Advisory Committee on the Microbiological Safety of Food

Ad Hoc Group on Vulnerable Groups

Report on the Increased Incidence of Listeriosis in the UK

Advises the Food Standards Agency on the Microbiological Safety of Food

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Acknowledgements

The *Ad Hoc* Group wishes to thank the people listed at Annex I and the Secretariat for their assistance.

The ACMSF accepts full responsibility for the final content of the report.

Contents

Summary

1. In this report the *Ad Hoc* Group has considered the change in epidemiology of human *Listeria monocytogenes* infection in the UK characterised by increased incidence of listeriosis from 2001.

2. This report follows information from the Health Protection Agency to the Advisory Committee on the Microbiological Safety of Food (ACMSF) which indicated that the incidence of listeriosis in England and Wales in 2005 remained higher than pre-2001 levels. In Scotland in 2005 the incidence was also significantly higher than in 2004 and from the period 1993 to 1999. A less pronounced increase in incidence was also reported in Northern Ireland. The disease occurred predominantly in older patients and presented as bacteraemia in the absence of CNS infection.

3. In June 2007 ACMSF referred this issue to its *Ad Hoc* Group on Vulnerable Groups for consideration as a priority. The Group met on six occasions over a period of 16 months to assemble information and review evidence relating to diagnosis, typing data, artefacts, case histories, social factors, changes in consumption habits and cumulative risk factors and to inform the development of ACMSF advice to the Food Standards Agency.

4. The Group set out several possible areas of activity to try to identify the cause of the change in epidemiology in the over 60s age group as a series of hypotheses. These were subjected to challenge. They considered information on the bacterium *Listeria monocytogenes* including its survival, virulence and behaviour in food and the food chain. The epidemiology of the bacterium was reviewed including transmission and trends in listeriosis in the UK, EU and other countries. UK data on human *L. monocytogenes* sub-types in relation to food exposure history and comparison with food isolate typing data were also examined. Blood culture and sampling trends in the general population, including the elderly, were discussed and changes in clinical assessment in the over 60s were also considered. Other areas of investigation included surveillance of *L. monocytogenes* in foods, shelf life, changes in chilled food production and food safety controls. The Group also examined social and behavioural factors in the over 60s age group including data on consumption patterns, consumer purchasing, storage and food handling behaviours. Other factors affecting vulnerable groups were explored including underlying medical conditions and changes in their care. Risk factors and underlying assumptions to assess whether the target population had become more susceptible to *L. monocytogenes* were evaluated, and UK and international consumer guidance on the risks posed by *L. monocytogenes* were reviewed.

5. Key conclusions and recommendations arising from the work of the Group were:

- The majority of cases of human listeriosis appear to be sporadic and foods associated with transmission are predominantly ready to eat, with extended (usually refrigerated) shelf life capable of supporting growth of *L. monocytogenes*. The reported increase in listeriosis since 2000 in the UK and some European countries has occurred almost exclusively in patients aged over 60 years presenting with listerial bacteraemia. However, there is no evidence for a common source relationship between these changes in presentation of listeriosis. Pan-European surveillance, epidemiological and microbiological investigations are recommended to investigate these changes in listeriosis in different Member States and to ascertain whether there are common generic or risk factors occurring in the UK and other countries. Studies to develop screening methods for *L. monocytogenes* isolates are also recommended to investigate differences in virulence and differences between isolates from different patient groups and time periods.

- The increase and shift in presentation of listeriosis cannot be attributed to improved diagnostics, as a comparative increase has not been reported in *L. monocytogenes* isolated from blood cultures from patients with CNS infections or pregnancy-associated cases. Similarly, levels of bacteraemia associated with other foodborne pathogens have not increased in the over 60s. To take account of any under-reporting of estimated cases of *L. monocytogenes* in the UK, work is needed to investigate and reduce the incidence of listeriosis in the over 60s. The ascertainment ratio for human listeriosis should also be estimated. Routine collection of denominator data for selected medical investigations associated with listeriosis infection would inform work to analyse infection trends and our understanding of changes in epidemiology associated with this organism.

- Elderly individuals are more likely to have underlying conditions which predispose to listeriosis than younger age groups. The increase in cases of listeriosis associated with the over 60s cannot solely be attributed to the general demographic increase of this age group in the population. The rate of listeriosis has increased three-fold in the over 60s from the early 1990s to the present. It is recommended that work is undertaken to investigate whether the management of underlying conditions in these age groups has contributed to the rise in listeriosis. Retrospective studies

and data collection should be conducted to identify which underlying conditions are most associated with listeriosis in this age group and UK infection surveillance should incorporate data on denominator populations and numbers of medical investigations undertaken (including blood cultures).

- Maintaining active surveillance for *Listeria* spp. in foods is important to inform control of this organism. Such surveys should examine a wide range of foods (shopping basket surveys) and account for food purchases at catering and retail outlets.

- Data on shopping and food behaviour and consumption patterns in the over 60s is limited. More information on the food consumption and food handling and storage behaviours in the home of this age group, including those who are vulnerable, is needed to inform factors contributing to the risk of listeriosis. In the absence of such information it is recommended that general consumer food safety advice should be developed and communicated to the over 60s (including those in vulnerable groups), as well as to those who prepare and provide their food and those who provide medical advice about the risks of listeriosis to these groups. Studies should be carried out to evaluate the impact of such advice on these groups. It is also recommended that the FSA refers this Report to its Social Science Research Committee to consider the food behaviour, storage and handling practices of elderly people in the home.

- The food industry has implemented many controls over the past two decades to prevent the contamination of foods with *L. monocytogenes* and the principles of food safety management are well established in the food industry. Evidence suggests that the incidence and levels of this organism at the points of production and sale are not higher than those detected in the late 1980s. The Group was unable to assess whether an increase in shelf life across chilled commodity areas or the development of new foods could account for an increased risk of listeriosis as limited information was available. However, the Group received *Ad Hoc* information from one supermarket chain that indicated that there had been no recent marked increase in the shelf-life of chilled foods. Therefore the Group was unable to assess whether an increase in shelf lives across chilled commodity areas or the development of new foods could account for an increased risk of listeriosis. It is recommended that any future advice to industry and enforcement authorities reiterates the importance of temperature and shelf life control, hygiene/cleaning and formulation of food in preventing contamination or limiting the

growth of *L. monocytogenes* in foods. The Committee also reiterates its advice that FSA should work with the food industry to ensure that formulations including salt levels of specific products are not changed without considering the impact of these changes on microbiological safety.

- The organism has been found in chilled ready-to-eat foods at a low level which probably represents a low risk provided storage time and temperature conditions are maintained at appropriate levels prior to consumption. The provision of durability instructions such as 'use by' dates on some perishable foods sold loose was found to be variable. One survey in the North West of England found use by information to be more common on retail, sliced, cooked meats from supermarkets (74%) than market stalls (6%); delicatessens (8%) or butchers (7%). Therefore it is recommended that the FSA reviews the need for consistent advice on such products.

6. The assessments made and the conclusions reached by the Group reflect evidence, oral and written, drawn from the scientific community, industry, government departments and Agencies, EFSA and the scientific literature. The Group's conclusions and recommendations are brought together at the end of the report.

Definition of a vulnerable group

7. For listeriosis, vulnerability is considerably increased within the following groups: elderly (i.e. people more than 60 years of age, regardless of whether they fall into other groups below) cancer patients, patients undergoing immunosuppressive or cytotoxic treatment, unborn and newly delivered infants, pregnant women, diabetics, alcoholics (including those with alcoholic liver disease) and a variety of other conditions. Rarely, infection can occur in patients without any known risk factors.

8. Although risk factors for listeriosis are well documented, identification of specific vulnerable groups, with the exception of pregnant women, is not straightforward. Immunocompromised individuals are acknowledged as being vulnerable to listeriosis, but the term is ill defined – a problem exacerbated by the use of other terms such as immunodeficiency. Indeed, many standard texts (Donnelly and de Pauw, 2005) do not attempt to define the term "immunocompromised", although in other settings, for example, prevention of severe infection following exposure to varicella zoster virus, immunocompromised is defined in detail (Anon, 2006).

9. A definition of a vulnerable group, such as the elderly, is necessary if public health initiatives designed at reducing the risk of listeriosis are to be directed to those individuals (or those responsible for their care) in the most effective manner. Yet there is no accepted definition of "elderly" or other similar terms such as "older adult". *NHS Direct* states, for example, that "older people" are at risk of listeriosis[1]. Better definition of at-risk groups would also serve to raise awareness of listeriosis among healthcare professionals caring for the elderly, particularly those with patients with additional risk factors such as underlying co-morbidities such as malignancy and autoimmune disease, especially those receiving immunosuppressive therapy (Mulley, 2008).

[1] NHS Direct web site: http://www.nhs.uk/conditions/Listeriosis/Pages/Introduction.aspx

Chapter 1: Introduction

1.1 In September 2005 and December 2006, the Health Protection Agency (HPA) alerted ACMSF Members to a change in the epidemiology of human *L. monocytogenes* infection in England and Wales. This change was characterised by an increase in the numbers of reported cases from 2001, which occurred predominantly in patients of 60 years of age and over, who presented with bacteraemia (the presence of bacteria in the blood) without central nervous system (CNS) infection. This increase, which represented a doubling in reported cases since 2001, occurred in most regions in England and Wales, in both genders, and could not be explained by outbreaks recognised during this time.

1.2 In Scotland in 2005, the incidence of listeriosis was significantly higher than in 2004 and the period 1993-1999. Furthermore, the clinical presentation in Scotland in 2005 was similar to that observed in England and Wales, with the disease occurring predominantly in older patients with bacteraemia in the absence of CNS infection. No significant increase was observed in Northern Ireland up to 2005. However, an increase was reported in 2006-07. Additional data were presented, which suggested that the altered epidemiological/clinical picture in England and Wales was not artefactual.

1.3 In June and December 2007, HPA confirmed that the increase in listeriosis had continued into 2007. Similar increases had also been reported in other European countries, including France and Germany. Following the introduction of a standard structured surveillance questionnaire for listeriosis in 2005, sufficient data were accrued for preliminary analysis. Initial investigations showed significant differences in the exposure histories of patients infected with different subtypes of *L. monocytogenes*. Separate analysis of data from routine reference typing of isolates from food indicated associations with the same or similar food types. From these findings it was hypothesised that specific food types gave rise to infection with specific *L. monocytogenes* sub-types.

1.4 In June 2007, ACMSF considered the high level of reporting of listeriosis in the UK. The Committee agreed that the change in epidemiology was more likely to be linked to social factors, including changes in dietary/food behaviour and food production rather than changes in the bacterium. It also identified a series of data gaps and issues requiring detailed consideration including diagnosis, typing, case histories, changes in consumption habits, and cumulative risk. The Committee referred this issue of listeriosis in the elderly to its *Ad Hoc* Group on Vulnerable Groups for further discussion as a priority[2].

[2] This Group was set up to examine potential microbiological safety risks to vulnerable groups including the elderly; and to define vulnerable groups in relation to foodborne disease, review key hazards, consider food consumption and behaviour patterns and to provide advice to these groups.

The ACMSF's approach to its work

1.5 The *Ad Hoc* Group met six times (over a period of 16 months) to consider documentary and verbal evidence relating to listeriosis in the elderly. To frame the scope of our deliberations we examined a series of hypotheses to establish the cause of the rise in listeriosis. Key issues for consideration included the validity of the increase, susceptibility of the target population and exposure levels. To investigate these hypotheses, we considered information on *L. monocytogenes,* including its survival, virulence and behaviour in food and the food chain. The epidemiology of the bacterium was reviewed, including transmission and trends in listeriosis in the UK, EU and other countries. Blood culture and sampling trends in the general population, including the elderly, were discussed and changes in clinical assessment in the over 60s were also considered. Other areas of investigation included surveillance of *L. monocytogenes* in foods, shelf life, changes in chilled food production and food safety controls.

1.6 We also examined social and behavioural factors in the over 60s, including data on food consumption patterns. Other factors affecting vulnerable groups were explored including underlying medical conditions and changes in vulnerable groups' care. Risk factors and underlying assumptions to assess whether the target population had become more susceptible to *L. monocytogenes* were evaluated and UK, EU and international consumer guidance on the risks posed by *L. monocytogenes* were reviewed.

1.7 It should be noted that the report uses the terms 'over 60' and 'the elderly' interchangeably. Where ages other than 'over 60' are used in this report (i.e. over 65) these relate to ages defined and used in specific data or studies that were considered by the Group.

Chapter 2: Hazard identification and characterization

2.1 Listeria is a genus of Gram-positive bacteria and comprises six species: *L. monocytogenes, L. ivanovii, L. innocua, L. welshimeri, L. seeligeri* and *L. grayi.* Listeriosis is the disease caused by *L. monocytogenes*, although very rare cases of infection in humans due to *L. ivanovii* and *L. seeligeri* have also been reported. In other animals, most cases are due to *L. monocytogenes* but with 10-15% due to *L. ivanovii* (McLauchlin 2005).

2.2 *Listeria monocytogenes* can be categorised using a number of different phenotypic and genotypic methods: the former have been now largely superseded by the latter. The most common methods currently used are molecular serotyping (based on the characterization of genes encoding or co-transcribed with the serotype antigens, Doumith *et al*, 2004) and amplified fragment length polymorphism analysis (AFLP, Guerra *et al*, 2002). Selected isolates can be characterised by pulsed-field gel electrophoresis (PFGE, Graves and Swaminathan 2001). These methods do not directly generate information on the virulence of individual isolates.

2.3 Complete genome sequences are publicly available for several different *L. monocytogenes* strains, as well as other *Listeria* species (Glaser *et al*, 2001; Nelson *et al*, 2004). There is now a considerable body of information available on the use of various animal and cell culture models, which have identified genes associated with the virulence of *L. monocytogenes* (Vazquez-Boland *et al*, 2001): most of which encode cell surface structures or secreted products. However, there is less information on polymorphisms, which occur naturally within these virulence genes and which might affect the ability of this bacterium to cause infection. Consequently tools for 'routine' screening of *L. monocytogenes* isolates for differences in virulence are not available.

2.4 Listeriosis occurs in a wide variety of animals, as well as humans, and most often affects the placenta, the central nervous system or the bloodstream. Amongst farm animals, listeriosis is most often diagnosed in sheep, cattle and goats. In humans, serious infection is most often recognized. Although subclinical infections do occur they are rarely identified (McLauchlin 2005).

2.5 In humans, infection is most often recognised in the immunocompromised, the elderly, pregnant women and unborn or newly delivered infants. Case-fatality rates of 20–40% or greater occur, dependent upon the patient group infected (Table 1). Cases can be classified as two groups; those associated with pregnancy (the pregnant or newly delivered women, the unborn or newly delivered infant) as well as the non-pregnant (McLauchlin 2005).

Table 1: Mortality rates in selected outbreaks of systemic listeriosis

Year	Country	Cases (deaths)	Mortality rate	Food vehicle
1980-81	Canada	41 (18)	44%	Coleslaw
1983	USA	49 (14)	29%	Milk
1983-7	Switzerland	122 (34)	29%	Soft cheese
1985	USA	142 (48)	34%	Soft cheese
1992	France	279 (63)	23%	Pork tongue in aspic
1998-9	Finland	25 (6)	24%	Butter
1999-2000	France	26 (7)	27%	Pork tongue in jelly
2000	USA	29 (7)	24%	Turkey meat

Adapted from Bell and Kyriakides. Listeria, 2nd ed, 2005, Blackwell.

Listeriosis in pregnancy

2.6 Maternal listeriosis occurs throughout gestation, but is rarely detected before 20 weeks. The mother is usually well with a normal pregnancy but may have mild symptoms (chills, fever, back pain, sore throat and headache and, sometimes, conjunctivitis, diarrhoea or drowsiness) or be asymptomatic until the delivery of an infected infant. Symptomatic women may have positive blood cultures. Underlying pathologies or immunosuppression have not been identified as risk factors for pregnancy-associated listeriosis (McLauchlin 2005).

2.7 With the onset of fever, foetal movements are reduced, and premature labour occurs within about 1 week. There may be a transient fever during labour, and the amniotic fluid is often meconium-stained and discoloured. Culture of the amniotic fluid, placenta or high vaginal swab (HVS) post delivery invariably yields *L. monocytogenes*. Fever in the mother resolves soon after birth and the HVS and faeces are usually culture-negative within 1 month. While the outcome of infection for the mother is usually benign, that for the infant is more variable and can be fatal or have long term sequelae in those that survive. Abortion, stillbirth and early-onset neonatal disease occur and probably reflect the gestation stage of exposure and/or infection. Maternal infection during pregnancy but without infection of the foetus can even progress to placental infection without ill effects for the foetus (McLauchlin 2005).

2.8 Neonatal infection usually presents as early (less than 2 days after delivery), or late (more than 5 days old) onset disease. Early neonatal listeriosis is predominantly a septicaemic illness, contracted *in utero* or during labour. Late neonatal infection is predominantly meningitic and can be associated with hospital cross-infection, contact with the post-natal environment or possibly

from the mother during delivery. Early onset disease represents a spectrum of mild to severe infection, which can be correlated with the extent of microbiological invasion: those most severe having invasion of the blood, central nervous system or internal organs. Neonates who die of infection usually do so within a few days of birth and have pneumonia, hepatosplenomegaly, abscesses in the liver or brain, peritonitis and enterocolitis. Diagnosis of early onset neonatal infection is by culture of blood and CSF as well as swabs from superficial sites, gastric aspirates, and meconium. Diagnosis of late onset infection is made by blood or CSF culture (McLauchlin 2005).

Listeriosis in non-pregnant individuals

2.9 Listeriosis in infants older than 1 month is very rare, except in those with underlying disease. In adults and juveniles the main syndromes are central nervous system (CNS) infection, or bacteraemia. Most cases occur in the immunocompromised, but about one-third of patients with meningitis and around 10% with primary bacteraemia are immunocompetent. A wide range of risk factors are associated with listeriosis and these include; cancers, autoimmune disease, treatment with immunosuppressive agents, alcohol-related disease, and diabetes mellitus (McLauchlin 2005).

2.10 The clinical presentation of meningitis is the same in all groups, but progression is more rapid in immunocompromised subjects. Gram stains of CSF deposits can be negative, and the clinical features of infection are such that it is not possible to distinguish between listerial meningitis from that due to other infectious agents. Diagnosis is by culturing CSF or blood (McLauchlin 2005).

2.11 Primary bacteraemia presents with a spectrum of severity with fever and other non-specific signs of infection. Rarer manifestations of listeriosis include arthritis, hepatitis, endophthalmitis, cutaneous lesions, and peritonitis in patients on continuous ambulatory peritoneal dialysis, endocarditis, and pneumonia. Diagnosis is almost always achieved by culture of blood or other clinical material (McLauchlin 2005).

2.12 Foodborne outbreaks of acute gastroenteritis with fever have been described. The foods associated with these outbreaks have been diverse, but heavily contaminated by the bacterium. Large numbers of *L. monocytogenes* are present in the stool and may also occur in blood in cases of severe infection. The ability to cause gastroenteritis may be specific to certain strains of *L. monocytogenes* and this presentation has not been recognised in all foodborne outbreaks (McLauchlin 2005).

2.13 The numbers of cases with a fatal outcome increases with age (Table 2).

Table 2: Reported deaths amongst non-pregnant listeriosis cases in England and Wales 1990-2007

	Death of patient (% of cases)			
Age Group	Yes	No	Not known	Total
0-9	2 (10%)	17 (81%)	2 (9%)	21
10-19	5 (16%)	26 (81%)	1 (3%)	32
20-29	4 (12%)	25 (76%)	4 (12%)	33
30-39	17 (22%)	39 (50%)	22 (28%)	78
40-49	29 (21%)	91 (66%)	18 (13%)	138
50-59	73 (27%)	152 (57%)	43 (16%)	268
60-69	151 (32%)	269 (57%)	48 (10%)	468
70-79	226 (37%)	308 (51%)	69 (11%)	603
80+	207 (44%)	211 (45%)	48 (10%)	466
Unknown	8	14	23	45
Total	**722**	**1152**	**278**	**2152**

Source: HPA unpublished data

Virulence of *L. monocytogenes*

2.14 Various animal and cell culture models have been developed to study the virulence of *L. monocytogenes* (Vazquez-Boland *et al*, 2001). Most of these have been based on either rats or mice or intracellular growth within mammalian cells growing *in vitro*. Non-human primate models have also been described. Some models bypass the intestines by injecting the bacteria into the peritoneum or blood, whilst others have used the oro-gastric route. Except for primates, these models do not include the complete foodborne route of exposure and are poor at investigating differences in virulence relevant to food-borne listeriosis. However, there is some evidence from them (together with that from epidemiological observations) that suggests that there are naturally occurring avirulent or virulence-attenuated strains: phenotypic and genotypic tests are not routinely available to characterise the expression of all virulence genes (see next paragraph) or identify differences in virulence. However for public health purposes, all *L. monocytogenes*, including those present in food, should be regarded as potentially pathogenic (McLauchlin 1997).

2.15 *L. monocytogenes* is a facultative intracellular pathogen, and multiple genes have been identified, which allow this bacterium to adhere to, invade and move within and between mammalian cells. Such genes include those which encode for proteins which are: cell surface-associated (internalins) involved with adhesion and induction of phagocytosis; secreted and involved with dissolving intracellular membranes and allowing the bacterium to escape into the cell cytoplasm (two phospholipases and a haemolysin); interacting with the host-cell cytoskeletal components and allowing intracellular mobility (actA protein; Vazquez-Boland *et al*, 2001).

Epidemiology of listeriosis and changing pattern of human listeriosis in England and Wales

2.16 Consumption of contaminated food is believed to be the principal route of infection and common source outbreaks, together with sporadic cases, occur. Infection can also be transmitted, albeit rarely, by direct contact with the environment, infected animals or by cross-infection during the neonatal period. The majority of cases are/appear to be sporadic. Foods associated with transmission are predominantly ready-to-eat, with extended (usually refrigerated) shelf-life, capable of supporting the growth of *L. monocytogenes*. Foods associated with transmission world-wide are shown in Table 3.

Table 3. Food products associated with the transmission of listeriosis worldwide

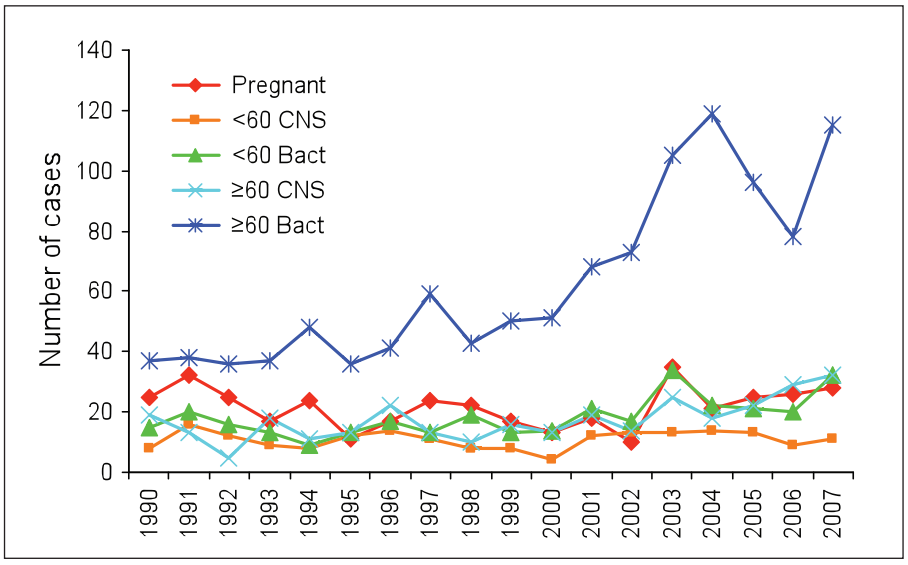
Dairy products	Meats	Fish	Vegetables	Complex foods
Soft cheese (Raw) milk Ice cream/ soft cream Butter	Cooked chicken Turkey Frankfurters Sausages Pâté and rillettes Pork tongue in aspic Sliced meats	Fish Shellfish Shrimps Smoked fish Cod roe	Coleslaw salad Vegetable rennet Salted mushrooms Alfalfa tablets Raw vegetables Pickled olives Rice salad Cut fruit (melons) Hummus	Sandwiches

Source of data from case and outbreak reports in the world literature. Wagner and McLauchlin. Biology in Handbook of *Listeria monocytogenes*. CRC Press, Boca Raton. 2008. pp3-25.

2.17 After the rise in cases in England and Wales associated, at least in part, with the consumption of pâté between 1987-9 (McLauchlin *et al*, 1991), the annual totals of reported cases declined during the 1990s to between 87 and 128 per year. However, since 2000 the annual number of listeriosis cases reported increased to 146 and 136 cases in 2001 and 2002 respectively, and to 182-237 cases from 2003-2007. Cases associated with pregnancy, with central nervous system infection and in people aged less than 60 years remained at similar levels. An increase in reports has occurred, almost exclusively in patients aged over 60 years with bacteraemia (Fig. 1; Gillespie *et al*, 2006). This increase is independent of demographic changes in the population and has resulted in an approximate tripling in the rate of the disease in those aged 60 years and over. In England and Wales: 3.3-4.7 cases per million were reported in 1990-1992 compared with 13.2 in 2007 (Fig. 2). A similar increase is observed when considering the total numbers of blood cultures and CSF specimens from which *L. monocytogenes* was isolated (Fig. 3). It is also of note from this Figure that the numbers of CSF specimens yielding *L. monocytogenes* has remained essentially the same since 1990.

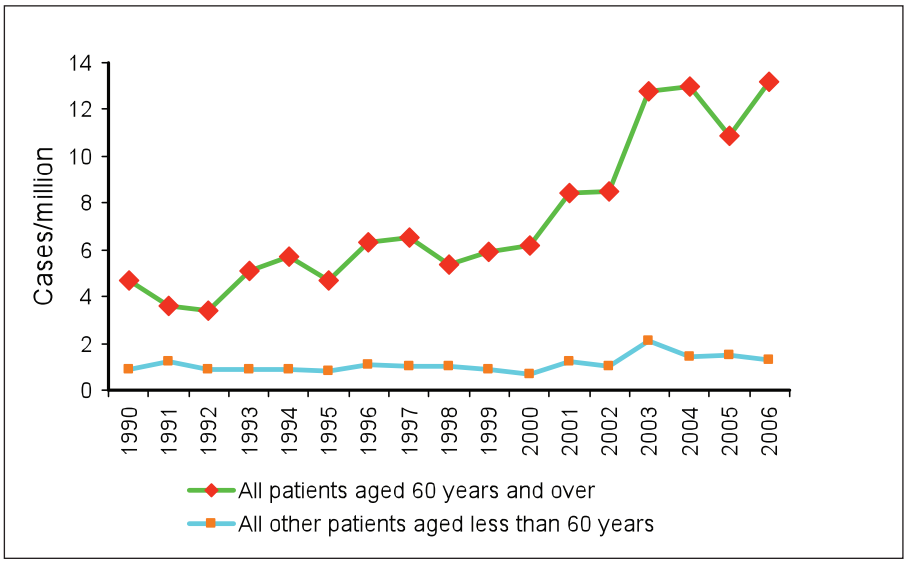
Fig. 1. Numbers of reported listeriosis cases: England and Wales 1990-2007

CNS = central nervous system infections.
Bact = bacteraemia in the absence of CNS infection.



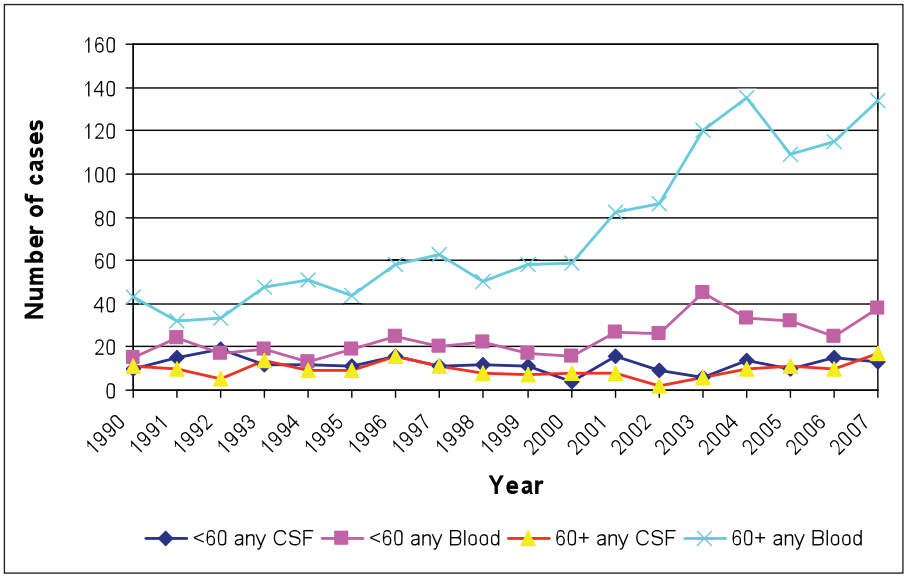
Source: HPA

Fig. 2. Age specific rates of listeriosis in England and Wales 1990-2006



Source HPA

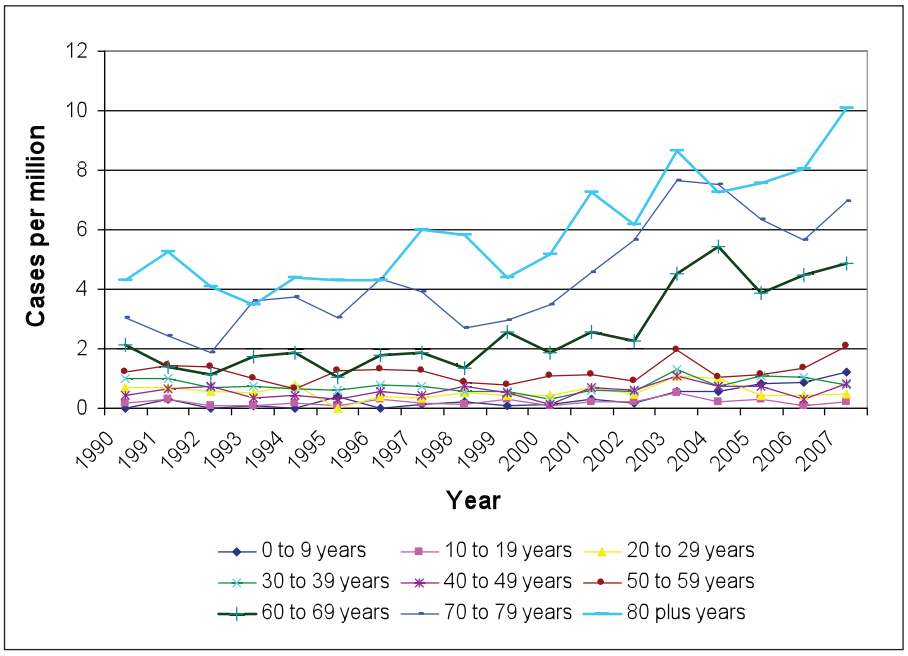
Fig. 3. Total *L. monocytogenes* isolations from blood and CSF



Source HPA

2.18 The rates of listeriosis have considerably increased in all groups aged 60 years and over, and show an increased rate with increasing age (Fig 4).

Fig. 4. Age group specific rates of human listeriosis in England and Wales



Source HPA

2.19 The proportion of cases in patients aged 60 years and over without underlying illnesses was not significantly different before or after 2000. Of all patients aged 60 years and over, 9% had no reported underlying illness for the period 1990 - 1999, and 6-14% for 2000 - 2007 (Table 4).

Table 4. Numbers of cases with and without underlying illnesses in all patients 60 years and over

	Numbers of cases (%) aged 60 years and over		
Year	With underlying condition	No underlying condition	Not recorded
1990-1999	383 (70%)	50 (9%)	115 (21%)
2000	53 (79%)	7 (10%)	7 (10%)
2001	68 (73%)	6 (6%)	19 (20%)
2002	70 (74%)	10 (10%)	15 (16%)
2003	102 (73%)	18 (13%)	19 (14%)
2004	65 (45%)	9 (6%)	71 (49%)
2005	76 (62%)	7 (6%)	40 (32%)
2006	93 (73%)	12 (9%)	22 (17%)
2007	124 (81%)	21 (14%)	7 (5%)

Source: HPA unpublished data

2.20 Whilst small outbreaks were recognized between 1999 and 2007, in association with consumption of hospital sandwiches, butter and sliced meats (Table 5), these represent a small proportion of the total number of cases and do not explain the overall increase. The increase in those aged 60 years and over was due to multiple strains of *L. monocytogenes* and occurred in all regions.

Table 5. Cases and clusters of human listeriosis in England and Wales 1999-2007 and associations with food vehicles[3]

Year	Region	Cases	Vehicle
1999	NE England	4	Hospital sandwiches
2003	NE England	17	Butter
2003	NE England	18	None identified
2003	S Wales	2	Hospital sandwiches
2003	SW England	5	Hospital sandwiches
2004	E Mids	6	None identified
2004	SE England	2	Hospital sandwiches
2005	NW England	1	Sliced meat
2006	London	1	Sliced meat
2007	London	1	Hospital sandwiches

Source: Gillespie *et al* 2006 and HPA unpublished data

2.21 A similar change in incidence of listeriosis has been reported in Scotland and Northern Ireland (ACMSF 2006, ACMSF 2007a, ACMSF 2007b) and in Germany (Koch and Stark, 2006). The rise in cases in Germany occurred together with changes in surveillance and raised diagnostic awareness (listeriosis became a notifiable disease in 2001) and resulted in a more than doubling of the numbers of reported cases between 2001 and 2005. The increase in cases in Germany occurred almost exclusively in patients aged 60 years and over and did not appear to be linked to any single common-source outbreak: the cases overall were predominantly sporadic in nature. Significant increases in cases were also reported in Belgium, Denmark, France, Lithuania, The Netherlands, and Spain (Denny and McLauchlin, 2008). There is no evidence for a common source relationship between these changes which have occurred in the UK with those in other countries.

3 All food vehicles contaminated with the same type of *L. monocytogenes* as infected the patients.

Conclusions

2.22 Human listeriosis is a rare but serious disease which occurs most often in patients with cancer, those undergoing immunosuppressive or cytotoxic treatment, the elderly (over 60 years of age), the unborn and newly delivered infants, the pregnant woman, diabetics, alcoholics (including those with liver disease) and a variety of other conditions.

2.23 Consumption of contaminated food is believed to be the principal route of infection and common source outbreaks together with sporadic cases occur.

2.24 The majority of cases are/appear to be sporadic and foods associated with transmission are predominantly ready-to-eat, with extended (usually refrigerated) shelf-life, capable of supporting the growth of *L. monocytogenes*.

2.25 Since 2000, the annual number of listeriosis cases reported has increased and the increase has occurred almost exclusively in patients aged over 60 years with listerial bacteraemia. This increase is independent of demographic changes in the population and has resulted in an approximate tripling in the rate of the disease in those aged 60 years and over in England and Wales: 3.3-4.7 cases per million were reported between 1990-1992 and 13.2 cases per million in 2007. However the degree of under-reporting of listeriosis in the UK has not been recently estimated.

2.26 A similar change in presentation of listeriosis has been reported in Scotland and Northern Ireland and Germany. Significant increases in cases were also reported in Belgium, Denmark, France, Lithuania, The Netherlands and Spain. There is no evidence for a common source relationship between these changes which have occurred in the UK and those in other countries.

Recommendations

2.27 Pan-European surveillance and epidemiological and microbiological investigations should be used to investigate changes in listeriosis in different Member States and to ascertain if there are common generic or risk factors occurring in the UK with those in other countries.

2.28 Studies should be undertaken to develop methods for screening *L. monocytogenes* isolates for differences in virulence and investigate the differences between isolates from different patient groups and time periods.

Chapter 3: Report rationale

3.1 This report focuses on our efforts to try to identify the cause(s) of the recent increase in *L. monocytogenes* cases in the over 60s. We chose to examine a series of four hypotheses. These are shown below together with brief details.

Our four main hypotheses

1. The rise in cases of listeriosis in immunocompromised people over 60 years of age is an artefact associated with improved case recognition.
2. The population predominantly affected by the recent increase has become more susceptible to infection with *L. monocytogenes*.
3. The pathogen, *L. monocytogenes* has become more virulent and "new" strains are more capable of causing infection which manifests as bacteraemia in this group of patients.
4. Levels of exposure have increased.

(1) The rise in cases of listeriosis in immunocompromised people over 60 years of age is an artefact associated with improved case recognition

3.2 We considered the possibility that the recent rises in listeriosis in England and Wales were an artefact. Thus are we now detecting infections previously missed because either patient management and/or laboratory testing protocols for the diagnosis had changed?

(2) The population predominantly affected by the recent increase has become more susceptible to infection with *L. monocytogenes*

3.3 One possible explanation for the recent increase in cases is that the population predominantly affected by the recent increase, immunocompromised people over 60 years of age, has become more susceptible to infection with *L. monocytogenes*. We thus reviewed evidence to determine whether the changes in treatments available to treat conditions more common in the over 60s could have had the side effect of increasing vulnerability to *L. monocytogenes* infection.

(3) The pathogen, *L. monocytogenes* has become more virulent and "new" strains are more capable of causing infection which manifests as bacteraemia

3.4 It is known with other foodborne pathogens such *Salmonella* spp. that bacteria can vary in their virulence attributes. We therefore examined the hypothesis that the strains of *L. monocytogenes* responsible for the recent rise in cases in the over 60s have virulence properties that are different from those identified in strains isolated from past cases.

(4) Levels of exposure have increased

3.5 Another possible explanation for the rise in cases of listeriosis in the elderly is that their exposure to the organism has increased as a result of increased contamination of foods, changes in processing and composition of foods, or changing patterns of consumption, or food storage in the over 60s. To examine this hypothesis, we received and reviewed evidence on food contamination levels with the pathogen and the frequency of *L. monocytogenes*-positive samples. We also reviewed available data on food purchase patterns, particularly those relevant to the groups with potentially increased risk of *L. monocytogenes* infection.

3.6 These hypotheses will be considered in the following chapter.

Chapter 4: Consideration of key hypotheses to explain the increase in listeriosis cases

Hypothesis 1: The rise in cases of listeriosis in immunocompromised people over 60 years is an artefact associated with improved case recognition

4.1 The increase in cases of listeriosis associated with elderly age groups cannot be attributed to the general demographic increase of this age group in the population alone. However the elderly are becoming an increasing proportion of the population (16% of the UK population were aged 65 and over in 2006, compared with 13% in 1971[4]). Furthermore, the increase in over 65s is about to undergo a marked acceleration over the next two decades. In 1991 there were approximately 9 million over 65s in the UK and in the following 10 years this increased to approximately 9.4 million (in 2001). By 2006, the numbers had increased to 9.7 million and it is estimated that this will be followed by a marked increase in over 65s, reaching approximately 10.5 million by 2011 and nearly 12.75 million by 2021. It is therefore especially important to understand the factors contributing to the increase in listeriosis in the group. Since this report was prepared the ACMSF has been made aware of an increase in the incidence of campylobacteriosis in the over 60s age group (ACMSF, 2009).

4.2 The surveillance of listeriosis in England and Wales is passive and such systems are prone to both under-ascertainment and pseudo-outbreaks following increased interest in the public health community. Although reporting artefacts cannot be excluded, no increased interest in listeriosis from 2000 onwards has been detected and reporting and referral patterns of individual laboratories could not be identified (Gillespie *et al*, 2006).

4.3 Improvements in laboratory methods (especially in the isolation of *L. monocytogenes* from blood) or changes in local clinical practice (e.g. more detailed investigations of patients with acute febrile illness presenting to primary care) might explain the increase in cases diagnosed or the altered clinical presentation.

4.4 The majority of diagnostic microbiology laboratories in the UK utilise one of a small number of commercial automated systems for blood culture. There have not been any changes in detection technologies that we believe would affect ascertainment of bacteraemia cases. All of the systems would readily support the isolation of *L. monocytogenes*.

4 http://www.statistics.gov.uk/cci/nugget.asp?ID=949

4.5 The national increase in the number of reported cases of bacteraemic listeria infection in older patients coincides with increased recognition of age discrimination in healthcare (Scott, 2000). A national director of older people's services was appointed for the NHS in England in November 2000 with a mandate to reduce ageism in healthcare (Anon 2000a). Subsequently the NHS launched a national plan in 2001 to ensure older people receive the same treatment as those under 65 (Kmietowicz, 2001). As a result of these initiatives, it is possible that the intensity of investigation of sepsis in the elderly has increased. However, other studies have challenged the extent of ageism in NHS healthcare and the practical impact of age discrimination is uncertain (Hubbard *et al*, 2003).

4.6 If there was a significant increase in the proportion of elderly patients with sepsis undergoing blood culture, at least some of the change in listeriosis epidemiology might be artefactual. National data are not routinely available on the number of blood cultures collected stratified by age group. However, data from a large Scottish diagnostic laboratory indicated that although there had been a steady increase in blood cultures submitted from 2000-2007, there did not appear to be any relative increase in the proportion of such samples submitted from patients over the age of 60.

Conclusions

4.7 *L. monocytogenes* will grow on most non-selective media; therefore improvements in microbiological media would be unlikely to increase the diagnosis of listeriosis (McLauchlin 2005). Although the introduction of mandatory reporting of meticillin-resistant *Staphylococcus aureus* bacteraemia in England in 2001 has led to an increase in blood cultures being taken, this is insufficient to explain the increase or shift in presentation described here (Anon 2000b, Anon 2005b). Further evidence that the increase was not due to improved diagnostics is provided by the absence of a significant increase in the isolation of *L. monocytogenes* from blood cultures from patients with CNS infections or from pregnancy-associated cases (Gillespie *et al*, 2008). In addition, there has not been an increase in bacteraemia caused by other foodborne pathogens (i.e. *Salmonella* and *Campylobacter*) in the over 60s. (Gillespie *et al*, 2008).

4.8 The degree of under-reporting of listeriosis in the UK has not been estimated recently. An ascertainment ratio of 2 (estimation of the numbers of cases of illness to the numbers reported to national databases for laboratory confirmed infections) for human listeriosis was estimated by Adak and colleagues (Adak *et al*, 2002). The amount of under-reporting (ascertainment ratio) for human listeriosis could be estimated by comparing the numbers of cases reported to national databases with the numbers of cases ascertained in a subset of diagnostic centres. Since the highest numbers of cases occur in those 60 years old and over and there is a possibility of surveillance artefact due to changes in diagnostic procedures having introduced bias, resources should be concentrated on investigation of incidence in this section of the population.

4.9 The Second Infectious Intestinal Disease Study will not address this problem. However, even if significant under-reporting of listeriosis has previously occurred, the FSA has recently estimated that *L. monocytogenes* is responsible for the highest numbers of deaths due to a food-borne pathogen (FSA 2007, Annual report of the Chief Scientist 2006/7). Since the highest numbers of cases occur in those 60 years old and over, resources should be concentrated to reduce the incidence in this section of the population.

4.10 Our ability to analyse infection trends and understand changes in the epidemiology would be enhanced by the routine collection of denominator data for selected medical investigations associated with infection.

Recommendations

4.11 The amount of under-reporting (ascertainment ratio) for human listeriosis should also be estimated.

4.12 UK surveillance of infection should be enhanced to incorporate data on the corresponding denominator populations, including numbers of relevant medical investigations, such as blood cultures, undertaken.

Hypothesis 2: The population predominantly affected by the recent increase has become more susceptible to infection with *L. monocytogenes*

4.13 Demographic changes in the population might have resulted in an over-representation of cases from particular age groups without a 'true' increase in risk. Life expectancy in the UK is increasing; therefore an increase in listeriosis in older patients is likely to occur. However, calculations controlling for the changing age structure in England and Wales during the surveillance period generates a consistent increase in risk amongst those aged 60 years and over in both sexes and in most regions. The risk of listeriosis increases with each successive age group (Fig. 4). Medical advances have resulted in the UK human population surviving for longer with chronic conditions (Anon 2005a) with a likely increased susceptibility to listeriosis. Whilst it has not been possible to obtain suitable denominator data required to examine such changes in detail, it is unlikely that they would result in a threefold increase in a single patient age group over a short time period without a concomitant increase in younger patients with similar underlying conditions. Furthermore, using the available data, no differences in the types of underlying illnesses could be detected between patients before and after the increase (Table 6). Whilst there have been changes in patient treatments which may have long term modulation of the immune system (e.g. statins and tumour necrosis factor-alpha inhibitors) it is not possible with current data to ascertain if these are increasing overall risk for listeriosis.

Table 6. Underlying illnesses in listeriosis patients aged 60 years and over: England and Wales

Underlying illnesses	1993-2000	2001-2004
Cancer	42%	43%
Autoimmune	13%	14%
Cardiovascular	13%	12%
Alcohol related	3%	4%
Renal	3%	5%
Diabetic	3%	3%
Hepatic and biliary	2%	1%
Other	20%	18%

Source: Gillespie *et al* 2006

Changes in medical practice which may render the elderly at increased risk of listeriosis

Treatment of haematological malignancy

4.14 There has been a trend for older patients to be treated more aggressively, with more intensive chemotherapy, often using chemotherapeutic agents which have only become available in the last 10 years. Indeed, national trial protocols are now tending not to state an upper age limit and it is left to the discretion of the enrolling clinician to assess patient's suitability for chemotherapy (Smith. Personal communication 2008). In the GELA (Groupe d'Etude des Lymphomes de l'Adulte) study, elderly patients with diffuse large B-cell lymphoma were randomized to two regimens CHOP and CHOP-R, the latter containing rituximab, which is a B lymphocyte-depleting monoclonal antibody (Coiffier *et al*, 2002). Patients treated with the latter manifest better outcomes than the former (Coiffier *et al* 2007) and CHOP-R is widely used in the UK in elderly individuals. Rituximab has been associated with listeriosis (Ng and Lim, 2001).

4.15 The combination of cyclophosphamide plus fludarabine (Rai *et al*, 2000), is increasingly used in the management of chronic lymphocytic leukaemia, which is predominantly a disease of the elderly and, following publication of the results of the MRC CLL4 trial, is now recommended as standard therapy for this condition (Catovsky *et al*, 2007). The association between listeriosis and fludarabine (a purine analogue) is well recognized (Hequet *et al*, 1997; Cleveland and Gelfand 1993; Anaissie *et al*, 1992).

4.16 The protein kinase inhibitor, imatinib, has now been recommended for some forms of chronic myeloid leukaemia (CML; NICE(a), 2003). The median age of diagnosis of CML is 67 years. Cases of listeriosis associated with patients taking this drug have been reported (Ferrand *et al*, 2005).

Management of solid organ malignancies

4.17 As with haematological malignancies, there have been changes in the management of those of solid organs over the last 10 years. For example, the new antimetabolites capecitabine and tegafur have been recommended by the National Institute for Health and Clinical Excellence for the management of metastatic colorectal cancer, a condition in which 40% of individuals are over 75 years at diagnosis (NICE(b), 2003). Similarly 50% of patients diagnosed with lung cancer are aged 70 years of age and over and there has been a trend to treat older patients more aggressively including the use of second line treatment for individuals with small cell disease.

Statins

4.18 Although this category of drugs was introduced in the late 1990s, their use has increased markedly since then, with prescriptions in England alone more than doubling in the three year period to 2007 (Department of Health(a), 2007). These drugs are not contra-indicated in the elderly and, indeed a recent meta-analysis demonstrated a clear benefit for statins in the elderly (defined as 65 years and over) (Afilalo *et al*, 2008). Statins are acknowledged to have immunomodulatory effects, especially on cellular immune function and they may even play some role in the prevention of solid organ transplant rejection (Steffens and Mach, 2006; Kobashigawa and Patel, 2006). The implications of this in terms of increasing risk of listeriosis are unclear. Interestingly, although *L. monocytogenes* HMG-CoA reductase is only weakly inhibited by these drugs (Theivagt *et al*, 2006), atorvastatin and lovastatin at physiological concentrations reduced intracellular proliferation of *Salmonella* Typhimurium both *in vitro* and in an animal model (Catron *et al*, 2004). Statins change cholesterol and membrane properties, which may decrease susceptibility to infection, but may also increase sensitivity to infection in other ways.

Disease modifying anti-rheumatic drugs (DMARDS)

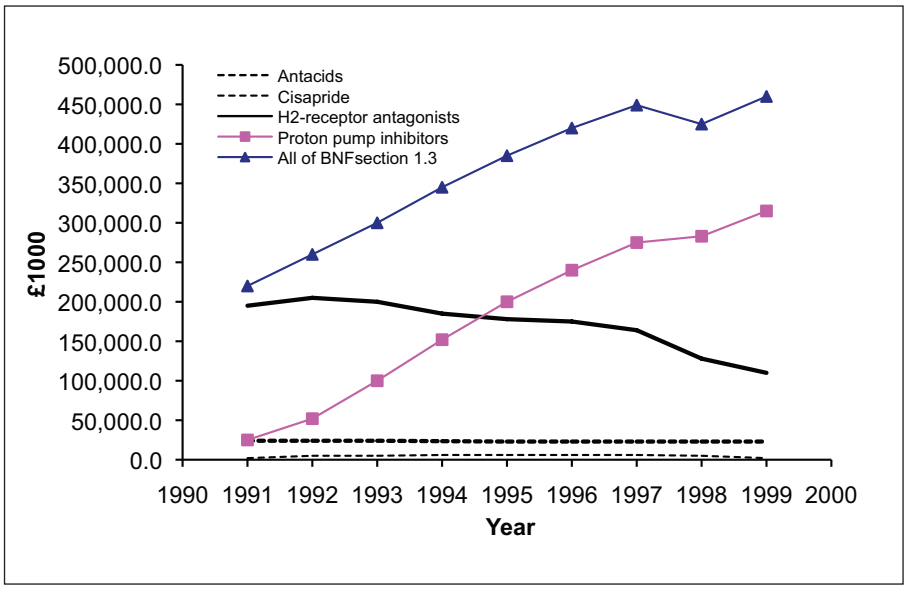
4.19 Although rheumatologists are less likely to employ aggressive DMARD therapy in elderly patients with rheumatoid arthritis (Fraenkel *et al*, 2006; Tutuncu *et al*, 2006), drugs such as etanercept, infliximab and leflunomide are widely used to treat such patients. These agents have a well recognized association with listeriosis e.g. (Kesteman *et al*, 2007; Schett *et al*, 2005).

Antisecretory Agents

4.20 Functional achlorhydria as a result of antisecretory drug therapy for dyspepsia-related conditions such as gastro-duodenal ulceration and gastro-oesophageal reflux disease is also an important risk factor for GI infection. Inhibition of stomach acid increases susceptibility to listeriosis in animal models (Schlech *et al*, 1993). An association between PPI and campylobacteriosis (Neal *et al*, 1996) and other gastro-intestinal (GI) infections

(Leonard *et al*, 2007) has been noted and there is increasing evidence to suggest that PPIs may be a risk factor for the development of *Clostridium difficile*-associated disease – although this still remains controversial (Lowe *et al*, 2006). Over recent years, proton pump inhibitors (PPI) have displaced H_2 receptor antagonists because of the near total achlorhydria induced by the former. Prescription Pricing Authority data show a steady rise in the cost of prescribing for dyspepsia since the introduction of PPIs. In 1999, £471 million was spent; £323 million on PPIs, £124 million on H_2RAs and £24 million on antacids. The costs and numbers of prescriptions for dyspepsia have risen steadily between 1991-1999, (Fig. 5). PPI prescribing has increased steadily, with little substitution of either antacids or H_2 receptor antagonists (H_2RAs). Indeed, following the introduction of the first generic PPI (omeprazole) in 2002 prescriptions doubled in the ensuing 5 years. PPIs are now one of the most frequently prescribed classes of drug (although <60-70% of prescriptions in either community or hospital settings are deemed inappropriate) (Forgacs and Loganayagam, 2008).

Fig. 5. Net cost of dyspepsia medication, England 1991-99



Source: http://hcna.radcliffe-oxford.com/dyspepsia.htm

Non-behavioural factors which may increase susceptibility to gastro-intestinal infection (and pathogens whose sole/primary portal of entry is the gastro-intestinal tract)

4.21 GI infection occurs more frequently in the elderly than in younger adults. Factors cited as contributing to the increased risk of infection are gastric atrophy, decreased intestinal mobility, altered regional microflora and gut mucus secretions (Klontz *et al*, 1997).

Immunosenescence

4.22 There are many mechanisms which contribute to the process of immunosenescence (Castle *et al*, 2007), but probably the most important of these is a decline in T lymphocyte function (Hakim and Gress, 2007; Aw *et al*, 2007) (e.g. decreased Th_1 response, thymic involution) which would predispose individuals to an increased risk of infections caused by facultative intracellular bacteria, such as *L. monocytogenes*. Declining T cell function in the elderly has been cited as an explanation for findings from a study which reported that the factors which increased the risk of contracting listeriosis were also associated with death in patients under 70 years, yet for patients over 70 years, the presence of a predisposing factor did not add to the risk of death (Gerner-Smidt *et al*, 2005).

Malnutrition

4.23 Malnutrition has increased in the elderly (British Association for Parenteral and Enteral Nutrition, 2003). For example, patients aged 80 years and over are five times more likely to be malnourished than those 50 years and under, and the importance of adequate nutrition for elderly patients in hospitals and care homes has recently been recognized with the publication of Improving Nutritional Care (Department of Health (b), 2007). Malnutrition has been reported as a risk factor for listeriosis (Gallagher and Watanakunakorn, 1988).

Other measures of increased susceptibility to listeriosis in the elderly

4.24 Underlying co-morbidities might predispose to listeriosis in the elderly and it would be of value to determine whether for a given age group there is more co-morbidity than in a comparator cohort of, say, 10 years ago. There are many tools to quantify co-morbidity such as the Charlson, Elixhauser and Kaplan Feinstein Indices, some of which are tailored for use in the elderly e.g. the Geriatric Index of Co-morbidity (CIG). However, an extensive literature search failed to identify studies which have addressed this hypothesis.

Conclusions

4.25 Medical advances have resulted in the UK human population surviving for longer. Elderly individuals are more likely to have underlying co-morbidities, which are acknowledged to predispose to listeriosis than those in younger age groups. Elderly patients are increasingly likely to receive immunosuppressive therapies for chronic conditions which are known to increase the risk of listeriosis. However, current data collection methods are insufficiently refined to determine the extent to which, if any, changes in the use of immunosuppresive or antisecretory therapies in elderly patients have resulted in an overall increased risk of listeriosis in this age group.

4.26 The increase in cases of listeriosis associated with elderly age groups cannot be attributed to the general demographic increase of this age group in the population.

Recommendations

4.27 Studies should be undertaken to investigate whether trends in the management of conditions which are treated with immunosuppressive or antisecretory agents might have contributed to the overall increase in the risk for listeriosis.

4.28 A retrospective case-controlled study could also identify with greater accuracy those underlying conditions which are most associated with listeriosis in the elderly.

4.29 Data collected prospectively as part of the investigation of cases of listeriosis should include more detailed information relating to underlying comorbidities and their drug management.

Hypothesis 3: The pathogen, *L. monocytogenes* has become more virulent and "new" strains are more capable of causing infection which manifests as bacteraemia

4.30 Changes in the virulence of *L. monocytogenes* might explain the change in disease presentation. However, the increase has involved multiple subtypes, making this unlikely. However, the growth and behaviour (*in vitro*, *in vivo*, in foods and in the environment) of current *L. monocytogenes* strains as compared with those isolated prior to the upsurge has not been examined. Furthermore, comparisons with strains from other European countries also experiencing an increase in incidence have not been performed.

4.31 Jacquet *et al.* (2004) reported that isolates from food were more likely to express a truncated version of the internalin A protein than those causing disease in humans. However, virulence is a product of the expression of multiple genes (Liu *et al*, 2007) and phenotypic and genotypic tests are not routinely available to characterise the expression of all virulence genes. Furthermore, since the upsurge was confined to a restricted patient age group, this is more likely to reflect increased risk due to higher exposure through consumption of specific food types and by differences in behavioural practices of food storage and preparation.

4.32. Complete genome sequences are available for several different *L. monocytogenes* strains and there is now a considerable body of information available on genes associated with the virulence of *L. monocytogenes*, most of which encode cell surface structures or secreted products. However, there is limited information on polymorphisms which occur naturally within these virulence genes which might affect the ability of this bacterium to cause infection. Although genes have been identified as essential for virulence of this bacterium, the exact roles in invasion of the entire host is less well understood. Patients involved with the recent upsurge with bacteraemia have been shown to be more likely to have disturbances of the gastrointestinal tract. Virulence

genes may have a role for survival and invasion of this organ. These genes might include putative virulence factors for survival in the stomach, e.g. glutamate decarboxylase and antiporter proteins *gad, betL, gbu* and *opuC*. These proteins result in a notable increase in cytoplasmic pH of the bacterium (Gahan and Hill 1999), thus potentially enhancing survival in the stomach. Having survived the stomach, there is some evidence that genes associated with bile salt tolerance and hydrolysis (*btlb* and *bsh*) are involved with survival in the small intestines as well as invasion via the bile duct (Dussurget *et al*, 2002). Finally, there is invasion of intestinal cells mediated by the internalin A and B surface proteins. Internalin A has been shown to be more important for invasion of intestinal epithelial cells and variations have been reported in this gene (Olier *et al*, 2003; Rousseaux *et al*, 2004; Jacquet *et al*, 2004). However, these are part of a family of surface located proteins and the roles of other internalins (*inlC, inlJ, inlE, inlF, inlG* and *inlH*) may also have a role in virulence (Sabet *et al*, 2005).

4.33. Characterisation (typing) methods are well developed and a variety of molecular methods (e.g. molecular serotyping, amplified fragment polymorphism and pulsed field gel electrophoresis) are routinely used for strain differentiation. However diversity within *L. monocytogenes* detected by these typing methods does not generate information on possible differences in the virulence of organisms. It has not been possible to exclude the possibility that the increase in incidence was due to changes in the bacterium. However, multiple strains were identified with the increase in listeriosis in patients over 60 years of age, hence these factors are likely to be of importance.

Conclusion

4.34 It is possible that specific pathogen factors occurring across multiple *L. monocytogenes* strains allow increased infection in older age groups. Changes in the food chain, such as alterations in food preservation technologies, may have served to select such strains. However, this is open to speculation and there is no *in vitro* evidence to support this hypothesis.

Recommendation

4.35 Work is needed to develop *in vitro* methods of investigating the frequency of specific genes or gene polymorphisms associated with differences in the pathogenicity of *L. monocytogenes*.

Hypothesis 4: Levels of exposure have increased

4.36 Common source foodborne outbreaks have been reported due to a single strain of *L. monocytogenes* which has a higher attack rate for specific members of the population (e.g. pregnant women, Linnan *et al*, 1988; non-pregnant immunocompetent adults Büla *et al*, 1995; or non-pregnant immunocompromised adults Fleming *et al*, 1988), despite the fact that food vehicles were on general sale

and were consumed by a much larger section of the population. The common source clusters which were identified (Table 5) constituted a small proportion of all cases and did not, therefore, account wholly for the increase in incidence. The upsurge overall had a similar seasonality to listeriosis in previous periods, occurred in conjunction with multiple underlying illnesses, in both sexes, across multiple regions and was caused by multiple *L. monocytogenes* strains. It is therefore unlikely that the upsurge reflects a 'conventional' common source food-borne outbreak confined to older members of the population.

4.37 Unusual clusters of listeriosis due to multiple *L. monocytogenes* strains occurring within distinct regions have been reported in Europe and the USA (Rocourt *et al*, 1982; Schwartz *et al*, 1989), which have some similarities to the current epidemiological pattern but on a national level and over a prolonged period. Possible explanations previously suggested have included additional cofactors (possibly infections), which increase susceptibility to infection, multiple food contamination events due to a common cause, or general changes in manufacturing and retailing practices for food. It was previously suggested that a co-infecting organism (probably in the enteric tract) might increase susceptibility to serious systemic listeriosis (Schwartz *et al*, 1989). This is certainly possible, although we are not aware of significant increases in enteric infections concomitant with the upsurge described here. Since listeriosis is predominantly food-borne, the upsurge may reflect multiple food contamination events, which, combined with changes in manufacturing processes or specific eating habits, results in increased exposure to this bacterium, and this will be discussed in the following section.

Listeria in foods

4.38 Foods traditionally considered high risk with regards to *L. monocytogenes* and thus listeriosis all generally have the following similar characteristics (Bell and Kyriakides, 2005)

- Manufactured with no processing step capable of destroying *Listeria* spp. eg. cooking or
- Exposed to post process contamination e.g. slicing
- Product with little or no preservation factors e.g. neutral pH, low salt, high moisture, etc.
- Sold with long shelf life under chilled conditions
- Consumed as a ready-to-eat product

4.39 Foods falling into these groups are therefore predominantly chilled, ready-to-eat foods such as:

- Cooked meats and pâté
- Ready meals (not designed to be fully cooked)

- Soft ripened cheeses
- Cooked fish and shellfish
- Dips (non pH-controlled)
- Sandwiches

4.40 The properties of *L. monocytogenes* favour transmission through food and a wide variety of food and food matrices will support the growth of this bacterium, which, especially in food with a long shelf life (>10 days), can become very heavily contaminated. Such 'problem' food types which support the growth of *L. monocytogenes* include soft cheese, milk, pâté, frankfurters and other sausages, cooked meat and poultry, smoked fish and shellfish, processed vegetables and some cut fruit including melon. Foods unable to support the growth of *L. monocytogenes* are defined in EC No. 2073/2005 as those with: pH ≤4.4; or $a_W \leq 0.92$; or pH ≤5.0 and $a_W \leq 0.94$. Microbiological models are available to predict the growth of this bacterium under defined conditions. Growth can be localised within specific areas of an individual food, either because of the source of contamination (i.e. within cut or contact surfaces or where raw products have been added) or because of the physicochemical properties of the foods such as in the areas of higher pH associated with the rind or with mould growth within a soft cheese. The tolerance of the bacterium to sodium chloride and sodium nitrite, and the ability to multiply, albeit slowly, at refrigeration temperatures (the doubling time at 4°C is 1 - 2 days) makes *L. monocytogenes* of particular concern as a post-processing contaminant in long shelf life refrigerated foods. The widespread distributionof *L. monocytogenes* and its ability to survive on dry and moist surfaces within food manufacturing environments for extended periods favours post-processing contamination of foods from both raw product and factory sites.

4.41 *Listeria* spp. grow well on a wide variety of non-selective laboratory media. However, for isolation from food and environmental sites, selective media are required. A variety of selective and differential media allowing the isolation of *L. monocytogenes* are now generally available, and the ability to isolate and recognise this bacterium is well within the capabilities of the majority of food, water and environmental testing laboratories. *L. monocytogenes* has been isolated from numerous types of raw, processed, cooked and ready-to-eat foods, as well as food production sites and the environment (Table 7).

4.42 Selective isolation methodologies are available with agreed and standardised protocols, which allow both presence/absence tests, as well as enumeration of the pathogen. The methods are robust, not least because of the limited phenotypic variation within this genus, and provide qualitative and quantitative data within the usual confines of sampling error and distribution of micro-organisms within food matrices.

Table 7: UK Food surveys of Listeria contamination in foods, 1997-2007

Meat and fish								
Survey title	Funded/ carried out by	Start date	End date	Food type	No. of samples tested	*L. monocytogenes*		
						Total no. positive	Prevalence rate (%)	Level
A UK wide microbiological survey of retail sliced cooked meats and pâtés with particular reference to *Listeria monocytogenes*	FSA	March 2007	Sept 2007	Sliced cooked meats	1,691	Report pending	Report pending	Report pending
				Pâtés	1,651	Report pending	Report pending	Report pending
Survey of the microbiological examination of freshly sliced cooked meat from the point of sale and after 48 hours refrigeration at 6°C with a focus on *Listeria* spp. (North West of England)[5]	North West LAs and FEMS NW testing laboratories	Sept 2006	Aug 2007	Sliced cooked meats at point of sale	1,127	82	7.3	15 samples 10-100 cfu/g **5 samples >100 cfu/g**
				Sliced cooked meats after 48 hours	1,127	Data not provided	Data not provided	21 samples 10-100 cfu/g **31 samples >100 cfu/g**
A UK wide microbiological survey of retail smoked fish with particular reference to the presence of *Listeria monocytogenes*[6]	FSA	July 2006	Nov 2006	Hot smoked fish	1,878	66	3.4	63 samples <100 cfu/100g **3 samples >100 cfu/g**
				Cold smoked fish	1,344	236	17.4	236 samples <100 cfu/g

5 Unpublished data from study undertaken by the Cheshire, Cumbria, Greater Manchester, Lancashire and Merseyside Food Liaison Group and the Health Protection Agency's Food and Environmental Microbiology Services North West. For more info see press release at http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1211528160312?p=1204186170287

6 http://www.food.gov.uk/science/surveillance/fsisbranch2008/fsis0508

Meat and fish *continued*								
Survey title	Funded/ carried out by	Start date	End date	Food type	No. of samples tested	*L. monocytogenes*		
						Total no. positive	Prevalence rate (%)	Level (cfu/g)
A UK wide survey of microbiological contamination of raw red meats on retail sale	FSA	March 2006	June 2007	Raw beef joints, steaks and chops	3,249	Available in 2009	Available in 2009	Available in 2009
				Raw pork joints, steaks and chops	1,693	Available in 2009	Available in 2009	Available in 2009
				Raw lamb joints, steaks and chops	1,056	Available in 2009	Available in 2009	Available in 2009
End of shelf life study of modified atmosphere packed and vacuum packed ready-to-eat meats from retail premises[7]	LACORS/HPA	Sept 2003	Mid Nov 2003	Modified atmosphere packed and vacuum packed ready-to-eat meats at end of shelf life	2981	143	4.8	96 samples <20 cfu/g 20 samples 20-100 cfu/g **27 samples >100 cfu/g** (range 10^2 –10^6)
Microbiological examination of cold ready-to-eat meats from catering establishments[7]	LACOTS/ PHLS	June 1998	July 1998	Cold sliced ready-to-eat meats	3494	Data not available	Data not available	8 samples 10-100 cfu/g **5 samples >100 cfu/g**

7 Further information and full survey reports are available on the LACORS website at: http://www.lacors.gov.uk/lacors/ContentDetails.aspx?id=3512&authCode=4988458

Fresh produce								
Survey title	Funded/ carried out by	Start date	End date	Food type	No. of samples tested	*L. monocytogenes*		
						Total no. positive	Prevalence rate (%)	Level (cfu/g)
Survey of *Listeria* on pre-packed mixed salads at retail[8]	LACORS/HPA	May 2005	June 2005	Pre-packed mixed salads	2,686	130	4.8	**2 samples >100 cfu/g**
Survey of pre-cut fruit, sprouted seeds, unpasteurised fruit and vegetable juice from production and retail premises in the UK	European Commission (sampling by LACORS/ PHLS)	July 2002	Dec 2002	Pre-cut fruit	997	78	7.8	Data not available
				Sprouted seeds	808	28	3.5	Data not available
				Unpasteurised fruit and vegetable juices	291	2	0.7	Data not available
The microbiological examination of open ready-to-eat prepared salad vegetables from catering and retail premises[7]	LACORS/ PHLS	Sept 2001	Oct 2001	Open ready-to-eat salad vegetables	2934	88	3.0	87 samples <20 cfu/g **1 sample 840 cfu/g**
The microbiological examination of bagged prepared ready-to eat salad vegetables from retail establishments [7]	LACORS/ PHLS	May 2001	June 2001	Pre-packed ready-to-eat salad vegetables	3849	90	2.3	88 samples <10 cfu/g 1 sample 10-100 cfu/g **1 sample >100 cfu/g**
The microbiological examination of ready-to-eat organic vegetables from retail establishments[7]	LACOTS/ PHLS	May 2000	June 2000	Ready-to-eat organic vegetables	3200	ND	ND	ND

8 Further information and survey report is available on the LACORS website at: http://www.lacors.gov.uk/lacors/ContentDetails.aspx?id=14949

Dairy								
Survey title	Funded/ carried out by	Start date	End date	Food type	No. of samples tested	*L. monocytogenes*		
						Total no. positive	Prevalence rate (%)	Level (cfu/g)
Study on the microbiological examination of cheeses made from raw or thermised milk from production establishments and retail premises in the UK[9]	European Commission (sampling by LACORS/HPA)	Sept 2004	Oct 2004	Semi-hard cheese, un-ripened (fresh) and ripened soft cheese	1,842	18	1.0	**16 samples >100 cfu/g**
The microbiological examination of butter from production, retail and catering premises for *Listeria monocytogenes* and other *Listeria* spp.[7]	LACORS/HPA	May 2004	June 2004	Butter from production, retail and catering premises	3,229	13	0.4	13 samples <10 cfu/g
Survey on *Listeria monocytogenes* in raw cow's milk[10]	MAFF	1998	1999	Raw cow's milk at retail farms in England and Wales	774	32	4.1	Data not available

9 Further information and survey report is available on the LACORS website at http://www.lacors.gov.uk/lacors/ContentDetails.aspx?id=16479

10 Defra UK Zoonoses Reports (1999 - 2006)

Sandwiches								
Survey title	Funded/ carried out by	Start date	End date	Food type	No. of samples tested	*L. monocytogenes*		
						Total no. positive	Prevalence rate (%)	Level (cfu/g)
NPHS Wales *Listeria* in hospital sandwiches survey[11]	LAs and NPHS Wales	Oct 2005	March 2006	Hospital sandwiches	950	Data not available	0.2	Data not available
				Retail sandwiches	588	Data not available	0.9	Data not available
Microbiological examination of sandwiches from hospitals and residential/care homes with a focus on *Listeria monocytogenes* and other *Listeria* spp.[12]	LACORS/HPA	April 2005	March 2006	Sandwiches	3,249	88	2.7	87 samples <10 cfu/g 1 sample <20 cfu/g

11 Meldrum RJ, Smith RM. Occurance of *Listeria monocytogenes* in sandwiches available to hospital patients in Wales, United Kingdom. 2007. *J. Food Prot.* 70(8):1958-60

12 Further information is available at http://www.hpa.org.uk/hpr/archives/2007/news2007/news3307.htm

Other								
Survey title	Funded/ carried out by	Start date	End date	Food type	No. of samples tested	*L. monocytogenes*		
						Total no. positive	Prevalence rate (%)	Level (cfu/g)
Focused shopping basket sampling linked to *Listeria monocytogenes* work programme 2006/07[7]	LACORS/HPA	May 2006	April 2007	Sliced meats (within shelf life)	1484	55	3.7	42 samples <10 cfu/g 3 samples 10-100 cfu/g **10 samples >100 cfu/g**
				Sliced meats (end of shelf life)	684	29	4.2	18 samples <10 cfu/g 4 samples 10-100 cfu/g **7 samples >100 cfu/g**
				Sandwiches	1088	76	7.0	63 samples <10 cfu/g 9 samples 10-100 cfu/g **4 samples >100 cfu/g**
				Hard cheese	1242	2	0.2	2 samples <10 cfu/g
				Confectionery products containing cream	515	4	0.8	4 samples <10 cfu/g
				Spreadable cheese	725	ND	ND	ND
				Butter	878	ND	ND	ND
				Probiotic drinks	368	ND	ND	ND

Other *continued*								
Survey title	Funded/ carried out by	Start date	End date	Food type	No. of samples tested	*L. monocytogenes*		
						Total no. positive	Prevalence rate (%)	Level (cfu/g)
A study of cleaning standards and practices in food premises[7]	LACOTS/PHLS	Sept 2000	Nov 2000	Cleaning cloths	1070	57	5.0	Not enumerated
Microbiological examination of baked egg custard tarts, soft ice-creams and cold mixes[7]	LACOTS/PHLS	Aug 1997	Oct 1997	Soft ice-cream mix (*L. monocytogenes* not detected in corresponding soft ice-creams)	597	2	0.3	2 samples <100 cfu/g
				Soft ice-creams (*L. monocytogenes* not detected in corresponding mixes)	1214	10	0.8	10 samples <100 cfu/g

4.43 Evidence provided to the group from a recent study conducted in the North West of England examining the contamination of cooked meats, sliced in retail stores demonstrated that *L. monocytogenes* was present in 7.3% (82/1127) of products tested on the day of purchase. Of these, five had levels ≥ 100cfu/g. Of the 82 samples that had the bacterium present on the day of purchase, a further 26 gave counts of *L. monocytogenes* ≥100cfu/g after storage at 6°C for 48h (range 100-2000cfu/g). The same survey reported that only 23% of products were labelled with the use by information although this varied significantly between establishments (Supermarkets 74%; Market stalls 6%, Delicatessens 8%, butchers 7%).[13]

4.44 Given the relatively low number of cases of listeriosis that occur every year, even taking into account recent increases, it is possible that poor control at a small number of food businesses manufacturing 'high risk' products could be a significant contributing factor.

4.45 The Group was unable to assess whether an increase in shelf life across chilled commodity areas or the development of new foods would account for an increased risk of listeriosis as limited information was available. However, the Group received *Ad Hoc* information from one large supermarket chain has shown no major recent increase in shelf life for cooked meats, sandwiches, soft cheeses, ready meals or pâtés over the period corresponding to the increase in cases of listeriosis although shelf life has increased by approximately 10-20% in many chilled foods over the last two decades. Information from the broader retail sector is not available.

4.46 It is clear, however, that consumer trends have resulted in foods being modified to reduce preservative factors in a bid to reduce the detrimental effects of key food components on public health. Reducing salt is probably the most significant feature of this trend, promoted by government and the FSA in terms of targets for industry to reduce salt in key foods and also at the public to reduce the consumption of salt.

4.47 It has been suggested that reduced controlling factors, together with improved hygienic production could create environments in food that offer less competition to organisms such as *L. monocytogenes*, as competitive microflora are not present in such high numbers. As such the bacterium can grow faster and thus present greater risk. This is clearly a possibility although such improved hygienic conditions should consequently reduce the likelihood of *L. monocytogenes* being present. In addition, it is generally the case that foods do continue to suffer from food spoilage and hence spoilage microflora continue to feature as components of food.

[13] http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1211528160312?p=1204186170287

Social factors – food handling and consumption patterns

4.48 Analysis of consumption patterns for the year to August 2007 for over 65s was presented to the *Ad Hoc* Group by a major retailer from data supplied by a major market research company TNS (Annex III). Over 65s shopping and eating habits were compared to total consumers and the following general trends were identified:

- Over 65s have more frequent, smaller shopping trips than average households. (Annex III, Figure 1)
- They are more likely to eat homemade, fresh and chilled foods and less likely to consume frozen or ambient stable foods (Annex III, Figure 2).
- They over-index (when compared to total consumers) at breakfast, in-home lunch and teatime occasions i.e. on average over 65s eat breakfast, in-home lunches and teatime food more than the general consumer (Annex III, Figure 3).
- In comparison with all other age groups, over 65s are the consumer group whose primary reason for the meal occasion is health and they are more concerned about managing health (Annex III, Figure 4).
- In terms of food groups that over 65s over-index, the top ten are (Annex III, Figure 5);
    - Marmalade (229); Semi-sweet biscuits (220); Fish/meat pastes (200); Packet soups (200); Fresh meat pies (200); Tinned fruit (200); Plain/savoury biscuits (193); Fresh soft fruits (168); Fresh/smoked fish (164); Custards (164).
- In terms of volume consumption, the top ten foods consumed by over 65s are as follows (Annex III, Figure 6);
    - Bread and rolls; Butter and margarine; Breakfast cereals; Fresh fruits; Total desserts; Total snacks; Fresh potatoes; Cold desserts; Cakes, tarts and pastries; Total sandwiches.
- In terms of food preparation, over 65s are more likely to consume their food cold rather than hot and consume considerably more cold foods at breakfast, lunch, teatime and for in-home snacks when compared with the total consumers (Annex III, Figure 7).

4.49 Data supplied by the BRC for over 60s food expenditure indicated that they over-indexed (in comparison with all buyers) in the following categories; Fresh other meat[14] and offal; Fresh meat and pastry; Fresh bacon steaks; Margarine; Chilled black and white pudding; Fresh/Chilled pastry; Lards and compounds; Butter; Fresh lamb and Fresh cream.

[14] "other meat" includes veal, game and venison

4.50 It was not possible to examine these data in terms of particular vulnerable groups but clearly this may be important as the patterns of behaviour for the elderly may not necessarily be representative of that for those with pre-existing conditions as the cases of listeriosis are occurring predominantly in the elderly with other risk factors.

4.51 An important consideration in relation to the increase in cases of listeriosis in the over 60s is the potential that food handling practices in this age group may be a contributory factor. Extended storage of chilled foods beyond the use by date or poor temperature could allow low levels of the bacterium to increase in foods to hazardous levels prior to consumption.

4.52 Information on the food safety perception and practices in older age groups was reviewed. A pilot study conducted in the UK in the early 2000s involving 9 elderly individuals (n=9 focus group; n=16 home observation & interview) indicated that most had not measured their refrigerator temperature and did not know what it should be. The majority gauged the correct temperature by the feel of the product. Use by dates were understood but not always followed due to the difficulty in reading labels. Items were purchased near the end of life as they were sometimes cheaper and they were often kept for up to a month before consumption (Hudson and Hartwell, 2002).

4.53 A larger study conducted in 1998 (Johnson *et al*, 1998) of over 65s concluded that refrigerator temperatures in 70% (451/645) were ≥6°C, with a high proportion also reporting difficulty in reading food labels, despite good knowledge of use by dates.

Conclusions

4.54 It is generally recognised that greatest risk of listeriosis occurs from consumption of foods where very high levels of *L. monocytogenes* occur and thus the aim must be to ensure foods do not have such high levels.

4.55 It was not possible to determine any particular factor in the shopping and consumption patterns for over 65s that is likely to increase their risk for contracting listeriosis, although the tendency to eat more homemade, chilled and fresh foods and to consume more food cold may be important factors. It was not possible to specifically identify the consumption patterns of vulnerable groups in this age group but clearly this may be important to identifying any additional risks.

4.56 Information on the food safety perception and practices in older age groups was limited but did identify factors that could contribute to growth of *L. monocytogenes* in already contaminated foods such as keeping foods beyond their use-by dates or not keeping them refrigerated at suitable temperatures.

4.57 While there is no recent national data source about the shopping, food storage, cooking and eating behaviours of all over 60s, the *Low income diet and*

nutrition survey (Nelson *et al*, 2007), has data on this for the over 60s in the most materially deprived households in the UK. People over 65, ethnic minorities and people with self reported illness were over-represented in this national sample of the bottom 15% in income of the UK population. Further analyses of this study would throw some light on the food purchase and handling behaviour of this group at risk of *L. monocytogenes* and provide a basis for identifying how to research this more generally among the over 60s.

4.58 In addition, it might be possible to gain further insight into how the over 60s manage food purchase, storage and cooking through analysis of existing time use studies. Diary-based studies are the more appropriate method of obtaining this information (Gershuny J. Personal communication, 2008). Analysis of the existing diary based study Home OnLine conducted between 1998 and 2001 would provide a useful starting point and if this proved fruitful, further research might be undertaken to look at more recent behaviour.

Recommendations

4.59 Maintaining targeted active surveillance for *Listeria* spp. in foods is important to understanding if the control of the bacterium is improving or deteriorating and regular surveys examining a wide range of commonly purchased foods (shopping basket surveys) that the bacterium can be a contaminant of may be useful. However, the potential for the bacterium to contaminate and grow in retail and catering bought foods is important and any survey should also consider such foods.

4.60 Information on the food consumption patterns of over 60s with particular reference to vulnerable groups in this age group is necessary in order to better inform risk management options.

4.61 A study on the food handling behaviours of over 60s including those in vulnerable groups is recommended in order to better understand factors potentially contributing to increasing the risk of listeriosis.

4.62 Studies in the home would be of particular benefit to include food storage behaviour, refrigerator temperatures, adherence to 'use by' date and analysis of foods for *L. monocytogenes*.

4.63 Data on control subjects and from listeriosis patients of similar age should be collected to identify risk factors and allow an evidence basis for food safety advice to vulnerable groups. Understanding the impact of this on the growth of the bacterium in food using modelling/challenge studies is recommended to assess the risks.

4.64 It is also recommended that the FSA refers this Report to its Social Science Research Committee to consider the food storage and handling practices of elderly people in the home.

Chapter 5: Risk management

Legislative limits

European limits

5.1 In the UK and the rest of Europe, Regulation (EC) 2073/2005 (as amended) establishes microbiological criteria for *L. monocytogenes* in ready-to-eat (RTE) foods. Three food safety criteria have been defined, establishing different limits according to the target group of consumers or the potential for the food to support growth of the bacterium. Any product which does not comply with these limits must be withdrawn from the market.

5.2 Criterion 1.1 applies to all RTE foods intended for infants or for special medical purposes. A limit of absence in 25g throughout the product shelf life applies.

5.3 Criterion 1.2 applies to all other RTE foods which support the growth of *L. monocytogenes*. Different limits apply depending on whether the manufacturer can demonstrate that growth has been taken into account in setting the product shelf-life, as follows:

a) A limit of ≤100 cfu/g applies throughout the product shelf-life where growth has been taken into account and manufacturers can demonstrate compliance with this limit.

b) A limit of absence in 25g applies at the end of the manufacturing process before the product is placed on the market where growth has not been taken into account (or manufacturers are unable to demonstrate compliance with the limit of ≤100 cfu/g throughout the shelf-life).

5.4 The Commission produced a Discussion Paper in February 2008 aiming to clarify the requirements of criterion 1.2 and promote harmonised implementation. Since this time, EC guidance on *L. monocytogenes* shelf-life studies has been developed, which may be sufficient to address the need for better harmonisation. In addition, the 1-5 December 2008 meeting of the Codex Committee on Food Hygiene agreed to advance Annex II on Microbiological Criteria for *Listeria monocytogenes* in Ready-to-Eat Foods to step 5/8 which provides for co-existence of US and EU approaches (i.e. absence in 25g and 100cfu/g) considered to give equal protection to public health. The Commission is currently reconsidering the need for changes to criterion 1.2 in light of these developments. The UK's strict interpretation for products under

1.2b is that there is no criterion for such products when they are placed on the market (i.e. when the manufacturer is unable to demonstrate compliance with the limit of ≤100 cfu/g). In practice, this means if *L. monocytogenes* is detected when such products are on the market, a risk assessment will be conducted by the appropriate authorities to determine whether any action is required to protect public health. Regulation 2073/2005 is unlikely to provide the legal base for action in these circumstances.

5.5 Criterion 1.3 applies to all other RTE foods unable to support the growth of *L. monocytogenes*. A limit of ≤100 cfu/g throughout the product shelf-life applies. Products with pH ≤ 4.4 or a water activity of ≤ 0.92, products with pH ≤ 5.0 and a water activity of ≤ 0.94, products with a shelf-life less than five days are automatically considered to belong to this category.

5.6 Prior to the introduction of Regulation (EC) 2073/2005 the European Commission's Scientific Committee on Veterinary Measures relating to Public Health (SCVMPH) opinion on *L. monocytogenes*, published 23 September 1999, recommended that the concentration of *L. monocytogenes* be maintained at levels below 100 cfu/g in ready-to-eat foods (European Commission 1999). It was the conclusion of the SCVMPH that levels below 100 cfu/g represent a very low risk for all population groups. The Public Health Laboratory Service (PHLS) guidelines, published 3 September 2000, state that levels below 100 cfu/g are acceptable, but that *L. monocytogenes* at 100 cfu/g or above should be considered unacceptable or potentially hazardous (Gilbert *et al*, 2000).

5.7 Regulation (EC) 2073/2005 was introduced in January 2006. The number of incidents[15] involving *L. monocytogenes* that have been reported to the Agency has increased since this legislation came into force (i.e. 2003; 12 incidents, 2004; 14 incidents, 2005; 10 incidents, 2006; 27 incidents, 2007; 17 incidents). However, it is possible that additional factors have also contributed to this increase (e.g. real effects, improved reporting or the use of themed food surveys). It would be worthwhile revisiting this observation once there is a better understanding of the basis for the increase in cases seen in the UK and other EU Member States.

US limits

5.8 Since the 1980s, the USA has operated a zero-tolerance policy for *L. monocytogenes* in ready-to-eat foods. Recently, the United States Food and Drug Administration has proposed a tolerance of up to 100 cfu/g *L. monocytogenes* for ready-to-eat foods that cannot support the growth of *L. monocytogenes*.

15 Please note that the Agency defines an incident as 'any event where, based on the information available, there are concerns about actual or suspected threats to the safety or quality of food that could require intervention to protect consumers' interests'. Not all of the incidents referred to in the figures above involved a breach of the legislation, although in all cases an investigation was conducted to determine whether there could be a risk to public health.

Food industry listeria controls

5.9 Food manufacturing controls to prevent contamination by *Listeria* spp. have improved over the last two decades, following the identification of contaminated food as a significant cause of listeriosis (Table 8). Chilled, ready-to-eat foods are produced using HACCP principles that aim to identify where the hazard can occur in the manufacturing process and at what steps measures can be put in place to eliminate the hazard or reduce it to an acceptable level (CFA, 2006).

Table 8: Changes in the rates of *L. monocytogenes* contamination of foods examined in England and Wales

Year	Region	Total number of samples	% with *L. monocytogenes*		
			Total	10^2-10^3/g	>10^3/g
Soft cheese					
1987	London	222	10%	0.5%	5%
<1989	England and Wales	1130	6%	NK	>1%*
1988-1989	England and Wales				
	Cow	1135	6%	<0.1%	1%
	Goat and ewe	617	4%	0	0.2%
1989-90	North Yorkshire	131	0	0	0
1991-92	Bristol	251	0.4%	0	0
1995	England and Wales	1437	1%	0	0
1991	England and Wales	356	0	0	0
Pâté					
<1989	England and Wales	696	17%	NK	>2%*
1989	South Wales	216	35%	3%	7%
1989	England and Wales	1698	10%	1%	2%
1989-90	North Yorkshire	161	10%	2%	0
1990	England and Wales	626	4%	1%	0.3%
1991-92	Bristol	40	0.5%	0	0
1993	England and Wales	29	3%	0	0
1994	England and Wales	3065	3%	0.2%	0.4%
2000	England and Wales	26	0	0	0
2000	North East England	72	1%	0	1%
2000	England, Wales, Scotland and Northern Ireland	1178	2%	0	0

NK = not known; *some samples enumeration not performed.
Data from McLauchlin J. *Listeria.* In Motarjemi Y, Adams M (eds). Emerging foodborne pathogens. Woodhead Publishing, Cambridge, 2006. pp406-428.

5.10 The bacterium is ubiquitous in the environment and therefore unless the food is subject to a cooking process (achieving a heat process equivalent to 70°C for 2 minutes) in a hermetically sealed container it is difficult to completely guarantee its absence from all chilled, ready-to-eat foods at all times. As most chilled foods are not treated in this way, most focus is placed on preventing contamination of foods from equipment and the environment and thus minimising the frequency with which the bacterium contaminates a food or alternatively preventing growth to high levels through shelf life restriction or product formulation.

5.11 Many foods that allow the growth of *Listeria* spp. are included in the FSA targets for salt reduction and include ready meals, cooked meats and sausages, cheeses and sandwiches (ACMSF, 2005). ACMSF has reviewed this advice and has recommended that manufacturers consider the impact on microbiological safety when making formulation changes to the key controlling factors such as salt in specific products (ACMSF, 2006).

5.12 Provided that producers of chilled, ready-to-eat food are operating to current recognised industry standards, disciplines will be in place in large manufacturing plants to segregate products and people between the 'raw' or 'low risk' side of the factory from the 'ready-to-eat' or 'high risk' side. Movement of products and equipment from the 'low risk' to the 'high risk' side of the factory occurs through a controlled area e.g. cooker or washer and movement of people occurs through changing areas where clothing including footwear and outer garments are changed to avoid contamination. Air flow and drainage is designed to ensure they flow from 'high risk' to 'low risk', thereby minimising transfer of contamination via these routes. (It should be noted that this situation may not be fully replicated in smaller production units, where the application of proportionate risk based controls may result in different arrangements.)

5.13 The level of control varies depending on the risk presented by the finished product in terms of potential for contamination and growth. For example, controls in place for cooked, sliced meat will be greater than those in factories producing ready-to-eat washed salads as the former have longer shelf lives and offer greater opportunity for growth of any contaminating organisms.

5.14 Such control includes measures to prevent *Listeria* spp. building up in the environment and on equipment, aspects recognised as key to preventing contamination of ready-to-eat foods. Hence, thorough cleaning and disinfection of the chilled, ready-to-eat food production environments occurs on a daily basis and more frequently for much of the equipment and product contact surfaces. Methods to reduce the spread of the organism in the environment such as use of low water pressures and minimising water usage during production are widely recognised and applied in the industry.

5.15 Analytical testing of both the environment and the product to verify that controls have been effective in managing the organism has been routinely applied for many years. It is recognised that microbiological testing can form an integral part of an effective HACCP plan (SANCO/4198/2001 Rev 21) and in 2006, such testing became a mandatory requirement under Commission Regulation on Microbiological Criteria for Foodstuffs (2073/2005/EC) (see 5.7).

5.16 The preventative measures in place in the food manufacturing industry today as described in paragraphs 5.9 – 5.15 are believed to be considerably higher than those in place two decades ago and there is no evidence of any changes recently that would have led to a significant increase in contamination of manufactured foods with *L. monocytogenes*. Indeed, data from recent surveys for *L. monocytogenes* in food indicate that whilst the bacterium does still occur in foods, it is not generally found at high levels and is present at much lower levels than was the case in the late 1980's.

5.17 Notwithstanding this, it is important to recognise there is a difference between manufacturing, catering and retail in considering the potential for food to become contaminated with *Listeria* spp. Catering and retail outlets, including delicatessens, handle a high volume of chilled perishable products that are not necessarily subject to the same controls to prevent contamination as those produced in major manufacturing units operating high/low risk principles. Such businesses often receive pre-packaged products e.g. bulk cooked meats, pâté, cheeses etc or they may make them on the premises themselves e.g. cooked meats. Once open, such perishable products are subject to cross contamination if equipment is poorly cleaned e.g. slicing machines, knives, etc, and the environment, people and pests. In addition, should the product already be contaminated with the bacterium or become contaminated during handling, preventing growth to high numbers is dependent on the adoption of strict temperature control and management of shelf life. Whilst many such products, once opened, are limited in shelf life for organoleptic reasons, the subsequent handling by the customer may also be important in ensuring the safety of the product and thus storage instructions including a durability indicator (Use By) and storage information (Store refrigerated) are important.

5.18 Identifying poor practices in a small number of businesses is likely to be very difficult. Many food businesses, especially those supplying large retail chains and catering companies, are subject to frequent certification audits to third party food safety standards e.g. BRC global standard for food safety (certification is currently held by approximately 10,000 food businesses) together with audits and visits by experienced food technologists from relevant customers; this is likely to identify poor management of *Listeria* spp. Without this, enforcement monitoring would be the only means of identifying poor practices. Improving the identification of poor practices is likely to be

important in identifying poor management of *Listeria* spp. in food businesses but it is questionable whether current industry/enforcement scrutiny is sufficient to identify this if it is happening in a small minority of businesses.

Consumer Advice

5.19 The FSA's consumer advice on listeriosis was originally targeted towards pregnant women and recommended that this group should avoid all types of pâté (including vegetable) and mould-ripened soft cheeses of the Brie, Camembert and blue-veined types. In the course of writing this report, the FSA consulted the *Ad Hoc* Group on whether this advice should be extended to vulnerable groups in addition to pregnant women. This action was considered necessary following several clusters of cases in healthcare settings and because the increase in listeriosis since 2001 mainly involved the over 60s with underlying medical conditions. The *Ad Hoc* Group was content to extend this advice and suggested that it should also emphasise existing advice on observing correct temperature control for foods that require refrigeration and on following use-by dates. The advice on the Agency's website was updated in July 2008.

5.20 The FSA's website[16] currently provides the following advice on listeriosis to consumers;

> "*Listeria monocytogenes* can cause illness in certain groups of people, such as pregnant women, unborn and newborn babies and people with reduced immunity, particularly those over 60 (these could include people who've had transplants, are taking drugs that weaken the immune system or with cancers affecting the immune system, such as leukaemia or lymphoma). Among these vulnerable groups, the illness is often severe and can be life-threatening.
>
> Listeria has been found in certain chilled ready-to-eat foods, such as pre-packed sandwiches, butter, cooked sliced meats, smoked salmon, soft mould-ripened cheeses and pâtés. Eating food containing high levels of *Listeria monocytogenes* is usually the cause of illness.
>
> Vulnerable people should avoid eating pasteurised and unpasteurised cheeses such as Camembert, Brie or chèvre (a type of goats' cheese), or others that have a similar rind, soft blue cheeses, and all types of pâté, including vegetable.
>
> Special care should also be taken to follow the storage instructions on the food label. Chilled foods should be kept out of the fridge for the shortest time possible and you shouldn't use food after its 'use by' date."

16 http://www.eatwell.gov.uk/healthissues/foodpoisoning/abugslife/

5.21 The Agency also advises pregnant women to ensure that any raw meat, shellfish or ready meals that they consume have been well cooked until they are piping hot throughout. This advice relates to other foodborne pathogens in general and not specifically to *L. monocytogenes*.

5.22 NHS Direct recognises that listeriosis may "affect older people, very young children and people with lowered immune systems" and that "Listeriosis is potentially harmful to unborn babies, so pregnant women need to be very careful to avoid the infection". NHS Direct currently provides the following advice on the prevention of listeriosis:[17]

"If you are pregnant:

- *Don't eat soft mould-ripened or blue-veined cheeses such as Brie, Camembert, stilton, and goat's cheese. You can still eat hard cheese, cottage cheese and yoghurts*
- *Don't eat pâté*
- *Avoid unpasteurised dairy products (including unpasteurised ice creams)*
- *You can drink probiotic yoghurt drinks and eat 'live' yoghurt as long as they have been pasteurised. Check the label*
- *Wash pre-packed salads thoroughly before eating*
- *The risk from cold (pre-cooked) meats and smoked salmon is fairly low, but you may wish to avoid them while you are pregnant*
- *Wash your hands before and after handling food*
- *Wash fruit and vegetables*
- *Cook food thoroughly (especially meat, eggs, chilled meals and ready-to-eat chicken)*
- *Check 'use by' dates"*

5.23 The HPA recognises that "Pregnant women, the elderly and people with weakened immune systems, including those suffering from cancer, AIDS or alcoholism, are more susceptible to listeria". HPA currently provides the following advice on the prevention of listeriosis:

17 Since this report was prepared, NHS Direct has published updated advice on preventing listeriosis. This can be found at: http://www.nhs.uk/conditions/Listeriosis/Pages/Introduction.aspx

"How can you avoid getting listeria?

Listeria is unusual because it not only grows at normal room temperature and up to about 40°C, but can grow at low temperatures, including refrigeration temperatures of below 5°C. It is, however, killed by cooking food thoroughly in conventional or microwave ovens and by pasteurisation.

- *Keep foods for as short a time as possible and follow storage instructions including 'use by' and 'eat by' dates*
- *Cook food thoroughly, especially meat, ensuring that it is cooked through to the middle*
- *Keep cooked food away from raw food*
- *Wash salads, fruit and raw vegetables thoroughly before eating*
- *Wash hands, knives, and cutting boards after handling uncooked food*
- *Make sure that the refrigerator is working correctly*
- *When heating food in a microwave follow heating and standing times recommended by the manufacturer*
- *Throw away left-over reheated food. Cooked food which is not eaten immediately should be cooled as rapidly as possible and then stored in the refrigerator*
- *Pregnant women, the elderly, and people with weakened immune systems should not help with lambing or touch the afterbirth"*

5.24 Examples of advice provided to vulnerable groups in relation to *L. monocytogenes* by the Authorities in other countries are provided in Table 9.

Conclusions

5.25 The food industry has implemented many controls to prevent the contamination of foods with *L. monocytogenes* in the last two decades and evidence suggests that the incidence and levels of the bacterium at the point of production and the point of sale are not higher than was detected in the late 1980's.

5.26 Shelf life management is a key control that can be exercised to reduce the opportunity for the bacterium to grow to high levels and whilst it is very difficult to gather data on shelf life increase over recent years, there is no evidence of marked increase in shelf lives across chilled commodity areas or

the development of new commodity foods that would account for increased risk of listeriosis. Further information on shelf life increases in ready-to-eat chilled foods over the last 10 years would be useful.

5.27 The bacterium has, however, been found to be present in a number of chilled ready-to-eat foods, usually at low levels, which probably represent a low risk, provided subsequent storage time and temperature conditions are maintained at acceptable levels prior to consumption.

5.28 Preservative factors are important in restricting the growth of the bacterium when present in foods and trends to reduce factors such as salt may lead to increased growth of the bacterium if present on such a food.

5.29 Advice to the public to date has focussed on pregnant women. In order to avoid the risk of listeriosis, the FSA advises pregnant women to avoid all types of pâté (including vegetable), mould-ripened soft cheeses of the Brie, Camembert and blue-veined types.

5.30 There seems to be very little specific advice targeting the elderly (Cates *et al*, 2006), and therefore it is possible that the increase in listeriosis in the elderly is in part a consequence of not having advice targeted at this age group.

Recommendations

5.31 It is recommended that, based on considerations of foods associated with transmission of listeriosis and the properties of the bacterium, that general advice should be developed and communicated to over 60s (including those in vulnerable groups), as well as those who prepare and provide their food and provide medical advice about the factors important to reduce the risk of exposure to *L. monocytogenes*. Studies should be carried out to evaluate the impact of such advice on these target groups and its effectiveness at reducing the incidence of listeriosis.

5.32 The principles of food safety management through the application of hazard analysis approaches such as HACCP are well established in the food industry. Universal adoption of these principles by the manufacturing, catering and retail industry, together with effective enforcement, is a recognised way of ensuring food safety. Any future advice to the industry and enforcement authorities given by the FSA should reiterate the particular importance of temperature and shelf life control, hygiene/cleaning (especially of equipment susceptible to contamination such as slicing machines) and formulation of a food in preventing contamination or limiting the growth of *L. monocytogenes* in foods.

5.33 The provision of durability instructions i.e. 'Use By' dates on perishable foods sold loose e.g. cooked sliced meats was found to be variable and it is recommended that the Food Standards Agency reviews the need for consistent advice on such products. Such instructions should also take account of age-related deteriorations in eyesight which may be very relevant to the target population for this advice.

5.34 FSA should work with industry to ensure that factors such as salt levels of specific products are not changed without considering the impact on the microbiological safety of the product (ACMSF, 2005).

Table 9: Examples of food safety advice on listeriosis provided to vulnerable groups by non-UK Authorities. Please note that this is not an exhaustive list, but is intended to provide examples of the advice provided by Authorities in other countries. Please also note that some of this food safety advice may relate to foodborne pathogens in general and is not specific to *L. monocytogenes.*

Country	Vulnerable groups	Advice on foods to avoid	Website
Australia and New Zealand	Pregnant women Older people (generally considered to be persons over 65-70 years) People of all ages whose immune systems have been weakened by disease or illness Anyone on medication that can suppress the immune system	• Cold meats; unpackaged ready-to-eat from delicatessen counters, sandwich bars etc. Packaged, sliced ready-to-eat • Cold cooked chicken; purchased (whole, portions, or diced) ready-to-eat • Pate; refrigerated pate or meat spreads • Salads (Fruit and vegetables); pre-prepared or pre-packaged salads (e.g. from salad bars, smorgasbords etc) • Chilled seafood; raw (e.g. oysters, sashimi or sushi), smoked ready-to-eat, or ready-to-eat peeled prawns (cooked) e.g. in prawn cocktails, sandwich fillings and prawn salads • Cheese; soft, semi soft and surface ripened (pre-packaged and delicatessen), (e.g. Brie, Camembert, ricotta, feta and blue. • Ice cream; soft serve • Other dairy products; unpasteurised dairy products (e.g. raw goats' milk)	www.foodstandards.gov.au/_srcfiles/Listeria.pdf
USA	Pregnant women Older adults People with cancer, AIDS, and other diseases that weaken the immune systems.	• Soft cheeses; Mexican-style soft cheeses (including queso blanco, queso fresco, queso de hoja, queso de creama and asadero), feta, Brie, and Camembert, blue cheeses and Roquefort. Cheeses made from raw milk. • Refrigerated pâtés or meat spreads. • Raw (unpasteurised) milk or foods that contain unpasteurised milk. • Hot dogs, luncheon meats and other ready-to-eat foods - *unless they're reheated until steaming hot.* • Meats and seafood - unless it's in a cooked dish	www.fda.gov

Country	Vulnerable groups	Advice on foods to avoid	Website
USA	Patients with cancer	Food safety is very important when your white blood cell (WBC) count is low. Infections can be picked up from food and drinks. You can reduce this risk as well by doing the following: • Avoid raw milk or milk products and any milk or milk product that has not been pasteurized, including cheese and yogurt made from unpasteurized milk • Do not eat raw or undercooked meat, fish, chicken, eggs, or tofu • Do not eat cold smoked fish • Do not eat hot dogs, deli meats, or processed meats (unless they have been cooked again just before eating) • Avoid any food that contains mold (for example, blue cheese, including that in salad dressings) • Avoid uncooked vegetables and fruits • Avoid uncooked grain products • Avoid unwashed salad greens • Do not eat vegetable sprouts (alfalfa, bean, and others) • Avoid fruit and vegetable juices that have not been pasteurized • Avoid raw honey (honey that has not been pasteurized) • Do not eat raw nuts or nuts roasted in their shells • Do not drink beer that has not been pasteurized (home brewed and some microbrewery beers); also avoid brewer's yeast • Do not eat any outdated food • Do not eat any cooked food that has been left at room temperature for 2 hours or more • Avoid any food that has been handled or prepared with unwashed hands • Talk with your doctor about any dietary concerns you may have, or ask to talk with a registered dietician.	www.cancer.org/docroot/ETO/content/ETO_1_2X_Infections_in_People_with_Cancer.asp

Country	Vulnerable groups	Advice on foods to avoid	Website
Canada	Pregnant women People with a weakened immune system	• Soft cheeses such as Brie, Camembert, feta and queso blanco fresco. • Refrigerated pâtés. • Although the risk of listeriosis associated with foods from deli counters, such as sliced packaged meat and poultry products, is relatively low, pregnant women and immunosuppressed persons may choose to avoid these foods. • Refrigerated smoked fish products unless you have cooked them, for example, in a casserole.	www.inspection.gc.ca/english/fssa/concen/cause/listeriae.shtml
Germany	People with a weakened immune system, older individuals and pregnant women	• Do not eat any foods of animal origin raw. • Refrain from eating smoked or marinated fish products, particularly vacuum-packed smoked salmon and gravadlax. • Do not eat any raw milk soft cheese and always remove the cheese rind. • Always prepare green salads themselves and do not use any cut packaged salads. • Use foods, in particular vacuum-packed foods, as soon as possible after purchase and well in advance of the 'best before' date.	www.bfr.bund.de/cd/10966

Chapter 6: Summary of Conclusions and Recommendations

Hazard identification and characterisation

Conclusions

6.1 Human listeriosis is a rare but serious disease which occurs most often in patients with cancer, those undergoing immunosuppressive or cytotoxic treatment, the elderly (over 60 years of age), the unborn and newly delivered infants, the pregnant woman, diabetics, alcoholics (including those with liver disease) and a variety of other conditions.

6.2 Consumption of contaminated food is believed to be the principal route of infection and common source outbreaks together with sporadic cases occur.

6.3 The majority of cases are/appear to be sporadic and foods associated with transmission are predominantly ready-to-eat, with extended (usually refrigerated) shelf-life, capable of supporting the growth of *L. monocytogenes*.

6.4 Since 2000, the annual number of listeriosis cases reported has increased and has occurred almost exclusively in patients aged over 60 years presenting with listerial bacteraemia. This increase is independent of demographic changes in the population and has resulted in an approximate tripling in the rate of the disease in those aged 60 years and over in England and Wales: 3.3-4.7 cases per million were reported between 1990-1992 and 13.2 cases per million in 2007. However, the degree of under-reporting of listeriosis in the UK has not been recently estimated.

6.5 A similar change in presentation of listeriosis has been reported in Scotland and Northern Ireland and Germany. Significant increases in cases were also reported in Belgium, Denmark, France, Lithuania, The Netherlands and Spain. There is no evidence for a common source relationship between these changes which have occurred in the UK and those in other countries.

Recommendations

6.6 Pan-European surveillance and epidemiological and microbiological investigations should be used to investigate changes in listeriosis in different Member States and to ascertain if there are common generic or risk factors occurring in the UK with those in other countries.

6.7 Studies should be undertaken to develop methods for screening *L. monocytogenes* isolates for differences in virulence and investigate the differences between isolates from different patient groups and time periods.

Consideration of key hypotheses to explain the increase in listeriosis cases

Hypothesis 1: The rise in cases of listeriosis in immunocompromised people over 60 years is an artefact associated with improved case recognition

Conclusions

6.8 *L. monocytogenes* will grow on most non-selective media; therefore improvements in microbiological media would be unlikely to increase the diagnosis of listeriosis (McLauchlin 2005). Although the introduction of mandatory reporting of meticillin-resistant *Staphylococcus aureus* bacteraemia in England in 2001 has led to an increase in blood cultures being taken, this is insufficient to explain the increase or shift in presentation of listeriosis described here (Anon 2000b, Anon 2005b). Further evidence that the increase was not due to improved diagnostics is provided by the absence of a significant increase in the isolation of *L. monocytogenes* from blood cultures from patients with CNS infections or from pregnancy-associated cases (Gillespie *et al*, 2008). In addition, there has not been an increase in bacteraemia amongst other foodborne pathogens (i.e. *Salmonella* and *Campylobacter)* in the over 60s. (Gillespie *et al*, 2008).

6.9 The degree of under-reporting of listeriosis in the UK has not been estimated recently. An ascertainment ratio of 2 (estimation of the numbers of cases of illness to the numbers reported to national databases for laboratory confirmed infections) for human listeriosis was estimated by Adak and colleagues (Adak *et al*, 2002). The amount of under-reporting (ascertainment ratio) for human listeriosis could be estimated by comparing the numbers of cases reported to national databases with the numbers of cases ascertained in a subset of diagnostic centres. Since the highest numbers of cases occur in those 60 years old and over and there is a possibility of surveillance artefact due to changes in diagnostic procedures having introduced bias, resources should be concentrated on investigation of incidence in this section of the population.

6.10 The Second Infectious Intestinal Disease Study will not address this problem. However, even if significant under-reporting of listeriosis has previously occurred, the FSA has recently estimated that *L. monocytogenes* is responsible for the highest numbers of deaths from a food-borne pathogen (FSA 2007, Annual report of the Chief Scientist 2006/7). Since the highest

numbers of cases occur in those 60 years old and over, resources should be concentrated to reduce the incidence in this section of the population.

6.11 Our ability to analyse infection trends and understand changes in the epidemiology would be enhanced by the routine collection of denominator data for selected medical investigations associated with infection.

Recommendations

6.12 The amount of under-reporting (ascertainment ratio) for human listeriosis should also be estimated.

6.13 UK surveillance of infection should be enhanced to incorporate data on the corresponding denominator populations, including numbers of relevant medical investigations, such as blood cultures, undertaken.

Hypothesis 2: The population predominantly affected by the recent increase has become more susceptible to infection with *L. monocytogenes*

Conclusions

6.14 Medical advances have resulted in the UK human population surviving for longer. Elderly individuals are more likely to have underlying co-morbidities, which are acknowledged to predispose to listeriosis than those in younger age groups. Elderly patients are increasingly likely to receive immunosuppressive therapies for chronic conditions which are known to increase the risk of listeriosis. However, current data collection methods are insufficiently refined to determine the extent to which, if any, changes in the use of immunosuppressive or antisecretory therapies in elderly patients have resulted in an overall increased risk of listeriosis in this age group.

6.15 The increase in cases of listeriosis associated with elderly age groups cannot be attributed to the general demographic increase of this age group in the population.

Recommendations

6.16 Studies should be undertaken to investigate whether trends in the management of conditions which are treated with immunosuppressive or antisecretory agents might have contributed to the overall increase in the risk for listeriosis.

6.17 A retrospective case-controlled study could also identify with greater accuracy those underlying conditions which are most associated with listeriosis in the elderly.

6.18 Data collected prospectively as part of the investigation of cases of listeriosis should include more detailed information relating to underlying comorbidities and their drug management.

Hypothesis 3: The pathogen, *L. monocytogenes* has become more virulent and "new" strains are more capable of causing infection which manifests as bacteraemia

Conclusion

6.19 It is possible that specific pathogen factors occurring across multiple *L. monocytogenes* strains allow increased infection amongst older age groups, and these factors may have been selected to increase within the food chain, for example by changes in the food chain including food preservation technologies. However, this is open to speculation and there is no *in vitro* evidence to support this hypothesis.

Recommendation

6.20 Work is needed to develop *in vitro* methods of investigating the frequency of specific genes or gene polymorphisms associated with difference in the pathogenicity of *L. monocytogenes*.

Hypothesis 4: Levels of exposure have increased

Conclusions

6.21 It is generally recognised that greatest risk of listeriosis occurs from consumption of foods where very high levels of *L. monocytogenes* occur and thus the aim must be to ensure foods do not have such high levels.

6.22 It was not possible to determine any particular factor in the shopping and consumption patterns for over 65s that is likely to increase their risk for contracting listeriosis, although the tendency to eat more homemade, chilled and fresh foods and to consume more food cold may be important factors. It was not possible to specifically identify the consumption patterns of vulnerable groups in this age group but clearly this may be important to identifying any additional risks.

6.23 Information on the food safety perception and practices in older age groups was limited but did identify factors that could contribute to growth of *L. monocytogenes* in already contaminated foods such as keeping foods beyond their use-by dates or not keeping them refrigerated at suitable temperatures.

6.24 While there is no recent national data source about the shopping, food storage, cooking and eating behaviours of all over 60s, the *Low income diet and nutrition survey* (Nelson *et al*, 2007), has data on this for the over 60s in the most materially deprived households in the UK. People over 65, ethnic minorities and people with self reported illness were over-represented in this national sample of the bottom 15% in income of the UK population. Further analyses of this study would throw some light on the food purchase and handling behaviour of this group at risk of *L. monocytogenes* and provide a basis for identifying how to research this more generally among the over 60s.

6.25 In addition, it might be possible to gain further insight into how the over 60s manage food purchase, storage and cooking through analysis of existing time use studies. Diary-based studies are the more appropriate method of obtaining this information (Gershuny J. Personal communication, 2008). Analysis of the existing diary based study Home OnLine conducted between 1998 and 2001 would provide a useful starting point and if this proved fruitful further research might be undertaken to look at more recent behaviour.

Recommendations

6.26 Maintaining targeted active surveillance for *Listeria* spp. in foods is important to understanding if the control of the bacterium is improving or deteriorating and regular surveys examining a wide range of commonly purchased foods (shopping basket surveys) that the bacterium can be a contaminant of may be useful. However, the potential for the bacterium to contaminate and grow in retail and catering bought foods is important and any survey should also consider such foods.

6.27 Information on the food consumption patterns of over 60s with particular reference to vulnerable groups in this age group is necessary in order to better inform risk management options.

6.28 A study on the food handling behaviours of over 60s including those in vulnerable groups is recommended in order to better understand factors potentially contributing to increasing the risk of listeriosis.

6.29 Studies in the home would be of particular benefit to include food storage behaviour, refrigerator temperatures, adherence to 'use by' date and analysis of foods for *L. monocytogenes*.

6.30 Data on control subjects and from listeriosis patients of similar age should be collected to identify risk factors and allow an evidence basis for food safety advice to vulnerable groups. Understanding the impact of this on the growth of the bacterium in food using modelling/challenge studies is recommended to assess the risks.

6.31 It is also recommended that the FSA refers this Report to its Social Science Research Committee to consider the food storage and handling practices of elderly people in the home.

Risk Management

Conclusions

6.32 The food industry has implemented many controls to prevent the contamination of foods with *L. monocytogenes* in the last two decades and evidence suggests that the incidence and levels of the bacterium at the point of production and the point of sale are not higher than was detected in the late 1980s.

6.3 Shelf life management is a key control that can be exercised to reduce the opportunity for the bacterium to grow to high levels and whilst it is very difficult to gather data on shelf life increase over recent years, there is no evidence of an increase in shelf lives across chilled commodity areas or the development of new commodity foods that would account for increased risk of listeriosis. Further information on shelf life increases in ready-to-eat chilled foods over the last 10 years would be useful.

6.34 The bacterium has, however, been found to be present in a number of chilled ready-to-eat foods, usually at low levels, which probably represent a low risk, provided subsequent storage time and temperature conditions are maintained at acceptable levels prior to consumption.

6.35 Preservative factors are important in restricting the growth of the bacterium when present in foods and trends to reduce factors such as salt may lead to increased growth of the bacterium if present on such a food.

6.36 Advice to the public to date has focussed on pregnant women. In order to avoid the risk of listeriosis, the FSA advises pregnant women to avoid all types of pâté (including vegetable), mould-ripened soft cheeses of the Brie, Camembert and blue-veined types.

6.37 There seems to be very little specific advice targeting the elderly (Cates *et al*, 2006) and therefore it is possible that the increase in listeriosis in the elderly is in part a consequence of not having advice targeted at this age group.

Recommendations

6.38 It is recommended that, based on considerations of foods associated with transmission of listeriosis and the properties of the bacterium, that general advice should be developed and communicated to over 60s (including those in vulnerable groups), as well as those who prepare and provide their food and provide medical advice about the factors important to reduce the risk of exposure to *L. monocytogenes*. Studies should be carried out to evaluate the impact of such advice on these target groups and its effectiveness at reducing the incidence of listeriosis.

6.39 The principles of food safety management through the application of hazard analysis approaches such as HACCP are well established in the food industry. Universal adoption of these principles by the manufacturing, catering and retail industry, together with effective enforcement, is a recognised way of ensuring food safety. Any future advice to the industry and enforcement authorities given by the FSA should reiterate the particular importance of temperature and shelf life control, hygiene/cleaning (especially of equipment susceptible to contamination such as slicing machines) and formulation of a food in preventing contamination or limiting the growth of *L. monocytogenes* in foods.

6.40 The provision of durability instructions i.e. 'Use By' dates on perishable foods sold loose e.g. cooked sliced meats was found to be variable and it is recommended that the Food Standards Agency reviews the need for consistent advice on such products. Such instructions should also take account of age-related deteriorations in eyesight which may be very relevant to the target population for this advice.

6.41 FSA should work with industry to ensure that factors such as salt levels of specific products are not changed without considering the impact on the microbiological safety of the product (ACMSF, 2005).

Annex I

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Annex II
Ad Hoc Group on Vulnerable Groups

Terms of reference

To examine the potential risks to vulnerable groups including the elderly in relation to the microbiological safety of food by:

- considering factors that make people vulnerable in order to define vulnerable groups in relation to foodborne disease
- identifying key hazards for key vulnerable groups for review
- assessing the impact of changing patterns of food consumption and behaviour on risks to these groups
- assessing/reviewing the value/adequacy of current advice and controls and whether it is appropriate
- advising the ACMSF on the need for changes in advice/recommendations on vulnerable groups and identifying gaps/research needs.

Chair

Professor Tom Humphrey (current)
Professor Paul Hunter (April 2007 to December 2007)

Members

Mr John Bassett
Mr Alec Kyriakides
Dr Richard Holliman
Mrs Jenny Morris
Ms Susan Davies (to March 2008)
Professor John Coia
Dr Jim McLauchlin
Ms Ceridwen Roberts
Professor Kevin Kerr

Assessors

Dr Judith Hilton (FSA)
Mr Stephen Wyllie (Defra)

Secretariat

Dr Lucy Foster
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Annex III

Worldpanel Usage methodology

Worldpanel Usage is the UK's leading, and only continuous monitor of Food and Drink consumption In and Out of Home.

Sample of 11,000 individuals in 4,200 households

Complete food and drink diary for 2 weeks every 6 months

Record all consumption of food and drink (providing us with the complete consumption picture from In home/lunchbox to food service and impulse channels)

Staggered sample so every day of the year is covered

Representative Sample (total GB)

Annual individual and household attitudinal/lifestyle questions
Data delivered quarterly

Current data periods are: 3 months to August – delivered in Nov, 3 months to Nov – delivered in February, 3 months to Feb – delivered in May, 3 months – to May – delivered in August

Figure 1: Over 65's have more frequent, smaller shopping trips

Total Households		Over 65's
55.7bn (+4%)	Spend £	13.0 bn (+3%)
2,261 (+4)	AWP £	2,148 (+3%)
216 (+2%)	Frequency	289 (+1%)
10.48 (+2%)	Trip Spend £	7.41 (+2%)

TNS Worldpanel Usage

Source: TNS Worldpanel 52w/e 25th March 07

Figure 2: Adults 65+ are more likely to eat homemade foods, fresh foods and chilled foods.

They are less likely to consume frozen and ambient foods.

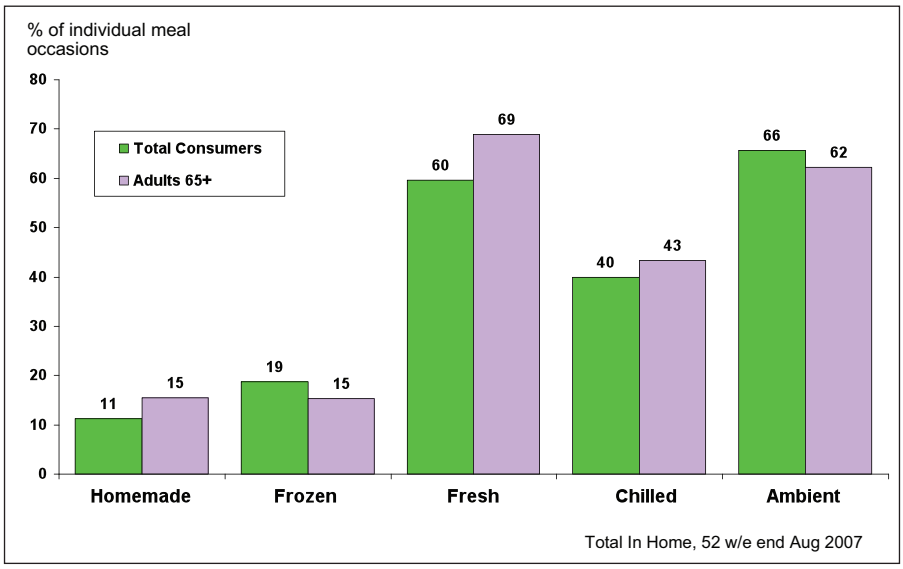


Figure 3: Adults 65+ overindex at the breakfast, in home lunch and teatime occasions. They are also more likely to snack in the home. They are low lunchbox consumers and are less likely to consume snacks out of the home.

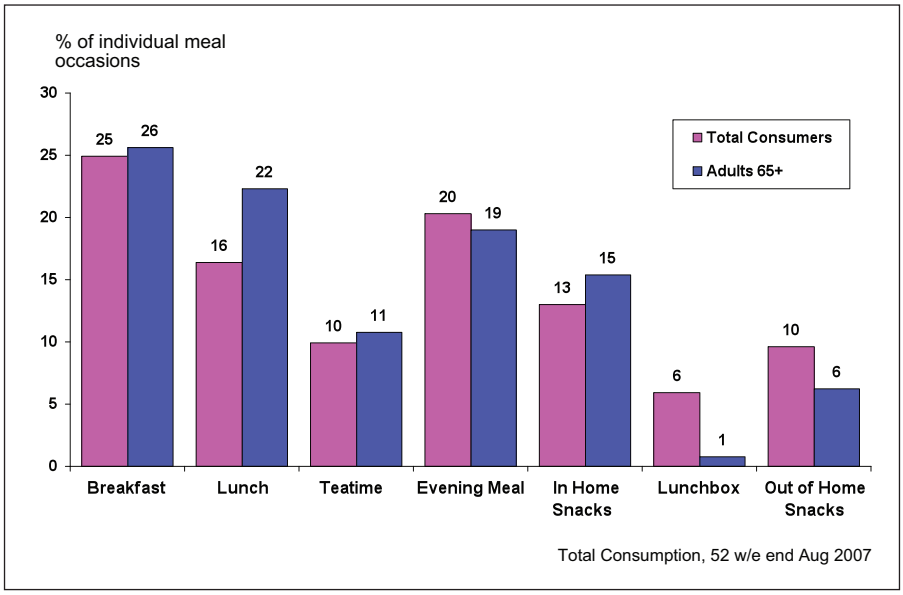
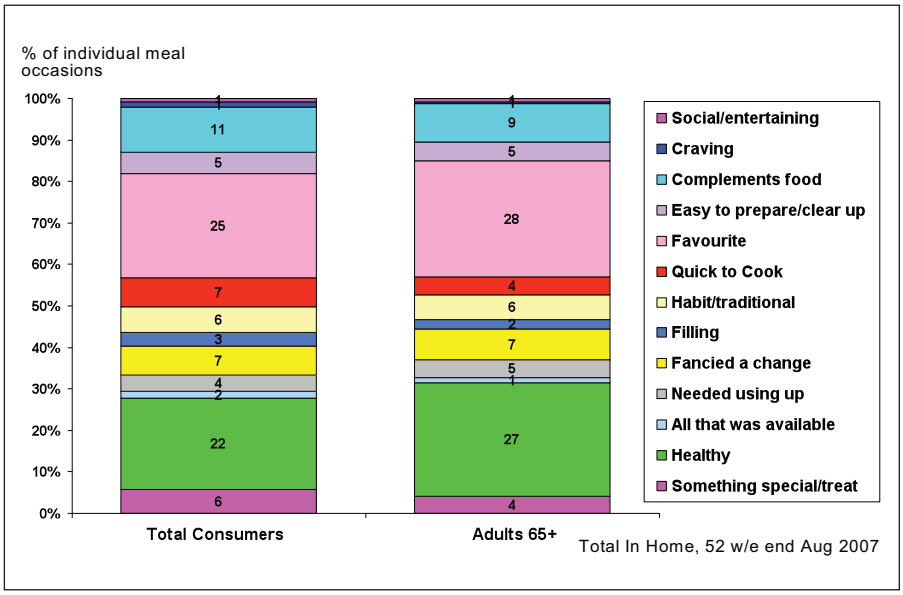


Figure 4: Adults 65+ are more likely to consume for health and 'favourite'. This group is the most traditional and also the most health conscious.

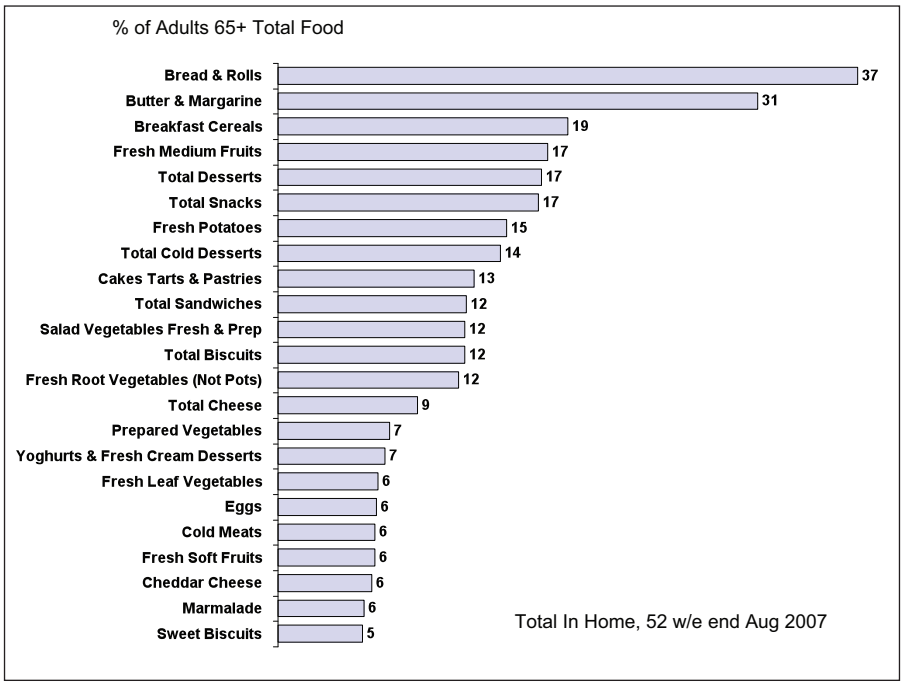


TNS Worldpanel Usage

Figure 5:

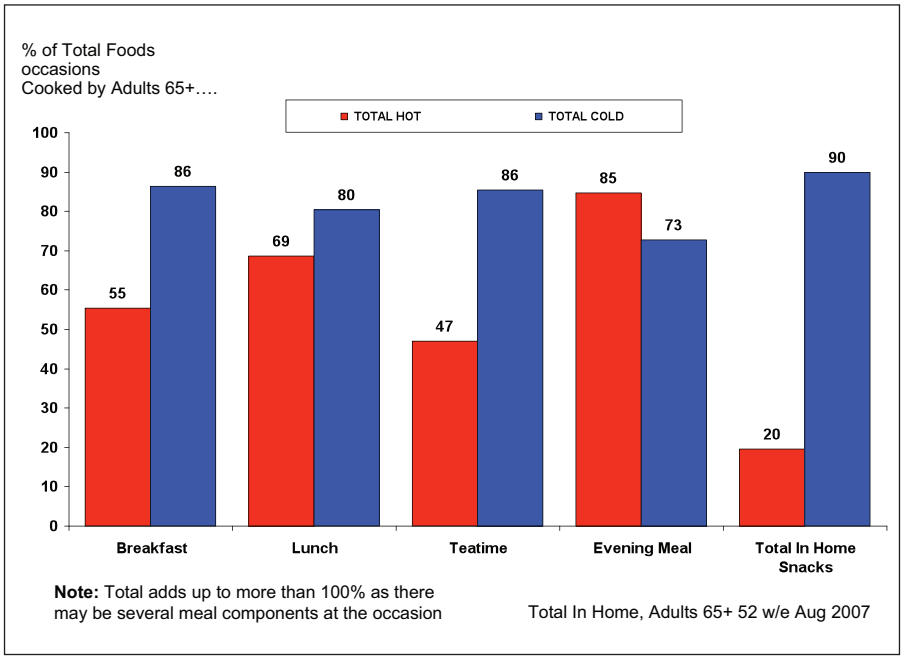
TNS Worldpanel Usage

Figure 6: Top foods consumed by Adults 65+ in volume.



TNS Worldpanel Usage

Figure 7: Adults 65+ have more cold foods at the Breakfast, Lunch, Teatime and In Home Snacks occasions. The evening meal occasion is more about hot food.



TNS Worldpanel Usage

List of Tables and Figures

Tables

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Glossary of Terms and Abbreviations

Terms

Achlorhydria	Absence of production of acid in the stomach.
ActA protein	Protein expressed by *L. monocytogenes* involved in motility of the organism within a host cell.
Acute disease	A disease which has rapid onset and lasts for a relatively short period of time. It can also refer to a very severe or painful disease.
Amniotic fluid	Protecting fluid which fills the amniotic sac which surrounds the foetus during pregnancy.
Animal model	A study using animal(s) that uses conditions similar to those seen in humans to be representative of what would occur in the human population.
Antibody	Protein found in the blood and other body fluids that recognises and binds to foreign substances (or antigens).
Antigen	A molecule, usually a protein or carbohydrate, recognised as "foreign" by the immune system.
Antimetabolite	A chemical or drug which interferes with normal biochemical functions of a cell.
Ascertainment ratio	Ratio of the estimation of the numbers of cases of illness in the population to the numbers reported to national databases for laboratory confirmed infections.
Asymptomatic	Without symptoms.
Atorvastatin	Type of statin.
Avirulent	Not showing virulence.
a_w	Water activity the amount of free water in a given substance (eg food substance). Free water is not the total water present in a substance, it can vary depending on other things in the product, for example the salt and sugar content.
Bacteraemia	Presence of bacteria in the bloodstream.

B-cell (B lymphocyte)	Type of lymphocyte
B-cell lymphoma	Type of cancer affecting B lymphocytes
Blood culture	Procedure for detecting the presence of an organism in blood.
Campylobacteriosis	Gastro-intestinal infection caused by a member of the genus *Campylobacter*. In humans this is usually *C. jejuni.*
Capecitabine	An antimetabolite drug.
Cases	Those identified as having a particular condition.
Cellular immune function	Mechanisms to protect against disease (immunity) at the cellular level.
Cerebritis	Infection of the brain.
cfu/g	Colony forming units per gram – a measure of the numbers of a microorganism within a sample.
CHOP	Type of chemotherapy treatment for non-Hodgkin's lymphoma.
CHOP-R	Type of chemotherapy treatment for non-Hodgkin's lymphoma containing rituximab.
Chronic condition	Long lasting health-related condition.
Chronic lymphocytic leukaemia.	Type of cancer affecting white blood cells
Chronic myeloid leukaemia	Type of cancer affecting white blood cells.
Clostridium difficile	Species of Gram positive spore forming bacteria - can be associated with disease particularly hospital acquired infections.
Clostridium difficile-associated disease	Spectrum of disease from mild diarrhoea to life -threatening colitis (inflammation of the colon) caused by *C. difficile.* Nearly all cases follow treatment with antibiotics.
Cofactors (possibly infections)	Required for the activity of an enzyme.
Colorectal	Involving the colon (large bowel) and rectum.

Co-morbidity	Disease or condition which exists independently of another.
Comparator cohort	Controls for a cohort study - used to compare to cases.
Continuous ambulatory peritoneal dialysis	A method for removing waste from the blood, as well as excess fluid, when the kidneys are incapable of this (i.e. in renal failure). Continuous ambulatory peritoneal dialysis (CAPD), the most common type, needs no machine and can be done at home. Exchanges of fluid are done periodically throughout the day.
Contra-indicated	To indicate inadvisability, for example the inadvisability of a medical treatment.
Cumulative risk	The risk that an event will occur as time progresses.
Cutaneous lesion	Wound of the skin.
Cyclophosphamide	Type of drug used to treat cancer.
Cytoplasm	The fluid that fills most cells.
Cytoskeletal	Of or pertaining to the cytoskeleton - cellular "scaffolding" or "skeleton" contained within the cytoplasm.
Cytotoxic treatment	Any treatment that is toxic to cells.
Demographic	Population characteristics.
Denominator data	Lower portion of a fraction used to calculate rate or ratio - i.e. the population at risk.
Diary based studies	Study where participants use a diary as research tool to record data from individuals.
Disease modifying anti-rheumatic drugs (DMARDS)	A class of drugs used to slow the progression of anti-immune diseases.
Dyspepsia	Indigestion.
Encephalitis	Acute inflammation of the brain.
Endocarditis	Inflammation of the inner layer of the heart.
Endophthalmitis	Inflammation of the inner eye.
Enteric infections	Infection of the gut/intestinal system.

Enterocolitis	Inflammation of the gut/intestines.
Enumeration	To count/quantify/define numerically. Enumeration tests are used to establish the amount of a specific micro-organism that is present in a sample.
Enzyme	A molecule which catalyses (increases the rate) of chemical reactions.
Epidemiology	The study of the occurrence, transmission and control of disease in a population.
Etanercept	A disease-modifying anti-rheumatic drug (DMARD).
Facultative intracellular bacterium	A bacterium which, although capable of independent existence, can survive, and in some cases multiply, within cells.
Fludaribine	Type of chemotherapeutic drug used to treat haematological malignancies.
Gastric atrophy	Condition where stomach muscles become weak and shrink.
Gastroenteritis	Inflammation of gastrointestinal tract.
Gastro-intestinal	Digestive tract.
Gene	A discrete section of DNA with a specific function. For example a gene may contain all the DNA to code for a protein.
Generic (as applied to pharmaceuticals)	Drug sold after the patent for the original formulation has expired.
Genome	All the genetic material for an organism.
Genotypic	Relating to genotype – the genetic make-up of an organism.
Genus	A level of the biological classification of organisms based on the fundamental properties of the organisms.
Gestation	Carrying an embryo/foetus inside female animal i.e. during pregnancy.
Gram stain	Method of using dyes to categorise bacteria.
H_2-receptor antagonist (H_2-RA)	Type of drug used to reduce acid production by the stomach.

Haematological malignancy	Type of cancer which affects the blood, bone marrow or lymph nodes.
Haemolysin	Substance that can cause lysis of red blood cells.
HMG-CoA reductase	Enzyme involved in the production of cholesterol
Hepatitis	Inflammation of the liver.
Hepatosplenomegaly	Enlargement of liver and spleen.
Host-cell	A cell that contains foreign molecules, such as viruses, or bacteria. For example, a cell can be host to a virus.
Imatinib	A protein kinase inhibitor.
Immunocompromised	Used to describe someone who has an impaired immune system - usually due to treatment or underlying illness.
Immunodeficiency	See immunocompromised.
Immunomodulatory	Adjusting or regulating immune system.
Immunosenescence	General decline in the function of the immune system as an individual ages.
Immunosuppressive	Inhibit/prevent immune system action.
Infliximab	A monoclonal antibody which may be used as a disease-modifying anti-rheumatic drug (DMARD)
in vitro	In laboratory environment.
in vivo	Inside a living organism.
Internalins	Cell surface associated proteins which allow attachment to cells and are involved with viruses being taken internalised within cells.
Intestinal mobility	Ability of gut to move, or ability for things to pass through the gut.
Intracellular	On the inside of a cell.
Isolate	Pure culture of bacteria originating from a particular sample.
L. monocytogenes HMG-CoA reductase	Enzyme that increases isoprenoid synthesis.
Leflunomide	A disease-modifying anti-rheumatic drug (DMARD).

Listeria monocytogenes	Gram-positive pathogenic bacteria that can cause listeriosis in humans.
Listeriosis	A rare but potentially life-threatening disease caused by *Listeria monocytogenes* infection. Healthy adults are likely to experience only mild infection, causing flu-like symptoms or gastroenteritis. However, *L. monocytogenes* infection can occasionally lead to severe blood poisoning (septicaemia) or meningitis.
Lovastatin	Type of statin.
Lymphocyte	Type of white blood cell and part of the immune system.
Malignancy	Tumour that can invade and destroy nearby tissue, and possibly spread to other parts of the body.
Meconium	Earliest infant stools.
Meningitic/meningitis	Inflammation of the meninges of the brain and the spinal cord.
Meta-analysis	Statistical technique in which the results of several sets of data from studies examining the same research question are pooled and subject to further analysis.
Metastatic	Spread of cancer beyond the originating tissue or organ.
Meticillin-resistant *Staphylococcus aureus*	MRSA – A subtype of the *Staphylococcus aureus* bacterial species that is resistant to common types of antibiotics.
Microflora	All the microorganisms in a given environment or location.
Monoclonal antibody	Antibody produced by one type of lymphocyte derived from a single parent cell. Can be used to target particular antigens found on cancer cells.
Neonatal	Infant in first four weeks after birth.
Non-selective laboratory media	The substance that is used in the laboratory to grow bacteria.
Notifiable disease	A disease that must be reported to the competent authority when diagnosed.
Omeprazole	Drug used to reduce stomach acid, in the group known as protein pump inhibitors.

Pathogen	Organism able to cause disease/illness.
Peritonitis	Inflammation of the membrane lining (peritoneum) covering the intestinal tract and surrounding the stomach.
pH	A measure of how acidic or alkaline something is. Low pH is acidic, High pH is alkaline.
Phagocytosis	Process whereby cells or microorganisms ingest particulates.
Phenotype	Observable characteristics of an organism.
Phospholipases	Enzymes that hydrolyse phospholipids.
Pneumonia	Inflammatory illness of the lung.
Polymorphisms	Alternatives of the same gene, or part of DNA, within a species.
Presence/ absence test	Common microbiological test to determine whether a specific microorganism is present without enumeration.
Protein kinase inhibitor	Chemotherapeutic agent which acts by inhibiting protein kinase in rapidly dividing cells.
Proton pump inhibitor	Type of drug used to reduce acid production by the stomach.
Pulsed-field gel electrophoresis	Technique used to separate DNA fragments by size.
Regional microflora	Bacteria found in all individuals at particular body sites (e.g. the large bowel).
Rheumatoid arthritis	Long lasting disorder that causes the immune system to attack the joints, leading to inflammation of the joints and other organs of the body.
Rillettes	A coarse pâté-type product
Rituximab	A monoclonal antibody used to target B-lymphocytes.
Salmonella Typhimurium	Specific type of *Salmonella* bacteria, full name *Salmonella enterica* serovar Typhimurium.
Salmonella spp	A genus of gram negative bacteria which can cause salmonellosis in humans.
Selective media	Media that will only allow specific types of bacteria to grow.

Septicaemic	Bacteria present in the blood, where symptoms are seen (blood poisoning).
Serotyping	A method of distinguishing types of bacteria (serotypes) within a single species by defining their antigenic properties (see antigen) on the basis of their reaction to known antisera.
Statin (or HMG-CoA reductase inhibitor)	Type of medication used to lower blood levels of cholesterol.
Steroids	A group of hormones that occur naturally in the body and medications based on them.
Strain	A population of organisms within a species or sub-species distinguished by typing.
Subclinical	Infection which does not show symptoms, or before the symptoms appear.
Symptomatic	Displaying symptoms of a disease.
Systemic	Throughout the whole body.
T-lymphocyte	Type of lymphocyte.
Tegafur	An antimetabolite drug.
Th_1	Type of T lymphocyte involved in directing other cells of the immune system.
Thymic involution	Shrinking of the thymus gland with ageing. The thymus is an important organ for maturation of T-lymphocytes.
Typing	Any method used to distinguish between closely related organisms.
Varicella zoster virus	Virus in the herpes family that causes chickenpox and shingles.
Virulence	The capacity of a microorganism to cause disease.
Virulence attributes	Characteristics of bacteria microorganism that allow it to cause disease.
White blood cell count	White blood cells form part of the immune system, so the white blood cell count indicates how well the immune system is functioning.

Abbreviations

BRC	British Retail Consortium
CNS	Central Nervous System
CSF	Cerebrospinal fluid
DMARD	Disease modifying anti-rheumatic drug
EFSA	European Food Safety Authority
GELA study	Groupe d'Etude des Lymphomes de l'Adulte study
HPA	Health Protection Agency
MRSA	Meticillin-resistant *Staphylococcus aureus*
MRC	CLL4 trial Medical Research Council Chronic Lymphocytic Leukaemia Trial 4
PFGE	Pulsed-field gel electrophoresis
AFLP	Amplified fragment length polymorphism
CML	Chronic myeloid leukaemia
NICE	National Institute for Health and Clinical Excellence
GI	Gastro-intestinal
PPI	Proton pump inhibitor
CIG	Geriatric Index of Co-morbidity
H_2RA	H_2 receptor antagonist
RTE	Ready-to-eat
TNS	A market research company
CLL	Chronic lymphocytic leukaemia

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Published by Food Standards Agency
July 2009
FSA/1439/0709