Relative Risk of Listeriosis in Foodborne Diseases Active Surveillance Network (FoodNet) Sites According to Age, Pregnancy, and Ethnicity

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Background. Quantitative estimates of the relative risk (RR) of listeriosis among higher-risk populations and a nuanced understanding of the age-specific risks are crucial for risk assessments, targeted interventions, and policy decisions.

Method. The RR of invasive listeriosis was evaluated by age, pregnancy status, and ethnicity using 2004–2009 data from the Foodborne Diseases Active Surveillance Network (FoodNet). Nonparametric logistic regression was used to characterize changes in risk with age and ethnicity. Adjusted RRs and 95% confidence intervals (CIs) were evaluated using negative binomial generalized linear models.

Results. Among non–pregnancy-associated cases, listeriosis incidence rates increased gradually with age (45–59 years: RR, 4.7; 95% CI, 3.3–6.8; >85 years: RR, 53.8; 95% CI, 37.3–78.9; reference: 15–44 years). The RR was significantly higher for Hispanics than for non-Hispanics (RR, 1.8; 95% CI, 1.3–2.5). Among women of reproductive age (15–44 years), pregnant women had a markedly higher listeriosis risk (RR, 114.6; 95% CI, 68.9–205.1) than nonpregnant women. The RR was higher for Hispanic than non-Hispanic women, regardless of pregnancy status, and this increased during the study period (2004–2006: RR, 1.9; 95% CI, 1.0–3.3; 2007–2009: RR, 4.8; 95% CI, 3.1–7.1).

Conclusions. This study quantifies the increases in risk of listeriosis among older persons, pregnant women, and Hispanics in the United States. Additional research is needed to better describe the independent effects of age on risk while accounting for underlying conditions. These estimates are needed both to optimize risk assessment models and to inform targeted interventions and policy decisions.

Listeria monocytogenes causes an estimated 1600 invasive infections and 260 related deaths in the United States each year [1]. Pregnant women and their fetuses or neonates, older adults, and persons with underlying conditions that impair cell-mediated immunity are at a particularly high risk of invasive listeriosis [2–4]. According to surveillance data for 2004–2009, the crude incidence rate of listeriosis in the general US population equals 0.27 cases per 100 000 population; incidence rates among pregnant women and adults aged ≥65 years equal 3.42 and 1.21 cases per 100 000 population, respectively [5].

Listeria monocytogenes risk assessments have used a crude, empirical categorization of subpopulations based on older age, defined as ≥60 years, and pregnancy status [6, 7]. However, in published studies of listeriosis, persons aged >50, >60, or >65 years have been inconsistently categorized as older adults [3, 8, 9]. Such differences in definitions complicate the direct comparison of age-specific incidence rates across studies and can affect the results of risk assessments based on these estimates. Importantly, demographic characteristics such as socioeconomic status, language, and ethnicity also may affect risk and are therefore important to consider in estimating population-specific relative risks (RRs) [8, 10–12]. As a case in point,

listeriosis incidence rates in the United States are considerably higher among pregnant women of Hispanic ethnicity than among non-Hispanic pregnant women, emphasizing the need to account for the ethnic composition of study populations [5, 8].

Higher-risk population subgroups need to be more precisely defined to further our understanding of the behavioral, biological, and clinical risk factors that affect the risk of listeriosis. A comprehensive understanding of the risk factors for listeriosis, including quantitative, robust, and subpopulation-specific RR estimates, is crucial for refining risk assessments. These assessments, in turn, will be invaluable to inform targeted interventions and policy decisions. The aim of this study was to provide quantitative estimates of the RRs of laboratory-confirmed, invasive listeriosis based on age, pregnancy status, and ethnicity.

METHODS

Active Surveillance Data on *L. monocytogenes* Cases

Epidemiological data from the Foodborne Diseases Active Surveillance Network (FoodNet) and population estimates from the US Census Bureau were used to define higher-risk population subgroups in this study. FoodNet is a collaborative active surveillance program of the Centers for Disease Control and Prevention (CDC), 10 participating state health departments, the US Department of Agriculture's Food Safety and Inspection Service, and the Food and Drug Administration [13]. For the analysis, surveillance data and case definitions were consistent with methods described by Silk et al in this issue [5]. Briefly, all cases reported between 1 January 2004 and 31 December 2009 in patients who were residents of the FoodNet catchment area were included in this study. Pregnancy-associated cases were defined as isolation of *L. monocytogenes* from pregnant women, fetuses, or infants aged <31 days. Documented mother–infant pairs (ie, isolates obtained from both mother and infant) were counted as single pregnancy-associated cases.

In this study, neonatal cases (ie, isolates obtained from fetuses or infants aged <31 days) were attributed to a pregnant woman during the same year, from the same state, and of the same ethnicity as the neonate because the demographic characteristics of the mother were unknown. Ages of these mothers were imputed by randomly sampling from the empirical distribution of ages among pregnancy-associated cases of the corresponding ethnicity (non-Hispanic population: range, 17–36 years; median, 31 years; mean, 29 years; Hispanic population: range, 14–43 years; median, 23 years; mean, 25 years).

Demographic Data on Population at Risk

Population denominator data were obtained from the US Census Bureau's annual population estimates for counties in the FoodNet catchment area for the years 2004–2009. Data for persons aged ≥85 years were available in aggregated form only, whereas data for the remaining age groups were available for each year of age. For each combination of year, state, and ethnicity, the number of pregnant women in the catchment area was estimated as described in this issue [5]. The population size for the subpopulation of nonpregnant women was estimated by subtracting the estimated number of pregnant women from the total number of women of reproductive age, defined here as 15–44 years.

Statistical Analysis

A nonparametric logistic regression model [14] was initially used to explore the relationship between age and the incidence of listeriosis, stratified by sex and ethnicity. This method estimates a regression curve using a local likelihood approach for a vector of binomial observations [14], with a smoothing parameter set to 5 years. The initial analysis was carried out on all cases, regardless of pregnancy status. For comparison purposes, the upper bound of the 95% confidence interval (CI) of the incidence rate for non-Hispanic males aged 15–44 years was defined as a conservative estimate of the reference rate for the general population.

Subsequently, a negative binomial generalized linear model was used to quantify the RR of listeriosis according to the considered covariates [15, 16]. A first analysis evaluated the effect of time period (ie, 2004–2006 or 2007–2009), state, sex, age group, and ethnicity on the rate of listeriosis in the nonpregnant population. The initial model included the time period of *L. monocytogenes* isolation, state, sex, ethnicity, and age group, defined as an ordinal variable with the following age groups: >31 days to 14 years, and 15–44 , 45–59 , 60–69 , 70–79 , 80–84, and ≥85 years. To evaluate covariates and relevant 2-way and higher-level interaction terms for inclusion in the final model, a stepwise forward model selection approach was used based on evaluation of Akaike's information criterion [17]. The state was deliberately included in all models.

A second set of generalized linear models was developed specifically for pregnancy-associated cases and non–pregnancy-associated cases among women of reproductive age. The selected model included year, state, and ethnicity. Model selection was performed as described above. All statistical analyses were performed in the R statistical software package (R Foundation for Statistical Computing, Version 2.13.0 [18]).

RESULTS

A total of 762 cases of invasive listeriosis were recorded in the FoodNet catchment area from 2004 to 2009. Sixty-four cases were excluded from analysis owing to incomplete records (61 records had missing data for ethnicity, 1 record
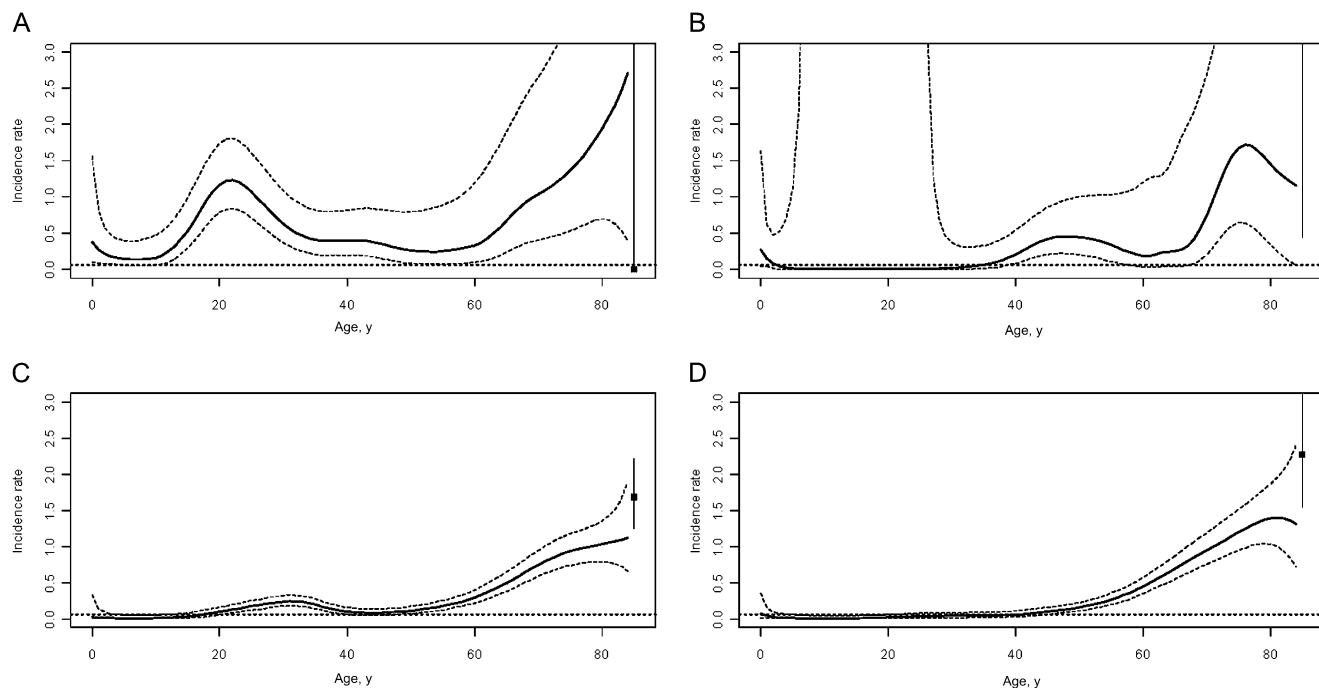
Figure 1. Incidence rate of listeriosis (per 100 000 population) by age (range, 0–84 years) for Hispanic women (*A*), Hispanic men (*B*), non-Hispanic women (*C*), and non-Hispanic men (*D*), as estimated by nonparametric logistic regression [14]. Continuous lines represent estimates; dashed lines, 95% confidence interval (CI) bands. As a reference, horizontal dotted lines represent upper 95% Poisson CI of the incidence rate among non-Hispanic men aged 15–44 years (0.063 cases per 100 000 population). Black squares represent estimates for persons aged ≥85 years and the 95% Poisson CI. Data are from the Foodborne Diseases Active Surveillance Network (FoodNet), 2004–2009.

had missing data for sex, and 2 records had missing data for pregnancy status).

Nonparametric Logistic Regression–Based Incidence Rate Estimates

The nonparametric logistic regression results illustrate the overall relationships between incidence rates and age, stratified by ethnicity and sex (Figure 1). The listeriosis incidence rate was elevated for infants (ie, aged >31 days), women of reproductive age, and older populations. The incidence rate among Hispanic women of reproductive age was significantly higher than among non-Hispanic women of the same age. For non-Hispanic males aged 15–44 years, the crude listeriosis incidence rate was 0.041 cases per 100 000 population, with a Poisson 95% CI of .026–.063 cases per 100 000 population. This upper 95% CI bound of .063 cases per 100 000 population subsequently served as a conservative reference rate for the general population (Figure 1). Based on the nonparametric logistic regression analysis, this incidence rate was significantly exceeded for non-Hispanic men aged ≥46 years (nonparametric logistic regression estimate: 0.109 cases per 100 000 population; 95% CI, .071–.169) and non-Hispanic women aged ≥49 years (nonparametric logistic regression estimate: 0.106 cases per 100 000 population; 95% CI, .069–.163).

The CI bands surrounding the estimates for the Hispanic populations (Figure 1*A* and 1*B*) were wider than for the respective non-Hispanic populations (Figure 1*C* and 1*D*) owing to the smaller population sizes. Indeed, only 8 cases were recorded for Hispanic men aged ≥60 years, and no cases were reported for Hispanic men aged 5–30 years (Figure 1*B*). Nevertheless, the listeriosis rate was significantly elevated for Hispanic men aged 40–60 years, with 54% of all cases in the Hispanic men subpopulation occurring in this age group (Figure 1*B*). Among persons aged ≥85 years, the crude incidence rate was 2.3 cases per 100 000 population (95% CI, 1.5–3.2) for non-Hispanic men and 1.7 cases per 100 000 population (95% CI, 1.3–2.2) for non-Hispanic women. No cases were recorded among Hispanic women aged ≥85 years, and only 2 were recorded among Hispanic men in this age group, precluding precise estimation of the incidence rates for these subpopulations.

Generalized Linear Model–Based Incidence Rates

The best-fitting parametric generalized linear model for non–pregnancy-associated cases included interactions between age group and ethnicity and between study period (ie, extending over 3-year periods) and sex (Table 1). Overall, the incidence rate of non–pregnancy-associated listeriosis was significantly

Table 1. Relative Risk of Non–Pregnancy-Associated Invasive Listeriosis, Negative Binomial Generalized Linear Model, FoodNet Data, 2004–2009

Variable	Relative Risk	95% CI
Sex (study period)		
Men (2004–2006)	1.0	Reference
Men (2007–2009)	0.8	.6–.9
Women (entire study period)	0.6	.5–.8
Age group, years		
0–14[a]	0.5	.3–1.0
15–44	1.0	Reference
45–59	4.7	3.3–6.8
60–69 (non-Hispanic)	17.6	12.5–25.3
60–69 (Hispanic)	6.3	1.8–16
70–79	28.8	20.6–41.2
80–84	37.6	25.5–56.0
≥85	53.8	37.3–78.9
Ethnicity		
Non-Hispanic	1.0	Reference
Hispanic	1.8	1.3–2.5

The state variable (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, or Tennessee) was forced in the model. Results are not reported for this variable.

Abbreviation: CI, confidence interval.

[a] The youngest age group was 32 days to 14 years.

Table 2. Relative Risk of Invasive Listeriosis Among Women of Reproductive Age, Negative Binomial Generalized Linear Model, FoodNet Data, 2004–2009

Variable	Relative Risk	95% CI
Pregnancy status		
Nonpregnant	1.0	Reference
Pregnant	114.6	68.9–205.1
Ethnicity (study period)		
Non-Hispanic (entire study period)	1.0	Reference
Hispanic (2004–2006)	1.9	1.0–3.3
Hispanic (2007–2009)	4.8	3.1–7.1

The state variable (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, or Tennessee) was forced in the model. Results are not reported for this variable.

Abbreviation: CI, confidence interval.

higher for the Hispanic population (RR, 1.8; 95% CI, 1.3–2.5) than for the non-Hispanic population. The significant interaction between age group and ethnicity appeared to be caused by a significantly lower RR for the Hispanic population aged 60–69 years compared with the non-Hispanic population of the same age (Figure 1B). For men, the RR was significantly higher during the first 3-year period than during the second 3-year period, but such temporal trends were not observed among women. The RR for women was lower than for men in the first study period. Importantly, the listeriosis risk for persons aged 45–59 years was significantly higher than that for those aged 15–44 years (RR, 4.7; 95% CI, 3.3–6.8). The RR continued to increase with age, reaching a value of 53.8 (95% CI, 37.3–78.9) for persons aged ≥85 years. No significant interaction between age group and study period was observed, suggesting that the age effect remained constant during the study period.

The best-fitting parametric generalized linear model specific to women of reproductive age included pregnancy status and an interaction between ethnicity and study period (Table 2). No significant interaction was observed between ethnicity and pregnancy status, suggesting similar impacts of ethnicity among pregnant and nonpregnant women. The RR of invasive listeriosis for pregnant women compared with nonpregnant women of reproductive age was 114.6 (95% CI, 69–205). The

RR for Hispanic women was higher than for non-Hispanic women: it was estimated to be 1.9 (95% CI, 1.0–3.3) during the 2004–2006 period and 4.8 (95% CI, 3.1–7.1) during the 2007–2009 period.

DISCUSSION

Our study confirms previous results showing higher listeriosis incidence rates among older adults and among women of reproductive age, particularly Hispanic women [4, 5, 8], in whom risk increased across the study period in the United States [5]. Importantly, our results quantify the dramatic progressive increase in the risk of listeriosis that occurs between 45 and 84 years of age, with a significant exception for the Hispanic population aged 60–69 years. This finding indicates that commonly used threshold values to define older populations (eg, 60 or 65 years) [3, 8, 9] may be too simplistic, especially for certain types of efforts, such as risk assessments. An international group of experts recently suggested the use of 5-year age intervals for the analysis of surveillance data to allow for refined characterization of the listeriosis risk among older populations, and our results clearly support their recommendation [19]. Our results also indicate that risk reduction strategies could effectively target a larger fraction of the population earlier in life, including persons in their 50s and early 60s; nonetheless, the inexorable increase of risk with age indicates that prevention efforts could also be intensified for persons of older ages.

However, further research, which accounts for immunocompromising and chronic conditions, is clearly needed to determine the extent to which older age is independently associated with a greater risk of listeriosis. Indeed, the increased prevalence of comorbid conditions among older persons could explain a large fraction of the increase in RR observed with

age [20]. A correlation between various comorbid conditions that affect cell-mediated immunity and the risk of invasive listeriosis has been well established [4]. However, few quantitative evaluations of the RR of listeriosis in patients with such comorbid conditions have been reported to date [2, 3, 21]. Recently, Goulet et al reported that only 35% of non–pregnancy-associated cases in France occurred among individuals without underlying disease [21]. Among individuals without underlying disease, the age group–specific incidences of listeriosis were 8 and 20 times higher, respectively, for the populations aged 65–74 or >74 years, compared with the incidence in the population aged <65 years without underlying disease [21]. These estimates are lower than the estimates we report without considering comorbid conditions, suggesting a confounding effect of age and comorbid conditions in our analysis.

Although there is a need for further, more in-depth studies that account for health status in estimating epidemiological risks of listeriosis, data on immunocompromising conditions and underlying comorbid conditions are not systematically collected among FoodNet sites. Reliable collection of data regarding the presence of well-defined comorbid conditions as a key component of the epidemiological investigations following listeriosis cases or outbreaks may expeditiously generate the data needed to evaluate the impact of comorbid conditions on listeriosis incidence. To characterize clinical conditions as potential risk factors for invasive listeriosis, the CDC is revising the standardized questionnaire for the *Listeria* Initiative, an effort conducting enhanced, national surveillance for sporadic and outbreak-associated listeriosis cases [22].

The reasons for the higher incidence rate among Hispanic men aged 50–60 years (nonparametric logistic regression) and the lower incidence rate among the Hispanic population aged 60–69 years (parametric and nonparametric logistic regression), compared with the respective corresponding non-Hispanic populations, are currently not clear. This observation has not been reported before, and further studies are needed to explore these apparent variations in listeriosis incidence rates in greater detail.

The RR of pregnancy-associated listeriosis among women of reproductive age reported here (RR, 115; 95% CI, 69–205) is similar to another estimate recently reported in France for pregnant women compared with the population aged <65 years without underlying conditions (RR, 116) [21]. Among Hispanic women of reproductive age, the RR increased during the study period. Although the markedly elevated incidence rate observed in Figure 1 may in part reflect the higher relative fertility rate among Hispanics and decreasing fertility rates in non-Hispanic women of childbearing age [23], the parametric generalized linear model controlled for the potential confounding effect of varying fertility rates and confirmed a dramatically higher

incidence rate of listeriosis. The ethnicity-specific differences in risk observed in this study may be attributable to differences in diet or food consumption habits [5, 24]. Furthermore, a recent British study demonstrated that listeriosis incidence was highest in the most economically deprived areas of England [12]. Therefore, socioeconomic factors related to ethnicity may also contribute to the observed differences in RR between Hispanic and non-Hispanic population subgroups. Future risk assessment may help explain this higher incidence and its increasing trend. Following others [5, 8], ethnicity rather than race was considered in this study. The high frequency of missing data for race in the FoodNet database impaired the analysis of the relationship between race and listeriosis. Additional statistical methods, such as imputation methods [25], could help in such analysis.

In conclusion, our results provide crucial insights for risk assessment efforts; they demonstrate that a significant increase in listeriosis incidence begins among persons as young as 45 years, and that incidence rates subsequently increase steadily with age. The high RR of listeriosis that we found for pregnant women illustrates the extraordinary importance of pregnancy. This study additionally highlights some of the complex interactions with ethnicity and time period. Future studies need to consider >1 population subgroup among older adults and to evaluate the independent effects of sex, ethnicity, and co conditions in each age group. Mathematical dose–response models, which represent key components of microbial risk assessments, should incorporate these complex interactions to more accurately reflect dose–response relationships in these subpopulations. In addition, our results highlight the particular public health importance of risk communication and prevention strategies targeted at Hispanic populations, including but not limited to women of reproductive age. The RR estimates derived in this study will further help to refine the definitions of susceptible subpopulations for risk assessments and can contribute to a more standardized, comparable, and evidence-based classification of higher-risk population subgroups in the future.

Notes

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