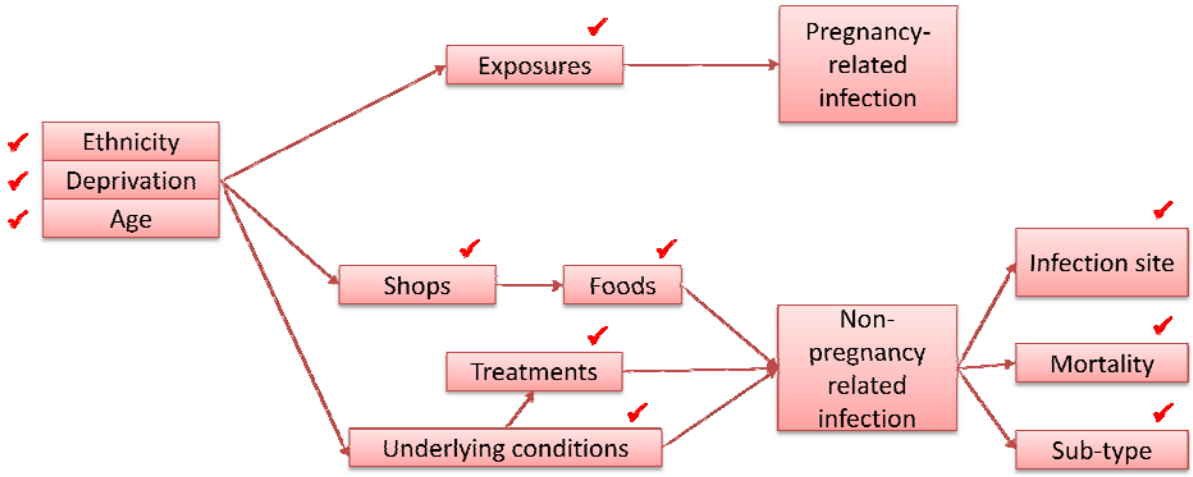
Few studies have attempted to quantify the risk of listeriosis by concurrent conditions or medication and none have used the systematic method employed in Papers 2 and 4. While methods and measures differed, the most notable concurrent conditions identified in Paper 2 - with the exception of systemic connective tissue disorders - are supported by the findings of two previous smaller studies: malignancies (particularly of the blood)[51;52], liver disease[52], kidney disease[51;52], diabetes[51;52] and alcoholism[51;52]. These studies also identified

conditions we did not, most notably transplantation[52] and AIDS[51;52] but the former might reflect the limitations of the employed coding strategy and the latter could be a function of the study period. Previous population based studies investigating risk of disease associated with medication also identified antacid therapy[51], steroid therapy[51] and gastric acid inhibitors[53] but not medications used to treat malignant disease. Smaller studies investigating mortality risk factors supported the findings from Paper 3 that age[5;13] and non-haematological cancers[3;5] are associated with a fatal outcome. Market research data had not been previously used to investigate the consumption patterns of cases of infectious disease as presented in Paper 6. In addition, the impact of deprivation on the risk of listeriosis, as presented in Paper 5, had not been previously explored in detail. Listeriosis has previously been reported as disproportionately affecting pregnant women from ethnic minorities - Hispanic women in the United States[54-56] and women living in an Australian household where a language other than English was spoken[53] – as per the findings of Paper 7. However, the identified sustained increase in pregnancy related cases in ethnic minorities has not been reported elsewhere.

The identified distal and proximal factors to listeriosis and post infection outcomes have been investigated in this portfolio (Figure 5). We have identified high risk groups for listeriosis that were previously unrecognised or for which the evidence base was not robust enough to be used for targeting the dissemination of food safety messages. It is vital to provide an evidence base for the public and clinicians to instil confidence in the reasoning of health protection messages, including food safety. These studies indicate that there is added value to actively targeting

appropriate food safety advice at a wider range of vulnerable groups. We recommend that vulnerable, yet currently neglected, groups highlighted here be targeted in the future and that risk by underlying condition (and associated medication) and prevalence of underlying conditions (Supplement, Paper 2) be considered in conjunction with relative severity of outcome when prioritising these groups.

Figure 5: Investigated elements of the hypothesized causal pathway for listeriosis



The primary aim of this investigation was to better characterise the population at risk of listeriosis in England and Wales using routine surveillance data. To make the best use of these data, we made comparisons with other datasets. However, for analyses in papers 2, 5 and 6, only English comparison data were available. Given the assumed similarity amongst the English and Welsh populations in terms of socio-economic and exposure factors and a common healthcare service, these populations were considered to be homogenous with regard to risk factors for listeriosis and, hence, these findings are generalisable. In addition, limitations of

proprietary data representative of national food consumption patterns meant that findings of paper 6, with regard to foods more commonly consumed amongst listeriosis cases than panel members, were limited to those aged over 60 years. There might be systematic differences in consumption patterns between age groups and therefore it would be unwise to generalise these findings beyond this demographic. However, it has been within this age group that the majority of the increase was observed. Furthermore, these findings can only be considered to be representative of the more severe cases which require hospitalisation (an inherent bias to the case-capture mechanism used by the national listeriosis surveillance system) and should not be used as an evidence base for less severe forms of disease.

The calculation of increased rates among listeriosis cases for certain medications (paper 4) and underlying conditions (Paper 2) used prescriptions and hospitalisation episodes denominator data, respectively, rather than the prevalence of those taking these medications and living with these conditions in the population. While we have made the best use of surveillance data, these two pieces of work should be considered as having generated advanced hypotheses only. It should be noted that our methods utilised standardised coding to systematically calculate rates and this has advantages over using a variety of sources to calculate population prevalence. Furthermore, while these two studies were limited by being based on univariable analyses, the findings of both were largely congruent and seemingly validate one another to some extent. A case-review methodology that would enable the investigation of interactions between medications and underlying conditions,

respectively, as well as the independent effects of each on the risk of listeriosis would be a useful next step in this research stream.

Paper 3 used all other conditions as the reference population for investigation of the effect of concurrent conditions on mortality among listeriosis cases rather than healthy controls in order to better represent the population at risk of contracting and dying of infection. It should be noted that this approach may underestimate the effect of specific concurrent conditions on mortality. In addition, the data driven approach employed to construct a categorical concurrent condition variable for multivariable analysis might have masked conditions with the least prevalence.

By assigning cases to socio-economic groups on the basis of their home postcode as in Paper 5, the effect of individual level socio-economic status is masked and individuals take on the characteristics of their locality and this might increase the potential for ecological fallacy. Also, this analysis considered the indices of deprivation to be static during the study period (assigning scores for 2007 for the period 2001 to 2007) and this might not adequately represent areas which have undergone extreme social change during this period.

Using name based classification for identifying an individual as belonging to an ethnic minority, as in Paper 7, is likely to have underestimated pregnancy related cases who consider themselves as belonging to an ethnic group other than white British. Consequently, the risk of pregnancy related listeriosis associated with ethnic minorities might be greater than that reported. Data on live births by country of origin of mother are also likely to be an imperfect denominator for incidence

calculations and might have affected risk estimates. Furthermore, case-case comparisons do not indicate the magnitude or direction of risk and these findings should be tested by other methodologies.

We have identified and or/quantified high risk groups for listeriosis and factors that relate to the increase in bacteraemic cases but we have not addressed the cause of the increase in listeriosis cases in England and Wales, and nor was this the aim of this portfolio. Paper 1 did consider the change in prescription rates of acid suppressing medication and found that the increase in cases did mirror the increase in prescriptions of proton pump inhibitors. Further work is required to review how changes in food and medication exposures and the prevalence of high-risk conditions may have been associated with this increase. There are also other hypotheses with regard to this increase, including: a decrease in exposure to the pathogen in food several decades ago resulted in an increase in the average age of infection[57]; the susceptible population has become more susceptible to infection; or *L. monocytogenes* has become more virulent. It has also been postulated that two sudden increases in monthly counts of cases in 2001 and 2003 may have been the result of major agricultural disturbance but no causative link was demonstrated[58] and this is unlikely to explain the sustained increased.

While the use of surveillance data is limited compared to bespoke studies designed to address a null hypotheses, they do provide timely information for action. Such action may be an investigation of a putative outbreak or, as in this case, response to a change in the population disproportionately bearing the burden of disease. Since 2009, there has been an apparent decline in the number of non-pregnancy related

cases of listeriosis in England and Wales to levels not observed since 2001 (Figure 6). Furthermore, this decline has predominantly been observed amongst those over 60 years of age presenting with bacteraemia in the absence of CNS infection (Figure 7). There is no evidence to indicate that this decline is a consequence of a reporting artefact. The reasons for this decline remain unclear but changes in approaches towards and resource dedicated to the control of listeriosis have likely been informed by this surveillance-driven research portfolio.

Figure 6: Trends in listeriosis cases by patient type in England and Wales, 1990 to 2011

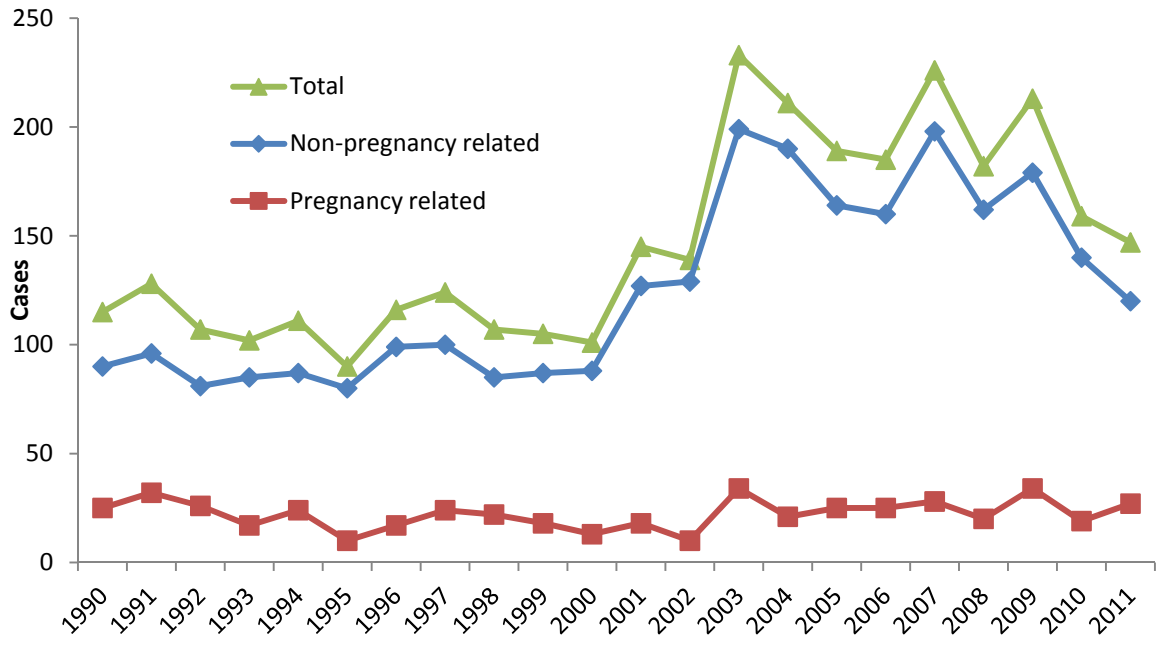
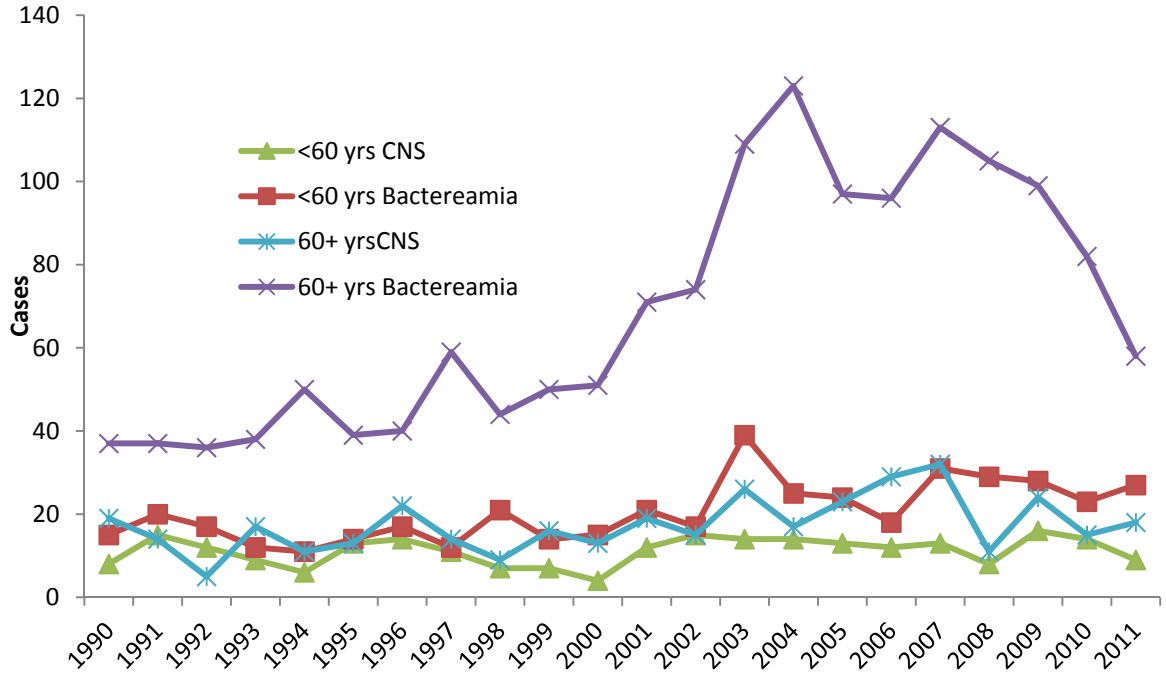


Figure 7: Trends in non-pregnancy related listeriosis cases by age and clinical presentation in England and Wales, 1990 to 2011



During the period of increased incidence in England and Wales (2001 to 2009; annual mean rate, 3.58 cases per 1,000,000 population), incidence was comparable in France (2001 to 2006, 3.1 to 4.6 cases per 1,000,000 population)[31] and Germany (2001 to 2005, 2.6 to 6.2 cases per 1,000,000 population)[32], both of which also experienced increased rates. Incidence in the USA - where no increase in cases was observed during this perio - ranged from 2.5 to 3.2 cases per 1,000,000 population between 2004 and 2009[56].

Recent annual figures in England and Wales still remain above those observed in the 1990s. Fluctuations have also previously been observed, though not of this magnitude, and caution is advised when interpreting this as a secular trend. Furthermore, large, fatal outbreaks of listeriosis still occur: an outbreak in the Czech

Republic in 2006 linked to soft cheese resulted in 78 identified cases and 13 deaths[59]; in Canada in 2008, an outbreak resulted in 57 cases and 23 deaths[60]; and, most recently, in 2011, an outbreak involving multiple *L. monocytogenes* strains linked to whole cantaloupes from a single farm in Colorado, USA, resulted in 146 cases and 30 deaths[61] across 28 states. Clearly, due diligence with regard to listeriosis control is imperative and this disease should remain a public health priority given its potential severity.

There are two main methods of disease control: provision of adequate dietary advice on the avoidance of high-risk foods to those at increased risk of infection and severe outcome by an appropriate delivery mechanism; and reduction in the contamination of food products, especially those provided to high-risk groups. Given the widespread distribution of *L. monocytogenes* in the environment and animal intestines, and its capacity to persist in food production environments, reducing contamination in food products remains challenging and is likely to be limited in success. A change in current policy on the tolerable levels of *L. monocytogenes* in foods in the UK from 100 colony forming units/gram (within shelf life) to match that in the USA (zero tolerance) would be an appropriate step to this end. However, such a change would have an intrinsic negative effect on UK trade within the European Union, throughout which the current UK criteria are a minimum standard. Furthermore, while the incidence of listeriosis decreased in the US between 1996 and 2003 from 4.1 cases per 1,000,000 population to 3.1 per 1,000,000 - and has since remained stable[56] - the extent to which this is as a result of the zero tolerance policy is unknown[55].

A pragmatic first step in protecting the population from listeriosis through reducing exposure in foods would be to enforce a zero tolerance policy for *L. monocytogenes* in foods served to those most at risk – those hospitalised with high risk conditions and/or receiving high risk treatments. While this is likely to increase the procurement costs of foods for hospitals, it is inappropriate that some of those most at risk of listeriosis are being served high risk foods, as is currently the situation. Nosocomial outbreaks associated with the consumption of high risk foods, including sandwiches with high risk fillings, have been reported[62-66]. This situation is compounded by the fact that food storage conditions on hospital wards can be inadequate. To resolve this situation, the type of food served should be selected to minimise the risk of food-borne infection[67], health care workers need to be better educated on risk and severity of listeriosis and improved systems to monitor food storage on wards need to be implemented. Clearly, such systems would need to balance food safety with the availability of food to a population with restricted access.

The inherent problems with removing contamination from foods only re-enforces the importance of adequate dietary advice on the avoidance of high-risk foods to those at increased risk of infection and severe outcome. This must be done in balance with the nutritional needs of these high risk groups and it might be most appropriate to suggest alternative foods when recommending those to avoid.

In February 2010, this body of work was presented informally to the FSA and, in March 2010, formally to the Advisory Committee on the Microbiological Safety of Food (ACMSF). The ACMSF is a statutory committee that provides expert advice to

the government on questions relating to microbiological issues and food and the FSA is the governmental department responsible for food safety to which the HPA provide routine data and commentary on gastro-intestinal infections, including listeriosis. The ACMSF had been apprised of the increase in human listeriosis in England and Wales in September 2005 and received updates in June 2006, December 2006, June 2007 and December 2007 where presented data suggested that the altered epidemiological and clinical picture in England & Wales was not artefactual. To both the FSA and ACMSF, it was recommended that advice on the avoidance of listeriosis be actively targeted to a wider range of vulnerable groups, as per the groups identified in this portfolio of work, using appropriate methods of delivery.

In June 2010, the FSA announced its food-borne disease strategy for the period 2010 to 2015[68]. *L. monocytogenes* was identified as a priority pathogen for this period, and the FSA has committed to ensure that "consumers understand the risk from Listeria and know how to minimise it". Initially this strategy will focus on two groups: those with cancers of the blood and pregnant women from ethnic minorities. The FSA reviewed the findings of the research presented here and the situation and approach in other countries in order to rationalise which groups should be prioritised for targeting, given limited resources.

Pregnant women are a well established high risk group for listeriosis and both healthcare practitioners and patients are likely to be receptive to better focused and more appropriate communication strategies to reach a high risk sub-group - pregnant women from ethnic minorities whose first language might not be English.

Our study on the role of ethnicity in pregnancy related listeriosis could not identify certain ethnic minorities at increased risk that should be targeted; a review of what languages would be most suitable and how best to deliver this information was to be undertaken by the FSA and based on the current demographics of mothers to babies born in the UK.

While there are several cancers which would appear to result in increased risk of infection and associated mortality, cancers of the blood had the highest risk and prevalence of disease amongst cases (Supplement, Paper 2). In the first instance, existing dissemination channels for cancer patients were to be explored for delivery of information on the avoidance of high risk foods to this group, as an adjunct to existing information provided soon after cancer diagnosis. If the use of existing networks proves to be effective, this means of delivering food safety information may later be rolled out to those affected by a wider range of cancers and other high risk groups that have similar information networks already in place.

6. Conclusion

The observed increasing trend in the incidence of listeriosis has been driven by non-pregnancy related infections. We have identified and quantified high risk foods and those most at risk of listeriosis and associated mortality as a result of age, underlying condition, medication, ethnicity and/or socio-economic factors. When targeting defined sub-populations for food safety messages it is important to provide the public and clinicians with appropriate evidence in order to instil confidence in the devised strategy. This research indicates that there is added value in actively targeting such advice at a range of vulnerable groups other than white British pregnant women. Risk of disease by underlying condition and associated medication should be considered in conjunction with prevalence of underlying conditions and relative severity of outcome when prioritising groups. Additional vulnerable groups that need to receive appropriate food safety advice include those with cancers, liver disease, connective tissue disorders, the elderly and pregnant women whose first language is not English.

While, like all epidemiological studies, limitations exist for each study presented here, the repeated identification of certain high risk groups throughout this portfolio of published work provides robust and compelling evidence on which to base policy for targeting appropriate food safety messages to those most at risk of listeriosis and fatal outcome. In the current resource limited landscape of public spending, the British Government are implementing a focused campaign informed by the findings of this research and it is hoped that this will result in fewer vulnerable people contracting this severe, yet largely avoidable disease.

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Appendix 1. The published work

Disease presentation in relation to infection foci for non-pregnancy-associated human listeriosis in England and Wales, 2001 to 2007. *J Clin Microbiol.* 2009; 47: 3301-3307

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Disease Presentation in Relation to Infection Foci for Non-Pregnancy-Associated Human Listeriosis in England and Wales, 2001 to 2007▽

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Listeriosis is a rare but severe food-borne disease, affecting unborn or newly delivered infants, the elderly, and the immunocompromised. The epidemiology of listeriosis in England and Wales changed between 2001 and 2007, with more patients ≥60 years old presenting with bacteremia (but without central nervous system [CNS] involvement). In order to explain this increase and understand the altered disease presentation, clinical, microbiological, and seasonal data on bacteremic cases of *Listeria monocytogenes* infection identified through national surveillance were compared with those for patients with CNS infections. Logistic regression analysis was applied while controlling for age. Bacteremic patients, who presented more frequently with gastrointestinal symptoms, were more likely to have underlying medical conditions than CNS patients. This was most marked in patients with malignancies, particularly digestive organ malignancies. Treatment to reduce stomach acid secretion modified the effect of nonmalignant underlying conditions on outcome, i.e., patients with an underlying condition who were not taking acid-suppressing medication were equally likely to have a bacteremic or a CNS infection. However, this type of therapy did not modify the effect of malignancies on the likelihood of having a bacteremic or a CNS infection. The increase in the incidence of human listeriosis among patients ≥60 years old in England and Wales between 2001 and 2007 appears to have occurred in those with cancer or other conditions whose treatment included acid-suppressing medication. Therefore, this vulnerable patient group needs specific dietary advice on avoiding risk factors for listeriosis.

Listeria monocytogenes is an opportunistic bacterial pathogen that causes listeriosis and most often affects the immunocompromised, the elderly, pregnant woman, and their unborn or newly delivered infants. The disease is transmitted predominantly via contaminated food and is estimated to be the greatest cause of food-related deaths in the United Kingdom (7). A large outbreak of listeriosis, affecting mostly pregnant women and associated with the consumption of imported pâté, occurred in the United Kingdom in the late 1980s (16). Consequently, specific advice provided to pregnant women and immunocompromised individuals on foods to avoid in order to minimize the risk (Department of Health, Advice to vulnerable groups on pâté stands, press release 189/369, 1989; Department of Health and Social Security, Advice from the Chief Medical Officer: listeriosis and food, DHSS PL/CMO 89, 1989), has subsequently been reiterated and preferentially targeted at pregnant woman (Food Standards Agency, http://www.eatwell.gov.uk/agesandstages/pregnancy/?lang=en).

The epidemiology of listeriosis in England and Wales changed between 1990 and 2007 (9). The incidence almost doubled (an average of 191 cases were reported annually between 2001 and 2007 versus 110 between 1990 and 1999), with the increase occurring mainly among patients aged ≥60 years presenting with bacteremia in the absence of central nervous system (CNS) infection (Fig. 1). These changes are independent of recognized outbreaks, gender, season, ethnicity, socioeconomic status, region, or *L. monocytogenes* subtype and are not thought to be artifactual. Similar patterns have been reported subsequently in other European countries (4, 10).

The purpose of this study was to identify clinical and epidemiological factors that might explain this increased incidence and altered disease presentation by interrogating surveillance data for listeriosis cases reported in England and Wales between 2001 and 2007.

MATERIALS AND METHODS

Surveillance of listeriosis in England and Wales. The Health Protection Agency Centre for Infections coordinates the surveillance of listeriosis in England and Wales. Cases are ascertained by the voluntary electronic reporting of laboratory-diagnosed cases from microbiology laboratories (approximately 80% of instances), by the voluntary referral of cultures for identification and subtyping (approximately 80% of instances) (5, 19), or by both means (approximately 60% of instances). Epidemiological and microbiological data from the two systems are combined, deduplicated, and stored in a bespoke electronic database. Additional clinical data are sought from the consultant medical microbiologist responsible for each case, using a standard questionnaire (12) modified in 2005 to include symptom data.

Study population. Cases of listeriosis were defined as those with clinically compatible illnesses where *L. monocytogenes* was isolated from normally sterile sites, usually blood or cerebrospinal fluid. Pregnancy-associated cases (all maternal-fetal and neonatal patients) were not considered in this analysis. Non-pregnancy-associated cases (illness in patients >1 month old) were categorized further into those with CNS infections (isolation of *L. monocytogenes* from cerebrospinal fluid or brain tissue, clinical evidence of CNS infection, or both),

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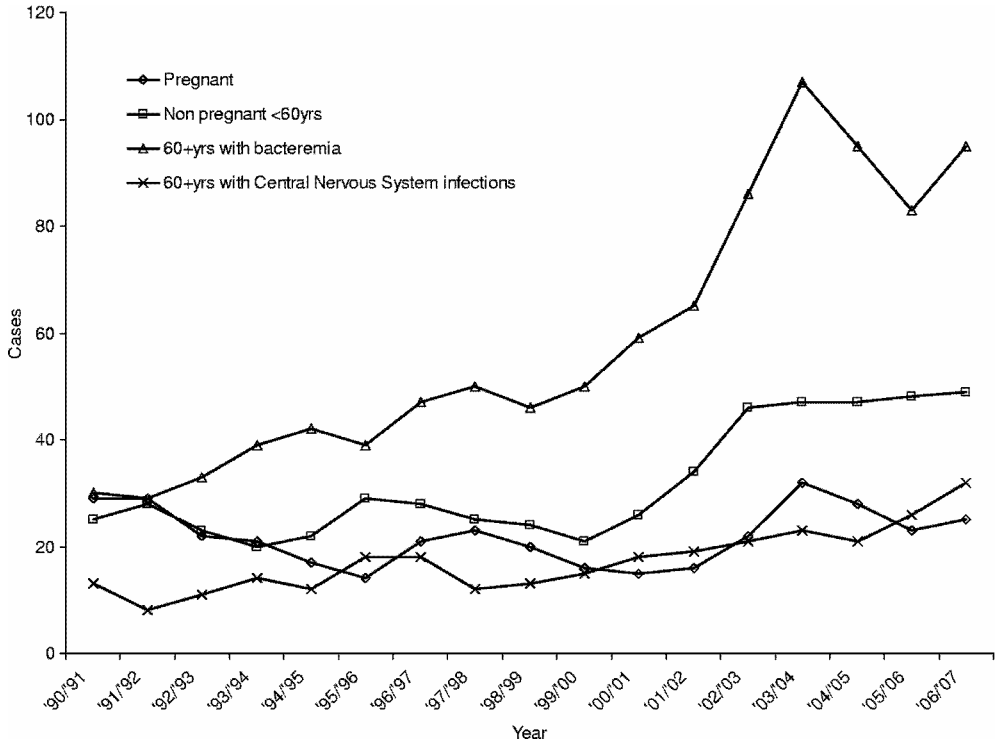

FIG. 1. Trends in human listeriosis in England and Wales, 1990 to 2007 (Health Protection Agency, unpublished data).

those with bacteremia in the absence of CNS infections (isolation of *L. monocytogenes* from blood but without microbiological or clinical evidence of CNS infection), and those with other conditions not included in these two categories.

Statistical analysis. Data manipulation and statistical analysis were undertaken using Stata, version 10, and were restricted to non-pregnancy-associated cases reported in England and Wales between 2001 and 2007, where a clinical questionnaire was returned and where the patient presented with a CNS infection or bacteremia. The descriptions of patients' underlying condition were grouped by two authors (I.A.G. and C.P.), and cancers were classed further according to the *International Statistical Classification of Diseases and Related Health Problems*, version 10 (22). More than one underlying condition can be reported for each patient. The study date was derived using onset and specimen dates as available (70% and 30%, respectively, with a median lag of 1 day between these dates [range, 0 to 33 days]). The season (winter [December to February], spring [March to May], summer [June to August], or autumn [September to November]) was defined using the study date. The lag time to clinical investigation was calculated from the date of onset to the date of the first specimen collection or the admission date as available, and these lag times were grouped as either as $\leq$1 day or $\geq$2 days, based on a median of 1 day (range, 0 to 28 days). Differences in proportions were assessed using the chi-square test and Fisher's exact test, and the nonparametric test was used for the comparison of medians. Individuals with missing data were omitted from the analyses involving those data.

An outcome variable was created to compare bacteremic infections with CNS infections, and single-variable analysis was initially used to investigate the associations between this outcome and the reported clinical features. Because the increase in the incidence of bacteremia occurred predominantly in patients aged $\geq$60 years, logistic regression was applied to calculate odds ratios (ORs), 95% confidence intervals (CIs), and significance tests while controlling for age. Variables associated with the outcome at a level of >90% (i.e., $P < 0.1$) were considered for further investigation. Logistic regression was applied to obtain maximum-likelihood estimates of the effect of exposures on the outcome while controlling for potential confounding factors. The model was simplified in a stepwise manner using the likelihood ratio test. Interactions between the factors included in multiple-variable analyses were investigated in the same way. Patient age was retained in the model throughout.

RESULTS

Reporting rates and mortality data. Clinical questionnaires were received for 925 of 1,167 non-pregnancy-associated listeriosis cases reported in England and Wales between 2001 and 2007 (79% response rate). The response rate was high (i.e., >70%) in each study year except 2004, when only 99 of 190 questionnaires were received (52% response). Data from this year were excluded from further analysis, giving an 85% response rate (826/977) for the remaining years. Twenty-seven cases (3%) reported during this time were linked to recognized clusters or outbreaks.

Bacteremia (693 cases) and CNS infections (224 cases) made up 94% of all cases; for the remaining 60 cases, either *L. monocytogenes* was isolated from other sites (ascitic fluid, joint aspirates, and other sites) (40 cases) or the cases could not be classified (20 cases). Questionnaire receipt was independent of age (means, 67 and 66 years) and gender (57% and 50% male; $P = 0.13$ by the χ^2 test), but questionnaires were received less frequently for bacteremic infections (571/693 [82%]) than for CNS infections (207/224 [93%]) ($P < 0.001$ by the χ^2 test). Among cases of bacteremic infection, questionnaire receipt was independent of age (means, 70 versus 67 years; $P = 0.06$ by the t test). Mortality data were available for 748/778 patients with clinical questionnaires (96%), and death rates were sim-

TABLE 1. Demographic, microbiological, and clinical factors associated with bacteremic and CNS infections for 780 cases of non-pregnancy-associated listeriosis in England and Wales, 2001 to 2003 and 2005 to 2007[a]

Parameter	No. (%) of cases		OR (95% CI)
	Bacteremia (n = 571)	CNS (n = 207)	
Gender			
Female	245 (43)	91 (44)	1.0
Male	326 (57)	116 (56)	1.1 (0.8–1.5)
Season			
Spring	123 (22)	52 (25)	1.0
Summer	192 (34)	66 (32)	1.3 (0.8–2)
Autumn	160 (28)	64 (31)	1.1 (0.7–1.8)
Winter	96 (17)	25 (12)	1.7 (0.9–2.9)
L. monocytogenes serotype			
4b	129 (23)	59 (29)	1.0
1/2a	75 (13)	26 (13)	1.4 (0.8–2.4)
1/2b	32 (6)	8 (4)	1.8 (0.8–4.2)
1/2c	13 (2)	3 (1)	2.2 (0.6–8.3)
Other/untyped	322 (56)	111 (54)	
Presentation lag			
≤1 day	228 (40)	97 (47)	1.0
≥2 days	182 (32)	81 (39)	1.0 (0.7–1.4)
Not known/recorded	161 (28)	29 (14)	
Presence or absence of underlying condition			
No underlying condition	53 (10)	50 (26)	1.0
Underlying conditions	489 (90)	146 (74)	3.1 (2.0–4.8)
Malignancies	241 (44)	57 (29)	1.8 (1.3–2.6)
Digestive organs	45 (19)[b]	2 (4)[b]	5.6 (1.3–23.9)[c]
Respiratory and intrathoracic	23 (10)[b]	5 (9)[b]	1.0 (0.4–2.9)[c]
Lymphoid, hematopoietic, and related tissue	95 (39)[b]	30 (53)[b]	0.6 (0.3–1.1)[c]
Breast	16 (7)[b]	6 (11)[b]	0.7 (0.3–1.9)[c]
Other known[d]	27 (11)[b]	9 (16)[b]	0.7 (0.3–1.6)[c]
Unknown[e]	33 (14)[b]	5 (9)[b]	1.6 (0.6–4.4)[c]
Postoperative	20 (4)	6 (4)	1.3 (0.5–3.4)
Renal	56 (11)	12 (8)	1.4 (0.7–2.7)
Diabetes	42 (9)	13 (9)	0.9 (0.5–1.7)
Liver	16 (3)	5 (3)	1.1 (0.4–2.9)
Autoimmune	81 (17)	31 (21)	0.8 (0.5–1.4)
Cardiovascular	79 (16)	26 (18)	0.7 (0.4–1.2)
Alcohol related	21 (4)	15 (10)	0.5 (0.2–0.99)
Other	59 (10)	24 (12)	0.7 (0.4–1.1)
Not known/recorded	29 (5)	11 (5)	
Immunosuppressive treatment			
No	341 (60)	132 (64)	1.0
Yes	92 (16)	36 (17)	1.3 (0.8–2.1)
Not known/recorded	138 (24)	39 (19)	
Cytotoxic drugs			
No	347 (61)	147 (71)	1.0
Yes	84 (15)	21 (10)	2.1 (1.2–3.6)
Not known/recorded	140 (25)	39 (19)	
Steroids			
No	297 (52)	113 (55)	1.0
Yes	133 (23)	55 (27)	1 (0.7–1.5)
Not known/recorded	141 (25)	39 (19)	
Treatment to reduce stomach acid secretion			
No	152 (27)	78 (38)	1.0
Yes	93 (16)	27 (13)	1.7 (1.04–2.9)
Not known/recorded	326 (57)	102 (49)	

[a] Single-variable logistic regression analysis controlling for age.
[b] As a proportion of all malignancies.
[c] In comparison to all other malignancies.
[d] Eye, brain, and other parts of the CNS; male genital organs; urinary tract; female genital organs; bone and articular cartilage; thyroid and other endocrine glands; lip, oral cavity, or pharynx; mesothelial and soft tissue.
[e] Ill-defined, secondary, and unspecified neoplasms, or those of uncertain or unknown behavior.

ilar for bacteremic infections (216/546 [40%]) and CNS infections (89/202 [44%]) within this group ($P = 0.27$ by the χ^2 test).

The ages of patients with bacteremia ranged from 3 to 102 years (median, 72 years; interquartile range, 61 to 80 years), while those of patients with CNS ranged from <1 year to 97 years (median, 65 years; interquartile range, 52 to 74 years)—a significant difference ($P < 0.001$). The single CNS patient less than 1 year old was a 57-day-old infant, and therefore the infection did not meet the criteria for being considered pregnancy associated. Within the bacteremic group where mortality data were available ($n = 546$), there was no difference between those aged <60 years and those aged ≥60 years with regard to mortality (36/109 [33%] versus 180/437 [41%], respectively; $P = 0.12$ by the χ^2 test). Where mortality data were available for CNS cases, however ($n = 202$), patients aged ≥60 years experienced higher mortality than those aged <60 years (71/132 [54%] versus 18/70 [26%]) ($P < 0.001$ by the χ^2 test).

Clinical features of bacteremic and CNS infections. On single-variable analysis controlling for age, bacteremic cases were no different from CNS cases in terms of gender, season, *L. monocytogenes* serotype, or lag period between the onset of symptoms and clinical investigation (Table 1). Bacteremic patients were more likely to have an underlying condition (most noticeably malignancies, and digestive-organ malignancies in particular) than CNS patients but were less likely to have alcohol-related conditions. Bacteremic patients were more likely to be treated with cytotoxic drugs or to receive treatment to reduce stomach acid secretion. There was no difference between bacteremic and CNS cases with regard to treatment with immunosuppressive drugs or steroids.

Initial multiple-variable logistic regression analysis ("model 1") revealed that the effect of alcohol-related conditions was no longer significant (OR, 1.5; 95% CI, 0.9 to 2.8; $P = 0.16$) when the analysis was controlled for all other nonmalignant underlying conditions (OR, 2.4; 95% CI, 1.4 to 4.0; $P < 0.001$) and for malignancies (OR, 3.0; 95% CI, 1.7 to 5.4; $P < 0.001$). Malignancies were examined further by comparing malignancies of the digestive organs with other "known" malignancies (i.e., excluding ill-defined, secondary, and unspecified neoplasms, or those of uncertain or unknown behavior) ("model 2"); both remained independently associated with the outcome when the analysis was controlled for nonmalignant underlying conditions and patient age (ORs, 17.0 [95% CI, 3.9 to 74.3; $P < 0.001$] and 3.0 [95% CI, 1.8 to 5.0; $P < 0.001$], respectively). When included in this model, neither the effect of cytotoxic drugs (OR, 1.6; 95% CI, 0.9 to 3.0; $P = 0.11$) nor treatment to reduce stomach acid secretion (OR, 1.4; 95% CI, 0.8 to 2.4; $P = 0.23$) remained significant. However, the latter interacted significantly with malignancies, and therefore its effect on each stratum was investigated further ("model 3") (Table 2). Treatment to reduce stomach acid secretion modified the effect of nonmalignant underlying conditions on the outcome of interest, in so far as patients who had an underlying condition but did not have treatment to reduce stomach acid secretion were equally likely to have a bacteremic or a CNS infection. However, treatment to reduce stomach acid secretion did not modify the effect of malignancies on the likelihood of having a bacteremic or a CNS infection.

Symptoms and signs of *L. monocytogenes* bacteremic and CNS infections (2005 onward). Fever was the single most common symptom reported by both patient groups (77% and 83% for bacteremic and CNS infections, respectively [Fig. 2]). Bacteremic patients were more likely to experience abdominal pain, respiratory or cardiovascular symptoms, and diarrhea. Patients with CNS infections were more likely to have headache, confusion, impaired consciousness, nuchal rigidity, seizures, and myoclonus. Logistic regression analysis revealed that the associations with abdominal pain, diarrhea, respiratory or cardiovascular symptoms, nuchal rigidity, and seizures remained independently significant when the analysis was controlled for underlying conditions and malignancies as described above ("model 2").

Reported mortality for bacteremia patients who experienced abdominal pain, nausea, or diarrhea did not differ from that for patients who did not report these symptoms (Table 3). The same was observed for CNS patients, although lower numbers were available for comparison.

TABLE 2. Clinical factors associated with bacteremia and CNS infections for non-pregnancy-associated listeriosis in England and Wales, 2001 to 2003 and 2005 to 2007[a]

Underlying condition	Treatment to reduce stomach acid secretion	OR (95% CI)
None		1
Nonmalignant underlying condition	No	1.5 (0.8–2.7)
	Yes	3.2 (1.5–6.6)
	Not known/recorded	3.4 (2.0–5.8)
Known nondigestive malignancy[b]	No	3.1 (1.5–6.4)
	Yes	2.5 (1.1–5.8)
	Not known/recorded	3 (1.7–5.5)
Malignancy of the digestive organs	All[c]	16.7 (3.8–73)

[a] Final multiple-variable logistic regression analysis controlling for age.
[b] Respiratory and intrathoracic; lymphoid, hematopoietic, and related tissue; breast; eye, brain, and other parts of the CNS; male genital organs; urinary tract; female genital organs; bone and articular cartilage; thyroid and other endocrine glands; lip, oral cavity, or pharynx; mesothelial and soft tissue.
[c] Numbers of patients were insufficient for stratification by status of treatment to reduce stomach acid secretion.

DISCUSSION

This study highlights hitherto unrecognized differences between the clinical presentations of *L. monocytogenes* infections in England and Wales. In the absence of point source exposures, it is impossible to measure the incubation period in individuals, but these data suggest that disease presentation occurs contemporaneously for bacteremic and CNS infections. Given this, the CNS infection is unlikely to be a sequela of bacteremia for most patients in this study population. While it is acknowledged that less severe presentations of the disease (e.g., influenza-like illness or gastrointestinal disturbance) might be underreported, this study suggests that the severity of disease for patients who experienced gastrointestinal symptoms was similar to that for patients who did not.

Bacteremic patients were more likely to have underlying conditions than those with CNS infections, and specific malignancies (especially digestive-organ malignancies) were especially prevalent in the bacteremia group. The former observa-

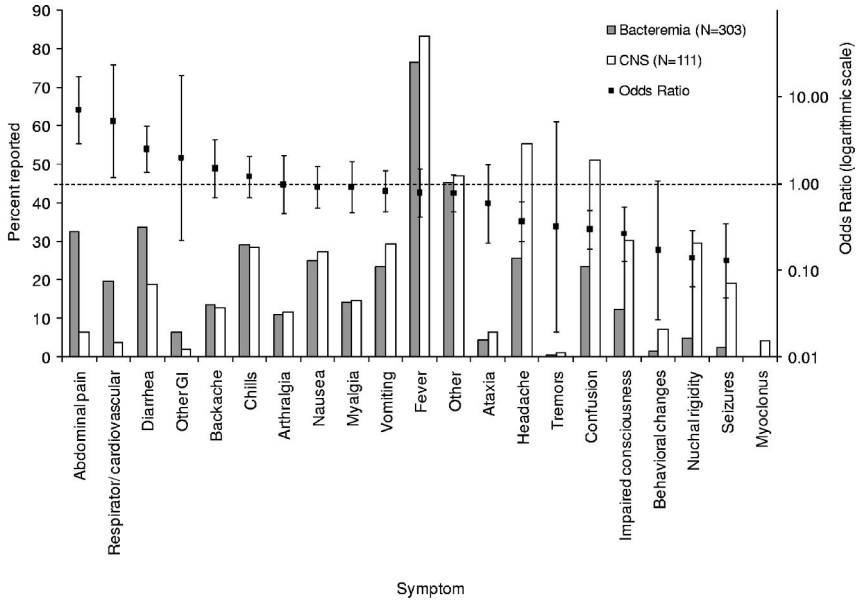

FIG. 2. Reported symptoms for non-pregnancy-associated *L. monocytogenes* bacteremic and CNS infections in England and Wales, 2005 to 2007.

tion concurs with Danish (8) and French (11) studies of listeriosis mortality, while the latter concurs with previous United Kingdom (15) and French (11) studies, and with more-recent findings from France (10), although leukemic patients predominated in the latter French study. The disparity in presentation by underlying pathology might reflect the degree of medical surveillance, the rapidity of onset, or the severity of infection in this patient group, since bacteremia in previously healthy individuals will be recognized only under unusual circumstances when blood cultures are collected (e.g., during outbreaks [2]), or when the disease is of high severity.

The higher prevalence of gastrointestinal symptoms in the bacteremia group is of note. It is not clear, however, if these symptoms result from the listeriosis, pathogenicity changes in the microorganism, another infectious agent, or patients' concurrent pathologies or treatments. Not all *L. monocytogenes* strains can cause gastrointestinal disturbance (2, 14), and since the current increase is caused by many different strains (9), it is unlikely that a single genetic change in *L. monocytogenes* has occurred. It has been suggested previously that another infectious or toxic agent leads to increased susceptibility to *L. monocytogenes* infection (21). Surveillance data from England and Wales provide little evidence for this: of 614 cases of *L. monocytogenes* infection reported electronically between 2004 and 2007, none had a reported gastrointestinal coinfection as part of the listerial episode or an antecedent gastrointestinal infection in the previous 90 days (I. A. Gillespie, unpublished observations). Many enteric pathogens are underdiagnosed in fecal specimens (1), however, and feces from listeriosis cases are rarely investigated; hence, a gastrointestinal coinfection

TABLE 3. Reported mortality among patients with *L. monocytogenes* bacteremic and CNS infections experiencing selected gastrointestinal symptoms

Symptom	Bacteremia		*P*	CNS		*P*
	No. (%) of patients who:			No. (%) of patients who:		
	Died	Survived		Died	Survived	
Abdominal pain						
Yes	28 (35)	52 (65)	0.65	1 (17)	5 (83.3)	0.21
No	62 (38)	101 (62)		37 (43)	50 (57.5)	
Nausea						
Yes	19 (31)	42 (68.9)	0.24	9 (36)	16 (64)	0.56
No	72 (40)	110 (60)		29 (43)	39 (57.4)	
Diarrhea						
Yes	25 (30)	58 (70)	0.10	8 (44)	10 (55.6)	0.70
No	66 (41)	95 (59)		30 (40)	46 (61)	

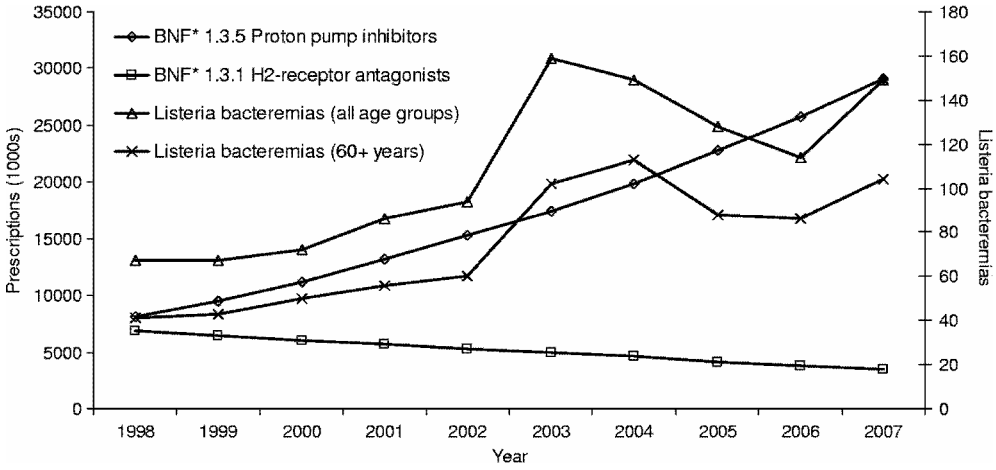

FIG. 3. Reported non-pregnancy-associated *Listeria monocytogenes* bacteremic infections in relation to prescribed proton pump inhibitors and H2 receptor antagonists, England, 1998 to 2007. (Prescription data are unpublished data from the Prescription Prescribing Authority.) BNF, British National Formulary.

would be detected less frequently in this patient group. Finally, existing pathologies (or their treatments) may alter the alimentary canal in such a way as to predispose to gastrointestinal symptoms, which may or may not have an infectious etiology. Such phenomena might explain the observed association between digestive-organ cancers and the group experiencing more gastrointestinal symptoms.

In comparison to patients' underlying conditions, information on patients' treatments was reported less frequently, and steps are required to improve the completeness of this information in routine national surveillance of listeriosis. Nevertheless, the observed associations with patient treatments warrant further comment. The association between cytotoxic drug use and bacteremia is perhaps unsurprising given the association with malignancies described above. This effect diminished when malignancies were controlled for, suggesting either that, in this instance, the malignancy is more important than the treatment itself, that a wide variety of cytotoxic treatments was described, or that missing data played a part.

Treatment to reduce stomach acid secretion was associated with bacteremic infections on single-variable analysis and modified the effect of underlying conditions on logistic regression analysis, missing data aside. Stomach acid inhibitors are used to treat a variety of conditions (13), but this drug class increases the risk of acquiring *Campylobacter*, *Giardia*, and *Salmonella* species infections (3, 17, 18) and increases susceptibility to listeriosis in animal models (20). Furthermore, the incidence of *L. monocytogenes* bacteremia in England closely mirrors overall prescribing patterns for proton pump inhibitors in England (Fig. 3); the number of such prescriptions increased by 257% between 1998 and 2007. Further work to investigate the role of proton pump inhibitors in human listeriosis is required. If an effective stomach acid barrier is absent, however, lower *L. monocytogenes* levels in foods may increase the likelihood of infection, and efforts should be made to reduce the exposure of vulnerable groups. The current European legal limit for *L. monocytogenes* in ready-to-eat foods not intended for infants or for special medical purposes ($\leq$100 CFU/g during shelf life [6]) may not be stringent enough to reduce the risk of infection to acceptable levels for those undergoing therapy to reduce stomach acid secretion.

Patients with CNS infections had fewer underlying conditions than the bacteremia group and presented with various neurological symptoms. The comparative lack of gastrointestinal symptoms in the CNS group suggests that the initial stages of the disease process in the alimentary tract might differ from those for the bacteremia group.

In conclusion, the increase in the incidence of *L. monocytogenes* bacteremia among people aged $\geq$60 years in England and Wales between 2001 and 2007 appears to relate to patients with cancer and, to a lesser extent, to patients with other conditions whose treatment leads to stomach acid suppression. Individuals are living longer with chronic conditions requiring immunocompromising treatments; hence, the population at risk of developing infections with opportunistic pathogens such as *L. monocytogenes* is increasing. Cancer cases represent a large proportion of listeriosis cases in England and Wales; therefore, the provision of targeted food safety advice to this group prior to, during, and after treatment might reduce the impact of subsequent infection. National surveillance of listeriosis in England and Wales must capture information on patients' treatments, in addition to their underlying pathologies, more effectively.

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Concurrent Conditions and Human Listeriosis, England and Wales, 1999–2009. *Emerg Infect Dis.* 2011; 17: 38-43

Concurrent Conditions and Human Listeriosis, England, 1999–2009

Piers Mook, Sarah J. O'Brien, and Iain A. Gillespie

The epidemiology of listeriosis in England and Wales changed during 2001–2008; more patients ≥60 years of age had bacteremia than in previous years. To investigate these changes, we calculated risk for listeriosis by concurrent condition for non–pregnancy-associated listeriosis cases reported to the national surveillance system in England during 1999–2009. Conditions occurring with *L. monocytogenes* infection were coded according to the International Classification of Diseases, 10th Revision, and compared with appropriate hospital episode statistics inpatient denominator data to calculate incidence rates/million consultations. Malignancies (especially of the blood), kidney disease, liver disease, diabetes, alcoholism, and age ≥60 years were associated with an increased risk for listeriosis. Physicians should consider a diagnosis of listeriosis when treating patients who have concurrent conditions. Providing cancer patients, who accounted for one third of cases, with food safety information might help limit additional cases.

Listeriosis is a rare but serious foodborne disease caused by the bacterium *Listeria monocytogenes*. Three groups of persons are disproportionately affected: the elderly, the immunocompromised, and pregnant women and their unborn or newborn infants. The clinical signs of disease in these persons include septicemia, meningitis, and miscarriage. Pregnant women can transmit the infection to the fetus, for whom the result can be deadly. However, these women may not have clearly overt signs or symptoms of infection. Case-fatality rates range from 20% to 50% (*1*). The susceptibility of healthy persons to symptomatic listeriosis is substantially less than that of persons with underlying conditions.

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Persons with cancer, diabetes, AIDS, and liver or kidney disease are often predisposed to severe infection and death after infection with *L. monocytogenes*. This predisposition is a consequence of suppressed T-cell–mediated immunity (*2*) caused by the condition or its treatment. Similarly, pregnant women, the elderly, and those receiving immunosuppressive therapy are also at risk because of impaired or modulated immune function.

The epidemiology of listeriosis in England and Wales has changed since 2001 (*3*). Incidence has increased (2.1 cases/million population during 1990–2000 vs. 3.6 cases/million population during 2001–2009), and more cases have been found in persons ≥60 years of age who had bacteremia (but not meningitis). Similar patterns have been reported in other countries in Europe (*4–6*). The reasons for these changes are not fully understood, but they do not seem to be caused by surveillance artifacts and are not associated with sex, season, geography, ethnic or socioeconomic differences, underlying conditions, or *L. monocytogenes* subtype (*3*). We have showed that the increase occurred in persons with cancer or other conditions whose treatment included acid-suppressing medication (*7*). In view of recent trends, we examined national surveillance data for England to quantify the role of concurrent conditions in persons with listeriosis and stratified these conditions to examine risks for persons ≥60 years of age.

Methods

The Health Protection Agency Centre for Infections has coordinated national surveillance of listeriosis in England and Wales since 1990. Cases are included in the system by voluntary referral of cultures to the national reference laboratory or by electronic reporting of confirmed cases from local laboratories. Clinical data, including details of patients' concurrent conditions, are subsequently sought from the consultant clinical microbiologist involved in the

care of the case-patient. Microbiologic data from local and reference laboratories and clinical and risk factor data are linked for each case, deduplicated as necessary, and stored in a bespoke Microsoft Access database (Microsoft, Redmond, WA, USA) Access database.

A case of listeriosis is defined as a person with clinically compatible illness and from whom *L. monocytogenes* was isolated from a normally sterile site. Cases are subsequently classified as either non–pregnancy-associated (persons >1 month of age) or pregnancy-associated (a maternal–fetal or maternal–neonatal pair; such pairs were considered a single case). In this study, we included non–pregnancy-associated cases reported from laboratories in England for which a clinical questionnaire was available and showed that at least 1 reported concurrent condition was present. We included cases reported during April 1, 1999–March 31, 2009 because denominator data were arranged by fiscal years. These cases included sporadic cases and cases that were identified as being part of common source foodborne outbreaks.

Authors (P.M. and I.A.G.) reviewed each reported concurrent condition and assigned an International Classification of Diseases, 10th Revision (ICD-10) (*8*) code when appropriate. Rules for assigning codes were developed at the outset to ensure standardized coding throughout the study (online Technical Appendix, www.cdc.gov/EID/content/17/1/38-Techapp.pdf). These rules were validated by a third author (S.J.O.), a clinically qualified investigator, who also reviewed any coding disparities. Counts were calculated of all persons and those ≥60 years of age for each ICD-10 chapter (ICD-10 codes are aggregated into 22 chapters) and subgroup (within each chapter).

Hospital episode statistics finished consultant episodes (FCE) data, which were aggregated by ICD-10 code, age group (0–14 years, 15–59 years, 60–74 years, and ≥75 years), and fiscal year, were obtained from the Health and Social Care Information Centre (*9*) and used as denominator data. These data describe episodes of continuous admitted patient care under a specific consultant for National Health Service hospital inpatients in England, and a primary diagnosis is assigned to each episode by using ICD-10 coding. To ensure reliable confidence intervals (CIs), we calculated incidence rates/million FCEs and 95% CIs for each ICD-10 chapter and subgroup in which there were ≥10 cases. Two ICD-10 chapters not used by hospital episodes statistics to code primary diagnoses, external causes of morbidity and mortality (V01–Y98) and codes for special purposes (U00–U99), were not considered. Relative risks (RRs) and corresponding 95% CIs were calculated as appropriate when ≥10 cases were reported for a concurrent condition subgroup or chapter. Analysis was then repeated for case-patients ≥60 years of age.

Data were stored, manipulated, and summarized by using Microsoft Access, and incidence rates and RRs were calculated by using Microsoft Excel. Differences in proportions and changes in proportions over strata were assessed by using the χ^2 test and the χ^2 test for trend, respectively.

Results

A total of 1,239 ICD-10–coded concurrent conditions were reported by 1,413 case-patients with non–pregnancy-associated listeriosis in England during April 1, 1999–March 31, 2009 (Figure). Of those patients who reported ≥1 underlying condition, 21 (2.2%) were identified as being part of a common source outbreak. Characteristics of case-patients with and without a completed clinical questionnaire are shown in Table 1. Overall, 9.1 cases of listeriosis/million FCEs were reported over the study period (95% CI 8.6–9.6) (online Appendix Table, www.cdc.gov/EID/content/17/2/38-appT.htm). Compared with all other reported conditions, higher rates of disease were reported for the following chapters (in order of highest to lowest RR): endocrine, nutritional, and metabolic diseases (RR 5.3, 95% CI 4.2–6.6); neoplasms (RR 4.9, 95% CI 4.4–5.5); mental and behavior disorders (RR 3.1, 95% CI 2.4–4.1); diseases of the circulatory system (RR 1.4, 95% CI 1.2–1.6); diseases of the digestive system (RR 1.3, 95% CI 1.1–1.5); and diseases of the musculoskeletal system and connective tissue (RR 1.3, 95% CI 1.1–1.6) (Table 2).

Within these chapters, only certain subgroups showed increased rates: diabetes mellitus; malignant neoplasms of the lymphoid, hematopoietic, and related tissues; eye, brain, and other parts of the central nervous system (CNS); respiratory and intrathoracic organs; digestive organs; breast; male and female genital organs; thyroid and other endo-

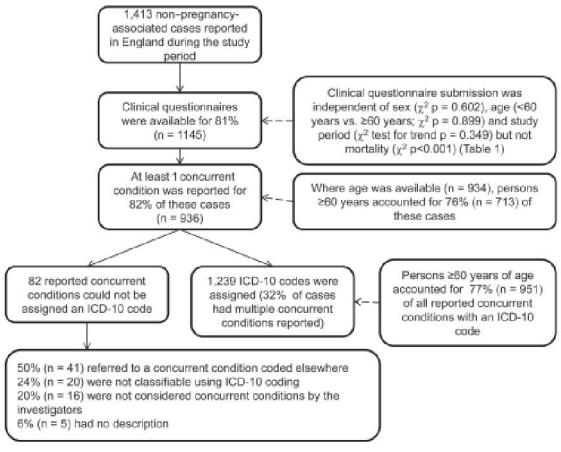

Figure. Study population and reported International Classification of Diseases, 10th Revision (ICD-10)–coded concurrent conditions for 1,413 case-patients with non–pregnancy-associated listeriosis, England, April 1, 1999–March 31, 2009.

Table 1. Characteristics of case-patients with non–pregnancy-associated listeriosis, England, 1999–2009*

Characteristic	No. (%) case-patients	
	CQR, n = 1,145	No CQR, n = 268
Fiscal years		
1999–2000 and 2000–2001	133 (85.3)	23 (14.7)
2001–2002 and 2002–2003	229 (89.8)	26 (10.2)
2003–2004 and 2004–2005	228 (63.9)	129 (36.1)
2005–2006 and 2006–2007	253 (81.1)	59 (18.9)
2007–2008 and 2008–2009	302 (90.7)	31 (9.3)
Sex		
M	642 (56.1)	145 (54.1)
F	503 (43.9)	122 (45.5)
Unknown	0	1 (0.4)
Age group, y		
<60	277 (24.2)	63 (23.5)
≥60	866 (75.6)	193 (72)
Unknown	2 (0.2)	12 (4.5)
Status		
Died	445 (38.9)	25 (9.3)
Did not die	664 (58)	159 (59.3)
Unknown	36 (3.1)	84 (31.3)

*CQR, clinical questionnaire received.

crine glands; mental and behavior disorders caused by psychoactive substances (alcohol-related in 96% of reports); hypertensive diseases, other forms of heart disease, and diseases of arteries, arterioles, and capillaries; diseases of the liver and noninfective enteritis and colitis; and systemic connective tissue disorders (Table 2). In addition, several subgroups were associated with increased risk even when the corresponding chapter was not: renal failure, diseases of blood and blood-forming organs, and chronic lower respiratory diseases (Table 2).

Concurrent conditions were disproportionately reported for persons ≥60 years of age (χ^2 $p<0.001$), and the rate of listeriosis for this age group (16.8/million; 95% CI 15.8–17.9) was significantly higher than that for younger persons (RR 4.6, 95% CI 4.1–5.3) (Table 2). When the RR for each chapter for persons ≥60 years of age (using persons <60 years of age as the reference population) was calculated, the following were associated with increased risk: endocrine, nutritional and metabolic diseases; genitourinary system diseases; diseases of the musculoskeletal system and connective tissue; neoplasms; certain infectious and parasitic diseases; diseases of the digestive system; and mental and behavior disorders (Table 2). In instances where the risk for each subgroup in persons ≥60 years of age could be calculated and compared with that for persons <60 years of age, all subgroups of previously identified chapters were associated with increased risk.

Discussion

We analyzed surveillance data that included detailed denominator data by using an internationally recognized diagnostic classification system and found that a wide variety of conditions seem to increase the risk for serious infection with *L. monocytogenes*. Malignancies accounted for more than one third of conditions, and cancer patients had a 5-fold increased risk for development of listeriosis. Cancers of the blood seemed to have the greatest effect. Other high-risk conditions included diabetes mellitus; alcoholism; certain diseases of the circulatory system and the musculoskeletal system and connective tissue; noninfective enteritis and colitis; and diseases of the liver and kidney. For most high-risk conditions, the risk for infection was higher among older patients.

Case identified by the national surveillance program in England are laboratory confirmed, and most cases result in serious illness requiring hospitalization or death. Given this finding, a hospitalized population better represents the population at risk than a community population, which was used in previous studies (*10,11*).

The response rate to the clinical questionnaire that captured information on concurrent conditions was high and not influenced by age or sex of the case-patient, which minimized differential ascertainment of clinical data. However, we could not assess concurrent conditions for which completed clinical questionnaires were not returned. This issue indicates that the role of some conditions might be underestimated if clinicians were unwilling to return questionnaires and disclose information for certain case-patients (e.g., those with AIDS). Similarly, but less likely, reporting bias might exist if the propensity to report certain concurrent conditions were affected by the presence or absence of others conditions, or if only concurrent conditions considered relevant to *L. monocytogenes* infection were reported. Concurrent conditions were reported by the clinical microbiologist rather than by the consultants responsible for the care of the patients with concurrent conditions. These consultants might be better informed of existing concurrent conditions. However, hospital microbiologists need to be aware of such conditions to provide treatment accordingly, and questioning several consultants for each case-patient may have a negative effect on questionnaire response because questionnaires might be lost if passed between multiple consultants.

Misclassification was minimized by grouping conditions only to 3-character ICD-10 code levels. Although we acknowledge that such grouping might mask high-risk conditions apparent at the 4-character ICD-10 code level, routine surveillance data were not specific enough to further discriminate among conditions. In some instances, in which treatments were reported in the absence of relevant conditions (e.g., chemotherapy, dialysis, splenectomy), we made assumptions about the conditions requiring such treatment and coded accordingly (online Technical Appendix). Although these assumptions could inflate the inci-

dence rates for certain conditions, they occurred relatively infrequently and were not used for treatments that could be prescribed for a range of conditions (e.g., broad-spectrum antimicrobial drugs).

Table 2. Relative risks for ICD-10 conditions for case-patients with non–pregnancy-associated listeriosis, England, 1999–2009*

Chapter and subgroup (code)	Relative risk (95% CI)	
	Versus other conditions	Age ≥60 y vs. <60 y
Certain infectious and parasitic diseases (A00–B99)	1.3 (0.9–2.0)	2.5 (1.1–5.9)
Neoplasms (C00-D48)	4.9 (4.4–5.5)	2.9 (2.3–3.6)
Digestive organs (C15–C26)	3.1 (2.4–3.9)	NC
Respiratory and intrathoracic organs (C30–C39)	4.8 (3.5–6.5)	NC
Breast (C50)	2.9 [2.1–4.1)	2.6 (1.4–5.2)
Female genital organs (C51–C58)	1.9 (1.07–3.5)	NC
Male genital organs (C60–C63)	2.9 (1.7–5.1)	NC
Eye, brain, and other parts of central nervous system (C69–C72)	7.3 (4.2–12.7)	NC
Thyroid and other endocrine glands (C73–C80, C97)	2.7 (2.0–3.6)	3.2 (1.6–6.4)
Lymphoid, hematopoietic, and related tissues (C81–C96)	17.6 (15.1–20.6)	2.8 (2.0–3.9)
In situ and benign neoplasms and others of uncertainty D00–D48)	0.7 (0.4–1.1)	NC
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50–D89)	1.3 (0.9–2.0)	0.8 (0.4–1.8)
Anemias (D50–D64)	1.0 (0.6–1.7)	NC
Diseases of blood and blood-forming organs (D65–D89)	2.3 (1.3–4.0)	NC
Endocrine, nutritional and metabolic diseases (E00–E90)	5.3 (4.2–6.6)	6.3 (3.5–11.2)
Diabetes mellitus (E10–E14)	11.4 (9.0–14.5)	4.9 (2.7–8.8)
Mental and behavior disorders (F00–F99)	3.1 (2.4–4.1)	1.7 (1.01–2.8)
Due to psychoactive substance (F10–F19)	12.3 (9.4–16.1)	4.7 (2.7–8.1)
Diseases of the nervous system (G00–G99)	0.6 (0.4–1.0)	NC
Diseases of the eye and adnexa (H00–H59)	NC	NC
Diseases of the ear and mastoid process (H60–H95)	NC	NC
Diseases of the circulatory system (I00–I99)	1.4 (1.2–1.6)	NC
Hypertensive diseases (I10–I15)	8.0 (5.2–12.2)	NC
Ischemic heart diseases (I20–I25)	0.8 (0.5–1.1)	NC
Other forms of heart disease (I30–I52)	2.4 (1.9–3.1)	NC
Cerebrovascular diseases (I60–I69)	0.7 (0.4–1.2)	NC
Diseases of arteries, arterioles, and capillaries (I70–I79)	2.1 (1.2–3.5)	NC
Diseases of the respiratory system (J00–J99)	0.9 (0.7–1.1)	NC
Chronic lower respiratory diseases (J40–J47)	1.8 (1.3–2.5)	NC
Other diseases of respiratory system (J80–J99)	1.7 (0.95–3.1)	NC
Diseases of the digestive system (K00–K93)	1.3 (1.1–1.5)	1.9 (1.4–2.6)
Noninfective enteritis and colitis (K50–K52)	4.3 (3.3–5.6)	2.3 (1.4–3.8)
Other diseases of intestines (K55–K63)	0.5 (0.3–0.9)	NC
Diseases of liver (K70–K77)	22.4 (17.7–28.4)	2.2 (1.4–3.6)
Diseases of the skin and subcutaneous tissue (L00–L99)	NC	NC
Diseases of the musculoskeletal system and connective tissue (M00–M99)	1.3 (1.1–1.6)	4.5 (2.7–7.3)
Arthropathies (M00–M25)	1.7 (1.3–2.2)	NC
Systemic connective tissue disorders (M30–M36)	18.3 (12.6–26.6)	NC
Diseases of the genitourinary system (N00–N99)	1.2 (0.99–1.5)	5.3 (3.2–8.6)
Renal failure (N17–N19)	12.2 (9.8–15.1)	1.7 (1.02–2.7)
Pregnancy, childbirth, and puerperium (O00–O99)	NC	NC
Certain conditions originating in the perinatal period (P00–P96)	NC	NC
Congenital malformations, deformations, and chromosomal abnormalities (Q00–Q99)	NC	NC
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	NC	NC
Injury, poisoning, and certain other consequences of external causes (S00–T98)	NC	NC
External causes of morbidity and mortality (V01–Y98)	–	–
Factors influencing health status and contact with health services (Z00–Z99)	NC	NC
Codes for special purposes (U00–U99)	–	–
Total	NC	4.6 (4.1–5.3)

*ICD-10, International Classification of Diseases, 10th Revision; CI, confidence interval; NC, not calculated (for conditions with <10 cases); –, data not available.

Because only single-variable analysis could be performed, we could not assess the extent to which concurrent conditions were correlated, which led to the potential for uncontrolled confounding. Such method limitations might explain the high incidence associated with both diabetes and kidney disease and reinforce the need to consider these findings as highly refined hypotheses to be tested by other methods (*12*).

To our knowledge, few studies have attempted to quantify the risk for listeriosis by patient concurrent conditions. As part of a risk assessment of *L. monocytogenes* in ready-to-eat foods, researchers from the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) calculated the relative susceptibility to listeriosis for certain conditions (*10*). Furthermore, risk levels for listeriosis by predisposing condition in Denmark have also been estimated (*11*). Despite differences in methods between those studies and our study, several high-risk conditions were also identified in those studies: malignancies (most notably those of the blood), kidney disease (recorded as dialysis [*10*] and renal transplant [*11*]), diabetes, alcoholism, and increased age in all 3 studies; liver disease and pulmonary cancer in the WHO/FAO study and our study; and systemic lupus erythematosus in the study in Denmark and our study (as systemic connective tissue disorders). Such commonality would seemingly validate our estimates.

The absence of AIDS as a high-risk condition in our study and its presence in both previous studies (*10,11*), might reflect improved treatment for HIV infection that prevents AIDS and, consequently, *L. monocytogenes* infection (*13*) or highlight a reporting bias by the consultant microbiologist. A general transplantation status, identified as a condition leading to the highest relative susceptibility in the WHO/FAO study, was not coded in our study because it is a treatment. Noninfective enteritis and colitis and certain diseases of the circulatory system were identified as additional high-risk conditions in our study but not in the previous studies. These additional conditions might be the result of improved accuracy, use of ICD-10 coding and a hospitalized reference population instead of the general population, different susceptibility calculations, or changes in the prevalence of certain conditions in the interim period (the previous studies used data from 1992 [*10*] and 1989–1990 [*11*]). However, we acknowledge that links between these conditions and listeriosis have been reported (*14–18*).

With these caveats in mind, our findings have implications for clinical practice and food safety policy makers. The number and diversity of conditions that appear to increase the risk for listeriosis imply that physicians working in all specialties should consider listeriosis when treating patients with concurrent conditions and provide appropriate food safety advice. Similarly, current UK government food safety advice on avoidance of listeriosis, which is delivered passively and is specific mainly for pregnant women (*19,20*), should be communicated actively to all high-risk groups. In prioritizing advice, policy makers should consider not only the associated risk but also the prevalence of the concurrent condition. Cancer patients accounted for more than one third of listeriosis cases, and high risks were observed for most cancer subgroups. Because we are not aware of any appropriate food safety advice that is tailored specifically for cancer patients in the UK, emphasis on this group might help to prevent further cases.

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Concurrent Conditions and Human Listeriosis, England and Wales, 1999–2009

Technical Appendix

Coding Rules for Concurrent Conditions in Human Listeriosis, England and Wales, 1999–2009*

General Points

International Classification of Diseases, 10th Revision (ICD-10) codes assigned to the 3 character level (but analyses were limited to the subgroup level only).

Age has not been considered for coding unless stated in the open text underlying condition field.

Conditions were only presumed to be congenital if stated as such (see above point).

Conditions were presumed to be chronic if they could be either chronic or acute but were not described as either.

Symptoms of a condition were not coded (encephalitis, septicemia, cough).

Alcohol-related Pathologic Changes

Underlying conditions such as alcoholic, alcoholism, alcohol problem were assigned as mental or behavior diseases because of use of alcohol (ICD-10 code F10).

Conditions coded as alcoholic liver disease (K70) were, in addition, coded as mental or behavior diseases because of use of alcohol (F10).

In the absence of alcoholic, liver cirrhosis or failure was coded as fibrosis and cirrhosis of liver (K74) or other diseases of the liver (K76).

Malignancies

Cancer of the bowel was coded as malignant neoplasm of colon (C18).

Underlying conditions described as metastases, malignant tumor, cancer, cancerous growth have been coded as malignant neoplasm without specification of site (C80).

Only the primary cancer site was coded unless there was mention of a secondary site and no mention of the primary site.

Neutropenia, without any description of cause, was kept as a condition and coded as agranulocytosis (D70).

If a case with a defined malignancy was also described as being neutropenic, agranulocytosis was not coded.

Chemotherapy without any description of a malignancy or other condition was coded as malignant neoplasm without specification of site (C80).

The assumption was made that bone marrow transplant would most likely be a treatment for malignancies of the blood and, thus, in the absence of any other described conditions, was coded as other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue (C96).

Other Chronic Diseases

Ischemic heart disease was coded as chronic ischemic heart disease (I25) unless stated otherwise. Following on from the general presumption that conditions are chronic if not stated otherwise.

Nonspecified heart disease was coded as complications and ill-defined descriptions of heart disease (I51).

Any treatments or indications of heart disease (valve replacement, fibrillations) were coded as complications and ill-defined descriptions of heart disease (I51). However, they were only coded if there was no other mention (and coding) of heart disease.

Unspecified sinusitis was presumed to be chronic sinusitis (J32).

Hepatitis B and C were coded as chronic viral hepatitis (B18) if they were not defined as acute or chronic. Unspecified and autoimmune hepatitis was coded as other inflammatory liver diseases (K75).

Renal impairment was coded as chronic renal failure (N18).

Pyelonephritis was coded as acute tubulointerstitial nephritis (N10).

Miscellaneous

Dialysis was coded as chronic renal failure (N18) because it is a condition for which dialysis is a treatment.

Although there is a causal link between renal failure and diabetes, they were coded if they were described.

Tuberculosis was assumed to be bacteriologically and microbiologically confirmed (A15).

Nonspecified anemia was coded as other anemia (D64), aplastic anemia and acquired pure erythrocyte anemia were coded as acquired pure erythrocyte aplasia (erythroblastopenia) (D60), iron deficiency anemia was coded as iron deficiency anemia (D50), and auto immune hemolytic anemia was coded as acquired hemolytic anemia (D59).

Unspecified osteoporosis was coded as osteoporosis, without fracture (M81).

Cerebrovascular accident was coded as stroke, not specified as hemorrhage or infarction (I64).

Hypertension was coded as essential (primary) hypertension (I10).

Splenectomy was coded as diseases of spleen (D73).

If splenectomy and lymphoma were described, diseases of spleen (D73) were not coded.

Lupus was coded as systemic lupus erythematosus (M32).

Chest infection (lower respiratory tract infection and bronchitis) was coded as unspecified chronic bronchitis (J42) if qualified as being chronic or bronchitis, not specified as acute or chronic (J40) if it was not further qualified.

Ascites and jaundice were coded as other diseases of the liver (K76).

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Research

Concurrent Conditions and Human Listeriosis, England, 1999–2009

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Main Article

Table A1

ICD-10 diagnosis codes for concurrent conditions among patients with non–pregnancy-associated listeriosis, showing rate of identification/FCE for each condition and comparison of all patients with patients ≥60 years of age, England, 1999–2009*

	All patients			Patient age ≥60 y		
Chapter and subgroup (code)	**No. cases**	**FCE**	**No. cases/million FCE (95% CI)**	**No. cases**	**FCE**	**No. cases/million FCE (95% CI)**
Certain infectious and parasitic diseases (A00–B99)	21	175,8220	11.9 (7.39–18.3)	10	467,930	21.4 (10.2–39.3)
Neoplasms (C00–D48)	456	1,449,3620	31.5 (28.6–34.5)	368	860,9476	42.7 (38.5–47.3)
Digestive organs (C15–C26)	72	2,665,050	27.0 (21.1–34.0)	64	1,967,238	32.5 (25.1–41.5)
Respiratory and intrathoracic organs (C30–C39)	41	965,504	42.5 (30.5–57.6)	39	727,468	53.6 (38.1–73.3)
Breast (C50)	36	1,382,014	26.0 (18.2–36.1)	22	515,774	42.7 (26.7–64.6)

Chapter and subgroup (code)	All patients			Patient age ≥60 y		
	No. cases	FCE	No. cases/million FCE (95% CI)	No. cases	FCE	No. cases/million FCE (95% CI)
Female genital organs (C51–C58)	10	587,403	17.0 (8.2–31.3)	7	345,555	NC
Male genital organs (C60–C63)	13	490,644	26.5 (14.1–45.3)	13	389,305	33.4 (17.8–57.1)
Eye, brain, and other parts of central nervous system (C69–C72)	13	196,199	66.3 (35.3–113.3)	11	58,414	188.3 (94–336.9)
Thyroid and other endocrine glands (C73–C80, C97)	47	1,957,683	24 (17.6–31.9)	37	1,053,496	35.1 (24.7–48.4)
Lymphoid, hematopoietic, and related tissue (C81–C96)	187	1,359,740	137.5 (118.5–158.7)	145	753,816	192.4 (162.3–226.3)
In situ and benign neoplasms and others of uncertainty (D00–D48)	18	2,880,269	6.3 (3.7–9.9)	16	1,286,473	12.4 (7.11–20.2)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50–D89)	25	2,062,183	12.1 (7.85–17.9)	12	1,079,281	11.1 (5.75–19.4)
Anemias (D50–D64)	13	1,478,008	8.8 (4.68–15)	7	871,585	NC
Diseases of blood and blood-forming organs (D65–D89)	12	584,175	20.5 (10.6–35.9)	5	207,696	NC
Endocrine, nutritional and metabolic	83	1,831,366	45.3 (36.1–56.2)	69	804,961	85.7 (66.7–108.5)

Chapter and subgroup (code)	All patients			Patient age ≥60 y		
	No. cases	FCE	No. cases/million FCE (95% CI)	No. cases	FCE	No. cases/million FCE (95% CI)
diseases (E00–E90)						
Diabetes mellitus (E10–E14)	71	721,573	98.4 (76.8–124.1)	57	326,473	174.6 (132.2–226.2)
Mental and behavior disorders (F00–F99)	60	2,176,420	27.6 (21.0–35.5)	25	646,228	38.7 (25.0–57.1)
Due to psychoactive substance (F10–F19)	54	502,363	107.5 (80.8–140.3)	20	56,062	356.7 (217.9–550.9)
Diseases of the nervous system (G00–G99)	16	2,732,564	5.86 (3.35–9.51)	15	1,141,845	13.1 (7.35–21.7)
Diseases of the eye and adnexa (H00–H59)	1	4,392,414	NC	0	3,449,215	NC
Diseases of the ear and mastoid process (H60–H95)	0	858,208	NC	0	125,850	NC
Diseases of the circulatory system (I00–I99)	143	11,770,385	12.1 (10.2–14.3)	135	8,514,080	15.9 (13.3–18.8)
Hypertensive diseases (I10–I15)	22	306,847	71.7 (44.9–108.5)	18	193,565	93 (55.1–147)
Ischemic heart diseases (I20–I25)	29	4,079,434	7.11 (4.76–10.2)	27	2,992,521	9.02 (5.95–13.1)
Other forms of heart disease (I30–I52)	62	2,928,710	21.2 (16.2–27.1)	61	2,366,977	25.8 (19.7–33.1)
Cerebrovascular diseases (I60–I69)	10	1,656,546	6.04 (2.89–11.1)	10	1,410,024	7.09 (3.4–13)
Diseases of arteries, arterioles, and	14	747,731	18.7 (10.2–31.4)	13	590,657	22.0 (11.7–37.6)

Chapter and subgroup (code)	All patients			Patient age ≥60 y		
	No. cases	FCE	No. cases/million FCE (95% CI)	No. cases	FCE	No. cases/million FCE (95% CI)
capillaries (I70–I79)						
Diseases of the respiratory system (J00–J99)	66	8,441,191	7.82 (6.1–10.0)	61	4,237,898	14.4 (11.0–18.5)
Chronic lower respiratory diseases (J40–J47)	41	2,510,375	16.3 (11.7–22.2)	40	1,627,030	24.6 (17.6–33.5)
Other diseases of the respiratory system (J80–J99)	11	702,393	15.7 (7.82–28)	10	458,712	21.8 (10.5–40.1)
Diseases of the digestive system (K00–K93)	163	14607104	11.2 (9.5–13.0)	96	6288251	15.3 (12.4–18.6)
Noninfective enteritis and colitis (K50–K52)	60	1,582,958	37.9 (28.9–48.8)	33	547,430	60.3 (41.5–84.7)
Other diseases of intestines (K55–K63)	14	2,985,107	4.69 (2.56–7.87)	13	1,623,725	8.01 (4.26–13.7)
Diseases of liver (K70–K77)	72	373,347	192.9 (150.9–242.9)	38	124,000	306.5 (216.9–420.6)
Diseases of the skin and subcutaneous tissue (L00–L99)	6	2,913,757	NC	6	1,066,962	NC
Diseases of the musculoskeletal system and connective tissue(M00–M99)	97	8,106,829	12.0 (9.7–14.6)	77	3,758,159	20.5 (16.2–25.6)
Arthropathies (M00–M25)	60	3,925,790	15.3 (11.7–19.7)	52	2,016,907	25.8 (19.3–33.8)
Systemic connective	28	171,687	163.1 (108.4–235.7)	19	67,700	280.6 (169.0–438.2)

Chapter and subgroup (code)	All patients			Patient age ≥60 y		
	No. cases	FCE	No. cases/million FCE (95% CI)	No. cases	FCE	No. cases/million FCE (95% CI)
tissue disorders (M30–M36)						
Diseases of the genitourinary system (N00–N99)	94	8,529,328	11.0 (8.9–13.5)	73	3,392,932	21.5 (16.9–27.1)
Renal failure (N17–N19)	90	869,322	103.5 (83.3–127.3)	69	577,799	119.4 (92.9–151.1)
Pregnancy, childbirth, and puerperium (O00–O99)	0	1,2614,774	NC	0	45,099	NC
Certain conditions originating in the perinatal period (P00–P96)	0	1,928,377	NC	0	433	NC
Congenital malformations, deformations, and chromosomal abnormalities (Q00–Q99)	1	1,069,074	NC	1	38,859	NC
Symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified (R00–R99)	2	16,380,896	NC	2	7,580,878	NC
Injury, poisoning, and certain other consequences of external causes (S00–T98)	4	8,723,795	NC	1	3,213,017	NC
External causes of morbidity and mortality (V01–Y98)	0	–	–	0	–	–

Chapter and subgroup (code)	All patients			Patient age ≥60 y		
	No. cases	FCE	No. cases/million FCE (95% CI)	No. cases	FCE	No. cases/million FCE (95% CI)
Factors influencing health status and contact with health services (Z00–Z99)	1	10,621,404	NC	1	2,070,369	NC
Codes for special purposes (U00–U99)	0	–	–	0	–	–
Total	1,239	13,601,1909	9.1 (8.6–9.6)	951	56,531,723	16.8 (15.8–17.9)

*ICD, International Classification of Diseases, 10th Revision; FCE, finished consultant episodes; CI, confidence interval; NC, not calculated (for conditions with <10 cases); –, data not available.

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Main Article

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Human listeriosis in England, 2001-2007: association with neighbourhood deprivation. *Euro Surveill* 2010; 15(27): 7-16

Human listeriosis in England, 2001–2007: association with neighbourhood deprivation

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Listeriosis is a rare but severe food-borne disease that predominantly affects pregnant women, the unborn, newborns, the elderly and immunocompromised people. Despite the high mortality rate of the disease, its socio-economic determinants have not been studied in detail, meaning that health inequalities that might exist in relation to this disease are not apparent. Laboratory surveillance data on listeriosis cases reported in England between 2001 and 2007 were linked to indices of deprivation and denominator data using patients' postcodes. Incidence relative to increasing quintiles of deprivation was calculated by fitting generalised linear models while controlling for population size. Patient food purchasing and consumption data were scrutinised and compared with commercial food purchasing denominator data to further quantify the observed differences in disease incidence. For all patient groups, listeriosis incidence was highest in the most deprived areas of England when compared with the most affluent, and cases were more likely to purchase foods from convenience stores or from local services (bakers, butchers, fishmongers and greengrocers) than the general population were. Patients' risk profile also changed with increasing neighbourhood deprivation. With increased life expectancy and rising food prices, food poverty could become an increasingly important driver for food-borne disease in the future. While United Kingdom Government policy should continue to focus on small food businesses to ensure sufficient levels of food hygiene expertise, tailored and targeted food safety advice on the avoidance of listeriosis is required for all vulnerable groups. Failure to do so may enhance health inequality across socio-economic groups.

Introduction

Listeriosis is a rare but severe food-borne disease caused by the opportunistic bacterium *Listeria monocytogenes*. Pregnant women, the unborn, newborns, the elderly and immunocompromised people are most commonly affected, with high associated mortality reported. Symptoms range from mild influenza-like or gastrointestinal illness to miscarriage, stillbirth, septicaemia, meningitis or encephalitis. Throughout the 1990s approximately 110 cases were reported annually in England and Wales, but from 2001 to 2008 an average of 188 annual cases were reported. The reasons for this increase – which has occurred almost exclusively in patients aged 60 years or older presenting with bacteraemia – are largely unknown [1]. Similar increases have been reported elsewhere in Europe [2,3].

The socio-economic determinants of human listeriosis have not been studied in detail before, despite numerous population-based studies of the disease [4-12]. Some studies have described the socio-economic aspects of suspected (i.e. undiagnosed) [13-16] and confirmed [17-24] gastrointestinal infections, but health inequalities that might exist in relation to listeriosis have not been investigated. A longitudinal study of human listeriosis in Bristol in England between 1983 and 1992 found that social classes I and II (higher social classes) were over-represented among cases when compared with the general population (45% versus 28%) [25]. Only 29 cases were included in this study, however, and social class data were only available for 20 of these, hence the estimates were subject to sampling variability (note the 95% confidence intervals (CI) around the above proportions: 45% (95% CI: 23.2 to 66.8) and 28% (95% CI: 27.8 to 28.2)). In order to systematically study the role of neighbourhood deprivation in human listeriosis for a larger population and over a longer time period, English national laboratory surveillance data for the period 2001 to 2007 were interrogated.

National surveillance for listeriosis in England and Wales is coordinated by the Health Protection Agency Centre for Infections. Following the voluntary referral of *L. monocytogenes* isolates for confirmation and subtyping [26-28] and/or local electronic reporting of confirmed cases, standardised clinical and epidemiological data are sought from hospital microbiologists and public health practitioners respectively [29]. The data are supplied through completion of questionnaires, which have been in use since 1990 (for hospital microbiologists) and 2005 (for public health practitioners) [29]. Epidemiological data are not routinely sought when the patient is deceased but are sometimes received. All data are stored in a bespoke database.

Methods

Case definitions

For the purposes of surveillance, a case of listeriosis is defined as a person with a clinically compatible illness from whom *L. monocytogenes* was isolated from a normally sterile site. Cases are classified further as pregnancy-associated (all maternal–fetal patients and neonatal patients, with a mother–baby pair considered a single case) or non pregnancy-associated (when the illness occurs in patients more than one month of age). Patients' ethnicity – classed as 'ethnic' if deemed to be from an ethnic minority, or 'non-ethnic' if not – was assigned to all cases using patients' names (surname and first name as available). It is important to note that this classification, undertaken by two of the authors (IAG and PM), is distinct from patients' own classification of their ethnicity, based on the 2001 United Kingdom (UK) census [30] and captured on the standardised epidemiological questionnaire. Due to restrictions in the availability of denominator data, our study was limited to cases reported from laboratories in England.

Analysis 1. Listeriosis incidence calculations

On the basis of their home postcode, cases were assigned to the Office for National Statistics' lower super output areas (LSOAs) – the smallest geographical area for which aggregated census data are routinely released, comprising 32,482 areas in England and containing on average 1,500 residents per area. We then calculated the number of all non pregnancy-associated cases, non pregnancy-associated cases aged 60 years or older and pregnancy-associated cases resident in each LSOA in each year from 2001 to 2007. Respective population data (the number of all people, all people aged 60 years or older and all live births) for each LSOA in each year were obtained from the Office for National Statistics (the number of conceptions by LSOA were unavailable). These data were combined with 2007 multiple and individual indices of deprivation [31], giving 227,374 observations.

Subsequent data manipulation and analyses were undertaken using Stata version 10 [32].

The 2007 indices of deprivation consist of seven dimensions of deprivation (income; employment; health deprivation and disability; education, skills and training; barriers to housing and services; crime and disorder; living environment) which are weighted and combined [33] to create the overall index of multiple deprivation. A rank is also provided for each dimension and the overall index, where one is the most deprived LSOA and 32,482 the least. Variables were created to represent quintiles of each dimension rank and the index of multiple deprivation, but coded to compare the least deprived LSOAs with the most. As there were instances where there were no live births in certain LSOAs in some years, data for pregnancy-associated cases were grouped further (sums of cases and population counts;

Table 1

Characteristics of listeriosis cases included or excluded in the study on the basis of postcode availability, England, 2001–2007 (N=1,242)

Factor	Postcode available	
	Yes (n=1,179) Number (%)[a]	No (n=63) Number (%)[a]
Study year		
2001	112 (86)[b]	18 (14)[b]
2002	106 (81)[b]	25 (19)[b]
2003	202 (91)[b]	20 (9)[b]
2004	193 (100)[b]	0 (0)
2005	179 (100)[b]	0 (0)
2006	176 (100)[b]	0 (0)
2007	211 (100)[b]	0 (0)
Case type		
Non pregnancy-associated	1033 (88)	51 (81)
Pregnancy-associated	146 (12)	12 (19)
Age group		
<60 years	385 (33)	31 (49)
≥60 years	783 (66)	27 (43)
Unknown	11 (1)	5 (8)
Ethnicity (based on name)		
Ethnic	140 (12)	12 (19)
Non-ethnic	1033 (88)	44 (70)
Undetermined	6 (1)	7 (11)

[a] Column percentage, unless stated otherwise.

[b] Row percentage.

Table 2

Incidence of listeriosis in relation to various markers for increasing deprivation, England, 2001–2007 (N=1,242)

Increasing deprivation quintile	Incidence relative to the least-deprived quintile (95% confidence interval)			
	All cases	Non-pregnancy-associated cases		Pregnancy-associated cases[a]
		All	≥60 years	
Indices of multiple deprivation				
1 (least)	1	1	1	1
2	1.02 (0.84–1.23)	0.98 (0.80–1.20)	0.94 (0.74–1.18)	1.16 (0.54–2.51)
3	0.93 (0.77–1.13)	0.98 (0.81–1.20)	0.96 (0.76–1.21)	0.94 (0.42–2.10)
4	1.16 (0.97–1.40)	1.09 (0.90–1.33)	1.21 (0.96–1.52)	2.34 (1.24–4.40)
5 (most)	1.38 (1.16–1.65)	1.27 (1.05–1.53)	1.36 (1.09–1.71)	2.20 (1.18–4.08)
Income				
1 (least)	1	1	1	1
2	0.98 (0.82–1.19)	0.99 (0.82–1.21)	0.97 (0.77–1.22)	1.26 (0.58–2.74)
3	0.77 (0.63–0.94)	0.83 (0.67–1.02)	0.83 (0.66–1.06)	1.21 (0.56–2.62)
4	1.18 (0.98–1.41)	1.16 (0.96–1.40)	1.24 (1.00–1.55)	2.38 (1.24–4.60)
5 (most)	1.25 (1.05–1.49)	1.17 (0.97–1.42)	1.31 (1.04–1.64)	2.10 (1.10–4.00)
Employment				
1 (least)	1	1	1	1
2	1.18 (0.97–1.43)	1.15 (0.94–1.41)	1.10 (0.87–1.39)	1.35 (0.62–2.95)
3	1.15 (0.95–1.40)	1.17 (0.95–1.43)	1.07 (0.84–1.36)	1.32 (0.63–2.76)
4	1.22 (1.01–1.48)	1.16 (0.95–1.43)	1.22 (0.96–1.55)	2.31 (1.18–4.52)
5 (most)	1.61 (1.34–1.93)	1.50 (1.24–1.82)	1.43 (1.14–1.80)	2.68 (1.41–5.08)
Health deprivation and disability				
1 (least)	1	1	1	1
2	0.97 (0.80–1.18)	0.92 (0.75–1.13)	0.98 (0.77–1.24)	1.04 (0.47–2.33)
3	1.13 (0.93–1.36)	1.08 (0.89–1.32)	1.12 (0.89–1.42)	1.19 (0.55–2.59)
4	1.17 (0.97–1.41)	1.09 (0.90–1.33)	1.24 (0.98–1.56)	2.12 (1.09–4.12)
5 (most)	1.54 (1.29–1.84)	1.37 (1.14–1.66)	1.48 (1.18–1.85)	2.58 (1.36–4.89)
Education, skills and training				
1 (least)	1	1	1	1
2	0.88 (0.73–1.06)	0.87 (0.72–1.06)	1.02 (0.82–1.28)	2.10 (1.10–4.03)
3	0.84 (0.69–1.01)	0.78 (0.64–0.95)	0.89 (0.70–1.12)	1.78 (0.91–3.46)
4	1.01 (0.84–1.20)	0.95 (0.78–1.14)	1.11 (0.89–1.39)	2.29 (1.23–4.27)
5 (most)	1.08 (0.90–1.28)	1.02 (0.85–1.23)	1.20 (0.96–1.50)	1.73 (0.92–3.26)
Barriers to housing and services				
1 (least)	1	1	1	1
2	0.88 (0.74–1.06)	0.96 (0.79–1.16)	0.95 (0.76–1.19)	0.60 (0.35–1.02)
3	0.87 (0.72–1.04)	0.95 (0.78–1.15)	1.03 (0.83–1.29)	0.86 (0.52–1.40)
4	0.87 (0.73–1.04)	0.94 (0.77–1.14)	0.92 (0.73–1.15)	0.63 (0.36–1.11)
5 (most)	0.92 (0.77–1.09)	0.93 (0.77–1.13)	1.01 (0.80–1.26)	0.84 (0.54–1.31)
Crime and disorder				
1 (least)	1	1	1	1
2	0.92 (0.76–1.12)	0.90 (0.74–1.10)	1.01 (0.80–1.28)	0.95 (0.36–2.50)
3	1.19 (0.99–1.43)	1.07 (0.88–1.30)	1.23 (0.98–1.54)	1.76 (0.75–4.17)
4	1.20 (1.001–1.44)	1.17 (0.96–1.41)	1.32 (1.05–1.65)	2.21 (0.99–4.93)
5 (most)	1.20 (1.003–1.44)	1.09 (0.90–1.33)	1.43 (1.14–1.79)	2.53 (1.16–5.51)
Living environment				
1 (least)	1	1	1	1
2	1.02 (0.84–1.24)	1.00 (0.82–1.22)	0.96 (0.76–1.21)	1.73 (0.83–3.64)
3	1.11 (0.92–1.34)	1.09 (0.90–1.33)	1.05 (0.84–1.32)	1.22 (0.56–2.66)
4	1.28 (1.07–1.54)	1.24 (1.02–1.50)	1.32 (1.06–1.65)	1.90 (0.95–3.82)
5 (most)	1.21 (1.01–1.45)	1.04 (0.86–1.27)	1.12 (0.88–1.42)	2.71 (1.44–5.11)

[a] Calculated at the local authority rather than the lower super output area (LSOA) level.

averages of deprivation measures) and quintiles recalculated to allow analysis at the larger local authority level.

Estimates of the incidence of listeriosis relative to increasing deprivation were obtained by fitting generalised linear models with a count of cases per LSOA or local authority per year as the outcome variable. Incidence in each quintile relative to the lowest quintile of deprivation (least deprived) was calculated. Four sets of analyses were undertaken: all cases, all non pregnancy-associated cases, non pregnancy-associated cases aged 60 years or older and pregnancy-associated cases. In each, a log-link function was included to control for the underlying population (all people, people aged 60 years or older and all live births as appropriate) in each LSOA or local authority in each year. Chi-square tests and chi-square tests for trend, performed in Epi Info version 6.04d [34], were used to assess simple comparisons of proportions or trend in proportions respectively.

Analysis 2. Food purchasing comparison

To inform further on the findings of the incidence calculations, patients' food purchasing patterns were examined in relation to commercial denominator data. The standardised epidemiological questionnaire includes questions on various retail premises where cases had recently purchased food. These data, available from 2005 to 2007, were interrogated to obtain the number of cases reporting food shopping in different types of retailer. Commercial denominator data for the same time period and population were obtained from the Worldpanel Purchase database from the market research company Taylor Nelson Sofres (TNS, London). This database is the largest continuous consumer panel in Great Britain, capturing purchasing behaviour for 48,000 individuals in 25,000 households, and is used extensively by major retailers and manufacturers in the UK to understand consumer behaviour. Participants, chosen to be representative of Great Britain as a whole in terms of age, social class and region, record retail purchases by various means (e.g. bar code scanners, online surveys, till receipt scanning, etc.) and report to TNS fortnightly. Crude data were obtained from the database for the total number of individuals and the

Table 3

Characteristics of listeriosis cases, according to receipt of epidemiological questionnaires, England, 2005–2007 (n=566)

Parameter	Epidemiological questionnaire received	
	Yes (n=231) Number (%)[a]	No (n=335) Number (%)[a]
Patient type		
Pregnancy-associated	39 (17)	38 (11)
Non pregnancy-associated	192 (83)	297 (89)
Year		
2005	37 (21)[b]	142 (79)[b]
2006	50 (28)[b]	126 (72)[b]
2007	144 (68)[b]	67 (32)[b]
Gender		
Male	121 (52)	165 (49)
Female	110 (48)	168 (50)
Unknown	0 (0)	2 (1)
Age		
Median	65 years	68 years
Interquartile range	42–76 years	55–79 years
Quintile of increasing deprivation[c]		
1 (least)	44 (19.0)	59 (18)
2	35 (15.2)	79 (24)
3	41 (17.7)	54 (16)
4	48 (20.8)	72 (21)
5 (most)	62 (26.8)	67 (20)
Unknown	1 (0.4)	4 (1)
Mortality		
Died	62 (27)	111 (33)
Did not die	167 (72)	128 (38)
Unknown	2 (1)	96 (29)

[a] Column percentage, unless stated otherwise.
[b] Row percentage.
[c] Indices of multiple deprivation.

total number of individuals aged 60 years or older, and the food purchasing habits of both groups from various supermarkets, discount supermarkets, convenience stores (typically small retail stores selling limited produce over extended periods) and local services (corner shops, local butchers, bakers, greengrocers and fishmongers). Reported places for food shopping among cases and the general population were compared in Microsoft Excel 2007. Odds ratios (OR) and 95% CIs were calculated.

Analysis 3. Food purchasing, storage and consumption in relation to quintiles of multiple deprivation

Finally, the quintiles of the index of multiple deprivation calculated in analysis 1 above were combined with the standardised food purchasing, storage and consumption data from analysis 2 and data were stratified by quintiles of increasing neighbourhood deprivation. Changes in the upwards or downwards trend in relation to increasing deprivation were assessed using the chi-square test for trend.

Results

Study population

Between 2001 and 2007, 1,242 cases of human listeriosis were reported; of these, 1,084 (87%) were non pregnancy-associated and 158 (13%) were pregnancy-associated. Where patient age was available for non pregnancy-associated cases (n=1,072), 810 (76%) of cases were aged 60 years or older. Patients' home postcodes were available for 1,179 (95%) cases and all matched to an LSOA (Table 1). Postcode availability increased significantly over the surveillance period (chi-square test for trend P<0.001), but postcodes were more likely to be unavailable for patients aged under 60 years (chi-square test p=0.001) or for those defined as ethnic on the basis of their names (chi-square test p=0.04) (Table 1).

Incidence by quintiles of deprivation

The incidence of listeriosis increased with increasing relative neighbourhood deprivation (Table 2), with 38% (95% CI: 16 to 65) higher incidence in the most deprived quintile compared with the least. Incidence was positively correlated with all of the dimensions of deprivation (reflecting their intracorrelation and their

Table 4

Food purchase patterns for listeriosis cases (n=171) compared with those of the general population (n=60,415), England, 2005–2007

Premises	Food shopping by premises					
	All cases n (%)	Population[a] n (%)	OR (95% CI)	Cases aged ≥60 years n (%)	Population aged ≥60 years[a] n (%)	OR (95% CI)
Supermarkets						
Chain B	85 (49.7)	47,811 (79.1)	0.26 (0.19–0.35)	44 (42.3)	11,383 (75.2)	0.24 (0.16–0.36)
Chain G	63 (36.8)	37,238 (61.6)	0.36 (0.27–0.50]	35 (33.7)	8,063 (53.2)	0.45 (0.30–0.67)
Chain J	63 (36.8)	35,475 (58.7)	0.41 (0.30–0.56)	34 (32.7)	9,315 (61.5)	0.30 (0.20–0.46)
Chain A	55 (32.2)	30,596 (50.6)	0.46 (0.34–0.64)	35 (33.7)	8,000 (52.8)	0.45 (0.30–0.68)
Chain D	48 (28.1)	24,225 (40.1)	0.58 (0.42–0.81)	32 (30.8)	8,050 (53.2)	0.39 (0.26–0.59)
Chain K	27 (15.8)	19,935 (33.0)	0.38 (0.25–0.57)	13 (12.5)	5,259 (34.7)	0.27 (0.15–0.48)
Chain U	24 (14.0)	18,993 (31.4)	0.36 (0.23–0.55)	15 (14.4)	5,579 (36.8)	0.29 (0.17–0.50)
Chain P	15 (8.8)	10,025 (16.6)	0.48 (0.28–0.82)	7 (6.7)	3,372 (22.3)	0.25 (0.12–0.54)
Discount supermarkets						
Chain X	15 (8.8)	15,568 (25.8)	0.28 (0.16–0.47)	7 (6.7)	5,032 (33.2)	0.15 (0.07–0.31)
Chain Q	16 (9.4)	14,500 (24.0)	0.33 (0.20–0.55)	8 (7.7)	4,279 (28.3)	0.21 (0.10–0.44)
Chain C	7 (4.1)	7,605 (12.6)	0.30 (0.14–0.63)	4 (3.8)	2,004 (13.2)	0.26 (0.10–0.71)
Chain E	9 (5.3)	5,594 (9.3)	0.54 (0.28–1.07)	7 (6.7)	1,715 (11.3)	0.57 (0.26–1.22)
Convenience stores						
Chain H	4 (2.3)	3,534 (5.8)	0.39 (0.14–1.04)	1 (1.0)	1,184 (7.8)	0.11 (0.02–0.82)
Chain L	10 (5.8)	3,846 (6.4)	0.91 (0.48–1.73)	5 (4.8)	1,013 (6.7)	0.70 (0.29–1.73)
Chain M	26 (15.2)	1,952 (3.2)	5.37 (3.53–8.17)	17 (16.3)	668 (4.4)	4.23 (2.50–7.16)
Local services						
Corner shops	44 (25.7)	13,864 (22.9)	1.16 (0.83–1.64)	15 (14.4)	4,241 (28.0)	0.43 (0.25–0.75)
Butchers	35 (20.5)	8,300 (13.7)	1.62 (1.11–2.34)	17 (16.3)	3,510 (23.2)	0.65 (0.38–1.09)
Green grocers	35 (20.5)	7,155 (11.8)	1.92 (1.32–2.78)	16 (15.4)	3,148 (20.8)	0.69 (0.41–1.18)
Bakers	40 (23.4)	4,973 (8.2)	3.40 (2.39–4.86)	23 (22.1)	2,140 (14.1)	1.73 (1.08–2.75)
Fishmongers	21 (12.3)	1,631 (2.7)	5.05 (3.19–7.99)	11 (10.6)	938 (6.2)	1.79 (0.96–3.36)

CI: confidence interval; OR: odds ratio.

[a] Source: commercial market research data.

contribution to the overall index of multiple deprivation) except 'education, skills and training' and 'barriers to housing and services' domains. Incidence in non pregnancy-associated cases generally followed that for all cases and was more marked for those cases aged 60 years or older. The incidence of pregnancy-associated listeriosis showed a more marked association with increasing neighbourhood deprivation, with the strongest associations observed with the 'income', 'employment' and 'health deprivation and disability' domains.

Standardised patient exposure data (2005–2007)

Between 1 January 2005 and 31 December 2007, 231 epidemiological questionnaires were received for the 566 reported cases in England (response rate 41%), with the response rate increasing significantly over the surveillance period (chi-square test for trend p<0.001) (Table 3). Surveillance questionnaire receipt was independent of case type (chi-square test p=0.06), age (chi-square test p=0.09), sex (chi-square test p=0.5) and level of deprivation (chi-square test p=0.09), but not mortality (chi-square test p<0.001) (Table 3). A total of 20 non-standard and 40 partially completed questionnaires were excluded, leaving 171 for analysis.

Of the 32 cases classed as ethnic on the basis of their name, 29 described their ethnicity as something other than 'white British', compared with 16 of 138 cases classed as non-ethnic (positive predictive value: 90.6% (95% CI: 86.2 to 95.0); negative predictive value: 88.4% (95% CI: 83.6 to 93.2). One case classed as non-ethnic on the basis of their name did not describe their own ethnicity.

Food purchasing patterns in relation to the general population (2005–2007)

The use of supermarkets and discount supermarkets was underrepresented among cases of listeriosis when compared with the general population, while the use of national convenience store chain M, and most local services, was overrepresented (Table 4). This relationship was observed to a lesser extent for cases aged 60 years or older, but could not be determined for pregnancy-associated cases due to a lack of denominator data. Cases who reported food shopping at national convenience store chain M were equally distributed across all quintiles of deprivation (chi-square for trend test p=0.38), were infected with nine different *L. monocytogenes* subtypes and food shopping at this store was overrepresented in each study year: OR: 6.00 (95% CI: 1.75 to 20.56) in 2005; OR: 6.16 (95% CI: 2.72 to 13.91) in 2006; OR: 4.67 (95% CI: 2.7 to 7.97) in 2007, suggesting that this association did not represent a single outbreak due to a single or restricted range of *L. monocytogenes* strains.

Food purchasing, storage and consumption in relation to quintiles of multiple deprivation (2005–2007; data not shown)

As quintiles of neighbourhood deprivation increased, cases (n=171) were more likely to describe their ethnicity as something other than white British (chi-square test for trend p=0.01) and were more likely to report:

- avoiding soft blue cheese (chi-square test for trend p=0.04)
- avoiding pâté (chi-square test for trend p=0.01).

They were more likely to report eating:

- liver sausage (chi-square test for trend p=0.04)
- cold roast turkey (chi-square test for trend p=0.045)
- pre-packed cold turkey (chi-square test for trend p=0.048).

They were less likely to report eating:

- food from hotels (chi-square test for trend p=0.01)
- food from restaurants serving British cuisine (chi-square test for trend p=0.04)
- duck liver pâté (chi-square test for trend p=0.049)
- oysters (chi-square test for trend p=0.03)
- watercress (chi-square test for trend p=0.03).

They were more likely to report recent food shopping in:

- national supermarket chain G (chi-square test for trend p=0.001)
- national supermarket chain K (chi-square test for trend p=0.006)
- national discount supermarket chain X (chi-square test for trend p=0.004)
- local bakers (chi-square test for trend p=0.02)
- fishmongers (chi-square test for trend p=0.03)
- greengrocers (chi-square test for trend p<0.001).

They were no more likely to have acute or long-standing medical conditions (chi-square test for trend p=0.22).

Discussion and conclusion

Laboratory-based surveillance of human *L. monocytogenes* infection in England between 2001 and 2007 revealed that incidence was highest in the most deprived areas of the country. Additional analyses demonstrated that cases of listeriosis were more likely than the general population to purchase foods from convenience stores or from local services, and that among cases, food purchasing and consumption patterns changed with increasing deprivation. While cases of listeriosis form the numerator in each of the three analyses presented, the denominators are either different or are absent, and therefore the findings of each are not necessarily comparable.

Cases in this study comprise laboratory-confirmed cases reported to national surveillance. Reporting will be affected by disease severity, health-seeking behaviour and reporting artefacts, all of which will

have a bearing on incidence estimates. Infection with *L. monocytogenes* results in a range of symptoms, and laboratory surveillance will undoubtedly underascertain milder forms of the disease. Disease severity relates largely to the degree of exposure and susceptibility of the host, and both might be driven by socio-economic factors (income-related food consumption leading to a greater or lesser exposure; known associations between certain underlying conditions (e.g. cancer [35], general poor health [36,37], diabetes [38]) and socio-economic status). By using laboratory-confirmed cases we might therefore be biasing our estimates for certain socio-economic groups. Community-based studies would be prohibitively expensive for a disease as rare as listeriosis, however, and without undertaking such studies it is impossible to measure the extent or direction of this bias in our study.

Healthcare usage also differs by socio-economic status for patients in England with infectious intestinal disease. Tam *et al*. demonstrated that individuals in lower socio-economic groups (as defined by age at leaving full-time education and housing) were more likely to present with infectious intestinal disease to a general practice than community controls were [39]. This might explain some of the observed difference in incidence by socio-economic status in our study. Tam's study included all causes of infectious intestinal disease, however, and it is not possible to determine how this differential presentation might relate to listeriosis, which differs markedly from most gastrointestinal infections in terms of severity, symptoms and population at risk.

National surveillance of listeriosis in England and Wales is passive, hence our estimates might be affected if clinicians' reporting practices differ depending on their patients' socio-economic status. In their study of listeriosis in Bristol, Jones *et al*. noted that the incidence in 1988 (1.2 cases per 100,000 population) was higher than the national average (0.58 cases per 100,000 population), suggesting that not all cases were reported to national surveillance and thus creating the opportunity for this form of selection bias [25]. The confidence intervals surrounding the above estimates overlap (0.58 to 2.24 per 100,000 population for Bristol; 0.5799 to 0.5801 per 100,000 population for England and Wales), however, suggesting no actual difference between incidence at the local and national level, and that the majority of cases confirmed at the local level are reported nationally.

We applied 2007 indices of deprivation to surveillance data from 2001 to 2007, meaning that areas that hypothetically experienced extreme social change during this time might not be adequately represented by these indices for part of the surveillance period. Such changes will be exceptional over such a short period, so most of the data will be unaffected by this generalisation, and any effect will be minimised further by arranging the data in quintiles.

By assigning cases to socio-economic groups on the basis of their home postcode, the effect of socio-economic status at the individual level is masked and individuals take on the socio-economic characteristics of their local environment [13]. While the merits of assigning social class to individuals by postcode is debatable [40,41] and the potential for ecological fallacy is increased, this method is advantageous in that it does not rely on high response rates to questionnaires (a particular problem for a severe disease such as listeriosis) or to potentially sensitive questions required for establishing socio-economic status (e.g. on income). Furthermore, the opportunity for misclassification through the direct derivation of socioeconomic status, based on occupation, for example [23], is minimised.

With these caveats in mind, the association between listeriosis and increasing deprivation reported in this study differs from other studies on the socio-economic determinants of gastrointestinal infections, where incidence was often positively associated with increased socio-economic status [17-24]. With pâté and soft mould-ripened cheese historically considered high-risk foods for listeriosis in the UK, our *a priori* hypothesis was that listeriosis would be a disease of affluence. The breakdowns in food safety that give rise to listeriosis differ from other food-borne pathogens, however, and these could impact on the demographics of the population at risk. While inadequate cooking of and/or cross-contamination from contaminated raw poultry meat increases the risk of campylobacteriosis, and inappropriate storage of uncooked or undercooked egg-based products over short time periods can lead to salmonellosis, the risk of listeriosis increases with the growth of *L. monocytogenes* to hazardous levels in refrigerated long shelf-life products [42]. It is possible that such conditions arise more frequently with increased deprivation where refrigeration may be inadequate or unavailable. Additionally, financial pressures may encourage individuals to store food for longer than the food product's safe shelf-life. Alternatively, as general poor health and certain chronic conditions such as cancers and diabetes are associated with lower socio-economic status [35-38] it is therefore intuitive that *Listeria* incidence would be higher in poorer areas.

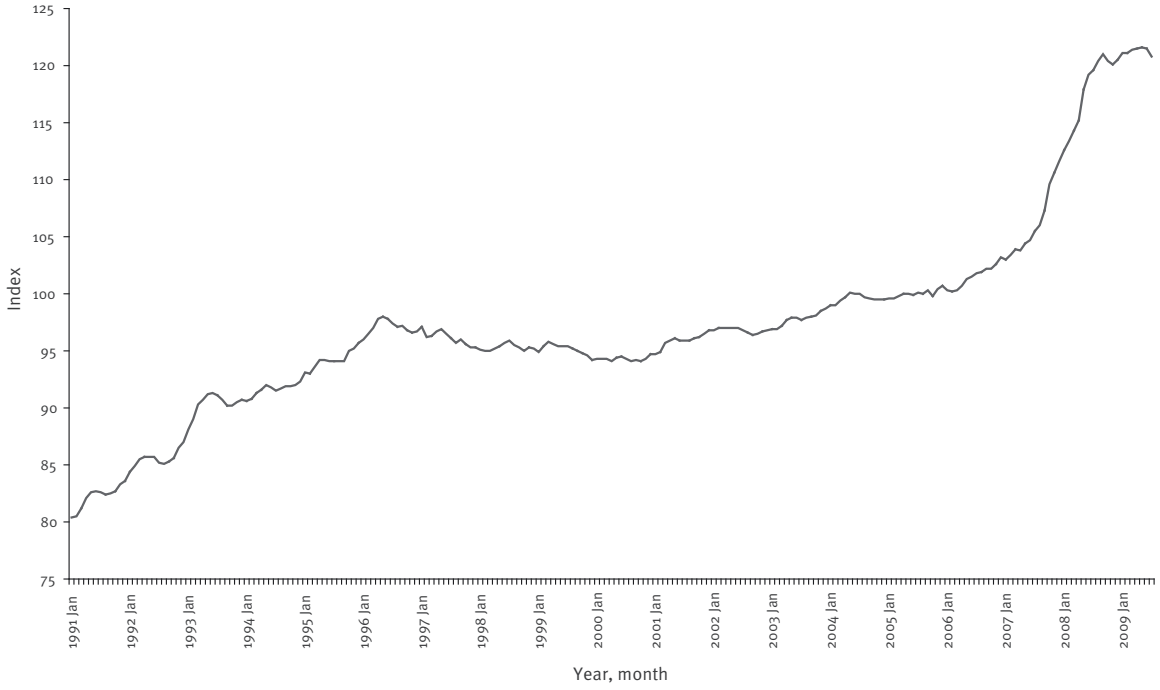
Home postcodes were available less often for ethnic patients, hence the observed association with increasing neighbourhood deprivation might be underestimated, as ethnic groups reside more frequently in more deprived areas of England [43]. As neighbourhood deprivation increased, cases were also more likely to report their ethnicity as something other than white British, suggesting that at least part of the overall association may be due to an increased risk of infection in ethnic minorities. Currently, specific UK Government food safety advice on minimising the risk of listeriosis is delivered passively (via a website [44]) and is targeted preferentially at pregnant women. Our study suggests that advice should be communicated proactively and effectively to all patient groups at risk

of listeriosis, especially where language barriers exist, or where access to the Internet is limited [45]. Advice should be extended to include information on safe use and storage of foods in the home to avoid listeriosis (e.g. refrigerate once opened, consume within the shelf life of the product, etc.).

Several factors should be considered while interpreting our comparisons of cases' exposures in relation to increasing neighbourhood deprivation, and their food purchasing patterns with that observed in the general population. Firstly, routine surveillance of listeriosis is problematic due to the severity of the disease and the population at risk. For this reason, the response rate to our epidemiological questionnaire, while improving, is lower than for other active surveillance systems for gastrointestinal infections in England, e.g. 77% for verocytotoxin-producing *Escherichia coli* infection in England (Health Protection Agency, unpublished data) and is better for patients who survive their infection. It is possible that certain exposures will be underrepresented in our surveillance dataset if those exposures are linked to increased mortality, e.g. foods containing higher concentrations of *L. monocytogenes* or certain subtypes, or those consumed more often by the most vulnerable. To date, studies of *L. monocytogenes* mortality [6,7,11] have focussed on host factors, making quantification of this potential bias impossible. Secondly, the population at risk of listeriosis in England is not the same as the population of England, as listeriosis patients are often individuals predisposed to opportunistic infections due to suppression of their T-cell-mediated immunity [46], and the conditions that give rise to this immunological state might alter their behaviour, including food purchasing patterns. People tend to keep the same shopping habits though, and while they might avoid some foods due to certain underlying conditions (or their treatments), they are less likely to change their favoured supermarkets or shops. Finally, individuals participating in surveys of any kind will differ systematically from the general population by virtue of their willingness to participate, and this bias might be more profound for market research surveys where participation is often rewarded financially. Market research data are used extensively by many business sectors, however, and therefore there is an economic pressure on market research companies for their study participants to be as representative as possible, and the denominator data used matched closely to the British population with regard to age and social class. This could be detrimental to our food purchasing comparison, as the numerator (listeriosis cases in England, skewed towards increased deprivation) differs from the denominator (commercial data, representative in terms of social class), and this might explain some or all of the observed differences in food

Figure

Non-seasonally adjusted product price index for food products (excluding beverages), United Kingdom, January 1991 – July 2009[a]



[a] Index set at 100 for 2005.
Source: [52].

purchasing. Further work could address this shortcoming by examining the food purchasing patterns of cases in relation to deprivation-matched population groups, but the provision of such detailed denominator data was prohibitively expensive for this unfunded study. Discussions of the findings from this study are still warranted, however, as shopping for food at several of the 'over-indexed' types of premises (those reported more often by cases than by the general population) also increased among listeriosis cases as neighbourhood deprivation increased.

The apparent overuse of national convenience store chain M by listeriosis cases may represent differential misclassification, as this chain is colloquially synonymous with small convenience stores in the UK, and therefore patients may report shopping there when they are in fact referring to any convenience store. Commercial data, on the other hand, will be ascribed correctly to the appropriate premises type, based on the comprehensive collection methods described previously. Similarly, the associations with local services might reflect the fact that, on average, a shopper would visit several shop types among their local services to purchase the variety of items that would be available in a single supermarket and therefore the numerator is inflated. Alternatively, residents in poorer areas may be limited to shopping locally due to poorer access to transportation. Convenience stores and local services generally represent the smaller end of the market in terms of business size, and this feature has been frequently linked to lower microbiological quality of foods in a number of surveys undertaken in England and Wales since 1994 [47]. Small businesses do not have access to the same level of food safety expertise [48] as larger retail companies do, and these food control deficiencies might increase the food safety risk for consumers. The 2006 'Safer food better business' initiative by the UK Government [49], designed to help small food businesses implement hazard-based control systems and to comply with food hygiene regulations, was therefore timely. Food safety management systems employed to satisfy legislation will only fully meet legal obligations, however, when they account for all relevant hazards and risks. Clearly *L. monocytogenes* and its associated food safety storage issues, which are different from those of other food-poisoning bacteria, must be considered carefully in food manufacturing and retail operations, particularly for foods sold to vulnerable individuals [50].

In conclusion, our study demonstrates that *L. monocytogenes* incidence was highest in the most deprived areas of England when compared with the most affluent, that cases were more likely to purchase foods from convenience stores or from local services than the general population were, and that patients' risk profile changed with increasing neighbourhood deprivation. Increasing 'healthy life expectancy' in the UK does not follow increasing life expectancy, meaning that in future, individuals may spend a greater part of their retirement in poor health [51]. With poor health in later life allied to increasing deprivation and recent rises in food prices (Figure [52]) predicted to continue, food poverty could become an increasingly important driver for listeriosis. While UK Government policy should continue to focus on small food businesses to ensure sufficient levels of food hygiene expertise, tailored and targeted food safety advice on the avoidance of listeriosis is required for all vulnerable groups within the community. Failure to do so will enhance health inequality across socio-economic groups.

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Listeria monocytogenes **infection in the Over-60s in England between 2005 and 2008: a retrospective case-control study utilizing market research panel data.** ***Foodborne Pathog Dis.*** **2010; 7: 1373-9**

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Emergence of pregnancy-related listeriosis amongst ethnic minorities in England and Wales. *Euro Surveill* 2010; 15(27): 17-23

Emergence of pregnancy-related listeriosis amongst ethnic minorities in England and Wales

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Listeriosis is a rare but severe food-borne disease that predominantly affects pregnant women, the unborn, newborns, the elderly and immunocompromised people. Following a large outbreak in the 1980s, specific food safety advice was provided to pregnant women and the immunocompromised in the United Kingdom. Following two coincident yet unconnected cases of pregnancy-related listeriosis in eastern European women in 2008, a review of the role of ethnicity in pregnancy-related listeriosis in England and Wales was undertaken in 2009. Cases reported to the national listeriosis surveillance scheme were classified as 'ethnic', belonging to an ethnic minority, or 'non-ethnic' based on their name, and trends were examined. Between 2001 and 2008, 1,510 cases of listeriosis were reported in England and Wales and, of these, 12% were pregnancy-related cases. The proportion of pregnancy-related cases classified as ethnic increased significantly from 16.7% to 57.9% (chi-square test for trend p=0.002).The reported incidence among the ethnic population was higher than that among the non-ethnic population in 2006, 2007 and 2008 (Relative Risk: 2.38, 95% confidence interval: 1.07 to 5.29; 3.82, 1.82 to 8.03; 4.33, 1.74 to 10.77, respectively). This effect was also shown when analysing data from January to September 2009, using extrapolated live births as denominator. Increased immigration and/or economic migration in recent years appear to have altered the population at risk of pregnancy-related listeriosis in England and Wales. These changes need to be taken into account in order to target risk communication strategies appropriately.

Introduction

Listeriosis is a rare but severe bacterial disease that predominantly affects pregnant women, the unborn, newborns, the elderly and immunocompromised individuals. In newborns, the elderly and immunocompromised individuals, the disease usually manifests as meningitis and/or septicaemia, with high mortality rates reported amongst these risk groups. Listeriosis is mainly transmitted via the consumption of foods contaminated with *Listeria monocytogenes* and recent estimates suggest that listeriosis is the greatest cause of food-related deaths in the United Kingdom (UK) [1]. It has been reported that pregnant women have a 12-fold increased risk of developing disease after the consumption of contaminated food when compared with the general population [2], indicating that pregnancy may constitute a disposition to acquiring listeriosis. Pregnant women rarely have central nervous system infection [3] but may experience fever, miscarriage, premature delivery or stillbirth. Pregnant women infected with *L. monocytogenes* may also be asymptomatic.

While most pregnancy-related infections are detected during the third trimester, listeriosis can develop at any time during pregnancy and, in some instances, asymptomatic pregnant women may still pass on infection to the fetus. Pregnancy-related cases of listeriosis are divided into early and late onset. An early onset case is defined as a newborn with symptoms at birth or within 48 hours of birth resulting from *in utero* infection from the mother. The term late onset is applied when a newborn develops symptoms more than 48 hours after birth and such infections are thought to be predominantly the result of infection during passage through the birth canal. While rare, there have also been reports of late onset cases being a consequence of nosocomial transmission via indirect contact with early onset cases, for example through common birthing staff or equipment [4,5]. Newborns born with listeriosis and who survive may have complications that include physical retardation and granulomatosis infantiseptica (pyogenic nodules distributed systemically).

Between 1985 and 1989, the number of cases of listeriosis in England, Wales and Northern Ireland nearly doubled before rapidly declining in 1990 [6].This upsurge in cases was, however, mainly caused by an outbreak which disproportionately affected pregnant women, and was related with consumption of pâté produced by a single manufacturer [7]. The suspension of sales of pâté from this manufacturer, whose pâté was highly contaminated with subtypes of *L. monocytogenes* indistinguishable from those isolated from cases, coincided with the dissemination of two government health warnings in 1989: one with regards to

the general risk of listeriosis and pâté [8] and a second one specifically targeted at vulnerable groups, which were defined at the time as pregnant women and people with impaired resistance to infection [9]. The aforementioned rapid decline in cases followed the second of these warnings.

The outbreak highlighted the risk to pregnant women of developing listeriosis after consuming pâté and reiterations of the health advice with regards to pâté and other high-risk foods still target this group [10]. Following two coincident but unconnected cases of pregnancy-related listeriosis in women of eastern European nationality during 2008, a review of pregnancy-related cases of listeriosis between 2001 and 2008 was undertaken using national surveillance data for England and Wales, to assess the role of ethnicity in this population and examine trends. A provisional investigation of cases between January and September 2009 was also carried out.

Methods

The Health Protection Agency Centre for Infections coordinates the surveillance of listeriosis in England and Wales. Cases are ascertained by the voluntary electronic reporting of laboratory-diagnosed cases and/or the referral of cultures for identification and subtyping. Epidemiological and microbiological data reported by these systems are combined, de-duplicated, and stored in a bespoke Microsoft Access 2003 database. Since 2005, supplementary clinical data are sought routinely from the consultant medical microbiologist responsible for the case, including onset date, date of hospital admission, principal listeria illness, clinical outcome, antibiotics and other drugs administered and symptoms [11]. In addition, exposure data with regards to travel, food consumption and food retailers are sought from the case or a relative of the case by environmental health officers in liaison with local health protection staff, using a standard exposure questionnaire [11]. Postcode data are employed to estimate socio-economic status using quintiles [12] of established indices of multiple deprivation [13].

A case of listeriosis is defined as an individual presenting with clinically compatible illness and from whom *L. monocytogenes* was isolated from a normally sterile site. Cases are classified as either non-pregnancy-related in individuals over four weeks old, or pregnancy-related where a mother and/or fetus/newborn of less than four weeks old are affected. An affected mother and newborn are classified as one pregnancy-related case. Pregnancy-related cases that involve a live birth are routinely stratified further into early and late onset cases, as described above.

All cases of listeriosis are routinely classified as either 'ethnic' (belonging to an ethnic minority) or 'non-ethnic' (not belonging to an ethnic minority) based on their first name and surname, where available. This classification is in addition to case-reported ethnicity, reported via the standard exposure questionnaire since 2005 and based on the 2001 UK census classification [14]. Name-based classification was used throughout the study period from 2001 to 2008, and used in analyses, while case-reported ethnicity data, were used to validate the name-based approach only. The numbers of live births, recorded in England and Wales from 2001 to 2008 and stratified by country of birth of mother, were obtained from the Office for National Statistics [15] and used as denominator data. The number of live births (i.e. not including stillbirths, miscarriages and abortions) to mothers who were born outside of the UK was used for comparative analyses with the number of pregnancy-related cases that were classified as ethnic, using the name-based approach. Similarly, the number of live births to mothers born in the UK was used for comparative analyses with the number of pregnancy-related cases that were classified as non-ethnic. Both denominator datasets included live births to mothers whose usual residence was outside of the UK, accounting for 1.1% of live births to mothers who were born outside the UK and 0.2% of live births to mothers born in the UK.

Statistical analyses were carried out using Stata version 10 and Epi Info. Trends in proportions were investigated using the chi-square test for trend while differences in proportions employed the chi-square test and Fisher's exact test as appropriate. Relative risks (RR) and corresponding 95% confidence intervals (CI) were calculated. Poisson regression was employed for multivariable analysis: incidence in pregnancy-related cases belonging to an ethnic minority, relative to pregnancy-related cases not belonging to an ethnic minority, were calculated whilst controlling for trend over the surveillance period. A log-link function was included to control for differences in the underlying population-live births to mothers born outside and inside the UK respectively in each year.

Linear regression models were fitted to live births to mothers born outside and inside the UK data for January to September, 2001 to 2008, and predictions (with corresponding 95% prediction intervals) for this denominator population were obtained for 2009 based on the linear trend of the previous years. For 2009, the RR was estimated using the number of provisional cases between January and September and estimated denominator predictions for this period. An uncertainty interval around the RR was calculated based on the CIs calculated for the upper and lower prediction intervals.

Results

Study population

Between 2001 and 2008, 1,510 cases of listeriosis were reported in England and Wales and, of these, 12% were pregnancy-related. The proportion of cases that were pregnancy-related did not change during the study period (chi-square test for trend p=0.866; Figure). Of all cases reported, 12.3% were classified as ethnic cases, 86.7% as non-ethnic cases and the remaining 1% could not be classified as ethnic or non-ethnic by

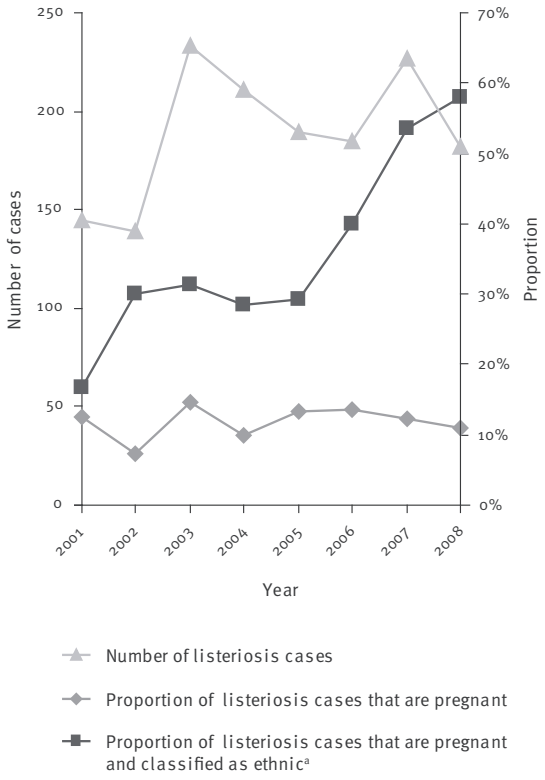
their name. Of the 181 pregnancy-related cases, 36.5% had ethnic names while 63% did not. One case in 2005 did not have a recorded name and, hence, ethnicity could not be established. This case was therefore not considered in these analyses. The proportion of pregnancy-related cases classified as having ethnic names over the whole study period was greater than that for non pregnancy-related cases (37% vs. 9% respectively; chi-square test p<0.001).

Incidence

Amongst pregnancy-related cases, there was a significant increase in the proportion of cases classified as ethnic, from 16.7% to 57.9% (chi-square test for trend P=0.002), during the study period (Figure). This change in proportion was not observed for non-pregnancy-related cases (chi-square test for trend p=0.124). The increasing proportion of pregnancy-related cases classified as ethnic was most noticeable in 2006, 2007 and 2008, during which years the reported incidences of ethnic cases were higher than that expected in the underlying population (RR: 2.38, 95%CI: 1.07 to 5.29; 3.82, 1.82 to 8.03; 4.33, 1.74 to 10.77; respectively) (Table 1). Poisson regression indicated that there was a significant increase in incidence of ethnic cases after adjusting for the trend observed over the study period (RR: 2.25, 95%CI: 1.66 to 3.05).

Figure

Total number of listeriosis cases (n=1,510), proportion of cases that are pregnant and proportion of pregnant cases classified as ethnic[a], England and Wales, 2001-2008



[a] Cases were classified as either ethnic or non-ethnic based on their name.

Pregnancy-related cases classified as ethnic and reported between 2006 and 2008 (the years with an observed significant increase) were distributed across eight of nine regions in England and in Wales. A greater proportion of these pregnancy-related cases classified as ethnic were reported in London (47.2% of all ethnic cases in England and Wales vs. 11.1% of all non-ethnic cases) when compared with elsewhere (52.7% vs. 88.9%; chi-square test p<0.001). This level was above that expected, based on the number of live births in London during this period (RR: 3.66, 95%CI: 1.23 to 10.89). Based on provisional case data for January to September 2009 (16 ethnic cases and 10 non-ethnic cases) and extrapolated live births denominator data for the same period (425,495 live births to mothers born within the UK and 128,148 live births to mothers born outside of the UK), there remains an increased risk associated with ethnic minorities for this period (RR: 5.31, 95% uncertainty interval: 2.33 to 12.20). All subsequent analyses relate to pregnancy-related cases, henceforth referred to as 'cases'.

Clinical data

There was no significant difference in the proportion of clinical questionnaires returned for ethnic and non-ethnic cases (91% vs. 94% respectively; Fisher's exact test p=0.553). There was also no difference in the proportion of infecting serotypes that were 1/2 compared with 4 between ethnic and non-ethnic cases (31% vs. 24% respectively; chi-square test p=0.390). When characteristics of ethnic and non-ethnic cases with a returned clinical questionnaire were compared, there was no significant difference in the recorded outcome of pregnancy, newborn survival, the stage of onset of symptoms in the newborn (early vs. late onset) or presentation with either meningitis or septicaemia in the newborn (Table 2). However, newborns born to ethnic mothers were more likely to present with symptoms of listeriosis at birth (chi-square test p=0.039) and these cases were more likely to come from more deprived areas (chi-square test for trend p<0.001), with almost half of the ethnic cases belonging to the most deprived group (Table 3).

Exposure data

There was no significant difference in the proportion of exposure questionnaires returned for ethnic and non-ethnic cases (58% vs. 47% respectively; chi-square test p=0.285). Of the 37 cases for which exposure and clinical data were available, 18 were classed as ethnic on the basis of their name. The cases defined as ethnic were more likely to describe their own ethnicity as 'non-white British', i.e. as something other than white British, compared with all cases (positive predictive value 94.4% and negative predictive value 68.4%)(Table 3). No single country or group of countries (e.g. countries within the Indian sub-continent)

predominated for cases who described themselves as non-white British (Table 4).

Cases defined as ethnic on the basis of their name were significantly more likely to consume pâté, cabbage or dill. In addition, they were more likely to shop in two national supermarket chains A and B or green grocers but less likely to shop in local bakeries (Table 5).

Discussion

We report a sustained increase in the incidence of pregnancy-related cases of listeriosis from ethnic

Table 1

Pregnancy-related listeriosis cases by name-based ethnicity classification[a] (n=180), number of live births to mothers born outside (n=1,055,827) and within the United Kingdom (n=4,110,279) and related relative risks, England and Wales, 2001-2008

Year	Number of ethnic[a] pregnancy-related listeriosis cases	Number of live births to mothers born outside the UK	Number of non-ethnic[a] pregnancy-related listeriosis cases	Number of live births to mothers born in the UK	Relative Risk (95% confidence intervals)
2001	3	98,115	15	496,519	1.01 (0.29-3.5)
2002	3	105,514	7	490,608	1.99 (0.52-7.71)
2003	11	115,593	24	505,876	2.01 (0.98-4.09)
2004	6	124,746	15	514,975	1.65 (0.64-4.26)
2005	7	134,334	17	511,501	1.57 (0.65-3.78)
2006	10	146,643	15	522,958	2.38 (1.07-5.29)
2007	15	160,083	13	529,930	3.82 (1.82-8.03)
2008	11	170,799	8	537,912	4.33 (1.74-10.77)
Total	**66**	**1,055,827**	**114**	**4,110,279**	

UK: United Kingdom.

[a] Cases were classified as either ethnic or non-ethnic based on their name.

Table 2

Characteristics of pregnancy-related listeriosis cases with a returned clinical questionnaire by name-based ethnicity classification[a], England and Wales, 2001-2008 (n=167)

Factor	Ethnicity of pregnancy-related listeriosis cases[a]	
	Ethnic	Non-ethnic
	(N=60)	(N=107)
Death related with pregnancy (miscarriage, stillbirth, or death)		
Yes	15/49	22/81
No	34/49	59/81
Pregnancy Outcome		
Live birth	47/57	71/91
Miscarriage	6 /57	16 /91
Stillbirth	2 /57	3 /91
Still pregnant	2 /57	1/91
Survival of live births		
Survived	32 /39	53/56
Died	7 /39	3 /56
Onset type of live births		
Early Onset (≤48 hrs)	28/38	30/43
Late Onset (>48hrs)	10/38	13/43
Symptoms of listeriosis in newborns		
Yes	38/45	40/60
No	7 /45	20/60
Meningitis in newborns		
Yes	11/16	3/6
No	5/16	3/6
Septicaemia in newborns		
Yes	14/17	12/15
No	3/17	3/15

[a] Cases were classified as either ethnic or non-ethnic based on their name, 'unknowns' were excluded in these analyses.

minorities in England and Wales between 2006 and 2008, with provisional case data suggesting that this increase continued into 2009 when compared with estimated population data. This increase was not observed amongst non pregnancy-related cases. An increase in pregnancy-related listeriosis in women born outside of the country was reported in Ireland in late 2007 [16]. Listeriosis has also been reported as

Table 3

Socio-economic status of pregnancy-related listeriosis cases with a returned clinical questionnaire by name-based ethnicity classification[a], England and Wales, 2001-2008 (n=161)

Socio-economic status	Ethnic[a] pregnancy-related listeriosis cases N=59	%	Non-ethnic[a] of pregnancy-related listeriosis cases N=102	%
IMD 1 (least deprived)	4/59	7	19/102	19
IMD 2	4/59	7	26/102	25
IMD 3	8/59	14	6/102	6
IMD 4	15/59	25	24/102	24
IMD5 (most deprived)	28/59	47	27/102	26

IMD: Indices of Multiple Deprivation [12].

[a]Cases were classified as either ethnic or non-ethnic based on their name, 'unknowns' were excluded in these analyses.

Table 4

Case-reported ethnicity data (as per 2001 census classification system) of pregnancy-related listeriosis cases by name-based ethnicity classification[a], England and Wales, 2005-2008 (n=37)

Case-reported ethnicity	Name-based ethnicity	
	Ethnic[a] (N=18)	Non-ethnic[a] (N=19)
White (British)	1/18	13/19
White (Non-British)	5 /18	2/19
Black African	2/18	1/19
White/Black Caribbean	0/18	1/19
Indian	4/18	1/19
Pakistani	1/18	0/19
Chinese	1/18	0/19
Other Asian	2/18	1/19
Other Ethnic	2/18	0/19
Total (other than white British)	**17/18**	**6 /19**

[a] Cases were classified as either ethnic or non-ethnic based on their name, 'unknowns' were excluded in these analyses.

Table 5

Food history of pregnancy-related listeriosis cases by name-based ethnicity classification[a], England and Wales, 2005-2008 (n=37)

Food history	Ethnic[a] pregnancy-related listeriosis cases (n=18)	Non-ethnic[a] pregnancy-related listeriosis cases (n=19)	p-value
Consumption of pâté	5/18	0/19	0.020[b]
Consumption of cabbage	8/16	1/19	0.005[b]
Consumption dill	5/16	0/18	0.016[b]
Shopped in national supermarket chain A	4/18	0/19	0.046[b]
Shopped in national supermarket chain B	8/18	1/19	0.008[b]
Shopped at green grocers	7/18	0/19	0.003[b]
Shopped at local bakeries	3/18	9/19	0.046[c]

[a] Cases were classified as either ethnic or non-ethnic based on their name, 'unknowns' were excluded in these analyses.

[b] Fisher's exact test.

[c] Chi-square test.

disproportionately affecting pregnant Hispanic women in the United States [17,18] and pregnant women living in a household where a language other than English was spoken in Australia [19]. To the authors' knowledge, the sustained increase reported in this study has not been previously described elsewhere. Pregnancy-related listeriosis cases comprise the minority of what is already a rare disease, and by this very nature any changes in incidence trends within this population will only become evident after a number of years.

Differences in health seeking behaviour and access to healthcare between ethnic minorities and the general population may impact on our incidence estimates, but this is difficult to assess. It is reasonable to assume that new migrants to the UK may find it more difficult to access the existing healthcare services than UK residents.

There appears to be no differential ascertainment of clinical and exposure data between ethnic and non-ethnic cases which minimises the likelihood of this form of bias affecting our findings. Analyses performed on those cases with a completed clinical questionnaire returned indicate that, compared to non-ethnic cases, ethnic cases were more likely to be from more deprived areas and newborns more often displayed symptoms of listeriosis at birth. It has previously been established that ethnic minorities reside disproportionately in more deprived areas [20] and this would explain the distribution of these pregnancy-related cases. Differential symptom presentation at birth may reflect differences in gestational age at time of infection (i.e. trimester) or route of infection (*in utero* or during passage through the birth canal) between ethnic and non-ethnic cases but this needs further investigation. Furthermore, we could not assess any differences in terms of clinical characteristics and exposures amongst those that did not have a completed clinical or exposure questionnaire returned in our analyses.

Cases' own description of their ethnic background was used to validate the name-based classification method of ethnicity employed in this study. The negative predictive value for this approach indicates that approximately 30% of cases defined as non-ethnic report their own ethnicity as something other than white British. Consequently, the number of pregnancy-related cases defined by their name as ethnic seems to underestimate the number of those belonging to an ethnic group other than white British. Therefore, the risk of pregnancy-related listeriosis associated with ethnic minorities is likely to be greater than that reported here. Regardless, any misclassification is likely to be non-differential over the study period and would therefore not affect the observed increase in pregnancy-related listeriosis in the ethnic group.

The reporting of certain foods and retail exposures differed between ethnic pregnancy-related cases and non-ethnic pregnancy-related cases. However, it is important to note that comparisons are not being made with controls without illness and hence, findings should not be considered as risk factors for infection [21]. Furthermore, such case-case comparisons would not indicate the magnitude or direction of risk among pregnancy-related cases and should only be used for hypothesis generation, which then need to be tested by alternative methodologies. If exposures were common to both ethnic and non-ethnic groups, they would have been underestimated or, indeed, would have remained unidentified using this method. It is important to bear in mind that ethnic minorities are a heterogeneous group who likely vary in their food preferences and behaviours. The sample size of this study did not allow for analyses of strata within this group. Nevertheless, the consumption of pâté was reported more commonly by ethnic than non-ethnic pregnancy-related cases, suggesting that food safety advice issued by the UK government is not reaching this at-risk population or is not being followed.

Incidence was calculated by comparing cases classed as ethnic or non-ethnic with the numbers of live births by country of origin of mother (non-UK born and UK born respectively). Differences between the numerator and the denominator may have affected the accuracy of our risk estimates. Firstly, live birth data will exclude instances of stillbirth or miscarriage – these are both included in the numerator - and, consequently, the risk of listeriosis will be over estimated. The denominator data employed in the analyses also included mothers whose usual country of residence was outside of the UK, while cases living outside the UK are not reported to this surveillance scheme and would not be represented in this numerator. While these mothers represent only a small proportion of the total, inflation of the denominator will lead to some underestimation of risk. The final, and perhaps most important, consideration is that the numerator refers to cases (mothers/newborns/both) stratified by ethnicity whereas the denominator refers to live births to mothers stratified by country of birth. A mother could, however, be born in the UK and belong to an ethnic minority but this was the best available proxy for ethnicity of mothers of live births. While there are limitations to using live birth data by country of origin of mother, there was a need to assess the observed increasing trend in the context of population change, and our study suggests that the increase in incidence is over and above what would be expected.

Conclusions

Increased immigration and/or economic migration in recent years appear to have altered the population most at risk of pregnancy-related listeriosis in England and Wales. The increase in the number of pregnancy-related cases belonging to an ethnic minority has disproportionately affected London, where migration has directly increased the number of new births in some local authorities [22]. Passive food safety messages, which highlight high-risk foods, appear not to be

reaching pregnant women from ethnic minorities or are not being followed by this emerging at-risk population. More specific and targeted routes of communication and materials, which should be both culturally-relevant and in a range of appropriate languages, are needed. Our findings should be considered by those targeting risk communication strategies to vulnerable groups. Studies to identify which ethnic minorities are most at risk would provide further valuable information on how to more effectively tailor communication strategies.

Acknowledgements

Thanks are extended to the hospital microbiologists, environmental health officers and public health professionals who contribute to this surveillance system.

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Appendix 2. Co-authors' statements of candidate's contribution

PhD by published work, Warwick Medical School, University of Warwick

Statement of contribution by Piers Andrew Nicholas Mook

Paper to be considered as part of the PhD by published work:

Gillespie IA, McLauchlin J, Little C, Penman C, Mook P, O'Brien S J. Disease presentation in relation to infection foci for non-pregnancy-associated human listeriosis in England and Wales, 2001 to 2007. *J.Clin.Microbiol.* 2009; 47: 3301-3307

Study circumstances: This study was carried out after a near doubling in the average number of cases of listeriosis reported annually in England and Wales between 1990 to 1999 and 2001 to 2007. This increase, which was not considered to be artefactual, occurred predominantly in patients aged over 60 years who presented with bacteraemia in the absence of central nervous system (CNS) infection. The aim of this study was to better understand the altered presentation, using national surveillance data to compare the clinical, microbiological and seasonal characteristics of bacteraemic cases with that for cases with CNS infection. This work was carried out by the Health Protection Agency, Gastrointestinal, Emerging and Zoonotic Infections Department, where Piers Mook was an epidemiologist.

Contribution of candidate: Piers Mook validated the employed coding scheme and provided comments on this manuscript.

I agree that Piers Andrew Nicholas Mook made the aforementioned contribution to this paper.

Name	Signature	Date
Iain Gillespie	[redacted]	30/1/12
Jim McLauchlin		14/02/12
Christine Little		14/02/12
Celia Penman		15/2/2012
Sarah O'Brien		03/02/12

PhD by published work, Warwick Medical School, University of Warwick

Statement of contribution by Piers Andrew Nicholas Mook

Paper to be considered as part of the PhD by published work:

Mook P, Gillespie IA, O'Brien SJ. Concurrent Conditions and Human Listeriosis, England and Wales, 1999–2009 . *Emerg.Infect.Dis.* 2011; 17: 38-43

Study circumstances: Underlying medical conditions that result in immuncompromisation can increase an individual's susceptibility to *L. monocytogenes* infection. This study was conducted to quantify the risk of disease by concurrent condition using an internationally recognised disease classification system (ICD-10) and Finished Consultant Episode data from Hospital Episode Statistics as the denominator. It was hoped that finding from this study might augment the current evidence base for policy makers to consider when targeting food safety advice to at vulnerable groups for listeriosis. This study was carried out by the Health Protection Agency, Gastrointestinal, Emerging and Zoonotic Infections Department, where Piers Mook was an epidemiologist.

Contribution of candidate: Piers Mook took a lead role in the study design, coding scheme and statistical method. He managed and coded the study data, performed the statistical analysis, took a lead in writing the manuscript in liaison with co-authors and responded to reviewers as corresponding author.

I agree that Piers Andrew Nicholas Mook made the aforementioned contribution to the paper.

Name	Signature	Date
Iain Gillespie	[redacted]	30/1/12
Sarah O'Brien	[redacted]	03/02/12

PhD by published work, Warwick Medical School, University of Warwick

Statement of contribution by Piers Andrew Nicholas Mook

Paper to be considered as part of the PhD by published work:

Mook P, Patel B, Gillespie IA. Mortality risk factors among human cases of listeriosis in England and Wales, 1990 to 2009. *Epidemiol.Infect.* 2011; Available on CJO 2011 doi:10.1017/S0950268811001051

Study circumstances: Listeriosis has a high case fatality ratio but there had been no previous assessment of what factors were prognostic on outcome of infection among cases in England and Wales. This study interrogated national surveillance data to identify risk factors for mortality among non-pregnancy related cases. This study was carried out by the Gastrointestinal, Emerging and Zoonotic Infections Department, where Piers Mook was an epidemiologist.

Contribution of cadidate: Piers Mook took a lead role in the study design, coding scheme and statistical method. He managed and coded the study data, performed the statistical analysis, took a lead role in drafting the paper in liaison with co-authors and responded to reviewers as corresponding author.

I agree that Piers Andrew Nicholas Mook made the aforementioned contribution to this paper.

Name	Signature	Date
Bharat Patel	[redacted]	5/3/12
Iain Gillespie		30/1/12

PhD by published work, Warwick Medical School, University of Warwick

Statement of contribution by Piers Andrew Nicholas Mook

Paper to be considered as part of the PhD by published work:

Mook P, Jenkins J, O'Brien SJ, Gillespie IA. Existing medications amongst listeriosis patients in England, 2007-2009. *Epidemiol.Infect.* 2011; Submitted

Study circumstances: In addition to the direct effect of concurrent conditions, treatments for these conditions might also result in immunocompromisation, which can increase an individual's susceptibility to *Listeria monocytogenes* infection. In order to investigate the relative role of existing medication on the risk of listeriosis, medications reported by non-pregnancy related cases were coded according to the British National Formulary (BNF) and compared with NHS prescription services data. This study was carried out by the Gastrointestinal, Emerging and Zoonotic Infections Department, where Piers Mook was an epidemiologist

Contribution of candidate: Piers Mook took a lead role in the study design, coding scheme and statistical method. He managed and coded the study data, performed the statistical analysis, took the lead role in drafting the paper in liaison with co-authors and responded to reviewers as corresponding author.

I agree that Piers Andrew Nicholas Mook made the aforementioned contribution to the paper.

Name	Signature	Date
John Jenkins	[redacted]	13/02/12
Sarah O'Brien		03/02/12
Iain Gillespie		30/1/12

PhD by published work, Warwick Medical School, University of Warwick

Statement of contribution by Piers Andrew Nicholas Mook

Paper to be considered as part of the PhD by published work:

Gillespie IA, Mook P, Little CL, Grant KA, McLauchlin J. Human listeriosis in England, 2001-2007: association with neighbourhood deprivation. *Euro.Surveill* 2010; 15: 7-16

Study circumstances: Putative socio-economic determinants had not been investigated in detail for this potentially severe disease. This study was carried out to investigate health inequalities which might exist in relation to listeriosis. Reported cases in England with postcodes were linked to Office for National Statistics Lower Super Output Areas, combined with 2005 Indices of Deprivation and merged with appropriate population data. Patient exposure data were interrogated and comparison made with commercial food purchasing denominator data to further quantify risk. This study was carried out by the Health Protection Agency, Gastrointestinal, Emerging and Zoonotic Infections Department, where Piers Mook was an epidemiologist.

Contribution of candidate: Piers Mook validated the coding scheme and reviewed the manuscript prior to submission.

I agree that Piers Andrew Nicholas Mook made the aforementioned contribution to this paper.

Name	Signature	Date
Iain Gillespie	[redacted]	30/1/12
Christine Little		14/02/12
Kathie Grant		14/02/12
Jim McLauchlin		14/02/12

PhD by published work, Warwick Medical School, University of Warwick

Statement of contribution by Piers Andrew Nicholas Mook

Paper to be considered as part of the PhD by published work:

Gillespie IA, Mook P, Little CL, Grant K, Adak GK. Listeria monocytogenes Infection in the Over-60s in England Between 2005 and 2008: A Retrospective Case-Control Study Utilizing Market Research Panel Data. *Foodborne.Pathog.Dis.* 2010; 7: 1373-9

Study circumstances: Standardised epidemiological exposure information has been sought on cases of listeriosis in England and Wales since 2005. However, the added value of these accrued data on informing on high risk exposures for disease is limited without some perception of the prevalence of these same exposures in the population at risk of listeriosis. The exposures of reported cases in England were compared to those of market research panel members representing the same population and time period (over 60 years between 2005 and 2008). This study used commercial denominator from the Worldpanel Usage database from the market research company Taylor Nelson Sofres and was carried out by the Health Protection Agency, Gastrointestinal, Emerging and Zoonotic Infections Department, where Piers Mook was an epidemiologist.

Contribution of candidate: Piers Mook was partially responsible for initiating this study, in that he suggested that it would be interesting to look at the findings from the deprivation study in the context of supermarket distribution. He discussed the methodology with the lead author throughout the development of this study and reviewed the analysis and manuscript prior to submission.

I agree that Piers Andrew Nicholas Mook made the aforementioned contribution to this paper.

Name	Signature	Date
Iain Gillespie	[redacted]	30/1/12
Christine Little		14/02/12
Kathie Grant		14/02/12
Goutam Adak		15/02/12

PhD by published work at Warwick Medical School, University of Warwick

Statement of contribution by Piers Andrew Nicholas Mook

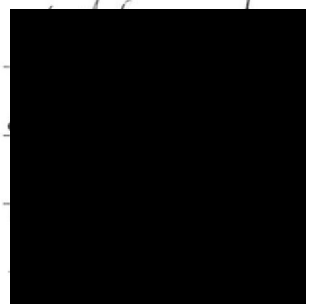
Paper to be considered as part of the PhD by published work:

Mook P, Grant KA, Little CL, Kafatos G, Gillespie IA. Emergence of pregnancy-related listeriosis amongst ethnic minorities in England and Wales. *Euro.Surveill* 2010; 15: 17-23

Study circumstances: While the annual rate of pregnancy-related listeriosis remained static in contrast to that for non-pregnancy related listeriosis for the period 2001 to 2008, two coincident yet unconnected cases of pregnancy-associated listeriosis in 2008 in eastern European women reported to the national listeriosis surveillance system for England and Wales prompted this study into the role of ethnicity in pregnancy-related listeriosis for this period. It was carried out by the Health Protection Agency, Gastrointestinal, Emerging and Zoonotic Infections Department, where Piers Mook was an epidemiologist.

Contribution of candidate: Piers Mook took a lead role in the study design, coding scheme and statistical method. He managed and coded the study data, performed the statistical analysis, took a lead role in writing the manuscript in liaison with co-authors and responded to reviewers as corresponding author.

I agree that Piers Andrew Nicholas Mook made the aforementioned contribution to this paper.

Name	**Signature**	**Date**
Kathie Grant		14/02/12
Christine Little		14/02/12
George Kafatos		14/2/12
Iain Gillespie		30/1/12

Appendix 3. National listeriosis surveillance questionnaires

Appendix 3.1 Clinical questionnaire

In strict medical confidence

Surveillance of Listeriosis, England and Wales.

1. Your details.

Microbiologist: _____ Date of completion: ____ /____ /____

Laboratory: _____

2. Specimen details.

Specimen reference no.: _____ Specimen date: ____ /____ /_____

Source of culture: Blood ☐ CSF ☐ HVS ☐ Other ☐ (please specify) _____

3. Patient details. ('patient' refers to positive isolate)

First Name: _____ Surname: _____

Town: _____ Postcode _____

Date of Birth: _____ Age ____ years Gender: Male ☐ Female ☐

Ethnicity: _____

4. Clinical details.

Date of onset of illness: ____ /____ /____ Did the patient die? Yes ☐ No ☐

Hospital of original admission: _____ Admission date: ____ /____ /____

Principal *Listeria* illness (tick all that apply):

Meningitis ☐ Septicaemia ☐ Gastroenteritis ☐ Other ☐ (specify): _____

What antibiotics have been used to treat this Listeria infection?

_____

Signs and symptoms (tick all that apply):

Nausea ☐ Vomiting ☐ Diarrhoea ☐ Abdominal pain ☐ Fever ☐ Chills ☐ Headache ☐

Myalgia ☐ Arthralgia ☐ Backache ☐ Seizures ☐ Ataxia ☐ Tremors ☐ Myoclonus ☐

Nuchal rigidity ☐ Confusion ☐ Other ☐ (specify)_____ _____

In strict medical confidence
Does the patient have an underlying illness/condition?

No ☐ Yes ☐ (specify): _____

Was the patient taking any of the following (please tick):

immunosuppressives ☐ cytotoxics ☐ steroids ☐ **or** No ☐ **or** Unknown ☐

If yes, please specify: _____

Does the patient have reduced Gastric Acid secretion? Yes ☐ No ☐ Unknown ☐

If yes, please specify: _____

5. **Pregnancy-associated cases.** (for non-pregnancy cases please go to section **6,** page 3)

i) Mother's details (if not recorded above)

First Name: _____ Surname: _____

Town: _____ _____ Postcode: _____

Date of Birth: ___ /___ /___ Age ___ years

Hospital of original admission: _____

ii) Details of the pregnancy.

Outcome of pregnancy: Live birth ☐ Still birth ☐ Miscarriage ☐ Still pregnant ☐

Date of Delivery / Miscarriage: ____ /____ /____

Expected Date of Delivery (EDD): ___ /___ /___ Gestation at pregnancy end: _____ weeks

During pregnancy did the mother have symptoms suggestive of Listeriosis? Yes ☐ No ☐

If yes, what were the main features of this illness (tick all that apply):

Flu-like (pyrexia / myalgia / headache / fatigue) ☐ Gastroenteritis ☐ Abdominal pain ☐ Night sweats ☐

Other ☐ *please specify*_____

Date of onset of this illness: ____ /____ /____ Gestational stage of first onset of this illness: _____ weeks

Was *Listeria* infection in the mother confirmed microbiologically? Yes ☐ No ☐

In strict medical confidence
iii) Details of the infant (if applicable)

First Name: _____ Surname: _____

Date of Birth: ____ /____ /____ Gender of infant: Male ☐ Female ☐

If a live birth, did the infant survive? Yes ☐ No ☐

If a live birth, was the infant ill with Listeriosis? Yes ☐ No ☐

If *yes*, please state age at onset? _____ days

Nature of the infant's *Listeria* illness:

Meningitis ☐ Septicaemia ☐ Other ☐ (specify) _____

Was the infant's infection (if present) due to vertical transmission from the mother? Yes ☐ No ☐

If yes, was cross contamination the cause? Yes ☐ No ☐

6. Linked cases.

Is it thought that this case could be linked to any other case(s)? Yes ☐ No ☐

If yes, please give their full Name(s): 1. _____

2. _____

Please tick if culture(s) have been sent for typing for: case 1 ☐ case 2 ☐

7. Food history.

Was the *Listeria* infection linked to suspect food Item(s) eaten by the patient? Yes ☐ No ☐

If yes, please specify: _____

Thank you for completing this questionnaire

Please return it in the pre-paid envelope provided.

- If you have any specific questions about this questionnaire or Listeria surveillance please call or write to: Piers Mook. Health Protection Agency Centre for Infections, 61 Colindale Avenue, London, NW9 5EQ. Tel. 020 8327 7486
- If you have any specific questions about Listeria typing please call or write to:

  Dr Kathie Grant. Food Safety Microbiology Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Ave, London NW9 5HT Tel. 020 8327 7118
- If cultures are available but have not been sent, please forward to:

  Dr Kathie Grant. Food Safety Microbiology Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London, NW9 5EQ. Tel. 020 8327 7118

Appendix 3.2 Trawling Questionnaire

In strict medical confidence Ref No ☐☐☐

Listeria monocytogenes
Trawling Questionnaire

Version 1 June 2005

- Any information supplied will be treated as strictly confidential.
- Please tick boxes (☐), or write in the spaces (____) provided.
- Please use black or dark blue biro/pen.
- **If you are answering on behalf of someone else, please remember that these questions refer to the *person that is/was ill* and not yourself.**
- "No" and "Not sure" answers are as important as "Yes" answers. If you leave a blank space we cannot interpret the intended answer.

Interviewee: Patient ☐ Proxy ☐ (relationship to patient) _____

Interviewer's name _____ Date of interview ____/____/____

SECTION 1. PERSONAL DETAILS

1.1 Forename (s): _____ **1.2** Surname: _____

1.3 Address: _____

_____ **1.4** Postcode. _____

1.5 Daytime telephone number: _____

1.6 Gender: Male ☐ Female ☐

1.7 Date of Birth: ____/____/____ dd/mm/yy **1.8** Age _____ years

1.9 Describe your ethnic background (please tick one):

White:

☐ British ☐ Irish ☐ Other (please state) _____

Mixed:

☐ White/Black Caribbean ☐ White/Black African

☐ White/Asian ☐ Other (please state) _____

Asian/Asian British:

☐ Indian ☐ Pakistani ☐ Bangladeshi

☐ Other (please state) _____

Black/Black British:

☐ Caribbean ☐ African ☐ Other (please state) _____

Chinese or other ethnic group:

☐ Chinese ☐ Other (please state) _____

1.10 GP's name: _____

1.11 Practice address: _____

1.12 Occupation (if currently unemployed, what was your most recent occupation; if retired, what was your main occupation):

_____

_____

1.13 Name and address of workplace/school/nursery/playgroup (as applicable):

_____

_____

SECTION 2. MEDICAL DETAILS

2.1 Did you have any acute or significant health problems in the month before your illness?

Yes ☐ No ☐ Not sure ☐

If yes, please describe _____

2.2 Did you have any other ongoing or long-standing medical conditions before your *Listeria* infection (e.g. heart problems, diabetes etc)?

Yes ☐ No ☐ Not sure ☐

If yes, please describe _____

2.3 Were you taking any medicine, either prescribed by your Doctor or bought from a chemist etc, in the two weeks before your illness?

Yes ☐ No ☐ Not sure ☐

If yes, please describe _____

2.4 Did you attend a health care facility (e.g. a hospital or a nursing home) in the 30 days before you became ill?

Yes ☐ No ☐ Not sure ☐

If yes please give details: (place, dates, food eaten etc.)

Hospital/nursing home visit or treatment	Date of visit/treatment	Discharge Date (if treated)
_____	____/____/____	____/____/____
_____	____/____/____	____/____/____
_____	____/____/____	____/____/____

SECTION 3. CASE HISTORY

3.1 When did you start to feel unwell with Listeria? ____/____/____ dd/mm/yy

3.2 Did you have any of the following symptoms (can tick more than one):

	Yes	No		Yes	No
Nausea	☐	☐	Headache	☐	☐
Vomiting	☐	☐	Muscle aches	☐	☐
Diarrhoea	☐	☐	Joint aches	☐	☐
Abdominal pain	☐	☐	Backache	☐	☐
Fever	☐	☐	Neck stiffness	☐	☐
Chills	☐	☐	Confusion	☐	☐
Other	☐	☐			

If other please specify: _____

3.3 Are you still ill with Listeria? Yes ☐ No ☐ Not sure ☐

If no, how many days were you ill for? _____ days

3.4 Were you admitted to hospital for this illness? Yes ☐ No ☐

If yes, which hospital? _____

3.5 Date of admission ____/____/____ Date of discharge ____/____/____

If exact dates are not known, how many days were you in hospital for? _____ days

SECTION 4. TRAVEL HISTORY

4.1 Did you spend any nights outside the UK in the **30 DAYS** before you became ill?

Yes ☐ No ☐

If **YES**, give details:

Country(ies) visited: _____

Dates of travel: departure ____/____/____ return ____/____/____

Addresses of places stayed (e.g. towns, hotels, campsites etc):

_____

_____

_____

4.2 Did you spend any nights away from home within the UK in the **30 DAYS** before you became ill? (e.g: includes staying at friends/relatives, business trips etc)

Yes ☐ No ☐

Dates of travel: departure ____/____/____ return ____/____/____

Addresses of places stayed : (eg: friend's house, towns, hotels, campsites etc)

_____

_____

_____

4.3 Did you go on any day trips within the UK in the **30 DAYS** before you became ill? (e.g. business/shopping trips etc)

Yes ☐ No ☐

Names and addresses of places visited (include post code if known or area e.g. Central London)

_____

_____

SECTION 5. FOOD HABITS

5.1 Do you follow any particular diets or only eat certain types of food?

No ☐

Yes - vegetarian ☐

Yes - vegan ☐

Yes - Kosher ☐

Yes - Halal ☐

Yes - organic food ☐

Yes - other ☐ _____

5.2 Do you avoid any of the following foods? (tick any that apply)

Soft/blue cheese ☐

Paté ☐

Raw fish (e.g. sushi) ☐

Smoked fish (e.g: smoked salmon etc.) ☐

Sliced uncooked meats (e.g: parma ham etc.) ☐

Butter ☐

Pre-cut/pre-packed fruits (e.g. fruit salad, melon etc.) ☐

SECTION 6. FOOD HISTORY

6.1 Did you eat any foods from any of the following in the **30 DAYS** before you started to feel ill?

	No	Yes	Date/location/brand etc
Coffee shop	☐	☐	_____
Bakers shop	☐	☐	_____
Sandwich bar	☐	☐	_____
Pub	☐	☐	_____
Canteen	☐	☐	_____
Hospital canteen	☐	☐	_____
Hospital snack bar	☐	☐	_____
Burger bar	☐	☐	_____
Pizza parlour	☐	☐	_____
Fast food restaurants	☐	☐	_____
Delicatessen	☐	☐	_____
British restaurant	☐	☐	_____
Ethnic restaurants	☐	☐	_____
Reception/wake	☐	☐	_____
Hotel	☐	☐	_____
Mobile caterer	☐	☐	_____
Airport	☐	☐	_____
Railway station/train	☐	☐	_____
Petrol station	☐	☐	_____
Other	☐	☐	_____

SECTION 6. FOOD HISTORY - BEEF

6.2 Did you eat any of the following **unheated/ready to eat** beef items in the **30 DAYS** before you became ill?

	No	Yes	Date/location/brand etc
Cold cooked beef	☐	☐	_____
Prepacked sliced beef	☐	☐	_____
Loose-sold sliced beef	☐	☐	_____
Prepacked salt beef	☐	☐	_____
Loose-sold salt beef	☐	☐	_____
Prepacked pastrami	☐	☐	_____

Loose-sold pastrami	☐	☐	_____

	No	Yes	Date/location/brand etc
Potted beef	☐	☐	_____
Tongue	☐	☐	_____
Brawn	☐	☐	_____
Other	☐	☐	_____

SECTION 6. FOOD HISTORY - PORK

6.3 Did you eat any of the following **unheated/ready to eat** pork items in the **30 DAYS** before you became ill?

	No	Yes	Date/location/brand etc
Cold roast pork	☐	☐	_____
Prepacked sliced ham	☐	☐	_____
Loose-sold sliced ham	☐	☐	_____
Prepacked smoked ham	☐	☐	_____
Loose-sold smoked ham	☐	☐	_____
Dry cured ham	☐	☐	_____
Dry fermented sausages	☐	☐	_____
Sausages	☐	☐	_____
Frankfurter sausages	☐	☐	_____
Sausage rolls	☐	☐	_____
Pork pies	☐	☐	_____
Scotch eggs	☐	☐	_____
Liver sausage	☐	☐	_____
Paté	☐	☐	_____
Other	☐	☐	_____

SECTION 6. FOOD HISTORY - POULTRY

6.4 Did you eat any of the following **unheated/ready to eat** poultry items in the **30 DAYS** before you became ill?

	No	Yes	Date/location/brand etc
Cold roast chicken	☐	☐	_____
Prepacked cooked chicken	☐	☐	_____
Prepacked sliced chicken	☐	☐	_____
Chicken sandwich meat	☐	☐	_____

Chicken pies	☐	☐	_____
Cold roast turkey	☐	☐	_____

	No	Yes	Date/location/brand etc
Prepacked cooked turkey	☐	☐	_____
Prepacked sliced turkey	☐	☐	_____
Goose liver pate (foie gras)	☐	☐	_____
Duck liver pate (foie gras)	☐	☐	_____
Other	☐	☐	_____

SECTION 6. FOOD HISTORY - FISH & SEAFOOD

6.5 Did you eat any of the following **unheated/ready to cook** seafoods in the **30 DAYS** before you became ill?

	No	Yes	Date/location/brand etc
Smoked salmon	☐	☐	_____
Mackerel fillets	☐	☐	_____
Smoked mackerel	☐	☐	_____
Salmon pâté/terrine	☐	☐	_____
Smoked trout	☐	☐	_____
Fish pâté/paste	☐	☐	_____
Jellied eels	☐	☐	_____
Other fish	☐	☐	_____
Cold seafood	☐	☐	_____
Oysters	☐	☐	_____
Prawns	☐	☐	_____
Mussels	☐	☐	_____
Squid/calamari	☐	☐	_____
Mixed seafood	☐	☐	_____
Other seafood	☐	☐	_____

SECTION 6. FOOD HISTORY - MILK & DAIRY

6.6 Did you drink or have in cereal any of the following milk products in the **30 DAYS** before you became ill?

	No	Yes	Date/location/brand etc
Cows milk			
Unpasteurised	☐	☐	_____
Pasteurised	☐	☐	_____

Sterilised/UHT	☐	☐	_____

	No	Yes	Date/location/brand etc
Goats milk			
Unpasteurised	☐	☐	_____
Pasteurised	☐	☐	_____
Soya milk	☐	☐	_____
Powdered milk	☐	☐	_____
Flavoured milk	☐	☐	_____
Other milk	☐	☐	_____

6.7 Did you eat any of the following dairy products in the **30 DAYS** before you became ill?

	No	Yes	Date/location/brand etc
Cream	☐	☐	_____
Butter	☐	☐	_____
Dairy spread (e.g. Clover etc.)	☐	☐	_____
Home made ice cream	☐	☐	_____
Other dairy products	☐	☐	_____

SECTION 6. FOOD HISTORY - CHEESE

6.8 Did you eat any of the following types of cheese in the **30 DAYS** before you became ill?

	No	Yes prepacked	Yes sold loose	Date/location/brand etc
Cheddar	☐	☐	☐	_____
Other hard cheese	☐	☐	☐	_____
Blue cheese	☐	☐	☐	_____
Camembert	☐	☐	☐	_____
Brie	☐	☐	☐	_____
Other soft cheese	☐	☐	☐	_____
Cheese spread	☐	☐	☐	_____
Goats cheese	☐	☐	☐	_____
Goats soft cheese	☐	☐	☐	_____
Other cheese	☐	☐	☐	_____

SECTION 6. FOOD HISTORY - SANDWICHES

6.9 Did you eat any sandwiches, rolls or filled baguettes that were **bought or served** away from home in the **30 DAYS** before you became ill?

Yes ☐ No ☐

If **YES** did the sandwiches contain:

	Yes	**No**	**Don't know**
Butter	☐	☐	☐
Margarine	☐	☐	☐

6.10 If **YES** did you eat any of the following types of sandwich?

	No	**Yes prepacked**	**Yes custom made**	**Date/location/brand etc**
Ham	☐	☐	☐	_____
Beef	☐	☐	☐	_____
Bacon/BLT	☐	☐	☐	_____
Chicken	☐	☐	☐	_____
Turkey	☐	☐	☐	_____
Other meat	☐	☐	☐	_____
Tuna sandwich	☐	☐	☐	_____
Salmon sandwich	☐	☐	☐	_____
Prawn/other seafood	☐	☐	☐	_____
Egg mayonnaise	☐	☐	☐	_____
Other egg	☐	☐	☐	_____
Hard cheese	☐	☐	☐	_____
Brie	☐	☐	☐	_____
Other	☐	☐	☐	_____

6.11 Did any of these sandwiches include any of the following extras?

	Yes	**No**
Cucumber	☐	☐
Lettuce	☐	☐
Onions	☐	☐
Tomato	☐	☐
Cress	☐	☐

SECTION 6. FOOD HISTORY - SALAD VEGETABLES & HERBS

6.12 Did you eat any of the following raw vegetables in the **30 DAYS** before you became ill?

	No	Yes prepacked	Yes sold loose	Date/location/brand etc
Basil	☐	☐	☐	_____
Bean sprouts	☐	☐	☐	_____
Broccoli		☐ ☐	☐	
Cabbage	☐	☐	☐	_____

	No	Yes prepacked	Yes sold loose	Date/location/brand etc
Carrots	☐	☐	☐	_____
Cauliflower	☐	☐	☐	_____
Coriander leaves	☐	☐	☐	_____
Courgettes	☐	☐	☐	_____
Cucumber	☐	☐	☐	_____
Dill	☐	☐	☐	_____
Gherkins	☐	☐	☐	_____
Lettuce	☐	☐	☐	_____
Mixed salad	☐	☐	☐	_____
Mushrooms	☐	☐	☐	_____
Onions (any)	☐	☐	☐	_____
Parsley	☐	☐	☐	_____
Peppers	☐	☐	☐	_____
Radishes	☐	☐	☐	_____
Spinach	☐	☐	☐	_____
Tomatoes	☐	☐	☐	_____
Water cress	☐	☐	☐	_____
Other	☐	☐	☐	_____

SECTION 6. FOOD HISTORY - FRUIT

6.13 Did you eat any of the following fresh fruit in the **30 DAYS** before you became ill?

	No	Yes	Date/location/brand etc
Ready-to eat fruit salads		☐	☐
Precut apples	☐	☐	_____
Precut peaches/nectarines	☐	☐	_____
Precut pineapple	☐	☐	_____
Precut mango	☐	☐	_____

Strawberries	☐	☐	_____
Raspberries	☐	☐	_____
Precut melon	☐	☐	_____
Other precut fruit	☐	☐	_____

SECTION 6. FOOD HISTORY - SHOPS

6.14 Have you bought any food from the following **shops** recently?

	No	Yes	Name/Branch/location
Aldi	☐	☐	_____
Asda	☐	☐	_____
Budgens	☐	☐	_____
Co-op	☐	☐	_____
Iceland	☐	☐	_____
Kwiksave	☐	☐	_____
Lidl	☐	☐	_____
Marks & Spencer	☐	☐	_____
Morrisons (Safeway)	☐	☐	_____
Netto	☐	☐	_____
Sainsbury	☐	☐	_____
Somerfield	☐	☐	_____
Spar	☐	☐	_____
Tesco	☐	☐	_____
Waitrose	☐	☐	_____
Local butchers	☐	☐	_____
Local bakers	☐	☐	_____
Local green grocers	☐	☐	_____
Local fish monger	☐	☐	_____
Corner shop/mini mkt	☐	☐	_____
Cheese shop	☐	☐	_____

Chinese grocers ☐ ☐ _____

Indian grocers ☐ ☐ _____

Greek grocers ☐ ☐ _____

Ethnic grocers ☐ ☐ _____

Other(s) ☐ ☐ _____

SECTION 6. FOOD HISTORY - BUYING HABITS

6.15 When you purchase food do you check the use by or sell by dates printed on the food items?

Always ☐ Sometimes ☐ Never ☐

6.16 Have you ever purchased food that has been sold AFTER the use by or best before date printed on the items?

Yes ☐ No ☐

6.17 Do you adhere to use by or best before dates on food you have purchased?

Always ☐ Sometimes ☐ Never ☐

6.18 Do you check the dates on tinned foods before consumption?

Always ☐ Sometimes ☐ Never ☐

6.19 How long do you keep loose meat products after purchasing from a butcher or butcher/deli counter at a supermarket?

Never ☐ < 3 days ☐ 3 to 6 days ☐ > 7 days ☐

6.20 In the last **30 DAYS** have you eaten any food that was **bought abroad?**

(e.g. bought by yourself or given to you as a gift)

Yes ☐ No ☐

If **YES,** please specify type of food and country of purchase

_____

_____

Thank you for completing this questionnaire

Would you mind if we contacted you at some point in the future for additional information, should the need arise?

Yes ☐ No ☐

If you have any specific questions about this investigation either now or in the future please call or write to:

Piers Mook
Health Protection Agency Centre for Infections
61 Colindale Avenue
London NW9 5EQ
Tel. 020 8327 7486
Fax. 020 8327 7112

Appendix 4. All publications by candidate

Gillespie IA, **Mook P**, Adak GK, O'Brien SJ, McCarthy NM. The 'case-chaos study' as an adjunct or alternative to conventional case-control study methodology. *Am J Epi*. 2012 [published online 8 August 2012]

Mook P, Jenkins J, O'Brien SJ, Gillespie IA. Prescribed medications and human Listeriosis in England, 2007-2009. *Epidemiol Infect*. 2012; 141(1): 36-44

Mook P, Patel B, Gillespie IA. Mortality risk factors among human cases of listeriosis in England and Wales, 1990 to 2009. *Epidemiol Infect*. 2011; 140(4): 706-715

Mook P, O'Brien SJ, Gillespie IA. Concurrent conditions and human listeriosis, England and Wales, 1999–2009. *Emerg Infect Dis*. 17: 38-43

Mook P, Grant KA, Little CL, Kaftos G, Gillespie IA. Emergence of pregnancy-related listeriosis among ethnic minorities in England and Wales. *Euro Surveill*. 2010; 15(27); 17-23

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