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Underlying Medical Conditions Associated with Invasive Listeriosis, United States, 1996-2014

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Underlying Medical Conditions Associated with Invasive Listeriosis,

United States, 1996-2014

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2012

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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By Hannah Kisselburgh

Background. Invasive listeriosis is a rare but severe foodborne disease that is estimated to have the highest hospitalization rate and one of the highest mortality rates of all foodborne infections in the United States. Pregnant women, the elderly, and people who are immunocompromised are generally at higher risk for invasive listeriosis. However, few studies have quantified the relative risk of listeriosis for various underlying medical conditions, making targeted prevention efforts difficult.

Methods. Underlying medical conditions associated with cases of listeriosis reported to the Centers for Disease Control and Prevention during 1996 to 2014 through the FoodNet active surveillance system in 10 sites across the United States were reviewed. Overall listeriosis incidence and condition-specific incidence rate ratios were determined using published estimates of the population with each condition.

Results. During 1996 to 2014, 2,142 cases of listeriosis were reported for an overall average annual incidence of 0.24 per 100,000 people. Compared to the overall incidence, the incidence of listeriosis was estimated to be 33 times higher for people with multiple myeloma, 21 times for leukemia, 12 times for cirrhosis, and 7 times for pregnancy-associated cases.

Conclusions. Of underlying medical conditions examined, hematologic cancers conferred the highest risk of listeriosis. Targeting prevention efforts towards risk groups that have a high incidence rate ratio of listeriosis and a high incidence of the condition in the U.S. may reduce the overall incidence, morbidity, and mortality.

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BACKGROUND

Invasive listeriosis is a severe foodborne disease caused by the bacteria *Listeria monocytogenes,* a Gram-positive bacillus that is widely found in nature. Unlike most foodborne bacteria, *L. monocytogenes* is capable of not only surviving, but growing, at refrigerator temperatures (4 degrees Celsius). This hardiness poses a problem for food safety, since refrigeration, one of the key interventions to prevent pathogen growth, does not inhibit *L. monocytogenes*. Additionally, this bacterium can form biofilms, which enhance environmental persistence and can facilitate the contamination of food in factories.[1]

With an estimated 1,600 cases in the United States annually, invasive listeriosis is rare, but severe. Of infections caused by 31 foodborne pathogens in the United States, listeriosis is estimated to have the third highest mortality rate, behind botulism and *Vibrio vulnificus*.[2] In healthy adults, *L. monocytogenes* infection may only cause a mild febrile illness. Invasive listeriosis occurs when the infection spreads beyond the gastrointestinal tract and causes sepsis or meningoencephalitis.[1] Although infection in pregnant women typically causes a mild or subclinical illness, this infection typically leads to severe disease in the fetus or neonate, commonly leading to fetal loss or neonatal death.[3] The incubation period of listeriosis can vary widely, ranging from one to 70 days, with pregnancy-associated cases being associated with a longer incubation period than neurologic infections.[4] Cell-mediated immunity is thought to be the primary mode of protection against *L. monocytogenes*, and people with impaired systems may experience septicemia; the innate immune system also plays an important role.[5] *L. monocytogenes* are capable of crossing the blood-brain barrier and the placenta, which accounts for the central nervous system and fetal infections commonly observed.[6]

Although it is known that listeriosis disproportionately affects people who are immunocompromised, age ≥65 years, and pregnant, no studies to our knowledge have systematically estimated the risk of listeriosis associated with various underlying conditions in the United States other than older age and pregnancy[1]. Such estimates have been published in France, but background rates of immunosuppressing conditions (e.g., diabetes) and risky food consumption (e.g., soft cheese) likely differs from the United States. Such U.S.-specific estimates would be useful in risk assessment and tailoring nutritional recommendations for people at highest risk. Indeed, a global review of *L. monocytogenes* control highlighted this area as a key data gap for conducting risk assessments and making food policy decisions.[7] Additionally, numerous listeriosis outbreaks have occurred in hospitals, and better risk estimates could provide important information for implementing hospital food safety recommendations.[8] This study seeks to determine medical conditions that place people at higher risk by estimating condition-specific listeriosis incidence rates and rate ratios compared with the general population. Previous students on incidence in the U.S. have demonstrated a decline in listeriosis incidence following recommendations by the Centers for Disease Control and Prevention (CDC).[9] Consequently, better information on which underlying conditions pose the greatest risk may help target nutrition education and increase awareness among clinicians.

In this thesis, I will first provide a review of the literature on associations between underlying conditions and listeriosis. The following section will examine the frequency of underlying conditions among a subset of U.S. cases of listeriosis that occurred during 1996–2014 reported by active public health surveillance. These data are then used to estimate condition-specific listeriosis incidence rates using published estimates of the number of U.S. residents with these underlying conditions as denominators.

Literature Review

Conditions Associated with Listeriosis

Pregnancy

Listeriosis disproportionately affects pregnant women, and these infections can lead to fetal loss or neonatal death.[1] Because national surveillance systems for listeriosis generally collect more complete data on pregnancy than on other underlying conditions apart from age, incidence estimates for pregnancy are relatively robust. Using 2004-2009 data from the FoodNet active surveillance system in 10 U.S. sites, Silk *et al.* reported 126 pregnancy-associated listeriosis cases, comprising about one-sixth of their total patients in the surveillance period.[10] In a similar study using the same data, Pouillot *et al.*, in a 2004-2009 surveillance analysis in the United States, found that the risk ratio of listeriosis in pregnant women was 114.6 (95% CI: 68.9, 205.1) when compared with non-pregnant women of reproductive age.[11] Similarly, in a 2001-2008 surveillance analysis, Goulet *et al.* used published prevalence estimates from French and European registry data to estimate risk ratios from surveillance data and a variety of conditions. Goulet *et al.* reported a risk ratio of 116 for pregnant women in France, among a cohort of 774,000 pregnant women, compared to people <65 years with no underlying conditions[4]. In a 2004 surveillance report for England and Wales, McLauchlin *et al.* reported an incidence of pregnancy-associated listeriosis of 2.83 per 100,000 live or still births during 1995 to 1999. Seven percent of these patients reported other immunocompromising conditions.[12] In an analysis of patients with listeriosis treated at a single hospital in Spain from 1986 to 2007, Muñoz reported that only 8% of cases were among pregnant women.[13]

Data from countries outside of North America and Europe are limited. Feng *et al.* conducted a systematic review of published case reports and laboratory isolates of listeriosis in China from 1964–2010 and found that 77 (52%) of 147 cases were pregnancy associated.[14] However, case reports may not adequately reflect the true distribution of underlying conditions among patients with listeriosis. In contrast, in an analysis in a Taiwan hospital, Huang *et al.* only had a single patient (2%) who was pregnant in in the eight year study period from 2001 to 2008, exemplifying the problem of using hospital-based rather than population-based surveillance data when calculating risk ratios and incidence estimates.[15] In a 1995-1999 analysis in Israel by Siegman-Igra *et al.*, 69 (43%) of the 161 total listeriosis patients were pregnancy associated. Of these, 28 (41%) experienced a fetal death or neonatal loss. The authors also conducted a review of ten recent case series, and found that 35% of listeriosis cases worldwide were pregnancy associated.[16]

In sum, pregnancy is a condition associated with invasive listeriosis, and high-quality incidence estimates exist for the United States and some European countries. This situation stands in marked contrast to the paucity of data available for most other underlying medical conditions.

Age

In addition to pregnancy, older age is a well-documented condition associated with listeriosis. In a 2004-2009 U.S. population-based surveillance study, Pouillot *et al.* used 15-year age groups to demonstrate the relative risk of non-pregnancy related listeriosis. People in the 0-14 year age category were at lowest risk, with a relative risk of 0.5 compared to the 15-44 year age group. Above age 44 years, risk increased substantially for each group, with a relative risk of 53.8 for people aged 85 years and older.[11] In their 2004-2009 U.S. surveillance report, Silk *et al*. found that over half of listeriosis cases were aged 65 years or older.[10] In a population-based 2001-2008 French surveillance analysis, Goulet *et al.* examined three age groups among people who did not have any other underlying conditions of interest: <65, 65-74, and >74 years. Compared to the youngest group, the risk ratios for the 65-74 year age group was 8 and the >74 year age group was 20.[4] The World Health Organization and the Food and Agriculture Organization (WHO/FAO) developed relative susceptible based on epidemiologic data and population estimates in France. They estimated a relative susceptibility of 7.5 for those ≥65 years of age, when compared to people <65 years of age with no underlying conditions.[17] In their systematic review of published listeriosis case reports and laboratory isolates of *L. monocytogenes* in China from 1964 to 2010, Feng *et al.* investigated ten-year age groups, divided into subcategories of immunocompromised, immunocompetent, pregnant women, and neonates. They found a sharp decline in number of cases after 28 days of age, with increasing rates from the 2-15 age group to the 36-45 age group among non-pregnant patients. Subsequent age groups saw a decrease in the overall number of cases.[14] In a surveillance report for England and Wales, McLauchlin *et al.* substantial increases in listeriosis incidence for each ten-year age group starting with ages 20-29. People aged 80 years and older experienced the highest incidence, or 10 per million.[12] In a surveillance study in England and Wales from 2001-2004 by Gillespie *et* al., the risk of listeriosis increased substantially after age 50 years (<1 case per million), with risk being highest for people aged 80 years and older (approximately 12 cases per million).[18] Additionally, in the 1995-1998 surveillance report in Israel by Siegman-Igra *et al.*, an upward trend of listeriosis cases by age, up to 79 years with a slight decrease in those 80 years and older.[16]

In a study by Bennion *et al.* in the United States that examined death certificate data from 1990-2005, the estimated annual mortality rate due to listeriosis was 0.13 per million for infants less than one year of age. This mortality rate then dropped to 0.02 deaths per million for the one to four-year age group and 0.01 deaths per million for the 5-14-year age groups. Each subsequent age group had a doubled mortality rate of the previous (15-24, 25-34, 35-44, 45-54 year groups), until reaching 0.48 per million for the 55-64 year age group. This number then increased dramatically to 2.12 for the 85 years and greater age group.[19]

Only two of the above studies investigated relative risk of listeriosis associated with various age categories, and each study used different age groups. Determining the relative risk of listeriosis by five-year age groups would be ideal.

Cancer

Cancer is a frequently reported condition among patients with invasive listeriosis, but the risk is not equally distributed among malignancies, and hematologic cancers appear to pose a higher risk than solid organ cancers. In a 2011 study of listeriosis surveillance data from France, Goulet *et al*. estimated the risk ratio for listeriosis posed by 18 types of cancer. Patients with any type of cancer had a risk ratio of 78 for listeriosis compared the general population under age 65 years with no major underlying conditions. The risk ratio point estimates ranged from 4 for kidney cancer to 1139 for chronic lymphocytic leukemia.[4] In a 2013 case-control study in Germany by Preußel *et al.* (109 cases and 1,982 controls), the odds ratio for listeriosis was 16.0 (95% CI: 6.51, 39.16) for hematologic cancers and 1.6 (95% CI: 0.93, 2.84) for solid tumors when compared to age frequency-matched population controls.[20] Similarly, in the WHO/FAO report based on France, people with hematologic cancers had a relative susceptibility of 1364, while pulmonary cancer was 229, gastrointestinal and liver cancers was 211, bladder and prostate cancers was 112, and gynecological was 66, when compared to people <65 years of age with no underlying conditions.[17] In a 2011 surveillance analysis in England and Wales, Mook *et al.* found that patients with cancer had a relative risk for listeriosis of 4.9 (95% CI: 4.4, 5.5) when compared to other conditions. Associations were found with cancers of the digestive organs, reproductive organs of both sexes, breast, eye, brain, and central nervous system, as well as lymphoid and hematopoietic cancers.[3] In an analysis of patients with listeriosis seen at a comprehensive cancer center during a 43-year period, Safdar and Armstrong found that two thirds (67%) of patients had a hematological cancer, with lymphoma being the most common type. Of the 34% with a solid organ cancer, nearly half (45%) had breast cancer.[21] In a study of listeriosis in Israeli hospitals, Siegman-Igra *et al.* found that 23 (40%) of 64 non-pregnancy associated listeriosis patients had hematologic cancer and an additional 22 (34%) patients had solid organ cancer.[16] A 2008 French surveillance report by Goulet *et al.* noted about 70 (30%) listeriosis cases with leukemia, 14 (6%) with breast cancer, 13 (5%) with lung cancer, and 20 (8%) with colon and rectal cancers on average for each year of the study, compared to an average of 237 reported listeriosis cases per year.[22] In an analysis of a 2010 Texas outbreak of listeriosis among hospitalized patients, Gaul *et al.* found that half of the ten patients were diagnosed with cancer.[23] Huang *et al.*, found that nearly half of 43 patients with listeriosis at a single hospital in Taiwan over an eight year period had some type of cancer.[15] In an analysis of cases at a large hospital in Spain over 22 years by Muñoz *et al.*, about 30% of patients with listeriosis had cancer.[13] Silk *et al.*, in a surveillance analysis, found that 104 (23%) of 443 patients reported a cancer diagnosis in FoodNet listeriosis patients over six years.[10] In a 2004 surveillance report for England and Wales, McLauchlin *et al.* estimated the incidence of listeriosis among those who did not report malignancies and among all people, including those who reported malignancies. The overall listeriosis incidence among patients without cancer was 1.2 cases per million, whereas the incidence among the entire population, including those with cancer, was estimated to be 1.7 per million. The greatest differences between these two groups are seen in the older age groups, suggesting age is also a factor.[12] In a 2006 surveillance report in England and Wales by Gillespie *et al.*, 43% of listeriosis patients age ≥60 years reported a cancer diagnosis.[18] In a case-control study using U.S. death certificate data by Bennion *et al.*, hematopoietic or lymphatic cancers were over five times more likely to be included on death records with listeriosis when compared to death records without listeriosis (OR=5.27). However, a similar association was not seen when considering all forms of cancer (OR=1.00).[19]

There is a variety of evidence examining the association between cancer and listeriosis. The evidence suggests that hematological cancers have the strongest association with listeriosis. However, to our knowledge, no studies estimate the incidence of listeriosis among cancer patients, especially leukemia, myeloma, and lymphoma patients in the United States.

Organ Transplant Recipients

Recipients of organ transplants are often on immunosuppressive drugs, which increase the risk of infectious diseases, likely including listeriosis. In the 2001-2008 French surveillance study, Goulet *et al.* determined that solid organ transplant patients had a risk ratio for listeriosis of 164 when compared to listeriosis cases under the age of 65 and having no underlying conditions being examined. However, it should be noted that this risk ratio was based on listeriosis in only ten patients with solid organ transplants.[4] In the 2012-2013 case-control study in Germany by Preußel *et al.*, the odds ratio for solid organ transplant recipients and invasive listeriosis was 3.89 (95% CI: 1.30, 11.62), compared to age frequency matched population control.[20] The 2004 WHO/FAO report based on French data estimates a relative susceptibility of listeriosis of 2,584 for people who had transplants, when compared to people <65 years of age with no underlying conditions.[17] Muñoz *et al.* found that about 11% of their patients in a single hospital in Spain underwent a solid organ transplant in their surveillance report.[13] Although there appears to be evidence that having a solid organ transplant is associated with listeriosis, there are only a few studies reporting associations, indicating a need for further investigation.

Renal Failure

Renal failure and hemodialysis can also make individuals more susceptible to invasive listeriosis. However, studies that have examined this association have used varying definitions that could dramatically affect results. For example, people on hemodialysis likely have a greater risk of listeriosis than patients with renal dysfunction not requiring dialysis. Goulet *et al.*, in their 2011 French surveillance study, found that the risk ratio of listeriosis in dialysis patients was 361 (n=46) when compared to those under the age of 65 and having no underlying conditions.[4] Similarly, though not as extreme, in the 2012-2013 case-control study in Germany Preußel *et al.*, determined that the odds ratio of listeriosis among people with renal disease was 4.62 compared to age frequency matched population controls.[20] In a 1999-2009 surveillance analysis in England, Mook *et al.* estimated a relative risk of 12.2 (95% CI: 9.8, 15.1) for people with renal failure when compared to other conditions.[3] The 2004 WHO/FAO report based on French data estimates a relative susceptibility of listeriosis of 476 for people on dialysis, when compared to people <65 years of age with no underlying conditions.[17] In their surveillance report, Huang *et al.* found that about 30% of the 43 patients at a single Taiwan hospital had renal failure.[15] In the Spanish surveillance study by Muñoz *et al.*, only about 8% of their patients suffered from renal disease.[13] In the 2004-2009 population-based U.S. surveillance analysis by Silk *et al.*, 48 (11%) people reported renal disease or dialysis among the 443 non-pregnancy associated cases that reported at least one underlying condition.[10] In the 2006 surveillance report in England and Wales, Gillespie *et al.* report only 4% of listeriosis cases ages 60 and older with any renal diseases.[18] Eleven (13%) patients in the Israeli surveillance analysis by Siegman-Igra had a diagnosis of renal failure, with four being treated by dialysis.[16] There appears to be evidence that renal disease and dialysis may be associated with invasive listeriosis, though further research could better quantify this finding.

Diabetes

Diabetes has been a focus of study for associations with listeriosis as well. Goulet *et al.* found a risk ratio of 34 for people with type 1 diabetes and 4 for type 2 diabetes compared with people <65 years with no underlying conditions in their 2011 cohort study in France. Although these may be seen as relatively large as far as risk ratios, they are some of the smallest risk ratios found in the study, indicating that diabetes may not be as important a condtion as other diseases.[4] Preußel *et al.*, though, found similar results in their case-control study in Germany with an odds ratio of 2.19 for diabetics when compared to age frequency matched population controls.[20] In the 1999-2009 surveillance study in England by Mook *et al.*, diabetes was found to have a risk ratio of listeriosis of 11.4 (95% CI: 9.0, 14.5) when compared to other conditions.[3] In a surveillance analysis, Huang *et al.* found that about 25% of patients at their Taiwanese hospital had a diagnosis of type 2 diabetes.[15] The 2004 WHO/FAO report based on French data estimates a relative susceptibility of listeriosis of 30 for people with insulin-dependent diabetes and 25 for people with non-insulin-dependent diabetes, when compared to people <65 years of age with no underlying conditions.[17] Similarly, Muñoz *et al.*, in their hospital in Spain, saw about 19% of their listeriosis patients with diabetes and in an outbreak report, Gaul *et al.* reported that two of ten patients had type 2 diabetes.[13,23] In the 2004-2009 U.S. surveillance study by Silk *et al.*, 63 (14%) of 443 listeriosis patients reported diabetes.[10] Of the 87 non-pregnancy associated cases in Israel, Siegman-Igra *et al.* reported ten (11%) patients with diabetes in their surveillance study.[16] In the 2006 surveillance report in England and Wales, Gillespie *et al.* report that only 3% of listeriosis cases ages 60 and older had diabetes.[18] Although there appears to be some evidence that diabetes is associated with listeriosis, further research is needed to quantify the incidence in the U.S.

Autoimmune Diseases

Both the pathogenesis and treatment of autoimmune diseases may influence the susceptibility to invasive listeriosis. In a 2011 cohort study in France, Goulet *et al.* investigated the association of rheumatoid arthritis, ulcerative colitis, and giant cell arthritis with invasive listeriosis and found risk ratios of 56, 54, and 365, respectively, when compared to those under the age of 65 with no underlying conditions.[4] In their age frequency matched case-control study in Germany (109 cases, 1,982 controls), Preußel *et al.* aggregated different types of autoimmune disorders and found an odds ratio of 3.53 (95% CI: 1.68, 7.41).[20] In their hospital surveillance report in Taiwan, Huang *et al.* found that almost 10% of the 43 patients had systemic lupus erythematosus.[15] Gaul *et al.* reported three of ten listeriosis patients with an autoimmune disorder in their Texas outbreak report.[23] In the 2006 surveillance report in England and Wales, Gillespie *et al.* report 13% of listeriosis cases ages 60 and older were diagnosed with an autoimmune disorder.[18] In a 2013 case series of patients in Colombia, Tobón, Serna, and Cañas described five (3%) listeriosis cases among 174 patients with systemic lupus erythematosus. Few studies have quantitatively described the association between specific autoimmune disorders and none have examined patients in the U.S.

Liver Diseases

Because of the proliferation of *Listeria monocytogenes* in the liver, people with liver disorders could be at higher risk for invasive disease. In their 2011 French cohort study, Goulet *et al.* determined a risk ratio of 122 for those with liver diseases, whereas Preußel *et al.*, found an odds ratio of 7.14 in their case-control study (using controls matched on age) in Germany.[4,20] In their 2011 study, Mook *et al.*, estimated a significant relative risk of 22.4 for those with liver diseases.[3] The 2004 WHO/FAO report based on French data estimates a relative susceptibility of listeriosis of 143 for people with liver disease, when compared to people <65 years of age with no underlying conditions.[17] In their analysis from a Taiwanese hospital, Huang *et al.* reported that 7% of patients had liver disease and 7% had chronic hepatitis, whereas Muñoz *et al.* reported that 18% of patients had liver disease in the hospital in Spain over an 11-year period.[13,15] Silk *et al.* found 25 (6%) listeriosis cases with cirrhosis, liver failure, or hepatitis among the 443 that reported at least one underlying condition in a surveillance analysis in the United States.[10] Gaul *et al.* specifically reported that three of ten patients had hepatitis C in the Texas outbreak report.[23] Less than 2% of the patients in the 2006 study of death records by Gillespie *et al.* had reported liver disease and 3.5% reported an alcohol related disease.[18] Safdar and Armstrong, in a study in a comprehensive cancer center, reported that 36% of listeriosis patients had advanced liver disease and 2% had cirrhosis.[21] In a surveillance analysis by Siegman-Igra *et al.*, ten (11%) patients reported chronic liver disease of 91 non-pregnancy associated cases, while the 2008 French surveillance report by Goulet *et al.* noted an average of 39 listeriosis cases with cirrhosis per year.[16,22] In a mortality study in the United States by Bennion *et al.*, the odds of liver disease being listed with listeriosis on death records was double the odds of liver disease being listed without listeriosis on the death record (OR=2.05).[19] Despite the number of studies reporting liver diseases, they are reported in an inconsistent manner that would necessitate further research to strengthen the potential association.

Immunosuppressive and Antacid Treatments

Immunosuppressive treatments, by their nature, make it difficult for the body to fight infections, including invasive listeriosis. Although not specifically an immunosuppressive drug, antacids can weaken the body's defenses against foodborne bacteria by neutralizing gastric acidity. In their case-control study, Preußel *et al.*, reported three different categories: chemotherapy, immunosuppressive medication, and radiation therapy. The highest odds ratio found in the study, 17.12, was from chemotherapy. The latter two had odds ratios of 6.52 and 5.77, respectively. The study also investigated antacid use, and found an odds ratio of 3.84.[20] In a 2009 case-control study, Gillespie *et al.* reported on a number of immunosuppressive treatment categories. Immunosuppressive treatments and steroids had non-significant results, with odds ratios of 1.3 and 1.0, respectively, whereas cytotoxic drugs and gastric acid reducers were significantly associated with listeriosis, with odds ratios of 2.1 and 1.7, respectively.[24] In the outbreak report by Gaul *et al.*, only three of ten patients with listeriosis did not list chronic steroid use, and of those three, one reported chronic use of antacids.[23] In their surveillance analyses, Huang *et al.* reported nearly 5% of listeriosis patients with asthma were treated with steroids, and Muñoz *et al.* reported almost 20% of patients with listeriosis under steroid therapy.[13,15] Similarly, Siegman-Igra *et al.* reported 31 (36%) of their 87 non-pregnancy associated listeriosis cases taking either steroids or undergoing chemotherapy.[16] Additionally, Safdar and Armstrong note that 68% of their listeriosis patients were on steroids and 77% received chemotherapy. It is important to note that these cases were in a comprehensive cancer center over a 43-year surveillance period, which may present skewed results on a true association.[21] While the evidence is beginning to form, many studies have reported only steroid use or other types of treatments. Further investigation on each of these type of immunosuppressive treatment is needed.

Respiratory Diseases

Diseases like chronic obstructive pulmonary disease (COPD) or asthma can influence a person's ability to fight disease. In their surveillance analysis, Huang *et al.* reported that two (5%) of 43 listeriosis patients had COPD and two had asthma, while Gaul *et al.* reported that half of their ten outbreak patients had respiratory diseases.[15,23] Muñoz *et al.* report about 15% of their 111 listeriosis patients had COPD in their surveillance analysis.[13] There are limited studies that suggest respiratory disease could be associated with invasive listeriosis, indicating further research is needed.

HIV/AIDS

HIV or AIDS can also affect one's ability to fight infection. In the 2011 French cohort study, Goulet *et al.* demonstrated a risk ratio of 55 for people with AIDS and 45 for people infected with HIV that did not progress to AIDS.[4] The 2004 WHO/FAO report based on French data estimates a relative susceptibility of listeriosis of 865 for people with AIDS, when compared to people <65 years of age with no underlying conditions.[17] The prevalence of HIV among patients with listeriosis across populations likely reflects the underlying prevalence of HIV in the population. In their surveillance reports, Muñoz *et al*. found that about 3% of their listeriosis patients were infected with HIV, while Silk *et al.* reported that 16 (4%) listeriosis cases had HIV.[10,13] In the analysis of listeriosis in a U.S. comprehensive cancer center between 1955-1997 by Safdar and Armstrong, two (2%) of 94 listeriosis patients were also diagnosed with AIDS.[21] In a mortality study in the United States by Bennion *et al.*, the odds of HIV and listeriosis being listed on a death record was four times the odds of HIV without listeriosis being listed on death records (OR=4.19).[19] There appears to be very limited research on the association between these two infections and further research is needed.

Heart Diseases

Heart disease could also be associated with invasive listeriosis, although older age may confound this relationship. Goulet *et al.* reported a risk ratio of 5 for people with heart disease compared with people without substantial comorbidities younger than 65 years. This risk ratio, was one of the lowest in the entire 2011 French cohort study and might be explained by age differences in the comparison groups.[4] In contrast, in an outbreak of listeriosis in Texas, Gaul *et al.* saw 90% of cases had cardiovascular disease.[23] In this outbreak, all patients had been hospitalized, and as described previously, other comorbidities and older age were common. Mook *et al.* found a non-significant relative risk of 0.8 for ischemic heart diseases and 0.7 for cerebrovascular disease, but a significant relative risk of 8.0 for hypertension.[3] Silk *et al.* found 45 (10%) cases of listeriosis with heart disease in a surveillance analysis in the United States. In the 2006 surveillance report by Gillespie *et al.*, about 13% reported a cardiovascular disease. A 2008 French surveillance report by Goulet *et al.* reported around ten listeriosis cases with heart valve problems.[22] Based on this limited research, it appears as though heart disease could be associated with listeriosis and should be further researched to solidify the determination.

Conclusion

Further research is needed on the incidence of listeriosis in the United States among people with most of the conditions described above. Investigating whether cancer, age, organ transplantation, renal failure, diabetes, autoimmune diseases, liver diseases, immunosuppressive treatments, respiratory diseases, HIV/AIDS, and heart diseases are associated with invasive listeriosis could lead to interventions to prevent this frequently fatal infection in the United States. Because of more consistent reporting, there is substantial research on the association between pregnancy and listeriosis. However, because pregnancy is already included in CDC recommendations regarding listeriosis prevention, this group could be used as a comparison for extending recommendations.[25] Further study is needed to examine conditions that could be important predictors of listeriosis.

There are clear gaps in the current literature. Only three of 20 studies provided comparisons of condition-specific incidence rates to control groups: the 2011 cohort study by Goulet *et al.*, the 2011 cohort study by Mook *et al.*, and the case-control study by Preußel *et al.* Additionally, Goulet *et al.* published the only study that systematically examined an extensive variety of underlying conditions.[4] The research currently-available fails estimate the risk of many possible conditions for this severe disease in the United States. The subsequent analyses will provide incidence rates and incidence rate ratios using active and passive surveillance in the United States. These analyses will contribute to the existing literature to better the understanding of the role of underlying conditions in invasive listeriosis.

Listeriosis is a rare, but serious foodborne infection. With a high mortality and disproportionate infection rate in those with underlying conditions, prevention is vitally important. Unfortunately, with limited research on exactly what groups are at the highest risk for the disease, focus on nutrition education and provider awareness is lacking. By conducting further research, more evidence can be provided on which groups need to be targeted for education about high risk foods and for providers who need to be aware of this rare disease.

METHODS

Information on invasive listeriosis cases in the United States has been routinely collected by CDC through both the *Listeria* Initiative since 2004 and FoodNet since 1996. The two surveillance systems exist to serve different purposes. FoodNet is an isolate-based active surveillance system that operates in 10 states, providing a representative sample of 15.2% of the United States population. Data from FoodNet are used to track incidence rates and progress towards Department of Health and Human Services Healthy People targets. FoodNet collected data on listeriosis patients' underlying conditions during 1996-2014 (similar data were not collected for other foodborne pathogens).[26] Data were collected in a non-standardized 'free text' format and had never previously been systematically examined. As such, the data were standardized as described in the Definitions section below. All cases reported to FoodNet during this time period were included in the analysis.

The *Listeria* Initiative (LI) is a passive surveillance system that collects demographic, clinical, and food exposure data from patients with listeriosis across the country, and its data are used during outbreak investigations to perform rapid case-case comparisons of food exposures to find the outbreak source. Some state health departments voluntarily report data on patients' underlying conditions to the LI. These LI data were used to supplement FoodNet data when available to provide additional information on underlying medical conditions. The CSTE case definition for listeriosis was applied: a clinically compatible case that is laboratory confirmed from either a normally sterile site or from placental or fetal tissue.[27] Cases that did not meet the CSTE case definition were excluded. Cases for which no information on underlying conditions was available were excluded from incidence calculations of underlying conditions. However, these cases were included in calculations of odds ratios and overall incidence.

In order to calculate the incidence of listeriosis among patients with various underlying conditions, estimates of the prevalence of each condition were needed. Such population prevalence data is not readily available for all conditions from a single source, but rather was obtained from published resources, often derived from population-based registries (Table 1). National population data, including age-specific figures, were obtained from the 2010 U.S. Census. These data were used to calculate the overall incidence and risk of listeriosis by age group. The overall cancer prevalence used was five-year prevalence data from the American Cancer Society.[28] Five-year prevalence was used to account for those at highest risk and not include people who had cancer but have since been cured or were in long-standing remission. Many of the specific cancer prevalence estimates used were published by the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute of the National Institutes of Health (NIH). The SEER program uses population-based registries to determine these prevalence estimates and is considered one of the best sources of cancer statistics in the country.[29] Other cancer prevalence estimates were obtained from reports published by the American Cancer Society.[28,30] Data for nearly all other conditions were obtained from CDC, the NIH, and the American Heart Association. For cirrhosis, this analysis used data from Scaglione *et al.*, who based their estimate of cirrhosis prevalence on surveillance data from the 1999-2010 National Health and Nutrition Examination Survey.[31] The intravenous (IV) drug use prevalence estimate used was developed by Mathers *et al.*, who performed systematic review of the published literature to estimate the prevalence in the US among 15 to 64 year olds.[32] All patients with reported IV drug use in this study are within that age range. For myelodysplastic syndromes, this analysis used a prevalence estimate from Ma, who estimated the prevalence using SEER data.[33] The published prevalence estimates were reduced to 15.2% of the original, to correspond to the FoodNet catchment area population. The average annual incidence per 100,000 people was calculated using FoodNet data and incidence rate ratios were determined using the total average annual incidence as the baseline. Age-adjusted incidence rate ratios for individual conditions could not be calculated because of a lack of age-stratified prevalence estimates.

Definitions

The underlying conditions were categorized into 44 groups of diseases (Table 2). Patients with a diagnosis of cancer were categorized into an overall group for all cancer types. Cancers were further categorized as for bladder; bone; breast; colon/rectal; ear, nose, or throat (ENT); gynecological (including cervical, uterine, and vulvar); kidney; leukemia; liver; lung;

lymphoma; multiple myeloma; pancreatic; prostate; skin; and stomach cancers. If cancer type was not specified, then the cancer was categorized as cancer type not specified. Illnesses in a pregnant woman or infant aged 30 days or less were classified as pregnancy-associated. Mother-infant pairs were considered a single case since the infections were presumed to have started with maternal infection. All solid and stem cell transplants were grouped into a single category of organ transplants, because type was frequently not specified. Immunosuppressive therapies included chemotherapy, radiation, steroids, and any immunosuppressive drugs, including tumor necrosis factor-alpha inhibitors (e.g., etanercept, infliximab). The category termed cardiovascular diseases and stroke included hypercholesteremia, hypertension, valve replacements, atherosclerosis, and myocardial infarctions. Diabetes included both type 1 and type 2 diabetes mellitus. Rheumatoid arthritis (an autoimmune disease) was separated from general arthritis wherever possible. Chronic kidney disease, sarcoidosis, systemic lupus erythematosus, hepatitis, cirrhosis, gastric ulcers, chronic obstructive pulmonary disease (COPD) and asthma, alcoholism, current smoker, and myelodysplastic syndromes, HIV/AIDS, and Crohn's/ulcerative colitis categories were included. Categories for other immunodeficiency, other autoimmune diseases, other inflammatory diseases, other infections, and all other diseases were created to encompass any diseases not already categorized. Three ten-year age groups for people 65 years of age and above were created for analysis as conditions of interest. Individuals could be placed in more than one category of underlying conditions, reflecting multiple comorbidities. Risk of listeriosis by five-year age categories was determined among non-pregnancy associated cases in the FoodNet catchment area only.

RESULTS

There were a total of 2,142 cases of listeriosis reported to FoodNet and LI from 1996 to 2014, which translates to a mean annual incidence of listeriosis was 0.24 per 100,000 people. Table 2 displays the number of cases, incidence rates, and incidence rate ratios for each category and Figure 1 displays incidence rates by underlying condition. Twenty-one percent (n=297) of cases were pregnancy associated. Among the non-pregnancy associated cases, 50% were female and the mean age was 66 years.

Because of the surveillance reporting method, no cases reported to FoodNet could be confirmed as being without underlying conditions (i.e., when no condition were listed, it was not possible to determine whether the patient lacked underlying conditions or whether that data field was not completed). Accordingly, incidence rates could not be determined for people without underlying conditions nor could this group be used as a comparison. Additionally, 808 cases were excluded from specific incidence rates due to universally blank fields for underlying conditions.

The incidence rates among people with underlying conditions varied from 0.02 to 11.59 per 100,000. The highest incidence (11.6 per 100,000) was among people with multiple myeloma, followed by leukemia at 7.45 per 100,000 and cirrhosis at 4.32 per 100,000. When compared to the overall incidence, the rate ratios of these diseases were 48, 31, and 18, respectively.

Pregnancy-associated cases and any cancer were the remaining conditions with incidences above 2 per 100,000 with the condition, with incidences of 2.60 per 100,000 pregnancies and 2.28 per 100,000 with cancer. The incidence rate ratios were 11 for pregnancy and 10 for any cancer.

Several conditions had an average annual incidence of 1 to 2 per 100,000: liver cancer, HIV/AIDS, systemic lupus erythematosus, and age 85 years or older. These groups had incidence rate ratios between 4.5 and 5.8. Conditions with incidences between 0.24 and 1.00 per 100,000 included brain cancer, colon/rectal cancers, lung cancer, lymphoma, pancreatic cancer, stomach cancer, rheumatoid arthritis, myelodysplastic syndromes, injection drug use, diabetes, age 65 to 74 years, and age 75 to 84 years. These groups' incidence rate ratios ranged from 1.1 to 3.9. The remaining conditions had incidence rates lower than the overall incidence of 0.24 per 100,000.

These conditions were bladder cancer, breast cancer, ENT cancer, kidney cancer, prostate cancer, skin cancer, Crohn's disease/ulcerative colitis, chronic kidney disease, hepatitis, non-rheumatoid arthritis, COPD/asthma, alcoholism, current smoker, and cardiovascular diseases and stroke. The incidence rate ratios ranged from 0.1 to 1.0.

Risk of listeriosis was determined for non-pregnancy associated cases by five-year age groups (Figure 2). The risk was lowest among people aged 5 to 14 years (0.01 per 100,000) and increased gradually to the 50-54 year age group (0.11 per 100,000). The risk then increased to 1.22 per 100,000 in the 85+ age group, with a risk ratio of 26 when compared to 35-39 year olds. The 0-4 year age group was only slightly increased to 0.03 per 100,000 from the lowest risk groups.

DISCUSSION

The strongest associations with listeriosis were found between multiple myeloma, leukemia, and cirrhosis, followed by pregnancy and cancer. Few studies have examined underlying medical conditions for invasive listeriosis while using comparison groups, and only three of these estimated risk. All four studies, as well as this study, indicate that people with hematologic cancers are among the highest risk for invasive listeriosis. In a German age-frequency matched case-control study, Preußel *et al.* estimated an elevated odds ratio for hematologic cancers.[20] In a French surveillance analysis for years 2001-2008, Goulet *et al.* estimated increased risk for chronic lymphocytic leukemia, acute leukemia, multiple myeloma, and non-Hodgkin's lymphoma[4]. In a surveillance analysis for England covering years 1999-2009, Mook *et al.* estimated an elevated risk for lymph and blood cancers.[3] Additionally, in a 2004 report, the World Health Organization and Food and Agriculture Organization (WHO/FAO) estimated an increased risk for people with cancers of the blood.[17] All of these results are comparable to the results of this study, where multiple myeloma was the condition with the highest incidence and an incidence rate ratio (IRR) of 48.32, while leukemia had an IRR of 31.05.

Lymphoma was lower, but still notable with an IRR of 4.51. These patients are often undergoing chemotherapy or radiation, which makes them more susceptible to infectious diseases as a result of the primary immune deficiency.[34] Solid organ cancers are typically associated with lower levels of immunosuppression compared with hematologic malignancies, and several types of solid organ cancer are typically less severe. For example, skin cancer (mostly non-melanoma) is remarkably common, but people have better survival.[35] The skin cancer incidence estimate in this study should be interpreted with caution as this category likely included a mixture of melanoma and non-melanoma skin cancers, which generally involve markedly different levels of immunosuppressive treatment and survival.

There are some differences in the results of this study compared to the results of the other three studies. This study estimated an IRR of 0.98 for people with chronic kidney diseases. The other studies estimated associations greater than one. Preußel *et al.*, Goulet *et al*., WHO/FAO estimated elevated associations of listeriosis with dialysis.[4,17,20] Mook *et al.* estimated an elevated risk for people with renal failure[3]. Possible explanations for differences in these studies and our study are that we were not able to differentiate between those with mild kidney failure and those with end-stage renal failure or those on dialysis. As a result, a potential association with dialysis or end stage renal diseases may be diluted by mild kidney failure, reducing the observed IRR. Kidney disease could affect the immune system, and people on dialysis generally have more severely impaired kidney function.[34] Thus, the greater the kidney dysfunction, the more likely to be on dialysis and the more likely to have an impaired immune system.

In this study, systemic lupus erythematosus had a markedly elevated rate ratio for listeriosis, suggesting that patients with this disease are at substantially higher risk of listeriosis than other immunocompromising conditions. This condition was not examined in the previous studies of listeriosis risk, except possibly aggregated under autoimmune diseases in the study by Preußel *et al.* This increased risk could be the result of chronic steroid use or other immunosuppressive treatments, which can be of higher intensity than treatment for other autoimmune diseases.[34]

Previous studies have demonstrated an increased risk of listeriosis at age 60 or 65 years and above.[3,4] This study suggests a gradient of increased risk with increasing age, starting as early as the teenage years, with risk increasing more steeply during a person's fifties. With increasing age, there is a decrease in immune function and the greater potential to develop chronic diseases, such as cancer. This makes older adults more susceptible to infectious diseases.[34]

A main limitation of this study is the inability to adjust condition-specific incidence comparisons by age, meaning that conditions that become more common with older age (e.g., heart disease and cancer) might appear to be associated with greater listeriosis risk when no such association exists. The risk ratios for multiple myeloma and leukemia may be inflated by age-based confounding, whereas risk ratios for lupus and HIV may be lower than if they were adjusted for age. The analysis is also limited by the non-standardized data collection instrument. Major diseases like cancer and organ transplants would seem more likely to be recorded rather than common and seemingly-unrelated ones like arthritis and heart disease (possibly explaining the lack of association with listeriosis despite their known associations with age). In addition, supplemental LI data was only available for a subset of the patients because LI began in 2004, while FoodNet data for this study begins in 1996. Although trends over time were not a focus of this study, there may be more complete data after 2004, resulting in undercounting of underlying conditions (but not total listeriosis cases) for early years. Undercounting, however, is more likely for common or relatively minor conditions, such as arthritis, which would further dilute any possible associations. Additionally, five-year prevalence was used for incidence estimates of all cancers. This was used to prevent the addition of lower risk individuals who had cancer in the past, but were cured or in long-standing remission. However, because of the nature of the data collection for FoodNet and LI, it is unknown if all of the cancer cases reported occurred in the last five years. As such, the estimates for cancer may be inflated. Additionally, it was not possible to examine the influence of more than one condition at a time, despite the fact that patients often have multiple comorbidities, as seen in the outbreak reported by Gaul et al, because few published prevalence estimates were available for combinations of conditions.[23]

Several other factors limited specific portions of the analysis. The lack of negative responses meant that analyses about immunosuppressive treatments could not be performed. Additionally, over 800 cases lacked information on underlying conditions, and it is not known if these patients had no underlying conditions or if the conditions were not reported. The data for FoodNet were included in free text fields and the data in LI contained a combination of free text and checkboxes. Consequently, the case definitions used for each underlying condition could not be confirmed to match the case definitions used for the prevalence data. For some conditions, like cancer, this is less likely to influence the association because diagnoses of cancer are reported to cancer registries, which were used for the prevalence data. Other conditions, such as lupus, may have a less straightforward case definition. In this case, the prevalence for confirmed and probable lupus was used to account for the potential uncertainty in diagnosis. Where this is not possible for other conditions, the associations may be inflated.

The prevalence data, although sourced from reputable national organizations, may not accurately capture the true prevalence of each condition in the U.S., and not all prevalence data was straightforward. All prevalence data used was a stagnant count for a single year, usually between 2005-2012. Consequently, the prevalence estimates do not reflect the changing incidence of the condition over time. This may lead to either inflated or reduced associations, depending on the condition and how its prevalence changed over time. Additionally, the prevalence data available was not always definitive. The calculations for lupus, for example, used 322,000 as the prevalence denominator. The number was calculated using NHANES and small published studies combined with census data to estimate a national prevalence. The data were only for adults and used 2005 population estimates from the U.S. Census Bureau. This number corresponds to both confirmed and probable lupus, rather than just confirmed.[36] The choice was made to use confirmed and probable prevalence estimate in order to provide a more conservative estimate and not provide a potentially inflated incidence. As another example, cirrhosis estimates also used NHANES data from 1999-2010. A cirrhosis diagnosis was determined by blood tests for aspartate aminotransferase-to-platelet ratio of >2 and abnormal liver function tests. The prevalence estimate used this information with a population denominator from the 2010 U.S. census.[31] For these conditions, differences in prevalence estimates compared with reported cases likely resulted in a diluted association for lupus and a potentially diluted or inflated association for cirrhosis.

Despite the limitations of the study, the analyses provide further insight into the association of underlying medical conditions with listeriosis. An important strength of the study is the use of data from FoodNet, given that it is an active surveillance system with a defined catchment area that allows extrapolation to the entire United States population.[26] As a result, although the data only covers a fraction of the US, it is generally applicable to the entire country. The prevalence estimates used as denominators for this study come from published resources of reputable, national health organizations. Additionally, the study examines a wide range of potential medical conditions in a quantitative way, which few studies have done previously.

Prevention of invasive listeriosis can occur through food safety interventions and targeted health education. In the United States, *L. monocytogenes* is considered an adulterant in a ready-to-eat product, and any such product testing positive for the bacteria must be disposed.[19,37] By comparison, in Europe, general ready-to-eat foods may have up to 100 colony forming units per gram of *L. monocytogenes.* These measures can reduce the risk of transmission through food but can never eliminate the risk, and certain foods are likely to remain risky. For this reason, the Centers for Disease Control and Prevention recommends that people at higher risk of listeriosis avoid certain types of foods, including ready-to-eat meats, soft cheeses, and smoked seafood.[19,25] Before these recommendations, in the early 1990s, incidence of listeriosis in the U.S. was around

0.8 per 100,000 and was reduced to 0.27 per 100,000 in 2004-2009.[9] While there are no known studies examining the influence of nutrition education, the decrease in overall incidence following CDC recommendations suggests that nutrition education may help decrease the incidence. Additionally, there is clearly a need for further awareness, as evidenced by hospitals continually serving high risk foods, such as deli meats, to ill patients.[8]

Using the results of this study, targeted nutrition education can take place by providers in an effort to prevent the occurrence of listeriosis. Given the underlying prevalence and the IRR, we would consider focusing prevention efforts towards people with multiple myeloma, leukemia, and cirrhosis. Although all of these conditions are less prevalent than pregnancy, the IRRs demonstrate a stronger association. Pregnant women are already considered to be at higher risk for listeriosis than the general population, with CDC recommendations extending to include them[25]. Perhaps “persons with weakened immune systems” could be further specified to include people with multiple myeloma, leukemia, and cirrhosis. Adapting a more specific definition, while still keeping a generalized statement, could bring further awareness to providers on who is most likely to be affected by listeriosis.

CONCLUSION

The results of this study assists in further identifying these high risk individuals, such as those with hematologic malignancies and cirrhosis and are similar to results found in previous studies. This study can further define the ages of older adults and the specific immune conditions that should be included for prevention education. Although age-adjusted IRRs could not be calculated, providers can consider all of the results to determine if a patient may need to consider a protective diet, avoiding high risk foods. Ideally, the greatest emphasis should be placed on conditions with both a high incidence and high prevalence. Manufacturing practice changes and increased awareness have both lead to a decreased incidence in listeriosis in the U.S. over time. By further expanding awareness and prevention, a continued decline in incidence may occur.

Additionally, the study recognized the importance of universal and uniform reporting on FoodNet surveillance forms. Beginning in 2015, FoodNet ceased collection of underlying conditions for patients with listeriosis. However, in 2016, these types of questions were added to the LI questionnaire. Rather than a single free text field, the new LI questionnaire will collect this information in a standardized way that includes an option for no predisposing conditions. Data collected with this new instrument will likely help further refine the findings of this study. While this study contributes to the existing research, additional cohort or case-controls studies could further define categories and allow for multivariable analyses of the most common conditions. For the conditions with the highest incidence – leukemia, multiple myeloma, and cirrhosis – studies could be completed to determine which factors are leading to the increased incidence, such as the pathophysiology of the disease or the treatment. By further defining the mechanism that increases risk, further nutrition prevention efforts can be determined or perhaps a new, more effective method of prevention could be discovered.

TABLES AND FIGURES
Tables

Table 1. Sources for Population Data

Condition	Source#	Year
Cancer	ACS[28]	2013
Bladder Cancer	ACS[28]	2014
Brain Cancer	SEER[38]	2012
Breast Cancer	ACS[28]	2014
Colorectal Cancers	ACS[28]	2014
ENT Cancers	SEER[39-41]	2012
Kidney Cancer	SEER[42]	2012
Leukemia	ACS[28]	2014
Liver Cancer	SEER[43]	2012
Lung Cancer	ACS[28]	2014
Lymphoma	ACS[28]	2014
Multiple Myeloma	SEER[44]	2012
Pancreatic cancer	SEER[45]	2014
Prostate Cancer	ACS[28]	2014
Skin Cancer	ACS[30]	2012
Stomach Cancer	SEER[46]	2012
Alcohol abuse	NIH[47]	2013
Arthritis	CDC[48]	2003
Cirrhosis	Scaglione *et al.*[31]	1999-2010
COPD/asthma	CDC[49,50]	2012, 2013
Crohn's and ulcerative colitis	CDC[51]	2004
Current Smokers	AHA[52]	2012
CVA/TIA	AHA[52]	2010
Diabetes	CDC[53]	2010
Heart Disease/CHF	AHA[52]	2014
Hepatitis	CDC[54]	2013
HIV/AIDS	CDC[55]	2012
IVDU	Mathers *et al.*[32]	2002
Kidney Disease	AHA[52]	1999-2004
Lupus	CDC[36]	2005
Myelodysplasia and aplastic anemia	Ma[33]	2012
Pregnancy	CDC[56]	2012
Rheumatoid Arthritis	CDC[57]	2005

#Citation Number
ACS: American Cancer Society
SEER: Surveillance, Epidemiology, and End Results Program of the National Cancer Institute
NIH: National Institutes of Health
CDC: Centers for Disease Control and Prevention
AHA: American Heart Association

Table 2. Incidence of Listeriosis, Risk Ratios, and Mortality

Underlying Conditions	Persons with Underlying Condition in FoodNet Catchment Area, no.‡	Listeriosis Patients with Underlying Condition, no. (1996-2014)	Mean No. of Listeriosis Patients with Underlying Conditions per Year	No. of Listeriosis cases per 100,000 persons with Underlying Condition	Incidence Rate Ratio§	No. Deaths Reported Among Patients with Listeriosis (1996-2014)	Case Fatality Ratio (%)
Cancer	741,661	321	16.89	2.28	9.50	76	24
Bladder Cancer	92,510	2	0.11	0.11	0.47	0	0
Bone cancer		2	0.11			0	0
Brain Cancer	22,620	3	0.16	0.70	2.91	1	33
Breast Cancer	471,200	14	0.74	0.16	0.65	5	36
Colorectal Cancers	182,400	9	0.47	0.26	1.08	1	11
ENT Cancer	63,193	1	0.05	0.08	0.35	0	0
Gynecological cancers		5	0.26			2	40
Kidney Cancer	57,141	1	0.05	0.09	0.38	0	0
Leukemia	48,064	68	3.58	7.45	31.05	13	19
Liver Cancer	7,712	2	0.11	1.37	5.69	0	0
Lung Cancer	65,374	9	0.47	0.72	3.02	2	22
Lymphoma (any/all)	116,686	24	1.26	1.08	4.51	3	13
Multiple Myeloma	13,628	30	1.58	11.59	48.32	5	17
Cancer, not specified		158	8.32			38	24
Pancreatic Cancer	6,947	1	0.05	0.76	3.16	1	100
Prostate Cancer	456,000	9	0.47	0.10	0.43	3	33
Skin Cancer	820,800	6	0.32	0.04	0.16	2	33
Stomach Cancer	11,678	2	0.11	0.90	3.76	0	0
Pregnancy-associated	600,832	297	15.63	2.60	10.85	55#	19
Organ Transplant		29	1.53			6	21
Immunosuppressive therapies		293	15.42			35	12
HIV/AIDS	182,400	40	2.11	1.15	4.81	4	10
Crohn's or Ulcerative Colitis	4,712,000	17	0.89	0.02	0.08	1	6
Rheumatoid Arthritis	228,000	15	0.79	0.35	1.44	1	7
Myelodysplastic Syndromes	9,120	1	0.05	0.58	2.41	0	0
Sarcoidosis		4	0.21			0	0

Table 2. Incidence of Listeriosis, Risk Ratios, and Mortality (continued)

Underlying Conditions	Persons with Underlying Condition in FoodNet Catchment Area, no.‡	Listeriosis Patients with Underlying Condition, no. (1996-2014)	Mean No. of Listeriosis Patients with Underlying Conditions per Year	No. of Listeriosis cases per 100,000 persons with Underlying Condition	Incidence Rate Ratio§	No. Deaths Reported Among Patients with Listeriosis (1996-2014)	Case Fatality Ratio (%)
Other immunodeficiency		13	0.68			3	23
Other autoimmune diseases		16	0.84			0	0
Other Inflammatory diseases		11	0.58			2	18
Other infections		20	1.05			5	25
Chronic Kidney Diseases	3,952,000	176	9.26	0.23	0.98	44	25
Hepatitis	661,471	13	0.68	0.10	0.43	3	23
Cirrhosis	96,265	79	4.16	4.32	18.01	21	27
Gastric ulcers		11	0.58			4	36
Arthritis	4,104,000	13	0.68	0.02	0.07	1	8
COPD/Asthma	5,722,496	131	6.89	0.12	0.50	24	18
Alcoholism	2,523,200	64	3.37	0.13	0.56	17	27
Current smoker	6,399,200	31	1.63	0.03	0.11	12	39
Injection Drug Use	282,318	16	0.84	0.30	1.24	2	13
Diabetes mellitus	2,857,600	245	12.89	0.45	1.88	43	18
Cardiovasular diseases and Stroke	12,707,200	284	14.95	0.12	0.49	71	25
Other diseases		357	18.79			68	19
Age 65-74	3,300,441	360	18.95	0.57	2.39	62	17
Age 75-84	1,985,291	353	18.58	0.94	3.90	83	24
Age 85+	835,002	194	10.21	1.22	5.10	45	23

‡FoodNet noted to be representative of the underlying population. Used National data and multiplied by the % represented by FoodNet
*Those with missing information on immunosuppressive therapies excluded from percentage
#Includes maternal, neonatal, and fetal death
§Referent: Overall incidence of listeriosis, 0.35 per 100,000

Figures

Figure 1. Incidence of Invasive Listeriosis by Condition

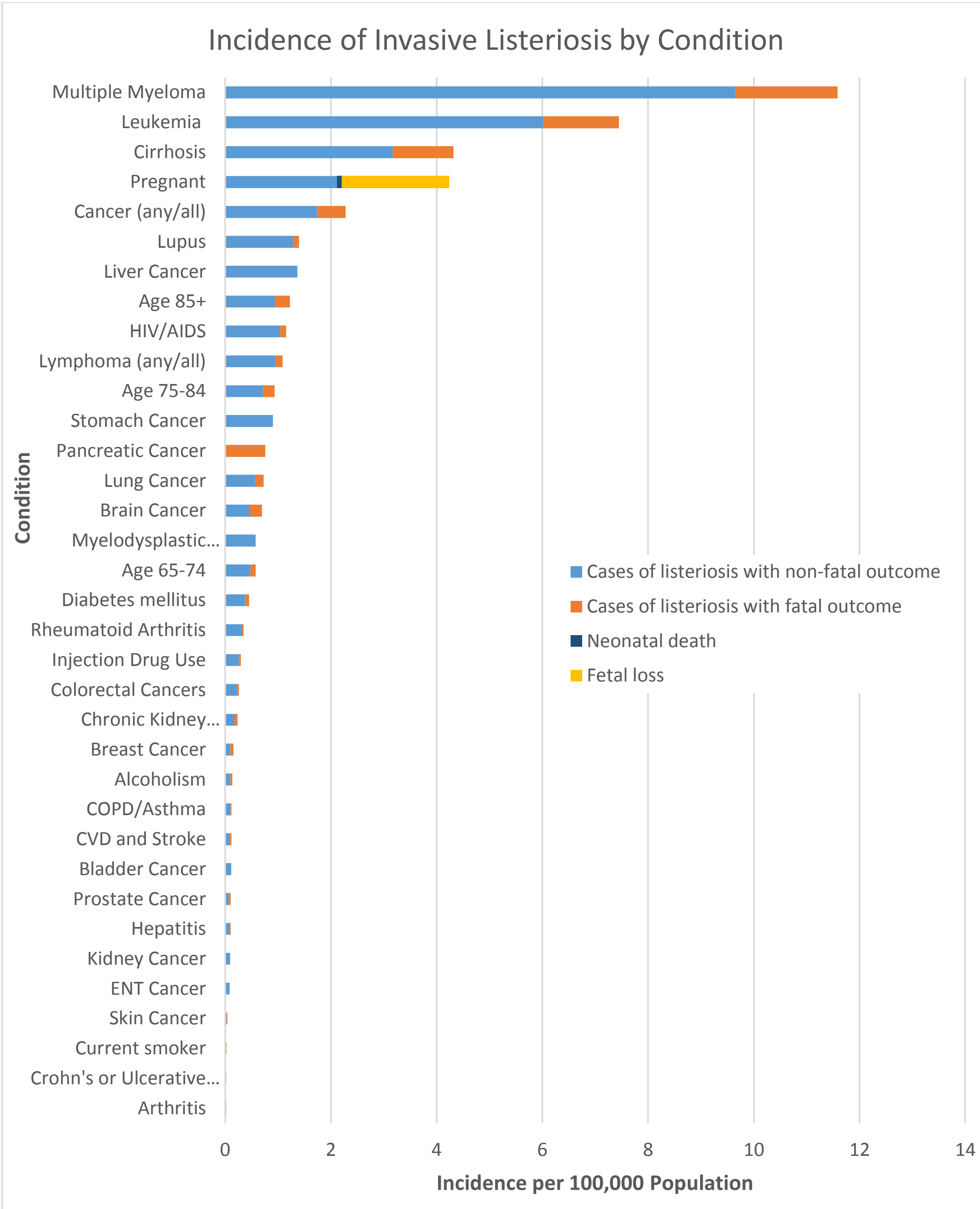
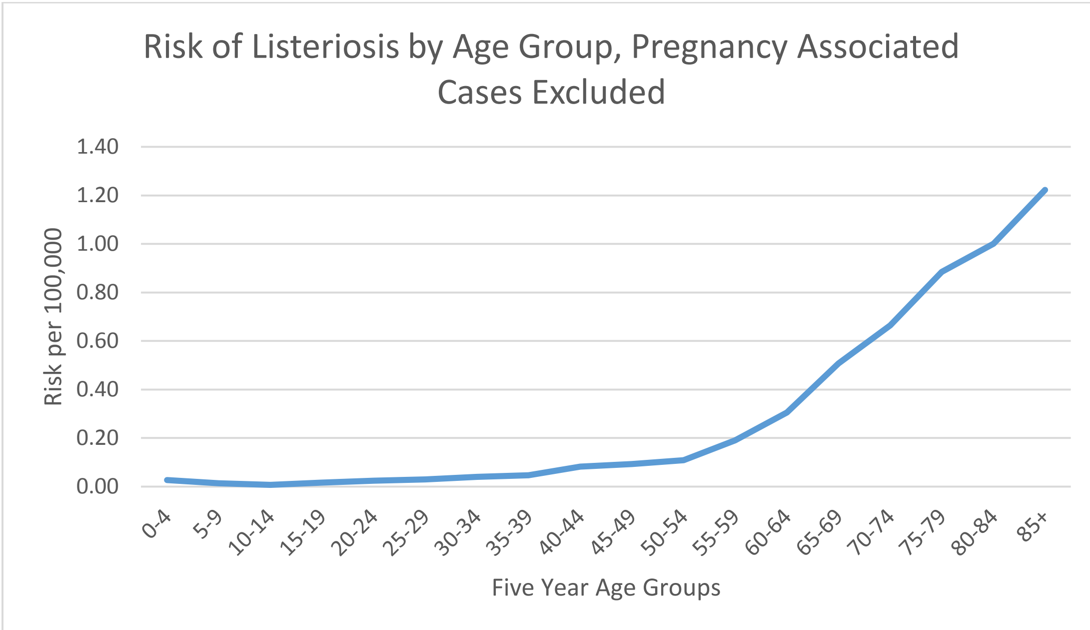


Figure 2. Risk of Invasive Listeriosis by Age Group, among non-pregnancy associated cases.



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