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General Interest

Role of the U.S. Food and Drug Administration in the Regulatory Management of Human Listeriosis in the United States

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ABSTRACT

From 1986 to 2006, the incidence of listeriosis in the United States dropped from approximately seven to three cases per million population, a reduction that most likely reflects the joint efforts of industry, government, consumers, and academia. Herein, we describe the U.S. Food and Drug Administration (FDA) strategy over the past three decades to combat listeriosis. Specifically, we discuss early actions taken to address outbreaks during the 1980s, policy decisions regarding the presence of *Listeria monocytogenes* in FDA-regulated foods, FDA compliance programs with *L. monocytogenes* components, enforcement actions to remove *L. monocytogenes*–contaminated products from the market (i.e., recalls) or to prevent entry of such products into the market (i.e., import detentions and refusals), research milestones, outreach and education efforts, and selected special projects. Evolving demographic trends in the United States may pose a challenge to further reduction of the incidence of listeriosis.

Between 1949 and 1957, roughly two decades after the first human infection with *Listeria monocytogenes* was reported, a large outbreak of listeriosis attributed to the consumption of unpasteurized milk and other dairy products was recognized in Halle, East Germany, one of the first documented reports of listeriosis linked to food consumption *(28).* The role of food as a vehicle for infection with *L. monocytogenes* was further established during the first half of the 1980s, when four outbreaks of human listeriosis were reported in North America and Europe *(1, 14, 19, 25).* The implicated foods included coleslaw made from cabbages grown in fields fertilized with raw manure from a flock of sheep that experienced fatal listeriosis prior to harvest *(25),* pasteurized whole or 2% milk *(14),* Mexican-style soft cheese *(19),* and Vacherin soft cheese *(1).* Together, the outbreaks demonstrated the proclivity of the organism to infect pregnant women and neonates, persons with compromised immune function, and the elderly.

During the late 1980s, case-control studies conducted to identify vehicles of infection for sporadic listeriosis revealed significant associations between illness and hot dogs that were not thoroughly reheated *(27),* undercooked chicken *(12, 26),* food purchased from store delicatessen counters *(26),* and Mexican-style soft cheese and feta cheese *(26).* Microbiological surveys of foods had also revealed that the pathogen could be recovered from a variety of foods, including leafy vegetables, raw milk, ice cream, soft-ripened cheeses, raw meats and poultry, fermented sausage, nonfermented ready-to-eat cooked meats, and various types of seafood *(43).* Underscoring the ubiquity of *L. monocytogenes,* a World Health Organization (WHO) Working Group on Foodborne Listeriosis convened in the late 1980s concluded that any food other than one processed in its final container could be expected to be contaminated sporadically with *L. monocytogenes (43).* The WHO also stated that correct use of a listericidal process (e.g., pasteurization or cooking procedures) would eliminate *L. monocytogenes* from food and that recontamination could be prevented by maintaining hygienic food practices *(43).*

Because of the practical difficulty of eliminating *L. monocytogenes* from all foods, collaborative efforts were undertaken by the food industry, scientists, and regulatory authorities to reduce the prevalence of *L. monocytogenes* in ready-to-eat foods that had been processed with one or more steps designed to eradicate the pathogen. Results from studies launched to define the incidence of infection in the United States (Fig. 1) suggest that this approach may have been effective; the incidence of listeriosis declined from approximately 7 cases per million population in 1986 to 3 cases per million population in 2006. The reduced incidence of listeriosis most likely reflects the joint efforts of industry, government, consumers, and academia. The purpose of this article is to describe the activities of the U.S. Food and Drug Administration (FDA) during the past three decades undertaken to combat this infectious disease. We discuss early actions the FDA took to address outbreaks of

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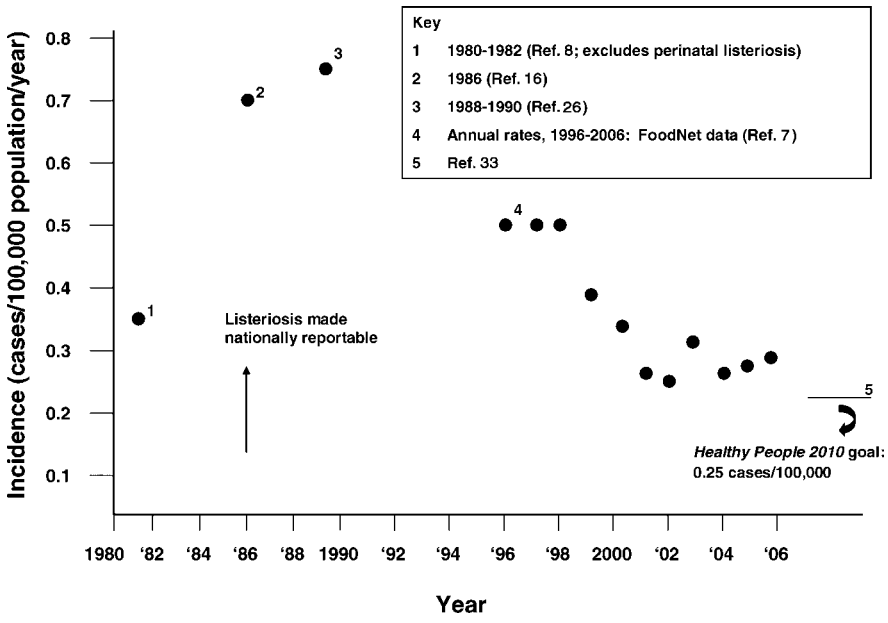

FIGURE 1. *Incidence of listeriosis, United States, selected years, 1980 through 2006.*

listeriosis that occurred in the 1980s, key policy decisions regarding the presence of *L. monocytogenes* in FDA-regulated foods, FDA compliance programs and field directives with *L. monocytogenes* components, enforcement actions to remove *L. monocytogenes*–contaminated products from the market (i.e., recalls) or to prevent entry of such products into the market (i.e., import detentions and refusals), research milestones, outreach and education efforts, and selected special projects (*L. monocytogenes* risk assessment and action plan).

EARLY ACTIONS

A spate of infectious disease outbreaks in the 1980s involving a variety of pathogens prompted the FDA to launch an intensive review of its regulatory approach to the dairy industry. These outbreaks involved *L. monocytogenes* contamination of pasteurized milk *(14)* and Mexican-style soft cheese *(19), Yersinia enterocolitica* contamination of pasteurized milk *(32),* and *Salmonella* contamination of pasteurized milk *(23).* The confluence of these outbreaks was notable because they spanned a relatively short period (1982 to 1985), involved multiple pathogens, and accounted for significant morbidity, with over 18,000 persons falling ill in Illinois alone following the consumption of pasteurized milk contaminated with antimicrobial-resistant *Salmonella (23).*

In response to these outbreaks, the FDA enhanced its program of dairy plant inspections, intensified surveillance for *L. monocytogenes* in dairy products, and invigorated training and standardization of federal and state milk specialists, ratings officers, and inspectors; these activities as a whole dovetailed into a new program called the Dairy Product Safety Initiatives. To address concerns that the FDA pasteurization process guidelines may not have been adequate to destroy *L. monocytogenes* in whole milk, the FDA conducted thermal resistance studies on the pathogen that indicated that the guidelines were, effective in eradicating *L. monocytogenes* from whole milk *(2, 4).* These findings and the microbiological survey results demonstrating that *L. monocytogenes* was present in the environment of approximately 3% of dairy plants led the FDA to conclude that when *L. monocytogenes* was found in pasteurized dairy products, its presence was due to improper pasteurization or to reintroduction in the postpasteurization environment *(5).*

Surveillance of human listeriosis and of dairy products for the presence of *L. monocytogenes* was a key component of the FDA's early response to outbreaks of listeriosis in the 1980s. On the human listeriosis front, in 1986 the FDA funded an active surveillance project conducted by the Centers for Disease Control and Prevention (CDC) designed to identify cases of invasive listeriosis in five states and Los Angeles County *(27).* For example, in a survey of raw milk samples collected in 1985 from bulk storage tanks in three regions of the United States, *L. monocytogenes* was detected in 4.2% of samples *(20).* In a separate survey conducted at approximately the same time, the pathogen was found in 2% of pasteurized milk samples derived from milk-producing plants *(35).* In comparison, in a survey in 2000 of 5,519 samples of pasteurized milk obtained at retail, only 1 sample (0.018%) yielded *L. monocytogenes.* Because other surveillance efforts identified *L. monocytogenes* contamination of soft cheeses imported from France as a recurring problem, the FDA surveyed a wide range of soft cheeses imported from multiple nations to determine the extent of *L. monocytogenes* contamination. A survey conducted in 1986 revealed that 18 (3%) of 583 samples of imported cheeses contained *L. monocytogenes* (13 samples originated in France, 4 in Italy, and 1 in Canada). To address this situation, the FDA enacted a policy of automatically detaining imported soft-ripened cheeses when the label stated the product had been manufactured from raw or unpasteurized milk. Concomitantly, the FDA collaborated with the Ministry of Agriculture in France to develop a certification program whereby only those plants certified by the French government as following good manufacturing

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practices were permitted to export soft-ripened cheese to the United States. In January 1987, the certification program was expanded to require the use of pasteurized milk and *Listeria* testing of soft cheeses, requirements that were designed to include goat cheeses. As part of the certification agreement, France provided the FDA with a list of certified production facilities, and each certified facility shipping into the United States provided certificates of analysis for each shipment of cheese that documented the presence of less than 1 CFU of *L. monocytogenes* per 25 g of soft cheese. This certification agreement remains in effect today.

In conjunction with these surveillance activities, the FDA developed detection and identification procedures that significantly enhanced the ability to confirm the presence of *L. monocytogenes* in dairy products. These developments are described below in the section entitled ''Research Milestones.''

POLICY DECISIONS

In 1985, the FDA promulgated a policy wherein the detection of *L. monocytogenes* in cooked ready-to-eat foods when using the FDA's detection method was deemed to be a violation of the Federal Food, Drug, and Cosmetic Act, sections 402(a) (1) and 402(a) (4). The Act prohibits the importation or distribution of adulterated foods in the United States. Section 402(a) (1) defines, in part, a food as being adulterated when it bears or contains any poisonous or deleterious substance that may render it injurious to health, whereas section 402(a) (4) defines a food as being adulterated when it has been prepared, packed, or held under unsanitary conditions under which it may have become contaminated with filth or may have been rendered injurious to health. In recognizing *L. monocytogenes* as a human pathogen capable of inducing injury, the FDA considered this organism in ready-to-eat food to be an added substance, and thus its presence constituted sufficient grounds to deem the food adulterated. This interpretation was affirmed by a U.S. District Court (*USA v Union Cheese Co,* 1995) *(29).* Accordingly, the FDA has consistently requested recall of ready-to-eat foods in which *L. monocytogenes* has been detected using current methodology when research has indicated that the cooking or heating instructions would not be adequate to achieve complete lethality *(29).* Since 1985, the FDA has classified recalls of ready-to-eat foods contaminated with *L. monocytogenes* as class I recalls, defined in the *Code of Federal Regulations* (CFR), Title 21, Part 7, ''Enforcement Policy'' as situations in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death. As described below, these recalls have involved a wide variety of ready-to-eat foods, including cheeses, ice cream, milk, fish, prepared salads, sandwiches, crab meat, smoked fish, and bakery products. In the majority of these instances, recalls take place in the absence of known illness.

Consistent with section 402(a) (4) of the Act, the FDA requires foods to be produced using proper sanitation and other measures codified in 21 CFR Part 110, ''Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Human Food.'' The FDA believes that the use of hazard analysis critical control point plans in conjunction with good manufacturing practices eliminates or greatly reduces *L. monocytogenes* levels in foods *(13).* In many instances, foods that contain *L. monocytogenes* have been produced in facilities that have deviated from good manufacturing practices, an observation supported by the recovery of *L. monocytogenes* from environmental samples taken from the facilities that produced the foods *(29).*

Whereas the term ''zero tolerance'' has often been used to describe the FDA's regulatory approach to the presence of *L. monocytogenes* in ready-to-eat foods, a more apt description is ''zero detection.'' The FDA considers the detectable presence of *L. monocytogenes* in ready-to-eat foods to be a hazard to health, and the limit of sensitivity of current official analytical methods is 1 CFU per 25-g sample.

In sum, the FDA's *L. monocytogenes* policy is based on this organism's potential to cause severe illness, its ability to grow in certain foods at refrigeration temperatures, the uncertainty and variability regarding the levels of ingestion that are likely to lead to infection in different susceptible subpopulations, and the influence of human host factors and food matrices in determining whether illness occurs *(13).* Because of the ability of *L. monocytogenes* to grow during cold storage, the FDA has consistently focused its concern on the presence and numbers of the organism in cooked ready-to-eat foods that are subjected to cold storage for significant periods of time. The FDA's long-standing policy regarding the presence of *L. monocytogenes* in ready-to-eat foods is currently under evaluation in response to a submission of a citizen petition filed with FDA in December 2003 by 15 trade associations that requests the agency to establish a permissible level of 100 CFU/g in foods that do not support the growth of *L. monocytogenes.* Having published the petition in the *Federal Register (36)* and having requested comments from the public, the FDA is currently reviewing comments addressing the proposed change in policy.

FDA COMPLIANCE PROGRAMS AND FIELD DIRECTIVES

Broadly speaking, the FDA carries out its day-to-day activities through compliance programs and field assignments. ''Compliance'' refers (i) to FDA's oversight activities of regulated entities to determine whether such entities adhere to federal statutes and their implementing regulations within FDA's purview and (ii) to the determination of actions required in instances where adherence may be lacking. Compliance programs provide directions to FDA field staff for the purpose of conducting regulatory and monitoring activities in specified food program areas. These activities include investigations, inspections, sample collections, sample analyses, and cooperative activities with state governments. Field assignments (e.g., retail cheese assignment) typically involve short-term activities and are more focused than compliance programs. Currently, the FDA maintains 23 food-related compliance programs (details regarding these programs are available at http://www.fda.gov/ora/cpgm/default.htm#Foods).

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TABLE 1. *Principal FDA-regulated food groups subjected to* Listeria monocytogenes *monitoring programs and dates such programs were incorporated into new or existing FDA compliance programs*

Food group	Fiscal year *L. monocytogenes* component added to new or existing program
Milk	1985
Cheese, ice cream	1985
Multi-ingredient ready-to-eat products[a]	1985
Medical foods	1988
Seafood	1992
Juice	2003

[a] Dinners (including gravies, sauces, specialties), fruits, vegetables, salads, egg products, bakery items, macaroni, dressings, spices, and nuts. In fiscal year 1990, the FDA added sandwiches to its *L. monocytogenes* monitoring program following a fatal case of listeriosis linked to contaminated turkey franks.

The FDA conducts its regulatory mission with the use of two additional tools: compliance policy guides and import alerts. Compliance policy guides provide formal guidance to FDA staff, regulated industries, foreign governments, and the general public concerning FDA policies. In 1980, the FDA issued a compliance policy guide for pathogens in dairy products (CPG 7106.08), a document that provided guidance for initiating legal action in instances where products were found to be improperly pasteurized, contaminated with pathogenic microorganisms, or prepared and packed under unsanitary conditions. Although the elements of compliance programs and field assignments often pertain to imported products, the FDA also issues import alerts, which often identify specific agents of concern (e.g., pesticides, aflatoxins, *Salmonella,* and *Listeria*) in imported products from specific countries or manufacturers.

Over the years, compliance programs and field assignments have been issued to establish programs to detect possible *L. monocytogenes* contamination of selected regulated foods (Table 1). Once established for each major food group, these *L. monocytogenes* monitoring programs generally remain in effect without interruption. Although dairy products were the focus of the first compliance program to address the issue of *L. monocytogenes* contamination, subsequent compliance programs have targeted other major food groups, including ready-to-eat products such as sandwiches, dinners, vegetables, fruits, and salads; medical foods; seafood; and juice.

Although not technically a compliance policy guide, FDA's *Food Code,* first published in 1993, serves as a reference document for state and local regulatory agencies that ensure food safety in retail food stores and other food establishments at the retail or institutional level (e.g., nursing homes and child care centers) *(41).* Presented in the *Food Code* are specific recommendations to prevent the occurrence and/or spread of *L. monocytogenes* during retail food preparation and production. These recommendations include employee practices, sanitization strategies, measures to prevent cross-contamination, and times and temperatures for cooking, cooling, and holding food. In 2007, the Association of Food and Drug Officials reported that 49 of 56 states and territories had adopted food codes patterned after the *Food Code*; these jurisdictions contain 82% of the U.S. population.

ENFORCEMENT ACTIONS

Two enforcement actions invoked regularly to prevent or minimize the marketing of food products contaminated with *L. monocytogenes* are recalls, i.e., the removal of *L. monocytogenes*–contaminated foods from the market, and import detentions and refusals, i.e., actions taken to prevent *L. monocytogenes*–contaminated foods from reaching the market.

A recall is defined as a firm's removal or correction of a marketed product that the FDA considers to be in violation of the laws it administers and against which it would initiate legal action, e.g., seizure. Recalls of foods are voluntary actions that take place as manufacturers and distributors carry out their responsibility to protect the public health and well-being from products that present a risk of injury. The FDA does not have authority to ''order'' a recall (except for infant formula products and certain drugs). Firms usually comply with a recall request; but if they refuse, the FDA can seek legal action under the Act for injunction of the firm, including a court request for recall of the product or seizure of available product. Regardless of the legal course, the FDA will ensure that the public is informed by issuing a press release. Guidelines regarding recalls are published in CFR, Title 21, Part 7. In addition, the FDA Enforcement Report (accessible at http://www.fda.gov/opacom/Enforce.html) is published weekly and contains information on recall actions taken in connection with agency regulatory activities.

When necessary, the FDA works with the food industry to remove *L. monocytogenes*–contaminated products from the market. The first such recall occurred following the outbreak of listeriosis linked to Mexican-style cheese in southern California in 1985. From 1986 through 2006, of the 5,494 recalls of foods monitored by the FDA's Center for Food Safety and Applied Nutrition, 511 (9.3%) involved foods contaminated with *L. monocytogenes* (Fig. 2). During this period, the mean annual number of *L. monocytogenes*–associated recalls was 24 (range, 14 to 38 recalls), with the greatest proportion of recalls involving seafood products (39% of recalls) and dairy products (cheese, ice cream, and milk: 34% of recalls) (Table 2). During this period, recalls of milk and ice cream products represented a declining proportion of *L. monocytogenes*–associated recalls, whereas recalls of multi-ingredient dinners became increasingly common.

The FDA requires that imported food products meet the same standards as domestic food products. Provisions within section 801 of the Act direct the FDA to refuse entry to any food that appears to be in violation. The FDA may detain products if they are not or appear not to be in compliance with the laws that the FDA administers. When a product violates FDA standards, subsequent entries of the product can be detained without physical examination, and

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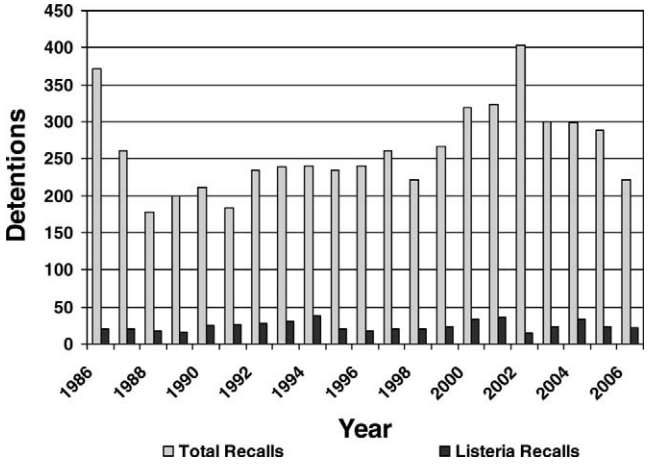

FIGURE 2. *Total number of FDA-regulated foods recalled (*n *= 5,494) versus number of foods recalled due to* L. monocytogenes *contamination (*n *= 511), by year, 1986 through 2006.*

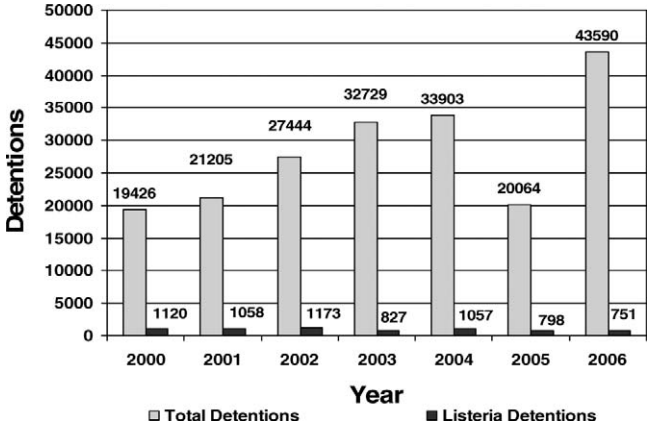

FIGURE 3. *Total number of FDA-regulated foods destined for import detained at port of entry (*n *= 198,361) versus number of foods detained due to possible* L. monocytogenes *contamination (*n *= 6,784), by year, 2000 through 2006.*

such products are placed on ''import alert.'' In such instances, to bring the product to market, the importer must prove that it complies with the FDA standards, and if such proof is not forthcoming, the importer is required to destroy or export the refused product.

From 2000 to 2006, approximately 198,000 food products destined for import were detained by the FDA pending proof that the products met FDA standards. Approximately 3.4% (6,780) of the detentions occurred because the products were potentially contaminated with *L. monocytogenes* (Fig. 3). Subsequently, 1,732 (annual range, 130 to 491) of the detained food products were refused entry because *L. monocytogenes* was recovered from the food. Seven nations accounted for 88% of the 1,732 refusals due to *L. monocytogenes* contamination: in descending order, France (58% of refusals), Mexico (14%), and Canada, Japan, People's Republic of China, United Kingdom, and Chile (less than 5% each). Soft and semisoft cheese products accounted for roughly 66% of *L. monocytogenes*–associated import refusals, and seafood products accounted for 25%. The remaining *L. monocytogenes*–associated import refusals involved fruit and fruit products (primarily avocado) (11% of refusals) and food specialties (primarily guacamole) (1%); less than 1% of refusals involved vegetable products, ice cream products, and other foods.

Guidance within chapter 9 of the FDA's *Regulatory Procedures Manual* allows travelers to carry personal food imports through U.S. Customs at ports of entry as long as the products transported are not intended for distribution in commercial venues or retail sales. In fiscal year 1994, in a survey of personal imports of cheeses from Mexico as part of the Domestic and Imported Cheese and Cheese Products Compliance Program, the FDA found that approximately 60% of samples were in violation for one or more reasons; 6.3% of the samples specifically yielded *L. monocytogenes.* In an additional survey conducted at approximately the same time of soft cheeses carried into the United States from Mexico in personal baggage, the FDA found that 30

TABLE 2. *Recalls of foods contaminated with* Listeria monocytogenes *monitored by the U.S. Food and Drug Administration, by food category and time interval, 1986 through 2006*[a]

	Time interval:									
	1986–1991		1992–1996		1997–2001		2002–2006		All years	
Food category	No.	%	No.	%	No.	%	No.	%	No.	%
Fish	30	23	73	54	50	38	44	38	197	39
Cheese	41	32	17	13	27	20	27	23	112	22
Dinners[b]	13	10	11	8	31	23	22	19	77	15
Ice cream	32	25	6	4	6	5	1	<1	45	9
Fruits, vegetables	0	<1	7	4	7	5	11	9	25	5
Salads	4	3	7	5	5	4	6	5	22	4
Milk	6	5	4	3	2	1	1	<1	13	3
Other[c]	2	2	9	7	5	4	4	3	20	4
Total	128	100	134	100	133	100	116	100	511	100

[a] The FDA regulates foods other than meat, poultry, and processed egg products, which are regulated by the U.S. Department of Agriculture.

[b] Multiple-food dinners, gravies, sauces, and specialties.

[c] Eggs, bakery items, macaroni, dressings, spices, and nuts.

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(53%) of 57 samples contained *L. monocytogenes* or other pathogens. Ample evidence indicates that a significant proportion of soft cheeses carried into the United States subsequently enters the market and is transported in this mode specifically to bypass the requirements of the Act and other applicable food laws, including labeling requirements and the requirements for prior notice and registration. Recommendations to address this practice of unlawful importation of cheese are currently under review by the FDA's Center for Food Safety and Applied Nutrition.

RESEARCH MILESTONES

For years, the FDA has maintained an active research program with respect to *L. monocytogenes.* Following the outbreaks of listeriosis in North America in the 1980s *(14, 19, 25),* the FDA made significant advances in the detection of *L. monocytogenes* in FDA-regulated foods *(2, 9).* Before this time, methods for the recovery and quantification of *L. monocytogenes* from foods were laborious and time-consuming; the task of recovery often required as long as a month. To speed the recovery process, the FDA developed a selective liquid enrichment broth and selective agar for the isolation and characterization of *L. monocytogenes* from dairy products *(20).* In 1988, the FDA announced a revised method that shortened the recovery time for *L. monocytogenes* from 11 days to 5 to 6 days *(34).* This improvement was followed by the development of the first DNA colony-probe hybridization assay for *L. monocytogenes,* which reduced the detection and identification time to 3 to 5 days at the same time that it provided a means for directly enumerating *L. monocytogenes* in a wide variety of foods *(11, 12).* These advances were instrumental in allowing the FDA to develop its current selective enrichment broth and selective agar method for recovering *L. monocytogenes* from a wide spectrum of foods *(9).* Subsequent work in molecular subtyping using pulsed-field gel electrophoresis allowed the FDA to link isolates recovered from foods with clinical isolates from listeriosis outbreaks *(22).* Currently, the FDA actively participates in and contributes to PulseNet USA, a national molecular subtyping network for foodborne bacterial pathogens, including *L. monocytogenes (17).*

When it became clear during the 1980s that listeriosis is primarily a foodborne disease, the FDA conducted studies on virulence factors associated with *L. monocytogenes.* An animal model was developed that offered insight into the relationship between doses of *L. monocytogenes* administered to mice and ensuing clinical responses *(31).* The immunocompromised mouse model also provided a means to distinguish virulent from avirulent *Listeria* species *(31).* Knowledge regarding infective doses was advanced further through FDA-sponsored studies that involved the use of pregnant monkeys as surrogates for humans *(30).* More recently, an in vitro invasion and replication system using a mouse hepatocyte cell, TIB73, was developed to assess the virulence potential of both food and clinical *L. monocytogenes* isolates *(24).* Using newer molecular biology tools such as phenotypic and genotypic microarrays, FDA researchers continue to study the virulence of *Listeria* species and their ability to survive and grow in different foods stored under various conditions. A more thorough understanding of these features could contribute to a further reduction in the incidence of foodborne listeriosis. Where appropriate, the FDA will continue targeted research into *L. monocytogenes* and listeriosis, building on its record of having published more than 125 articles on various aspects of the pathogen in the English language peer-reviewed scientific literature.

OUTREACH AND EDUCATION EFFORTS

The identification of food purchased from store delicatessen counters as a risk factor for listeriosis in the United States *(26)* prompted the FDA to collaborate with the U.S. Department of Agriculture Food Safety Inspection Service (USDA-FSIS) to issue recommendations for safe food handling procedures at retail delicatessen operations. At the same time, the FDA intensified *L. monocytogenes* outreach and educational campaigns to consumers, focusing on consumers deemed to be at highest risk for listeriosis. Working jointly with the CDC and the USDA-FSIS, the FDA sent information ''tear sheets'' regarding the risk of listeriosis during pregnancy to physicians and health organizations, and information booklets and a video on food safety were sent to senior centers and special feeding sites throughout the country.

In 2000, *Listeria*-message focus groups convened by the FDA found little awareness of *L. monocytogenes* as a food safety problem among the general public. Elderly participants and groups drawn from the general population tended to dismiss the wisdom and practicality of *Listeria*-specific recommendations such as reheating cold cuts. Pregnant women expressed a willingness to comply with recommendations aimed at protecting their babies. In 2001, the FDA issued a consumer advisory entitled ''How to Safely Handle Refrigerated Ready-To-Eat Foods and Avoid Listeriosis'' *(38).*

Joining with the Partnership for Food Safety Education, a nonprofit coalition uniting industry associations, professional societies in the fields of food science, nutrition, and health, consumer groups, and the U.S. government, the FDA initiated a program called BAC DOWN (http://www.fightbac.org), an education campaign that highlighted the importance of maintaining refrigeration temperature at 40°F (4.5°C) or below to reduce the risk of foodborne illness. A food safety educational program called MOMS TO BE was developed by the FDA for pregnant women and was distributed to health educators nationwide; it included an educator's guide, a video, an informational brochure, and a web site address (http://www.cfsan.fda.gov/~pregnant/pregnant.html). To provide physicians with the most current information regarding foodborne diseases, the FDA collaborated with the American Medical Association, the American Nurses Association, the CDC, and the USDA to design an educational program called ''Diagnosis and Management of Foodborne Illnesses. A Primer for Physicians and Other Health Care Professionals.'' The program, which contains a clinical vignette on *L. monocytogenes,* may be obtained from the American Medical Association (http://www.ama-assn.org/ama/pub/category/3629.html) or the *Morbid-*

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ity and Mortality Weekly Reports (Recommendations and Reports) *(6).*

To address an increase in the number of outbreaks of listeriosis within the Hispanic community in the United States, in 2005 the FDA initiated a program detailing the risks of consuming cheese made with unpasteurized milk. In this, Hispanic media and community health workers transmit the message to pregnant Hispanic women. A community outreach program tool kit developed for use by public health educators to inform Hispanics of the risks entailed in consuming cheese made from unpasteurized milk has been distributed to health departments and Hispanic organizations nationwide.

RISK ASSESSMENT

In the *Healthy People 2010 (33)* publication, one of the goals for national health promotion and disease prevention was for the federal food safety agencies to reduce foodborne listeriosis by 50% by the end of the year 2010, for a target of 0.25 case per 100,000 population. Although the incidence of listeriosis in the United States decreased between 1996 and 2001 from 0.5 to 0.27 case per 100,000 people per year, it failed to fall further after 2001 (Fig. 1). In 1999, the FDA and the USDA-FSIS began an *L. monocytogenes* risk assessment that focused on ready-to-eat foods and that could be used as an evaluation tool to help achieve the *Healthy People 2010* goal. The purpose of the assessment was to examine the available scientific data and information and estimate the relative risks of serious illness and death associated with consumption of 23 categories of ready-to-eat foods that could be contaminated with *L. monocytogenes.* The risk assessment was designed to answer the question, ''Which foods should receive the most regulatory attention in order to improve public health?'' The total U.S. population was modeled, as were three age-based population groups: perinatal (fetuses and neonates from 16 weeks after fertilization to 30 days postpartum), elderly (individuals >60 years of age), and the remaining population in an intermediate-age group. Foods included in the risk assessment were identified through a comprehensive review of the microbiological and epidemiologic literature, and each food was placed in 1 of 23 food categories.

Risk estimates for the food categories were expressed in terms of both the predicted number of cases per serving and per annum *(40).* The risk assessment supported the findings of epidemiologic investigations indicating that certain foods are more likely to transmit *L. monocytogenes* than others. For example, there was almost a 10,000,000-fold differential between risks associated with the highest ranking category (deli meats) and the lowest ranking food category (hard cheeses). Food categories with a higher predicted risk (e.g., deli meats and frankfurters not reheated) support the relatively rapid growth of *L. monocytogenes* under refrigerated storage conditions, are stored for extended periods before consumption, and are consumed extensively. The results of the risk assessment included development of new control strategies (such as reformulation of products) and/or consumer education programs as key steps in the prevention of listeriosis. The risk assessment authors also concluded that the strong association of foodborne listeriosis with specific population groups supported targeting susceptible population groups in prevention efforts. The model also was used to estimate the likely impact of intervention strategies (referred to as ''what-if'' scenarios). In one ''what-if'' scenario, consumer education aimed at maintaining home refrigerator temperatures at 40°F could substantially reduce the risk of listeriosis associated with consumption of deli meats.

In addition to the risk assessment efforts described above, the FDA currently is conducting risk assessments on smoked fish and soft cheeses and developing a risk profile for produce. The FDA also contributed to an FAO-WHO risk assessment of *L. monocytogenes* in ready-to-eat foods *(15).*

ACTION PLAN

In 2001, the FDA and the USDA-FSIS developed a *Listeria* action plan to reduce significantly the risk of illness and death caused by *L. monocytogenes* in ready-to-eat foods. The impetus for this effort was twofold: (i) to promote the *Healthy People 2010* goal of reducing the national incidence of listeriosis to 0.25 case per 100,000 population and (ii) to respond to outbreaks of listeriosis that occurred in 1998 and 1999 (linked to hot dogs) and another in 2000 that was associated with turkey delicatessen meat. The plan, which was updated in 2003 *(39),* complemented the work of the risk assessment team *(40).* Included in the plan were strategies for guidance, training, research, education, surveillance, and enforcement.

CONSUMER SURVEY OF KNOWLEDGE, ATTITUDES, AND BEHAVIOR

In 2001, the FDA in collaboration with the USDA-FSIS conducted a nationally representative telephone survey of food safety knowledge, attitudes, and behaviors of U.S. adults. The survey contained a section of questions about usual storage times for foods at risk for contamination by *L. monocytogenes* and about eating hotdogs directly from the package without cooking. These questions were designed to assist in developing communication and outreach efforts. The survey indicated that about 15% of respondents reported eating hot dogs directly from the package without cooking. Of those who reported eating hot dogs, 51% stated that they kept opened packages of hot dogs in the refrigerator for ≤3 days before consumption or storing them in the freezer, whereas 90% reported either eating hotdogs within a week or storing them in the freezer. Among respondents who ate cold cuts, 36% reported keeping opened packages in the refrigerator ≤3 days before consumption, and 89% ate them within 1 week. Among respondents who ate cooked meats, such as roasts or stews, 73% of respondents consumed them in ≤3 days and 98% consumed them within 1 week. Among respondents who ate opened soft cheeses, 29% of respondents consumed them in ≤3 days and 75% consumed them within 1 week. Among respondents who ate prepared salads, 72% usually ate them within ≤3 days and 98% ate them within 1 week.

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These data indicate that there are still persons who consume these products beyond 1 week of refrigeration, a period during which *L. monocytogenes,* if present, may multiply significantly in these types of foods.

DISCUSSION

The reduction in the incidence of listeriosis in the United States in the past two decades may reflect, in part, two major actions taken by local, state, and federal public health authorities and industry: (i) actions aimed at reducing the prevalence of *L. monocytogenes* in ready-to-eat foods, which in turn reduced consumer exposure to the pathogen, and (ii) actions taken to educate consumers about the risk of infection and the food vehicles responsible for infection. During this period, major efforts were expended by manufacturers of ready-to-eat foods to reduce the prevalence of *L. monocytogenes* in food processing areas and to inform consumers at high risk of infection about foods with the greatest potential for transmitting infection. However, although the reduced incidence is salutary, dropping from 0.5 case per 100,000 population in 1996 to 0.27 case per 100,000 population in 2001, the incidence to date still falls short of the *Healthy People 2010* goal of 0.25 case per 100,000 population. The upturn in incidence observed after 2001 (Fig. 1) underscores the challenges that remain if the *Healthy People 2010* goal is to be achieved.

As outlined in its action plan, the FDA is committed to a multipronged strategy to reduce the incidence of listeriosis in this country. The principal components of the strategy include working with manufacturers and processors of ready-to-eat foods to decrease the prevalence of *L. monocytogenes* in food production and processing arenas; collaborating with retail and institutional food service groups to decrease opportunities for the introduction and spread of *L. monocytogenes* within these facilities; disseminating information regarding effective listeriosis prevention measures to consumers and health providers; and reviewing, redirecting, and revising FDA enforcement and regulatory strategies (such as microbial product sampling) to maximize listeriosis prevention efforts.

Enhanced microbiological monitoring of cheeses produced in Mexico and other Central American countries and imported into the United States serves as an example of the FDA targeting resources to enhance listeriosis prevention efforts. Each year, an estimated 75 million kilograms of cheese is imported through border crossings between California and Mexico, and a significant portion is transported by couriers or in personal cargo *(18).* Because some of this cheese is made from unpasteurized (raw) milk, it carries the potential for contamination with various pathogens, including *L. monocytogenes.* In a microbiological survey of cheese transported into the United States in personal baggage across the Mexican border in 2003, the FDA determined that 82% of 57 entries were made from raw milk, 12% yielded *Salmonella,* and 8% yielded *L. monocytogenes.* These results are similar to those in another recently conducted survey of cheese entering the United States through a noncommercial land port of entry *(18).* Working with U.S. Customs at selected ports of entry, the FDA plans to expand its microbiological monitoring efforts of cheeses transported into the country from Mexico and Central America to ascertain both the volume imported and the frequency with which such cheeses contain microbiological pathogens. The goal ultimately is to restrict the entry of contaminated cheeses derived from raw milk, which is important because 28% of pregnancy-associated cases of invasive listeriosis from FoodNet sites from 1996 through 2003 occurred among Hispanic women, and pregnant Hispanic women are four times more likely to report consuming unpasteurized cheese than are non-Hispanic pregnant women *(42).* Consumption of cheese made from unpasteurized (raw) milk is a well-documented cause of listeriosis *(21).* For this reason, the FDA has an aggressive education campaign regarding listeriosis targeted at the Hispanic population.

Evolving demographic trends in the United States may pose additional challenges to the task of achieving the *Healthy People 2010* goal for listeriosis. Specifically, an aging population of persons ≥85 years of age is the fastest growing subgroup and will increase the number of persons living with immunocompromising medical conditions, a key risk factor for invasive listeriosis. From 1996 through 2003, two-thirds of cases of invasive listeriosis in FoodNet sites involved nonpregnancy-associated illnesses in patients ≥50 years old *(42).* The FDA views these challenges as a reason both to continue time-tested strategies to reduce the incidence of listeriosis (i.e., the support of active surveillance programs for human disease, enforcement of good manufacturing practice regulations, conduct of sanitary inspections, and selective sampling and testing of food products for the presence of *L. monocytogenes*) and to evaluate and, where appropriate, employ additional new and emerging strategies that may be useful for further reducing the incidence of listeriosis. As an example of the new strategies, in 2006 the FDA approved a *Listeria*-specific bacteriophage preparation for use on ready-to-eat meat and poultry products, the first approval by the FDA of a phage preparation as a food additive *(3)*; in 2007, the FDA extended GRAS (generally regarded as safe) approval for the phage preparation to be used on all food products. Another example of a new approach is the use of nisin, an antimicrobial polypeptide that has been recognized as GRAS and approved by the FDA for some cheese products (21 CFS 3:520-521, 1 April 2000). The antilisterial property of nisin and its ability to increase acid susceptibility of *L. monocytogenes (10)* should be useful for controlling listerial growth in a variety of foods. Other nontraditional food-processing technologies being assessed for their safety and usefulness are microwave and radio frequency processing, ohmic and inductive heating, high-pressure processing, pulsed electric fields, high-voltage arc discharge, pulsed light technology, oscillating magnetic fields, UV light application, ultrasound, and pulsed X rays *(37).*

In many ways, the reduced incidence of listeriosis in the United States illustrates the laudable results that may be achieved when industry, government, consumers, and academia collaborate for common food safety goals. However, as seen for many infectious diseases, when united

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fronts falter or collaborations wane, infections can reemerge. Hence, the challenge before us is to maintain a robust defense against listeriosis that highlights prevention as it strives to further reduce morbidity and mortality.

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