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Existing medications among non-pregnancy-related listeriosis patients in England, 2007–2009

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SUMMARY

To identify which medications were most commonly taken by non-pregnancy-related listeriosis patients prior to illness, we compared the medications reported by 512 cases identified via national surveillance in England between 2007 and 2009 with national prescription data, using British National Formulary (BNF) coding. Relative risks and corresponding confidence intervals were calculated, as appropriate, for BNF chapters and sections. Among listeriosis cases, the rates for cytotoxic drugs, drugs affecting the immune response and corticosteroids were significantly higher than for other medications. However, interactions between medications and how medications might confound or be confounded by concurrent medical conditions need to be investigated further. Nevertheless our findings suggest that targeting food-safety advice to prevent this foodborne disease in certain treatment groups is warranted.

Key words: British National Formulary, epidemiology, *Listeria monocytogenes*, listeriosis, medications, surveillance.

INTRODUCTION

Listeriosis is a serious but relatively rare foodborne disease, which can present clinically as bacteraemia, meningitis, meningoencephalitis, febrile gastroenteritis, miscarriage or stillbirth. The elderly, those with underlying conditions that compromise their cell-mediated immune function [1], and pregnant women and their unborn or newborn infants are disproportionately affected. The case-fatality rate is high, ranging from 19% to 44% in non-pregnancy-related cases [2–8].

Between 2001 and 2004, the epidemiology of listeriosis in England and Wales changed with more cases aged $\geqslant$60 years presenting with bacteraemia [2]. This increase has continued, with incidence rates of 3·6 cases/1 000 000 population between 2001 and 2009 *vs.* 2·1 cases/1 000 000 population between 1990 and 2000. Similar patterns have been reported in other European countries [9–11]. The reasons for these changes are still obscure, but surveillance artefacts,

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Table 1. *Characteristics of non-pregnancy-related listeriosis cases by exposure questionnaire (EQ) receipt and availability of medication data, England, 2007–2009 (row percentages for each criterion)*

	EQ returned		Medication status known		Medication received		Medication described	
Parameter	Yes ($n=354$)	No ($n=158$)	Yes ($n=311$)	No ($n=43$)	Yes ($n=271$)	No ($n=40$)	Yes ($n=216$)	No ($n=55$)
Year groups								
2007	120 (65%)	64 (35%)	109 (91%)	11 (9%)	99 (91%)	10 (9%)	75 (76%)	24 (24%)
2008	100 (65%)	54 (35%)	88 (88%)	12 (12%)	75 (85%)	13 (15%)	67 (89%)	8 (11%)
2009	134 (77%)	40 (23%)	114 (85%)	20 (15%)	97 (85%)	17 (15%)	74 (76%)	23 (24%)
Gender								
Female	159 (71%)	64 (29%)	140 (88%)	19 (12%)	124 (89%)	16 (11%)	101 (81%)	23 (19%)
Male	195 (67%)	94 (33%)	171 (88%)	24 (12%)	147 (86%)	24 (14%)	115 (78%)	32 (22%)
Age group								
<60 years	90 (70%)	39 (30%)	82 (91%)	8 (9%)	73 (89%)	9 (11%)	58 (79%)	15 (21%)
$\geqslant 60$ years	264 (69%)	119 (31%)	229 (87%)	35 (13%)	198 (86%)	31 (14%)	158 (80%)	40 (20%)
Concurrent condition								
Yes	277 (70%)	120 (30%)	247 (89%)	30 (11%)	226 (91%)	21 (9%)	181 (80%)	45 (20%)
No	35 (67%)	17 (33%)	31 (89%)	4 (11%)	19 (61%)	12 (39%)	14 (74%)	5 (26%)
Unknown	42 (67%)	21 (33%)	33 (79%)	9 (21%)	26 (79%)	7 (21%)	21 (81%)	5 (19%)
Mortality								
Died	88 (50%)	89 (50%)	70 (80%)	18 (20%)	64 (91%)	6 (9%)	49 (77%)	15 (23%)
Survived	235 (80%)	58 (20%)	213 (91%)	22 (9%)	183 (86%)	30 (14%)	145 (79%)	38 (21%)
Unknown	31 (74%)	11 (26%)	28 (90%)	3 (10%)	24 (86%)	4 (14%)	22 (92%)	2 (8%)

outbreaks or a number of demographic, clinical or microbiological factors appear not to be explanations [2].

People receiving immunosuppressive drugs, including steroids, and stomach acid-suppressing medication are predisposed to severe infection with *L. monocytogenes*. However, it is difficult to quantify the risks using a classical epidemiological approach for several reasons: (*a*) case fatality is high; (*b*) choice of an appropriate control group is complicated and (*c*) members of the public are increasingly reluctant to take part in research. To overcome these difficulties we compared existing medications among listeriosis cases with National Health Service (NHS) prescription data for England during the period of increased incidence to identify medications that were more commonly taken by this group of patients prior to illness.

METHODS

The national surveillance system for listeriosis in England and Wales, which is coordinated by the Health Protection Agency (HPA), Colindale, has been described previously [12]. Briefly, cases are identified through electronic reporting of laboratory-confirmed cases and/or by the voluntary referral of cultures to the Laboratory of Gastrointestinal Pathogens. Environmental health officers seek standardized epidemiological data [13], including information on prescribed medications and those bought over the counter taken in the 2 weeks before illness, from the case or from a close relative as available [13]. These medications could not be stratified retrospectively into those bought over the counter or those prescribed and consequently remained aggregated in these analyses. Epidemiological and microbiological data from the local and reference laboratories are linked for each case, de-duplicated as necessary and stored in a bespoke Microsoft Access database.

A case of listeriosis is defined as an individual presenting with clinically compatible illness from whom *L. monocytogenes* is isolated from a normally sterile site. Cases are classified further as either pregnancy-related or non-pregnancy-related (people aged >1 month). In this study, we included non-pregnancy-related cases, resident in England, for whom an exposure questionnaire was available and medication prior to illness was described. We considered medication data between 2007 and 2009. We retained cases that were identified as part of a common-source outbreak in these analyses [these account for a small minority of cases (eight, 1·6%)].

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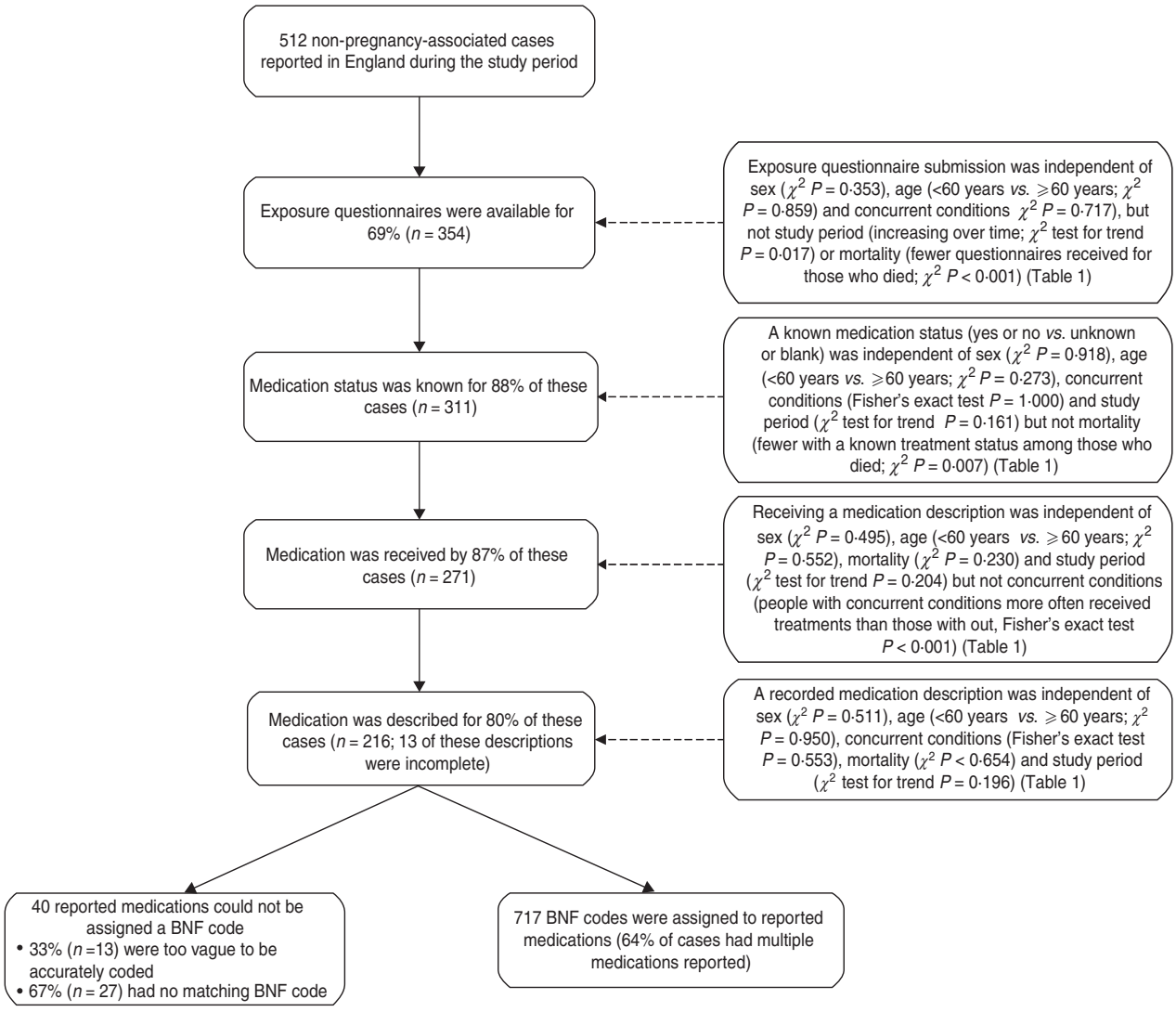

Fig. 1. Breakdown of study population and reported medications for 512 cases of non-pregnancy-related listeriosis, England, 2007–2009. BNF, British National Formulary.

Three of us (P.M., I.A.G., J.M.J.) reviewed each medication reported by the cases and assigned the corresponding British National Formulary (BNF) [14] chapter and section codes. Following initial review, differences in classification were resolved by consensus. Appendix 1 (available online) details the coding scheme employed for medications with multiple coding options, based on the concurrent condition experienced by the case, or where only a vague medication description (analgesics, antibiotics, etc.) was reported. We excluded from the analysis medications that could have been used to treat more than one reported concurrent condition. Prednisolone can be coded either by its function or for the concurrent condition that it was intended to treat. To ensure we investigated prednisolone (and therefore reported 'steroids') thoroughly we devised a second scheme for coding these medications (Appendix 1). These coding schemes were refined further so that we only used codes for which denominator data were available. Denominator data were available for the codes assigned to prednisolone in the primary and secondary coding schemes. Both coding schemes were validated by the clinically qualified investigator (S.J.O'B.), who also reviewed the coding ascribed to medications reported by a random selection of 10% of cases. Counts of all cases for each BNF chapter and section were calculated using both the primary and secondary coding scheme.

NHS prescription data for England, aggregated by BNF chemical substance summary level and year, were obtained from the NHS Prescription Services via Epact [15] and used as the denominators. An overall

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Table 2. *Relative risk for BNF-coded medications among non-pregnancy-related cases of listeriosis, England, 2007–2009**

BNF chapter and section	No. of prescriptions in England	Primary analysis		Secondary analysis	
		No. of reports by cases (*n*)	RR *vs.* other medications (95% CI)	No. of reports by cases (*n*)	RR *vs.* other medications (95% CI)
1. Gastrointestinal system	**191 811 591**	**78**	**1·4 (1·1–1·8)**	**84**	**1·5 (1·2–1·9)**
1·1 Dyspepsia and gastro-oesophageal reflux disease	14 565 197	1	—	1	—
1·3 Antisecretory drugs and mucosal protectants	108 069 544	58	1·9 (1·4–2·5)	58	1·9 (1·4–2·5)
1·4 Acute diarrhoea	4 712 768	2	—	2	—
1·5 Chronic bowel disorders	5 573 124	5	—	11	6·7 (3·7–12·2)
1·6 Laxatives	43 045 863	12	0·9 (0·5–1·7)	12	0·9 (0·5–1·7)
2. Cardiovascular system	**793 271 182**	**243**	**1·05 (0·9–1·2)**	**243**	**1·05 (0·9–1·2)**
2·1 Positive inotropic drugs	12 385 289	9	—	9	—
2·2 Diuretics	112 263 238	41	1·2 (0·9–1·7)	41	1·2 (0·9–1·7)
2·3 Anti-arrhythmic drugs	3 649 568	4	—	4	—
2·4 Beta-adrenoceptor blocking drugs and 2·5 Hypertension and heart failure	254 957 733	63	0·8 (0·6–1·1)	63	0·8 (0·6–1·1)
2·6 Nitrates, calcium-channel blockers, and other antianginal drugs	116 763 550	43	1·3 (0·9–1·7)	43	1·3 (0·9–1·7)
2·8 Anticoagulants and protamine	23 787 165	14	2·0 (1·2–3·4)	14	2·0 (1·2–3·4)
2·9 Antiplatelet drugs	112 471 248	34	1·02 (0·7–1·4)	34	1·02 (0·7–1·4)
2·12 Lipid-regulating drugs	155 913 696	35	0·7 (0·5–1·05)	35	0·7 (0·5–1·05)
3. Respiratory system	**166 633 769**	**26**	**0·5 (0·3–0·8)**	**28**	**0·5 (0·4–0·8)**
3·1 Bronchodilators	77 804 025	19	0·8 (0·5–1·3)	19	0·8 (0·5–1·3)
3·2 Corticosteroids	47 489 766	7	—	9	—
4. Central nervous system	**430 484 131**	**76**	**0·5 (0·4–0·7)**	**76**	**0·5 (0·4–0·7)**
4·1 Hypnotics and anxiolytics	48 527 008	2	—	2	—
4·2 Drugs used in psychoses and related disorders	23 449 955	3	—	3	—
4·3 Antidepressant drugs	107 864 336	6	—	6	—
4·6 Drugs used in nausea and vertigo	19 081 739	6	—	6	—
4·7 Analgesics	162 784 249	53	1·1 (0·8–1·5)	53	1·1 (0·8–1·5)
4·8 Antiepileptic drugs	34 751 062	5	—	5	—
4·9 Drugs used in parkinsonism and related disorders	10 036 197	1	—	1	—
5. Infections	**123 420 957**	**27**	**0·7 (0·5–1·1)**	**27**	**0·7 (0·5–1·1)**
5·1 Antibacterial drugs	104 678 305	19	0·6 (0·4–0·9)	19	0·6 (0·4–0·9)
5·3 Antiviral drugs	1 649 706	4	—	4	—
5·4 Antiprotozoal drugs	11 205 301	4	—	4	—
6. Endocrine system	**216 378 700**	**107**	**1·8 (1·5–2·2)**	**85**	**1·4 (1·1–1·7)**
6·1 Drugs used in diabetes	97 630 797	27	0·9 (0·6–1·4)	27	0·9 (0·6–1·4)
6·2 Thyroid and antithyroid drugs	62 437 615	11	0·6 (0·3–1·1)	11	0·6 (0·3–1·1)
6·3 Corticosteroids	18 637 330	57	11·1 (8·5–14·6)	35	6·6 (4·7–9·3)
6·4 Sex hormones	15 560 355	2	—	2	—
6·6 Drugs affecting bone metabolism	20 933 125	10	1·6 (0·9–3·0)	10	1·6 (0·9–3·0)
7. Obstetrics, gynaecology, and urinary-tract disorders	**57 690 639**	**10**	**0·6 (0·3–1·1)**	**10**	**0·6 (0·3–1·1)**

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Table 2 (*cont.*)

BNF chapter and section	No. of prescriptions in England	Primary analysis		Secondary analysis	
		No. of reports by cases (*n*)	RR *vs.* other medications (95% CI)	No. of reports by cases (*n*)	RR *vs.* other medications (95% CI)
7·4 Drugs for genito-urinary disorders	26 328 409	10	1·3 (0·7–2·4)	10	1·3 (0·7–2·4)
8. Malignant disease and immunosuppression	**10 616 055**	**54**	**18·5 (14·0–24·4)**	**54**	**18·5 (14·0–24·4)**
8·1 Cytotoxic drugs	386 607	35	320·9 (228·5–450·7)	35	320·9 (228·5–450·7)
8·2 Drugs affecting the immune response	3 361 954	18	18·5 (11·6–29·5)	18	18·5 (11·6–29·5)
8·3 Sex hormones and hormone antagonists in malignant disease	6 867 494	1	—	1	—
9. Nutrition and blood	**104 208 816**	**57**	**1·9 (1·5–2·5)**	**57**	**1·9 (1·5–2·5)**
9·1 Anaemias and some other blood disorders	30 010 654	25	2·9 (1·9–4·3)	25	2·9 (1·9–4·3)
9·2 Fluids and electrolytes	3 310 456	1	—	1	—
9·5 Minerals and 9·6 Vitamins	42 738 485	31	2·5 (1·8–3·6)	31	2·5 (1·8–3·6)
10. Musculoskeletal and joint diseases	**87 437 200**	**36**	**1·4 (1·01–2·0)**	**50**	**2·0 (1·5–2·7)**
10·1 Drugs used in rheumatic diseases and gout	68 707 041	34	1·7 (1·2–2·4)	48	2·5 (1·8–3·3)
10·3 Drugs for the relief of soft-tissue inflammation	15 914 712	2	—	2	—
12. Ear, nose, and oropharynx	**29 101 750**	**2**	—	**2**	—
12·2 Drugs acting on the nose	18 039 946	1	—	1	—
12·3 Drugs acting on the oropharynx	4 694 952	1	—	1	—
13. Skin	**109 748 396**	**1**	—	**1**	—
13·4 Topical corticosteroids	37 397 001	1	—	1	—
Overall (chapters 1–15)	**2 417 732 647**	**717**		**717**	

BNF, British National Formulary; RR, relative risk; CI, confidence interval.
* Only BNF chapters and sections reported by these cases are presented; counts of all sections and chapters are included in the chapter totals and overall total, respectively.

medication rate per million prescriptions and 95% confidence intervals (CI) were calculated. We considered denominator data with a BNF chapter of between 1 and 15; additional pseudo-chapters created by NHS Prescription Services to reference the drugs, dressings and appliances that are not considered in the BNF were not included in our analyses. Relative risks (RR) and corresponding 95% CIs were calculated as appropriate where there were 10 or more reports for a BNF chapter or section. All medications other than from the chapter or section in question were used for the comparison group. Analyses were conducted using both coding schemes. Data were manipulated and summarized using Microsoft Access 2007 while Microsoft Excel 2007, Stata release 11.0 (StataCorp, USA) and Epi Info (CDC, USA) were used to undertake statistical analysis, which included calculating rates, RRs and corresponding 95% CIs. Changes in proportions over strata and differences in proportions were assessed using the χ^2 test for trend and the χ^2 or Fisher's exact test, respectively. Furthermore, the potential for confounding between BNF sections, using each coding scheme, was assessed by constructing a Spearman's rank correlation coefficient matrix.

RESULTS

The characteristics of 512 non-pregnancy-related cases reported to the HPA during the study period are described in detail in Table 1 and Figure 1. BNF codes

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Table 3. *Correlation index for BNF sections* (*as per primary coding scheme*) *with significantly higher medication rates than other sections*

	Correlation coefficient							
BNF section	Antisecretory drugs and mucosal protectants	Anti-coagulants and protamine	Cortico-steroids	Cytotoxic drugs	Drugs affecting the immune response	Anaemias and some other blood disorders	Drugs used in rheumatic diseases and gout	Minerals and vitamins
Antisecretory drugs and mucosal protectants	1							
Anticoagulants and protamine	−0·0298	1						
Corticosteroids	0·0902	−0·0356	1					
Cytotoxic drugs	−0·1858*	−0·114	−0·0365	1				
Drugs affecting the immune response	0·0624	−0·0125	0·1351	−0·0765	1			
Anaemias and some other blood disorders	0·2250*	0·0297	0·1075	−0·1013	0·123	1		
Drugs used in rheumatic diseases and gout	0·0492	−0·0434	0·1416*	−0·1570*	−0·1139	0·2547*	1	
Minerals and vitamins	0·3756*	0·0115	0·097	−0·1605*	0·0965	0·2927*	0·1249	1

BNF, British National Formulary.
* $P<0·05$.

could be assigned for 717 medications reported by 216 cases who met our case definition (Fig. 1). With a total of 2 417 732 647 prescriptions reported in England during this time, the overall medication rate among these cases was 0·30 per million prescriptions (95% CI 0·28–0·32). Compared with all other BNF chapters, our primary analysis showed that the rate was most increased for the malignant disease and immunosuppression chapter (Table 2). The rates for cytotoxic drugs, drugs affecting the immune response and corticosteroid sections were particularly high, relative to other sections. Some other chapters and sections showed a moderately significant increase. Certain medications (central nervous system and respiratory system chapters and the antibacterial drugs section) were less common.

Those medications more commonly reported by these listeriosis cases in the 2 weeks before illness using the primary analysis coding scheme were also more commonly reported when the secondary scheme was employed. Here, cases were additionally more likely to report taking medications from the chronic bowel disorders section of the gastrointestinal system chapter.

There was relatively little correlation between BNF sections that had significantly higher rates than other sections, using either coding scheme (Tables 3 and 4). Where correlation was observed it was generally low.

DISCUSSION

We compared surveillance data on medications with detailed denominator data using a nationally recognized classification system and found a variety of medications with increased rates among non-pregnancy-related listeriosis cases. Some medications captured in the surveillance data and for which a BNF code was ascribed could have been obtained over the counter as well as by prescription but the denominator is prescription data only. Medications bought over the counter generally treat more common ailments while those used to treat severe underlying conditions, as tend to be those conditions concurrent to a *L. monocytogenes* infection, are generally prescribed. Therefore, while there is disparity between the numerator and denominator, we consider that we have made the best use of surveillance data to generate refined hypotheses which should be tested by other methods. Of particular note from our results were cytotoxic drugs, drugs affecting the immune response and corticosteroids. Drugs for anaemias and some other blood disorders, minerals and vitamins, antisecretory drugs and mucosal protectants, drugs used in rheumatic diseases and gout, and anticoagulants and protamine showed moderately increased rates. A significant effect was observed with corticosteroids regardless of coding strategy. The national listeriosis surveillance system identifies cases that are laboratory confirmed and

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Table 4. *Correlation index for BNF sections* (*as per secondary coding scheme*) *with significantly higher medication rates than other sections*

	Correlation coefficient								
BNF section	Antisecretory drugs and mucosal protectants	Chronic bowel disorders	Anti-coagulants and protamine	Cortico-steroids	Cytotoxic drugs	Drugs affecting the immune response	Anaemias and some other blood disorders	Drugs used in rheumatic diseases and gout	Minerals and vitamins
Antisecretory drugs and mucosal protectants	1								
Chronic bowel disorders	−0·0743	1							
Anticoagulants and protamine	−0·0298	−0·0589	1						
Corticosteroids	0·1528*	−0·033	−0·0186	1					
Cytotoxic drugs	−0·1858*	−0·0227	−0·114	0·0726	1				
Drugs affecting the immune response	0·0624	0·1074	−0·0125	0·1019	−0·0765	1			
Anaemias and some other blood disorders	0·2250*	0·0015	0·0297	−0·0723	−0·1013	0·123	1		
Drugs used in rheumatic diseases and gout	0·027	−0·0254	−0·0621	−0·0814	−0·1778*	−0·0796	0·2479*	1	
Minerals and vitamins	0·3756*	−0·083	0·0115	0·0642	−0·1605*	0·0965	0·2927*	0·1234	1

BNF, British National Formulary.
* $P<0·05$.

therefore at the more severe end of the clinical spectrum, with most resulting in hospitalization. Consequently, our findings here relate to the medications reported by such cases and not those with less severe disease who remain undiagnosed.

The response rate to the exposure questionnaire was satisfactory for all years and was not influenced by sex, age and concurrent conditions, indicating that differential ascertainment of exposure data was minimal. Response rate and known medication status were not independent of survival outcome, as might be expected. Receiving medication was independent of study period and the demographic factors considered here but not independent of a concurrent condition. It is logical that medications received prior to the *L. monocytogenes* infection were a function of existing conditions. A description of a medication on the exposure questionnaire was independent of all factors considered here but was only recorded for 80% of those patients reported to have received a medication. We could not asses the medications for which a description was not provided, nor where there were fewer than 10 reports for a BNF section.

Our study has several limitations. For a large proportion of cases we relied on descriptions of medication reported by relatives, increasing the potential for information bias. We attempted to minimize misclassification by not stratifying medications further than the BNF section code level. Limiting our analyses to this level might have masked certain medications within BNF sections but medication data collected from patients or next of kin as part of routine national surveillance were not specific enough to discriminate further confidently.

In this univariate analysis we could not fully assess the extent to which medications were correlated or the effect of interactions. Consequently, uncontrolled confounding might have impacted upon our findings. This is pertinent given that almost two thirds of cases with descriptions of medications and assigned BNF codes had more than one reported medication. It is important to note, however, that the denominator data used in this study will also be subject to the same constraints. Furthermore, these analyses could not be further stratified by age or concurrent condition because of limitations with the denominator data and so the measure effects reported here are not independent of these factors. For instance, medications within the nutrition and blood chapter are likely to be more often prescribed to older individuals and/or those with concurrent conditions.

The frequency of repeat prescriptions for a medication will be captured in the BNF denominator data, but the number of instances that a medication is taken by an individual is not captured in the surveillance data. It is likely that a differential in the frequency

of repeat prescriptions in the denominator will exist between chapters and sections, respectively, and this might affect the accuracy of our measures of effect. While we collected data on medications that were bought over the counter as well as those that were prescribed, we could not assess those in the former group without a BNF code. Furthermore, a report of 'chemotherapy' was coded only as a cytotoxic for the purposes of these analyses but a chemotherapy regimen may also include combination therapy with other drug classes, including immunosuppressants and/or steroids. As a result of this coding strategy, the potential exists for the effect of drugs other than cytotoxics in a combined chemotherapy regimen to have been underestimated here.

Antibiotics given to treat the *L. monocytogenes* infection were not included in this analysis while antibiotics prescribed for an unknown reason were retained. Antibiotics were prescribed less frequently among *Listeria* patients, compared to other treatments, possibly because antibiotics with anti-listerial activity prescribed for other infections conferred protection with regard to the *L. monocytogenes* infection. While the questionnaire seeks data on medications taken in the 2 weeks before illness, it is possible that antibiotics prescribed to treat the *L. monocytogenes* infection were reported inadvertently. Such misclassification would only have biased estimates towards the null, diminishing the observed effect.

Few population-based studies have quantified the risk of listeriosis by medications and no study has reviewed a cohort of cases to identify which medications are more commonly taken prior to illness using this method. Risk by certain predisposing conditions and medications in Denmark, using national prevalence data as the denominator, have been calculated [16]. Furthermore, a population-based case-control study investigating risk factors for listeriosis in Australia considered prior medications [17]. While there are methodological differences between these studies and ours, their finding support ours: the Danish study found that those receiving systemic steroid therapy and antacid therapy were of an increased risk while the Australian study found that use of gastric acid inhibitors was independently associated with an increased risk for non-perinatal listeriosis. Other studies have also reported links between listeriosis and drugs that fall into the medication groups reported in our study including: gastric acid suppressants [18–20]; and tumour necrosis factor-α inhibitors, particularly infliximab, used in the treatment of rheumatoid arthritis [21–25].

We have identified medications that would be used to treat conditions that have previously been associated with a quantified increased risk of listeriosis in England [12] and elsewhere [16, 26], which validate our findings. Nevertheless, we are unable to account for the effect of concurrent conditions in this analysis.

Surveillance could be strengthened with more specific medication data, ideally including BNF coding, collected from the hospital where the case was an inpatient. The way in which interactions between medications affect the risk of listeriosis and how medications might confound or be confounded by conditions concurrent to a *L. monocytogenes* infection requires further investigation. A case review of hospital patient medical records might be one appropriate method.

This study reinforces the need for clinicians to provide relevant food-safety advice to people in high-risk groups, either because of their underlying condition [12] or the treatment for it. In addition, policy-makers should consider these findings when targeting food-safety information on the avoidance of listeriosis to vulnerable treatment groups.

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SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S095026881200026X.

DECLARATION OF INTEREST

None.

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