Food Control 123 (2021) 107601

Contents lists available at ScienceDirect

Food Control

journal homepage: www.elsevier.com/locate/foodcont

Review

Alternative approaches to the risk management of *Listeria monocytogenes* in low risk foods

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ARTICLE INFO

Keywords:
Listeria
Epidemiology
Zero tolerance
Control
Risk assessment
Risk communication

ABSTRACT

Listeria monocytogenes is an important foodborne pathogen, which is associated with high hospitalization and case-fatality rates. Outbreaks due to food contaminated with this pathogen continue to occur globally. In terms of risk management, major food trade associations have come together in a non-competitive manner to develop excellent guidance documents on the control of this pathogen. In addition, regulatory agencies responsible for food safety have made significant advances to help control *L. monocytogenes*.

Many countries around the world have established microbiological criteria for *L. monocytogenes* of 100 cfu/g for low-risk foods that do not support the growth of the organism. In contrast, the US currently has a "zero-tolerance" approach for all ready-to-eat (RTE) foods, regardless of their risk profile, therefore all positive test results lead to a recall. A blanket "zero-tolerance" policy for all RTE foods provides a very strong disincentive for both zone 1 (product contact surface) and finished product testing, therefore potentially limiting the willingness of industry to frequently sample. To compensate for moving away from a zero-tolerance approach for low-risk foods, industry would likely be willing to do a higher frequency of testing, which would enable them to generate and use more data, including next generation tools, to inform risk-based decision-making, long before committing products to commerce. Moreover, analysis of various alternate sampling approaches demonstrates that using a 3-class sampling plan can even be more stringent than the current 2-class presence-absence zero-tolerance approach. In addition to more stringent testing, the benefits of not doing a recall on low-risk foods that do not support the growth of *L. monocytogenes* and that contain only low levels of the pathogen include i) not wasting limited industry and regulator resources; ii) not losing consumer confidence, iii) maintaining a secure and sufficient food supply, iv) decreased food waste, v) avoiding negative effects on the environment, and vi) avoiding unnecessary costly food recalls.

In this review, we provide for an alternative approach to "zero-tolerance" and argue that some of the actions that could be undertaken as part of a country's policy and/or regulatory approach to enhance the control of *L. monocytogenes* include: i) using alternate sampling approaches to the current 2-class sampling plans for low-risk foods that do not support the growth of the organism; ii) using big data to better inform microbial risk assessments; iii) performing a risk-benefit assessment; and iv) developing novel consumer food handling/risk communication strategies.

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https://doi.org/10.1016/j.foodcont.2020.107601
Received 19 June 2020; Received in revised form 31 August 2020; Accepted 2 September 2020
Available online 13 October 2020

As evidenced by many years of studying this foodborne pathogen, a multi-pronged approach to the control of *L. monocytogenes* in high-risk RTE foods is necessary to reduce risk. This approach should include evidence-based, globally harmonized definitions for RTE and non-RTE foods, along with guidance on how these definitions should be applied in any policy on *L. monocytogenes*.

1. Introduction

After a decade or more of US policy to regulate *L. monocytogenes* on the "presence of the hazard" through a stringent "zero-tolerance" program, the food industry and policy makers appear to be at a significant crossroads. Although many countries in the world have policies in place that make a clear distinction in the regulatory actions taken when low-risk or high-risk foods are found to be contaminated, from a risk standpoint the current US policy treats all *L. monocytogenes* contaminated RTE foods the same. However, in today's climate, it is recognized that risk-based policies that also consider multiple health, economic, and social factors including food security and food availability, should be more broadly adopted. Regulatory policies that consider all foods containing *L. monocytogenes* to have the same level of regulatory oversight and compliance action require a reassessment. This panel was put together to represent expertise in epidemiology, risk assessment, food microbiology, food science, and consumer behavior, and brings decades of experience in academia, research, government and industry. This discussion paper stresses the need for an alternative approach to deal with low-risk foods containing *L. monocytogenes* and recommends alternate concepts to help address the overall public health risks associated with this pathogen in RTE foods.

1.1. Susceptible consumers

Listeria monocytogenes is the causative agent of listeriosis, a serious foodborne illness with a high associated case-fatality rate. The population of susceptible consumers is increasing and may represent up to 30% of the general population. Individuals at risk for acquiring listeriosis include pregnant women, neonates, and those with a compromised immune system due to cancer, kidney disease, diabetes, HIV/AIDS, and advanced age (>65 years old). Refinements in demographic identification, such as consideration of the elderly population in two cohorts (60–75 years of age and >75 years), may reveal new information on specific populations at risk. In the US cantaloupe outbreak, the median age of patients who became ill was 78 years; the median age of persons who died was 81 years (McCollum et al., 2013). The US Census Bureau reports that in 2018, there were 52 million people aged 65 or older and the share of this demographic increased to 16% of the total population. Furthermore, the bureau indicates that by 2030 all US baby boomers will be age 65 years or older (US Census Bureau, 2019). In 2018, there were 52 million people age 65 and older, according to the Census Bureau's Vintage Population Estimates. Their share of the population grew as well, from 12.4% in 2000 to 16% in 2018.

The role of demographic changes in the US population on the burden of illness and incidence of listeriosis was recently examined (Pohl et al., 2017). The authors used FoodNet data from 2004 to 2009 to estimate the rates of listeriosis by subpopulation. They also evaluated the expected number of cases and incidence rates of listeriosis in the overall US population and the pregnant female subpopulation, as the demographic composition changed over time with respect to ethnicity, pregnancy status, and age distribution. Holding the incidence rate per subpopulation constant, the overall listeriosis incidence rate was predicted to increase from 0.25 per 100,000 in 2010 to 0.32 per 100,000 in 2030, due to changes in the population structure alone. Additionally, the pregnancy-associated incidence rate is expected to increase from 4.0 per 100,000 for pregnant women, to 4.4 in 2030 as the proportion of pregnant Hispanic women increases. The authors estimated that a reduction of 12% in the exposure of the US population to *L. monocytogenes* would be needed to maintain a constant incidence rate from 2010 to 2020 (current trend), assuming infectivity (strain virulence distribution and individual susceptibility) is unchanged. To reduce the overall US population incidence rate of listeriosis by one-third, to achieve the Healthy People 2020 goal, would require a reduction in exposure (or infectivity) to *L. monocytogenes* of 48% over the same time period. If older age groups are exclusively targeted, the required reduction in exposure would be even larger (67% for > 60 years and 89% for > 70 years). Due to demographic changes, an increase in incidence of listeriosis may occur, even though improvements in public health are being made.

1.2. Recent outbreaks

Outbreaks of illness and resultant deaths due to this pathogen continue to occur across the globe. The most significant outbreak occurred in South Africa between January 1, 2017 and July 17, 2018 and was linked to the consumption of RTE meat products referred to as polony (Smith et al., 2019). This outbreak resulted in 1060 laboratory-confirmed cases and 216 deaths, with an associated 27% case-fatality rate. Whole genome sequencing performed on clinical isolates demonstrated that 93% belonged to *L. monocytogenes* sequence type 6 (ST6). The same ST6 sequence type was identified in samples of polony, along with the processing environment where this product was manufactured. This is the largest and deadliest outbreak of listeriosis recorded globally to-date. To put the scope of this outbreak into perspective, in the US annually, 1455 cases of foodborne listeriosis from all sources are estimated to occur, resulting in 255 deaths (Scallan et al., 2011).

Notable outbreaks have more recently been linked to produce. While risk assessments predicted for instance, risks associated with sprouts and melons based on their ability to support the growth of *L. monocytogenes*, risk for other produce vehicles were not previously identified in risk assessments. The produce items involved in outbreaks include enoki mushrooms (Centers for Disease Control and Prevention, 2020a) lettuce and/or packaged salads, cantaloupe (McCollum et al., 2013; Wu et al., 2016) and rock-melons, stone fruit (Chen, Burall, Luo, et al., 2016), caramel apples (Angelo et al., 2017), celery, mung bean sprouts (Buchanan et al., 2017) and frozen vegetables. Unlike outbreaks linked to a singular, genetically homogeneous epidemic clone, produce outbreaks frequently involve multiple outbreak-associated clones. The US Centers for Disease Control and Prevention (CDC) findings associated with the 2011 US cantaloupe outbreak identified a total of 5 outbreak-associated subtypes of *Listeria* that infected 147 persons. This outbreak highlights the complexity of outbreaks. During the investigation of the 2010–2015 US ice cream outbreak (Chen et al., 2017), whole genome sequencing (WGS) was used to assess the genome level diversity of *L. monocytogenes* strains isolated from ice cream and the ice cream production environment. WGS differentiated outbreak-associated *L. monocytogenes* from epidemiologically unrelated strains that matched outbreak pulsed-field gel electrophoresis (PFGE)/multilocus sequence typing (MLST) profiles. Additionally, these authors demonstrated that WGS clustered outbreak-associated isolates exhibited multiple PFGE profiles. Single nucleotide polymorphism (SNP) analysis allowed simultaneous identification of a clonal complex (CC5) and discrimination of different outbreak strains in the same clone. WGS data suggested that certain ice cream varieties and/or production lines might have unique genotypes due to the acquisition of prophages. This scientific evidence demonstrates the necessity of molecular tools for

effectively linking outbreak strains with infected hosts, and for determination of the routes of food contamination.

The ice cream outbreak suggests that human listeriosis cases may occur after widespread distribution of products that are unable to support the growth of this pathogen but are persistently contaminated at low levels, if consumed by highly susceptible persons (Pouillot et al., 2016). However, a detailed examination of the outbreak strongly suggests that all known exposures related to this outbreak were likely due to the consumption of milkshakes rather than to the original ice cream product (Centers for Disease Control and Prevention, 2015a; Li et al., 2017). Additional information is needed to further inform the dose-response and probability of infection in highly susceptible subpopulations. Uncertainty in most dose-response models results from a lack of information on the impact of low-level exposure of *L. monocytogenes* in these highly susceptible populations. Recent quantitative modelling conducted by the European Food Safety Authority (European Food Safety Authority, 2018a) indicates that more than 90% of invasive listeriosis is caused by the ingestion of ready-to-eat (RTE) food containing $>$ 2000 cfu/g, and that one-third of cases are due to growth in the consumer phase. In addition, in Europe, the listeriosis incidence has increased among males 75 years of age and older and females 25-44 years of age (European Food Safety Authority, 2016). In fact, since the European Union (EU) started collecting human surveillance data, most listeriosis cases have been reported in people over 64 years of age. The number and proportion of cases reported for this age group has increased steadily from 2008 and continued to increase in 2017 and 2018. Human cases almost doubled in the age group greater than 84 years in the same time period (European Food Safety Authority, 2018b; 2019).

1.3. Food safety regulation in the United States

The US Food and Drug Administration (FDA) and the US Department of Agriculture's (USDA) Food Safety Inspection Service (FSIS) have different approaches and philosophies to food safety assurance. Despite scientific evidence that documents the same ecology and behavior of *L. monocytogenes* in different food processing environments, FSIS's approach to meat safety differs substantially from that used by the FDA to assure the safety of other foods. In the late 1990's to early 2000's, there were numerous large multi-state outbreaks of listeriosis linked to contaminated RTE meat products, including deli-meats and hot dogs. For example, a 2002 outbreak of listeriosis linked to turkey deli-meat sickened 54 patients, caused 8 deaths and led to fetal loss in 3 pregnant women (Gottlieb et al., 2006). The outbreak strain was isolated from the processing environment of one plant, and in turkey products and the processing environment of a second plant. More than 30 million pounds of products were recalled from the two implicated processing facilities, and this and other similar outbreaks led the FSIS to issue new regulations. To prevent future outbreaks, FSIS provided a flexible and practical framework for the meat industry to address *Listeria* control. A significant decline in outbreaks of illness and incidence of contamination of RTE meats has occurred as a direct result of collaborative efforts between the meat industry and academia, working through the American Meat Institute, along with USDA FSIS regulators.

FSIS has maintained a "zero-tolerance" policy for *L. monocytogenes* in RTE meat products, defined as products that are safe to consume without the need for further preparation, such as re-cooking. Hot dogs and deli-meats are examples of RTE meat products to which the FSIS *Listeria* Rule applies. RTE meat and poultry products are processed using a lethality step to reduce pathogen levels to the point that the probability of detecting a positive sample is very low. After these interventions have been applied, RTE products may become re-contaminated with *L. monocytogenes* from the processing environment. USDA Regulation, 9 CFR 430.4(a), states that *L. monocytogenes* is a hazard that must be controlled in RTE products exposed to the post-lethality environment. This is done through the implementation of strong pre-requisite programs such as sanitation and hygienic design. Based on a standard sampling plan, RTE products are considered adulterated, if they either contain *L. monocytogenes* or if they come into direct contact with a food contact surface that is contaminated with *L. monocytogenes*. The regulation provides processors with the flexibility of choosing one of three alternatives to meet the regulatory requirements. Under Alternative 1, if a processing establishment applies both a post-lethality treatment to reduce or eliminate *L. monocytogenes,* along with an antimicrobial agent or process (AMAP) to control *Listeria* growth, this product poses less risk for *Listeria* contamination. FSIS will subject the company to less stringent compliance sampling than would be done if neither of these treatments were used. Following slicing and packaging of processed meats, examples of post-lethality processes include applying steam or hot water pasteurization to package surfaces or subjecting packaged deli-meats or hot dogs to high hydrostatic pressure processing, a non-thermal process that destroys bacteria. Processors can also elect to reformulate their products to inhibit *Listeria* growth. Reformulating hot dogs or deli-meats with sodium lactate or potassium diacetate can inhibit the growth of *L. monocytogenes* (Seman et al., 2002). Under Alternative 2, processors apply either a post-lethality treatment or an antimicrobial agent. They would receive more stringent compliance sampling than a processing facility using Alternative 1, since the effectiveness of many anti-microbials dissipates with extended storage. Using Alternative 3, the establishment does not apply any post lethality treatment or antimicrobial agent or process, and instead relies on its sanitation program to control *L. monocytogenes*. These plants would be sampled more stringently than those using Alternatives 1 and 2. This is an example of risk-based compliance that provides processors of all sizes with flexibility for controlling a significant potential hazard presented to their products.

Prior to the Food Safety Modernization Act (FSMA), FDA policies required food companies to speciate *Listeria species* found in products or food contact surfaces. This approach essentially penalized food companies for finding *L. monocytogenes* contamination on food contact surfaces or in products, therefore discouraging *L. monocytogenes* testing. Notwithstanding product recalls and market withdrawals, in FDA's new approach under FSMA and its record-keeping and documentation provisions, any positive *L. monocytogenes* finding can result in negative consequences for the company and thus would severely curtail their attempts to immediately pinpoint and eliminate a *L. monocytogenes* niche by implementing robust 'seek and destroy' efforts. Food safety in all manufactured foods could be advanced by federal regulations that offer consistent approaches to *Listeria* control. The FSIS approach demonstrates a beneficial public health impact, albeit products that fall under FSIS jurisdiction are more likely to be amenable to the inclusion of post-lethality interventions. Based on FSIS's microbiological testing program for RTE meat and poultry products, the percent positive rate for *L. monocytogenes* decreased from 0.76% in 2003 to less than 0.2% in 2017, likely a result of both an emphasis on environmental sampling, as well as the requirement to use one of multiple alternatives for post-lethality exposed RTE products (Food Safety Inspection Service, 2018).

Regulatory policies that incentivize aggressive environmental monitoring and elimination of *L. monocytogenes* on food contact surfaces, offer an effective approach towards public health protection. Control of *L. monocytogenes* contamination in food processing facilities is challenging due to the abilities of *L. monocytogenes* to adapt to and resist standard methods used to control its presence. As stated by Buchanan et al. (2017), "Several authors have concluded that it is virtually impossible to permanently eradicate *L. monocytogenes* from food environments because of its ubiquitous presence in the environment and many potential avenues for entry into the facility. Therefore, elimination and exclusion of the organism must be actively managed, for example by adequate hygienic design of a facility's infrastructure and equipment, effective cleaning and sanitation, personnel practices and movement of people and materials into areas where food products are exposed."

The FDA has long upheld its policy of zero-tolerance for

L. monocytogenes in RTE foods (0/25 g) that was established in the 1980's (Shank et al., 1996). Most findings of *Listeria* are covered under two different adulteration standards: 1. The article of food bears and contains a poisonous or deleterious substance, namely *L. monocytogenes*, which may render it injurious to health, (Act, 21 U.S.C. 342(a1) and 2). The food may not be prepared, packed, or held under insanitary conditions or the requirements in FDA's good manufacturing practices (Act, 21 U.S.C. 342(a4)). In 2004, the food industry petitioned FDA to establish a regulatory limit of 100 cfu/g for *L. monocytogenes* in RTE foods that do not support growth of the microorganism. In 2008, the FDA issued draft guidance for control of *L. monocytogenes* in refrigerated or frozen RTE foods. A food is deemed low risk for *L. monocytogenes* if the pH of the food is less than 4.4, the water activity is less than or equal to 0.92, or the food is frozen. Foods satisfying these conditions do not support the growth of *L. monocytogenes*. The issue of whether a food can or cannot support the growth of *L. monocytogenes* is a critical one. This is because, as will be discussed later on (section 4), a number of risk assessments have demonstrated that preventing the growth of *L. monocytogenes* in RTE foods can reduce the risk of acquiring listeriosis by 1000 to 10,000-fold.

The definitions of RTE and non-RTE and what constitutes an adulterant are at odds in FSIS versus FDA regulations. FDA's 2008 Draft Guidance suggested, "For example, fresh and frozen crab meat and individually quick frozen peas and corn MAY be RTE foods." This interpretation is inconsistent with the FDA's designation of foods such as refrigerated cookie dough as "ready-to-cook" if they bear cooking instructions. In 2015, the FDA's Food Advisory Committee (FAC) revisited the question of whether frozen vegetables should be considered RTE, and specifically if they should be considered RTE even if they bear cooking instructions. The FAC was unable to come to a consensus on this issue.

In the last few years, outbreaks of illness and death have been associated with foods that met the criteria for not supporting growth of *L. monocytogenes*. The 2015 outbreak of listeriosis linked to ice cream revealed the presence of *L. monocytogenes* in 99% of tested ice cream samples at low levels, i.e., *L. monocytogenes* was detected in 99% (2307 of 2320) of the tested samples (lower limit of detection, 0.03 MPN/g), 92% of which were contaminated at $<$ 20 MPN/g (Chen, Burall, Macarisin, et al., 2016). In 2016, frozen vegetables were implicated as the source of a multi-state outbreak in the US, and recently a listeriosis outbreak in Europe has been attributed to frozen corn and other non ready-to-eat (NRTE) frozen vegetables produced by a processing plant in Hungary. With regards to the latter outbreak, the European Food Safety Authority published an expert scientific opinion concluding that the public health risk posed by *L. monocytogenes* in frozen vegetables is significantly lower in comparison to any other RTE food categories historically associated with the pathogen including RTE meat, fish and dairy products. Importantly, the report reiterated recognition of RTE foods that do not support the growth of *L. monocytogenes* and the basis for a 100 cfu/g regulatory tolerance (Koutsoumanis et al., 2020).

In the US, FDA is more likely to consider frozen corn as RTE food, as consumers are known to thaw and consume without following on-package cooking instructions. Other public health agencies (Food Standards Scotland, 2019) recently proactively issued guidance to consumers reminding them that frozen vegetables are NRTE foods and must be cooked prior to consumption. FSMA related guidance considers frozen vegetables labeled with cooking instructions to be "ready-to-cook (RTC) foods" (i.e., NRTE) and offers guidance to consumers regarding cooking instructions. We need globally harmonized public health approaches to definitions of RTE and NRTE foods.

The Codex document entitled "Guidelines on the Application of General Principles of Food Hygiene to the Control of *Listeria monocytogenes* in Foods", received final approval in 2007, and thus was agreed to by all parties present (188 Member Countries and 1 Member Organization - the EU), including the US. In general, these Codex guidelines provide advice to governments on a framework for the control of *L. monocytogenes* in RTE foods, with a view towards protecting the health of consumers and ensuring fair practices in food trade. The primary purpose of the Codex guidelines is to minimize the likelihood of illness arising from the presence of *L. monocytogenes* in these foods. The guidelines are applicable throughout the food chain, from primary production through to consumption. There were numerous risk assessments at the time that were considered in the development of the Codex microbiological criteria for *L. monocytogenes*.

Data from the US, Canada and Germany coupled with data particularly from the United Kingdom's (UK) chilled food manufacturing industry on *L. monocytogenes* and *Listeria* species monitoring in food and the production environment, as well as comparable listeriosis rates in the EU and US, led to acceptance by Codex of the coexistence of both the EU (100 cfu/g max) and US approaches to setting a microbiological criterion for *L. monocytogenes* in RTE foods that support its growth.

In terms of providing evidence that *L. monocytogenes* will grow in a RTE food, Codex has stated that member countries should accept, for example: i) food characteristics; ii) the study of naturally-contaminated food; iii) challenge tests; iv) predictive modelling; v) information from the scientific literature and risk assessments; vi) historic records or; vii) a combination of the above (Codex Alimentarius Commission, 2007).

2. History of US FDA's position on *L. monocytogenes* in RTE foods

The origins of the FDA policy and microbiological criteria for *L. monocytogenes* in RTE foods dates back to the mid-1980's when the US was in the middle of what became known as the Jalisco cheese outbreak. The large number of cases and the high case-fatality rate, particularly among neonates and stillborn fetuses put pressure on FDA to implement policies to prevent future outbreaks. The outbreak ultimately caused 142 cases and 48 deaths attributable to contaminated Mexican-style cheese (Linnan et al., 1988). To complicate matters, the available *Listeria* methods at the time for sampling dairy foods were qualitative in nature, and the limit of detection regulatory philosophy, adopted during a time of crisis, became in effect the FDA "zero-tolerance" policy.' An issue also arose with the size of the samples being analyzed for the organism. In summary, due to a typographical error, a mistake was made and what was supposed to be a sampling size of 10 $\times$ 25 g samples (250 g in total), became a sample size of 2 $\times$ 25 g (Archer, 2018).

Starting from this "zero-tolerance" baseline approach, there were some attempts by the FDA to try and move away from it. Some of the scientific reasoning explained by regulators revolved around the fact that if low numbers of *L. monocytogenes* could indeed cause illness, and the organism was widespread in nature and foods, why were there so few illnesses? Outside influences as well came from the World Health Organization (WHO), who stated in deliberations of their informal working group on the subject that it was not possible to guarantee a food free from *L. monocytogenes* if the food was i) raw, ii) a transformed raw food or iii) a processed food that was subsequently handled before consumption. Other influencers included Canada, who early on adopted an action level of 100 cfu/g in foods not supporting growth of the organism and Codex Alimentarius Commission (2007), who also adopted a similar limit of 100 cfu/g.

In mid-2004, a petition was filed by 15 US food trade organizations requesting that FDA amend the regulations (21 CFR part 109) so that *L. monocytogenes* would be recognized as an unavoidable contaminant, and that FDA should set a regulatory limit of 100 cfu/g of *L. monocytogenes* in foods in which the organism could not grow. Industry viewpoints at the time were strengthened by some published risk assessments, as well as the experiences of nations that had established the 100 cfu/g regulatory limit. This position was also supported by the Institute of Food Technologists and the American Society for Microbiology.

In response, the FDA published a 'Draft Guidance' Compliance Policy Guide (CPG) in early 2008 that defined the term 'RTE food', and separated its regulatory policy on RTE foods that support the growth of

L. monocytogenes, from those RTE foods that did not support the growth of the organism. For the latter, a food would be considered adulterated (under FD&C 402(a) (1)) when 100 cfu/g or more of *L. monocytogenes* would be present. This Draft Guidance on *L. monocytogenes* remained as a draft for 9 years.

In the years following the release of the 2008 CPG Draft Guidance, several events occurred that slowly started to change the thinking of the FDA on how they were going to regulate *L. monocytogenes*. These included:

i) a paper published by Pouillot, Hoelzer, Chen, & Dennis (2015) on revisiting the dose-response for *L. monocytogenes*;
ii) new information on dose-response modeling for *L. monocytogenes*, realizing that there could be as great as a 10,000-fold difference in virulence between strains, and lack of reliability on the extrapolation from high-to-low doses of *L. monocytogenes* (Chen et al., 2011). Thus, doubt began to emerge on the validity of the previous risk assessments that provided the basis for considering the establishment of a regulatory limit;
iii) new models that FDA started using showed that low numbers of *L. monocytogenes* could negatively affect highly susceptible people if highly virulent strains would be present in a food (Pouillot et al., 2016); and
iv) more recent listeriosis outbreaks linked to foods such as ice cream (Centers for Disease Control and Prevention, 2015a), peaches (Chen, Burall, Luo, et al., 2016; Chen, Burall, Macarisin, et al., 2016), celery (Gaul et al., 2013), caramel apples (Centers for Disease Control and Prevention, 2015b), and uncooked frozen vegetables (Centers for Disease Control and Prevention, 2016a) suggesting that low number of *L. monocytogenes* could potentially cause illness in highly susceptible individuals. However, it should be noted most of these new vehicles are foods that could support the growth of *L. monocytogenes* if handled inappropriately.

Thus, due to the above factors, FDA became concerned about the uncertainty associated with the 100 cfu/g standard for RTE foods that do not support growth, and started to question whether the proposed standard in the 2008 draft CPG sufficiently provided an appropriate level of protection for the most vulnerable individuals in at-risk subpopulations. As a result, in January 2017, FDA published a Revised Draft Guidance that removed the suggested 100 cfu/g regulatory limit for RTE foods in which *L. monocytogenes* cannot grow. Thus, the evolution of FDA's policy on *L. monocytogenes* had reverted to its original position, i.e., that of a "zero-tolerance" policy.

It is important to note a scientific critique of the Pouillot et al. (2016) manuscript specifically providing additional perspectives was submitted to the Federal Register (2008) in response to FDA industry guidance on the presence of *L. monocytogenes* in RTE foods (Food & Drug Administration, 2017).

Lastly, it's important to recognize the differences between the *L. monocytogenes* policies within the two primary federal food safety agencies in the U.S. While FDA's *L. monocytogenes* policy impacts a wider range of products than those that fall under FSIS jurisdiction, the latter agency explicitly precludes NRTE foods in its *Listeria* rule. FSIS's *L. monocytogenes* policy is largely directed towards RTE processed meats and addresses risks of post-lethality contamination. Furthermore, the agency clearly delineates alternative steps that firms can take to mitigate these risks. This risk-based FSIS approach also allows manufacturers to monitor the prevalence of *Listeria* spp. in the environment, without the need to further speciate. Even though FDA also augmented its monitoring guidance with a similar approach in 2017, the agency's current "zero-tolerance" approach to regulating *L. monocytogenes* impedes industry efforts to incorporate active seek and destroy as well as finished product testing programs in food manufacturing.

3. European Union (EU) regulatory approach

The EU *L. monocytogenes* legislation is set out in Commission Regulation (EC) No 2073/2005 of November 15, 2005 (as amended) on microbiological criteria for foodstuffs. As this is a Regulation and not another legal instrument, it is directly applicable in all Member States. The Regulation generally relates to finished manufactured foods and not to ingredients or raw materials used to manufacture that food. However, Food Business Operators (FBOs) producing/supplying raw materials may be affected by the Regulation through the application of criteria and corrective actions required by their customers' food safety management plans.

3.1. EU criteria for L. monocytogenes

The EU Scientific Committee on Veterinary Measures relating to Public Health (SCVPH) issued an opinion on September 23, 1999 on the evaluation of microbiological criteria for food products of animal origin for human consumption. It highlighted the relevance of basing microbiological criteria on formal risk assessment and internationally approved principles. The SCVPH issued at the same time a separate opinion on *L. monocytogenes*, recommending that it be an objective to keep the concentration of *L. monocytogenes* in food below 100 cfu/g. The EU Scientific Committee on Food (SCF) agreed with these recommendations in its opinion of June 22, 2000 (2073/2005) and established Food Safety Criteria (FSC) and Process Hygiene Criteria (PHC) for specific combinations of foods and microorganisms (European Union Commission Regulation, 2005).

In the EU, FSC applies only to foods placed on the market. Non-compliance with the FSC requires withdrawal and/or recall of affected batches from the market, investigation of the occurrence and implementation of effective corrective action. Failure to react accordingly is a breach of the law. FSC are set only for *L. monocytogenes*, and only for RTE foods. PHC apply to in-process foods and are used by FBOs to track control of their processes, and in certain circumstances, raw materials. However, PHC are not applied when the product has been placed on the market. Exceedance of a PHC requires the FBO to carry out investigation and corrective actions. Failure to react accordingly is a breach of the law.

Products placed on the market, but which are not yet at the retail level and which do not meet FSC, may be submitted to further processing by a non-retail FBO to eliminate the hazard in question, or use it for another purpose such as animal feed, provided no health risk is presented and authorities have agreed to this use.

Results that find *L. monocytogenes* levels of >100 CFU/g in any RTE food indicate that the food tested is in breach of the FSC and hence is considered under EU law to be an unacceptable food safety risk. Affected products must be withdrawn/recalled from the market and the Competent Authority notified (European Union Commission Regulation, 2005).

3.2. Practical application of the EU criteria for L. monocytogenes

For RTE foods other than those intended for infants and special medical purposes (criterion 1.1) the general limit of 100 cfu/g applies, whether or not *L. monocytogenes* will grow in the product. However, for RTE foods supporting the growth of *L. monocytogenes*, authorities can require FBOs that do not provide data to substantiate the efficacy of their controls and/or the scientific basis of the product shelf life, to implement criterion 1.2b (not detected in 25 g before the food has left the immediate control of the FBO producing it, i.e., placing foods on positive release) until sufficient data are gathered to demonstrate control of food safety including validity of shelf life. Further information on the EU criteria, and on the detection of *L. monocytogenes* in RTE foods can be found in the supplementary material.

4. Canadian Regulatory Approach

The Canadian policy on *L. monocytogenes* in RTE foods is based on the principles of HACCP. The policy was developed using a health risk assessment approach and uses as its foundation a combination of inspection, environmental sampling and end-product testing (Health Canada, 2011). It is understood that the risk of *Listeria* spp. contamination can be reduced, but cannot always be eliminated from the production environment or the finished product. Priority is therefore placed on RTE products in which the growth of *L. monocytogenes* can occur. The Health Canada policy covers all RTE foods sold in Canada, and provides for a definition of RTE. Non-RTE products are not covered by the policy.

In the policy, RTE foods are classified into two categories, based upon health risk. Category 1 contains products in which the growth of *L. monocytogenes* can occur. These products receive the highest priority for industry verification and control, as well as regulatory oversight and compliance activities.

Category 2 foods contains two subgroups: 2A) RTE food products in which limited growth of *L. monocytogenes* to levels not greater than 100 CFU/g can occur throughout the stated shelf-life e.g., durable life date shown as a "best before" date on the package; and 2B) RTE food products in which the growth of *L. monocytogenes* cannot occur throughout the expected shelf-life of that food. Both of these low risk product categories receive a lower priority with regards to industry verification and control, as well as regulatory oversight and compliance activities.

5. Hazards-based versus risk-based strategies for controlling foodborne listeriosis

Prior to 1981, listeriosis, the disease caused by *L. monocytogenes* was primarily considered a disease of domestic and feral animals. The disease was only rarely reported in humans, and it was often presumed that such cases resulted from exposure to infected animals. However, an outbreak of listeriosis in 1981 was traced to contaminated coleslaw in Nova Scotia, Canada made from cabbage that had been fertilized with sheep manure and held in cold storage prior to use (Schlech et al., 1983). This outbreak led to a re-evaluation of how listeriosis cases were investigated, i.e., these outbreaks tend to be highly dispersed geographically and are largely limited to individuals who have suppressed immune systems, including the elderly, pregnant women and their newborns, individuals with certain chronic diseases, and patients taking immunosuppressive medications. This led to the identification in the 1980's and 1990's of typically small listeriosis outbreaks in North America and Europe associated with pasteurized and unpasteurized milk, certain cheeses and other dairy products, various RTE meats, and smoked seafood products (Ryser & Buchanan, 2013). Listeriosis is considered a rare disease with an annual incidence in developed countries of between 2 and 5 cases per 1,000,000 persons. In the US, it is estimated that there are approximately 1600 cases of invasive listeriosis per year.

Between the initial 1981/1982 outbreak and the present, the US food safety agencies (FDA and FSIS) developed regulatory frameworks to deal with this emerging foodborne pathogenic microorganism. As pointed out earlier, the policies and frameworks for regulating *L. monocytogenes* were summarized by the then Director of the FDA Center for Food Safety and Applied Nutrition, Dr. Fred Shank and FDA co-authors (Shank et al., 1996) in "Food Control" in 1996, as part of a special issue that had representatives from various national governments (e.g., Canada, UK, France, Denmark). In developing its emerging policy towards the pathogen, the FDA took a "hazards-based approach," i.e., the detection of *L. monocytogenes* in a food sample would cause the food to be considered adulterated. However, in reaching this policy, they faced several challenges such as the ubiquitous nature of the microorganism, its ability to overcome a major means of controlling foodborne enteric pathogens (i.e., refrigeration), the low probability of infections even in high-risk patients, the limitations in available detection methodologies, and the epidemiological evidence that the bacterium was almost exclusively associated with RTE foods. So, in reaching their regulatory policy, they did consider the relative risk of the pathogen by articulating the testing program requirements.

While the early US policy is considered a hazard-based approach, a number of the decisions in developing those policies attempted to take into account some factors that affected the risk of invasive listeriosis. One of the key decisions related to the policies of FDA and FSIS for *L. monocytogenes* was the decision to restrict testing to RTE foods; raw foods that are intended to be cooked prior to consumption (i.e., RTC foods) were not covered. Secondly, the primary focus of the initial implementation of the regulatory policies was RTE foods where epidemiological associations had been established or anticipated (e.g., RTE meats and poultry, dairy products such as milk/cheeses/butter, RTE seafood products). If a product had a label that specifically stated that the product had to be cooked prior to consumption and had validated cooking instructions, this would not be considered a RTE food. The third "risk-based" decision captured in the hazards-based approach was a restriction on the size of the samples to be analyzed. For FDA regulated products, a "*Listeria*-free" product was based on a standard sampling plan that required that no *L. monocytogenes* were detected in two 25 g-samples of the product. The number of samples required could be considered a risk-based decision when compared to other pathogens such as *Salmonella enterica* where a high-risk food fed to high-risk individuals often has sampling plans requiring sixty 25-g samples. It is worth noting that despite limiting *L. monocytogenes* sampling to two 25-g samples, occasional positive samples with low levels of *L. monocytogenes* were detected.

The outbreaks and sporadic cases of listeriosis, as well as extensive research on the ability of various foods to support the growth of this bacterium, has provided a profile of the factors that affect the relative risk of a consumer contracting foodborne listeriosis. This includes highly detailed risk assessments that have been conducted by national governments, intergovernmental organizations (e.g., WHO, Food and Agriculture Organization of the United Nations (FAO), 2004), and research scientists (Buchanan et al., 2017, 1997; Bemrah et al., 1998; Lindqvist & Westoo, 2000; Hitchens & Whiting, 2001; Food & Drug Administration, 2003; Carrington et al., 2004; FAO/WHO, 2004; McLauchlin et al., 2004; Sanaa et al., 2000; Francois et al., 2006; Yang et al., 2006; Pouillot et al., 2009, 2012, Pouillot, Gallagher et al., 2015, 2016, 2007; Pérez-Rodríguez et al., 2007; Keeratipibul & Lekroengsin, 2008; Pradhan et al., 2009; Ross et al., 2009). These parameters include ability of the food to support the growth of *L. monocytogenes* at refrigeration (2–5 °C) or chill temperatures (6–9 °C), extended refrigerated storage, exceedingly high levels of *L. monocytogenes* in a food product, and mishandling on the part of the consumer, particularly inadequate refrigerated storage. It has been estimated that preventing the growth of *L. monocytogenes* in food decreases the risk of infection by > 1000-fold (World Health Organization and Food and Agriculture Organization of the United Nations, 2004).

The hazards-based policy remained in place until after the *L. monocytogenes* risk assessments by the US Food and Drug Administration and the US Food Safety Inspection Service (2003) and the World Health Organisation and Food and Agriculture Organisation (2004) and the Codex Alimentarius Commission recommended the adoption of a 2-tier international standard based on whether the food supported the growth of *L. monocytogenes* over the shelf life of the food product. As mentioned, the US supported the adoption of the Codex standard and, in 2008, FDA proposed to harmonize their *L. monocytogenes* policies. The rationale underlying this was that providing an incentive for manufacturers to reformulate their products so that they no longer supported the growth of *L. monocytogenes*, would improve public health. As mentioned earlier, the various risk assessments clearly demonstrated that preventing the growth of *L. monocytogenes* in RTE foods would reduce the risk of listeriosis cases by 1000-fold to 10,000-fold. It is worth noting that during the discussion of the 2-tier policy, the US largely achieved its

2000 and 2010 goals for reducing foodborne listeriosis cases. It is also worth noting that in 2006, FSIS introduced three alternatives for RTE meats and poultry based on: i) whether the product received a lethal treatment after final packaging; ii) whether the product contained an antimicrobial treatment or process before packaged; or iii) did not have either of the alternatives. The degree of microbiological testing required for verification was then dependent on the control alternative used by the manufacturer. It should be noted that among all the risk-based strategies implemented or considered, none absolutely assures the elimination of listeriosis. However, they do lay out a scientifically supportable framework for managing risks and improving public health, in an era where wasting food can have dire consequences even in the richest of developed countries.

6. Biology of *Listeria monocytogenes*

Listeria is one of the most intensely studied genera of bacteria during the past 30 years. This reflects its importance as a public health concern, as a tool for studying virulence and immune response, and as a challenge to traditional means of controlling foodborne pathogens.

6.1. Listeria taxonomy

Before 2009, six *Listeria* species were recognized, including *Listeria monocytogenes*, *L. innocua*, *L. seeligeri*, *L. ivanovii*, *L. welshimeri*, and *L. grayi*. Since 2009, >10 new *Listeria* species have been identified, including *L. marthii*, *L. fleischmannii*, *L. floridensis*, *L. aquatica*, *L. newyorkensis*, *L. cornellensis*, *L. rocourtiae*, *L. weihenstephanensis*, *L. grandensis, L. riparia*, *L. booriae*, *L. thailandensis*, and *L. costaricensis*. Among these species, only *L. monocytogenes* and *L. ivanovii* are considered pathogens. While *L. monocytogenes* is an important human foodborne pathogen, *L. ivanovii* is generally considered to only be an animal pathogen and has usually been associated with clinical cases in ruminants. The non-pathogenic *Listeria* species are, however, important from a food safety perspective, as detection of *Listeria* spp. (using tests that detect all pathogenic and non-pathogenic *Listeria*) is often used to identify conditions that could favor the presence or potential harborage of *L. monocytogenes* in food associated facilities, e.g., food processing plants.

Importantly, the different *Listeria* species represent four taxonomically distinct groups that have been proposed to represent distinct genera. *L. monocytogenes*, along with *L. innocua*, *L. marthii*, *L. seeligeri*, *L. ivanovii*, and *L. welshimeri* have been proposed to represent *Listeria sensu stricto*, while the remainder of the *Listeria* spp. represent three distinct groups with proposed genus names of *Paenilisteria*, *Mesolisteria*, and *Murraya* (Orsi & Wiedmann, 2016). Species grouped into these three proposed genera may have phenotypic characteristics that are fairly distinct from *L. monocytogenes* and members of the genus *Listeria sensu stricto*, which suggests that at least some of the genera may neither represent appropriate "indicator" organisms that indicate conditions that may allow for survival or presence of *L. monocytogenes*, nor represent appropriate, so called "index" organisms, which would indicate the likely presence of *L. monocytogenes*.

6.2. Listeria ecology and prevalence

In general, *Listeria* spp. appear to be relatively common in different environments, including in non-agricultural and non-food associated environments. For example, a study of >1800 soil, water, and other environmental samples collected in New York (NY) reported *Listeria* prevalence of 23.4 and 22.3% in urban and natural environments, respectively; *L. monocytogenes* prevalence in these same environments were reported as 4.4 and 1.4%, respectively (Sauders et al., 2012). A smaller study of soil samples in NY state reported *Listeria* and *L. monocytogenes* prevalence of 34.2 and 15%, respectively (Chapin et al., 2014; Strawn et al., 2013). While there is some evidence that the prevalence of *Listeria* and *L. monocytogenes* may differ regionally and by environments, studies in parts of the US other than NY and in different regions of the world often report a similarly high prevalence (Sauders et al., 2012). Overall, these studies and prior data suggest a considerable risk of *L. monocytogenes* contamination of foods throughout the farm-to-table continuum. This represents a particular challenge for foods that are consumed fresh and do not undergo a listericidal processing step (e.g., fresh produce). In addition, these data suggest that human exposure to *L. monocytogenes* is not uncommon. This is also consistent with an early FDA risk assessment (FDA, 2003), which also supported frequent human exposure to *L. monocytogenes*.

6.3. L. monocytogenes virulence characteristics

While regulatory agencies across the world consistently consider all *L. monocytogenes* strains a public health hazard, there is considerable evidence that the species *L. monocytogenes* includes strains that represent a wide range of virulence associated characteristics. Importantly, identification of *L. monocytogenes* strains that differ in their virulence is facilitated by a considerable detailed body of knowledge of *L. monocytogenes* pathogenesis and virulence genes (Bergholz et al., 2018; Orsi et al., 2011). Importantly, both "hypo-virulent" (or virulence attenuated) and "hyper-virulent" *L. monocytogenes* strains have been identified. The most important group of virulence attenuated *L. monocytogenes* is represented by isolates that contain premature stop codons (PMSC) in the virulence gene *inlA*, which encodes an internalin protein (InlA) that is essential for efficient attachment of *L. monocytogenes* to intestinal epithelial cells. This attachment is essential for subsequent invasion and systemic spread of *L. monocytogenes* present in the human intestinal lumen. To-date, at least 19 different *inlA* mutations that lead to PMSC that attenuate *L. monocytogenes* invasion of human intestinal epithelial cells have been reported (Van Stelten et al., 2011; Gelbícová, Pantucek, & Karpíšková, 2016). Different studies indicate that a considerable proportion of *L. monocytogenes* isolates obtained from RTE foods contain these types of PMSC For example, characterization of 502 *L. monocytogenes* food isolates from a retail survey conducted in the US in 2000 and 2001 reported that 45.2% of these isolates carried *inlA* PMSC (Chen et al., 2011). Importantly, the data from this survey were also used to complete a risk assessment, which suggested that the r value (probability of a single cell causing illness) was significantly lower for *L. monocytogenes* strains which had an *inlA* PMSC. More specifically, mean $\log_{10}$ r values were estimated to be −10.4, −13.8, and −12.8 for the subtypes with genes encoding a full-length InlA, for the subtypes carrying a PMSC in *inlA*, and for all *L. monocytogenes* isolates regardless of subtype, respectively. These calculations accounted for the growth of *L. monocytogenes* in foods, including observed differences in *L. monocytogenes* numbers in foods for different subtypes.

These data suggest that isolates with *inlA* PMSC are >3 logs less likely to cause disease, as compared to strains that encode the full length InlA. Virulence attenuation of *L. monocytogenes* strains with *inlA* PMSCs has also been confirmed in animal models (Maury et al., 2016; Van Stelten et al., 2016), as well as in studies with human tissue culture cells (Nightingale et al., 2005; Olier et al., 2003; Orsi et al., 2007). In addition, virulence attenuation of *L. monocytogenes* with *inlA* PMSC is also consistent with historical epidemiological observations. Specifically, *L. monocytogenes* serotype 1/2 c strains have historically been reported as being found frequently in some foods, but rarely in human cases (Doumith et al., 2004; Gianfranceschi et al., 2003; Orsi et al., 2011; Tamburro et al., 2010). More recent characterization of serotype 1/2 c strains found that the vast majority of them are characterized by *inlA* PMSCs (Doumith et al., 2004; Tamburro et al., 2010; Ward et al., 2010). While naturally occurring virulence attenuating mutations have also been reported in other genes (e.g., *prfA*), these mutations appear to be rather infrequent and hence are less relevant from a public health perspective (Maury et al., 2017; Roche et al., 2005; Velge et al., 2007).

With regard to strains that are potentially more virulent, a number of studies have defined outbreak associated clones or so-called epidemic clones of *L. monocytogenes* (Maury et al., 2016; Moura et al., 2016; Ragon et al., 2008). While these studies have identified a number of *L. monocytogenes* groups that are frequently associated with human listeriosis outbreaks, unlike for virulence attenuated strains with *inlA* premature stop codons, specific genetic features that could account for and have mechanistically been shown to be linked to hypervirulence have only recently been elucidated for some clonal groups (Maury et al., 2016). Importantly, MLST-based classification of *L. monocytogenes* into clonal groups has not only confirmed the existence of specific virulence attenuated clones with *inlA* premature stops codons, such as clonal complex (CC) 121, but also identified a number of lineage I clonal groups that appear to be hypervirulent and more likely to cause human disease, including CC1, CC6, CC2, and CC4 (listed in order of frequency among human isolates obtained in France, where this study was conducted).

While identification and characterization of hypo- and hyper-virulent clonal groups in *L. monocytogenes* provides an opportunity to further improve risk assessments, there remains a need to further characterize the relative likelihood of different clonal groups to cause human disease. While these efforts may ultimately lead to an enhanced focus on control of hyper-virulent clonal groups (for example, by assuring that interventions and control strategies are effective against these clonal groups), variation in host susceptibility to *L. monocytogenes* may provide a more practical approach to target control strategies (for example, by focusing risk communications on highly susceptible populations).

6.4. *Listeria monocytogenes* phenotypic and physiological characteristics

The ubiquitous nature of *L. monocytogenes*, in part, reflects its ability to adapt to changing conditions and resist control strategies designed to suppress or eliminate non-spore forming Gram-positive bacteria. The growth and survival characteristics of *L. monocytogenes* have been studied extensively (see Table 1 for *L. monocytogenes* growth requirements) and several predictive microbiology models have been published that provide rapid estimates of its behavior in foods and has allowed the development of quantitative microbiological risk assessments (Castro-Ibanez et al., 2015; Park et al., 2012; Pasonen et al., 2019; Pradhan et al., 2009).

For a non-spore forming foodborne pathogen, *L. monocytogenes* is relatively resistant to the various technologies used to reduce its presence in foods. Its thermal resistance has been well characterized, with D-values that indicate that heating temperature profiles in the 60–75 °C range can be used to effectively reduce *L. monocytogenes* and that heating to boiling (100 °C) would result in almost instantaneous inactivation of the pathogen (Mazzotta, 2001; De Jesús & Whiting, 2003; Murphy et al., 2003; Hassani et al., 2005; Fernandez et al., 2007). A number of alternative non-thermal technologies such as high-hydrostatic pressure (Gao et al., 2006; Lopez-Pedemonte et al., 2007; Van Boeijen et al., 2008), pulsed electric field (Unal et al., 2001; Saldana et al., 2010), cold plasma (Ziuzina et al., 2015; Jiang et al., 2017; Yadav et al., 2019) and ionizing and non-ionizing radiation (Bari et al., 2006, 2005; Konteles et al., 2009; Sommers & Rajkowski, 2008; Zhu et al., 2009), have been shown to be effective against *L. monocytogenes*. While *L. monocytogenes* is a challenge in certain classes of foods, it is not a "superbug" and there are multiple approaches and technologies for reducing the risk associated with this pathogen.

Table 1
Growth characteristics of *Listeria monocytogenes*[a].

	ICMSF	Aryani average (s.e.)	Aryani 2.5 percentile	Aryani min (out of 20)
T_{min}	−0.4	−2.2 (0.52)	−3.3	−3.0
pH_{min}	4.39	4.55 (0.081)	4.38	4.34
$a_{w,min}$	0.92	0.927 (0.003)	0.921	0.920
$NaCl_{max}$ (M)		1.97 (0.075)	2.13 (97.5th)	2.15 (max)
HLa_{max} (mM)		5.11 (0.31)	5.76 (97.5th)	6.06 (max)
$Log(D_{70})$ (log min)		−1.7 (0.23)	−1.2 (97.5th)	
Z		5.2		

[a] Source: International Commission on Microbiological Specifications for Foods (ICMSF), Book No. 5; Aryani et al. (2015a, 2015b).

7. Listeriosis – disease incidence

Clinical illness associated with *L. monocytogenes* infections ranges from self-limited gastroenteritis with fever, to invasive infections leading to hospitalization and possibly death. Serious invasive infections primarily occur in people with conditions that compromise normal immune system function. These include pregnant women and neonates, elderly people and people with other immunocompromising conditions (de Noordhout et al., 2014). Surveillance for listeriosis is based on laboratory confirmation of invasive infections (Scallan et al., 2011). Cases of invasive listeriosis are defined by isolation of *L. monocytogenes* from a normally sterile site (e.g., blood or cerebrospinal fluid), or from products of conception (e.g., placenta or fetal tissue) in the setting of miscarriage or stillbirth (Pohl et al., 2019). Febrile gastroenteritis is rarely diagnosed, in part because stool specimens are not routinely tested for *Listeria*. While this results in underestimation of the total public health burden of listeriosis, the largest share of that burden is borne by invasive infections that are under surveillance.

A population-based study of listeriosis cases in France from 2001 to 2008 compared the risk of acquiring listeriosis among persons with underlying conditions, to risks among persons under 65 years of age with no underlying conditions (Goulet et al., 2012). To illustrate the range of risks, persons with chronic lymphocytic leukemia had >1000-fold increase of listeriosis, persons with non-Hodgkins lymphoma had a 325-fold increased risk, pregnancy was associated with a 116-fold increase, HIV infection 45-fold increase, type 1 diabetes 34-fold increase, and age >74 years a 20-fold increase in risk of infection. While persons in the highest risk groups made up only 1% of the population in France, they accounted for 43% of illnesses and 55% of deaths (Goulet et al., 2012). People under 65 years of age with no underlying risk factors made up 75% of the population but accounted for only 10% of cases and 2% of deaths. This analysis from France typifies the risk patterns for listeriosis and the burden of illness borne by the relatively small percentage of the population at greatest risk for illness.

In the US, population based active surveillance for listeriosis has been conducted since 1996 by FoodNET, the Foodborne Diseases Active Surveillance Network. FoodNET analyzed incidence rates of invasive listeriosis by age, sex, race/ethnicity and pregnancy status in the US from 2008 to 2016 (Pohl et al., 2019). Compared to persons 15–44 years of age, the risk of listeriosis increased 25-fold for persons 70–79 years of age, 36-fold for persons 80–89 years, and 45-fold for persons more than 85 years of age. Compared to non-hispanic whites, hispanics, non-hispanic blacks and Asians all had approximately 2-fold increased risks of infection. The increased risk associated with ethnicity appears to be largely due to cultural food preferences, also reflected in the occurrence of outbreaks. Among women of child-bearing age, pregnant women had a 91-fold increased risk of infection (Pohl et al., 2019).

The global burden of listeriosis cases and deaths for 2010 were estimated for the World Health Organization (WHO) Foodborne Diseases Epidemiology Reference Group (de Noordhout et al., 2014). Based on a meta-analysis and modeling of reported incidence data, a global total of 23,150 cases (95% credible interval, 6061–91,247 cases) and 5463 deaths (95% credible interval, 1401–21,497 deaths) were estimated to have occurred. These cases correspond to an overall incidence rate of 0.34 cases and 0.08 deaths per 100,000 population. The estimates of incidence ranged from less than 0.1 cases per 100,000 among eastern European countries to 0.47 cases per 100,000 across much of Central

and South America. Data on incidence were lacking for 85 countries representing several large areas of the world. These countries distributed across Africa, the Middle East, and Southeast Asia accounted for almost half of the world's population (de Noordhout et al., 2014). Incidence rates for these countries were extrapolated from known sources and applied to local populations representing potentially important differences in risk. The imputed rates of 0.43 cases per 100,000, with 95% credible intervals ranging from 0 to 2.47 cases per 100,000, very likely underestimated the actual incidence in many countries.

The methods used to estimate the global burden of listeriosis preclude looking at trends over time. Trend data are primarily available for high income countries with well-developed health care delivery and public health systems. Incidence data from Australia, US, Canada, EU, UK, and France from 2007 to 2018 highlight recent trends (Fig. 1). Across this geographically diverse group of countries, incidence rates ranged from 0.2 to 0.5 cases per 100,000 population in 2007 to 0.25 to 0.55 cases per 100,000 in 2018. Trends towards increasing numbers of human listeriosis cases were particularly noted for the EU generally, and France in particular. Despite sharing the EU regulatory approach to *Listeria*, rates in the UK were similar to the US and remained steady or trended downwards (Australia Department of Health, 2019; European Centre for Disease Prevention and Control, 2018a,b; Centers for Disease Prevention and Control, 2019c; Public Health Agency of Canada, 2019a, b).

Over a longer timescale, rates in the US from 1996 through 2018, as reported by FoodNET, show a marked decline from 0.53 cases per 100,000 in 1998 to 0.25 cases per 100,000 in 2001 (Fig. 2). This marked decline was attributed to the reduction in the risk of *L. monocytogenes* from RTE meat and poultry products. The combined efforts of the USDA FSIS and industry led to better environmental controls in production facilities and reformulation of products to reduce their ability to support the growth of *L. monocytogenes*.

Because surveillance of listeriosis is largely based on recognition of severe infections, usually requiring hospitalization, surveillance of listeriosis is not as sensitive to issues such as access to health care or changing practices in diagnostic laboratory testing, as is surveillance for more common enteric foodborne pathogens. Thus, longitudinal surveillance data allow for a reasonable assessment of established public health goals. At the time that FoodNET was established, the national public health goal (Healthy People 2000) for listeriosis in the US was 0.5 cases per 100,000 population. Demonstration that this goal was met, allowed the Healthy People 2010 goal to be reduced to 0.24 cases per 100,000. Although this goal was never quite achieved, the incidence of listeriosis in the US has remained low (<0.4 cases/100,000) since 2000.

National surveillance data are used to measure the effectiveness of the food safety system. Increased occurrence of cases detected through routine surveillance is used to identify specific outbreaks. Investigation of outbreaks is critical to identifying emerging food safety hazards or failures to control known hazards. In the absence of effective, routine surveillance, outbreaks such as occurred in South Africa in 2017–2018 can become very large before being recognized (Smith et al., 2019). Increased use of molecular subtyping by public health laboratories has increased detection of outbreaks among reported cases and improved the ability of public health agencies to identify the source of outbreaks (Jackson et al., 2016).

General trends in increased occurrence of cases may reflect changes in risk that are associated with specific commodities or industry segments or may reflect changes in behavior patterns or demographics in the population. For example, consumption of Mexican-style soft cheeses has been associated with increased risk of listeriosis among the Hispanic population in the US (Ibarra-Sánchez et al., 2017). Furthermore, the aging demographics in high-income countries means that more people are at higher risk of developing listeriosis (Pohl et al., 2017). This could lead to increasing rates of illness, even if the underlying risk of exposure through the food supply remained constant. Aging populations may be contributing to the increasing rates of illness noted across Europe.

Aging populations imply that to maintain a low rate of listeriosis over time, the risk of transmission through the food supply must be continuously reduced. As a result, identifying the drivers for changes in observed rates of listeriosis in the population requires the integration of epidemiologic data with data from food and environmental monitoring programs conducted by regulatory agencies and industry.

8. Risk assessments of *L. monocytogenes* in foods

An exhaustive survey of published quantitative microbial risk assessments (QMRA) focused on *L. monocytogenes* is beyond the scope of this document, however, a short historical summary of some of the significant documents in the area is useful. This short history is summarized in Table 2. The first documented quantitative microbial risk

Fig. 1. Incidence* of reported listeriosis, 2007–2018 (Australia, United States, Canada, European Union, United Kingdom, and France)
* Rates of listeriosis per 100,000 population reported to Australia, the US, Canada, the EU, the UK and France, 2007–2018
Data sourced from National Public Health Systems.

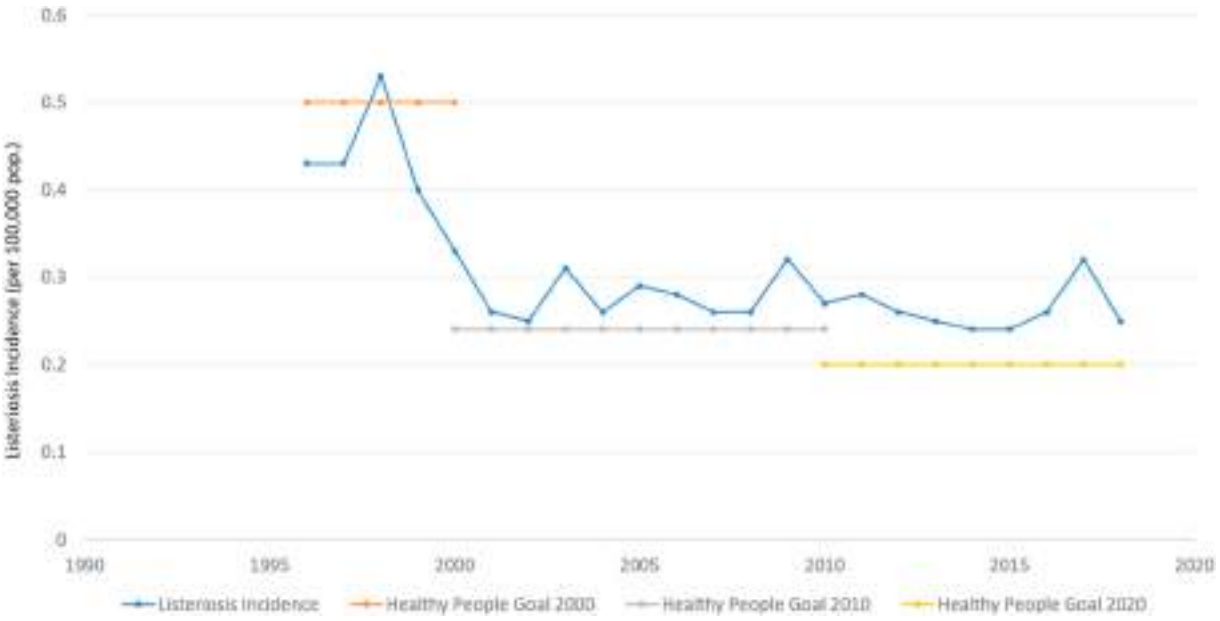

Fig. 2. Incidence of reported listeriosis in the USA, 1996–2018 (CDC, FoodNet).

Table 2
A chronological summary of selected publications from the *Listeria monocytogenes* quantitative microbial risk assessment literature.

Authors	Year	Topic	Region
Farber et al.	1996	Canada; Pâté and Soft Cheese	Canada
Bemrah et al.	1998	Soft Cheese Made from Raw Milk	France
Lindqvist & Westöö	2000	Smoked or Gravad Salmon and Trout	Sweden
FDA	2003	RTE Foods	US
Gallagher et al.	2003	Deli Meats	US
FAO/WHO	2004	RTE Foods	International
Ross et al.	2009	RTE Meats	Australia
USDA/FSIS	2010	RTE Meat and Deli Products	US
Endrikat et al.	2010	RTE Meat and Deli Products	US
Pradhan et al.	2009	Deli Meats	US
Akingbade et al.	2013	Retail Delicatessens	US
Pouillot et al.	2015a	Retail Delicatessens	US
Pouillot et al.	2015b	Dose Response Variability	US
Gallagher et al.	2016	Retail Delicatessens	US
Pouillot et al.	2016	Infectious Dose	US
Falk et al.	2016	At-Risk Populations	Canada
Pérez-Rodríguez et al.	2017	RTE Foods	EU
Buchanan et al.	2017	Literature Review	International
Ricci et al.	2018	RTE Foods	EU
Fritsch et al.	2018	Cold Smoked Salmon	France
Zoellner et al.	2019	Frozen Vegetables	US

assessment on *L. monocytogenes* in foods was published by Farber et al. (1996) and was specific to Canada. These were followed by more modest product focused risk assessments by Bemrah et al. (1998) for listeriosis risk from soft cheese made from raw milk, and by Lindqvist and Westoo (2000) on risks from smoked or gravad salmon and trout in Sweden. FDA and USDA published an extensive risk ranking for US foods posing a risk of listeriosis in 2003 (FDA, 2003), while USDA FSIS also published a risk assessment focused specifically on deli meats (Gallagher et al., 2003). These were shortly followed by a publication from FAO/WHO in 2004 (FAO/WHO, 2004) on *L. monocytogenes* in RTE foods as part of their microbiological risk assessment series. Ross et al. (2009) published a risk assessment specifically focused on RTE meats in Australia. International advances have continued to occur, with important updates recently coming from researchers in the EU (Pérez-Rodríguez et al., 2017; Ricci et al., 2018). Most recently, Zoellner et al. (2019) developed a quantitative microbial risk assessment to assess the lot-level listeriosis risk due to *L. monocytogenes* contamination in frozen vegetables consumed as a RTE food. The model estimated listeriosis risk per serving and the number of illnesses per lot, considering factors such as lot size, prevalence of contamination, and consumer handling prior to consumption. Scenarios simulating low levels of *L. monocytogenes* did not typically result in illness, while scenarios where more testing was performed increased the probability of finding a contaminated lot and reduced overall health risk.

One feature of risk assessments is their ability to be adapted and updated as new information becomes known, or for components of risk assessments to be published as stand-alone peer-reviewed articles. Five such examples arising from the US work on risks from RTE meat and deli products include the 2010 FSIS risk assessment (USDA/FSIS, 2010), a companion piece published in the Journal of Food Protection (Endrikat et al., 2010), a USDA-FDA collaboration (Akingbade et al., 2013), along with two other peer-reviewed articles (Pouillot, Gallagher et al., 2015; Gallagher et al., 2003).

Important advances relating to *Listeria* risk continue to be published, including refinements to dose-response modeling (Pouillot, Hoelzer et al., 2015), the development of user-friendly interfaces (Falk et al., 2016) and the incorporation of genomic data (Fritsch et al., 2018). For a more detailed and comprehensive summary of all the surrounding literature on the topic, the reader is directed to a recent review by Buchanan et al. (2017).

9. Recent outbreaks of listeriosis

The occurrence of cases detected through routine surveillance is used to identify specific outbreaks. Increased use of molecular subtyping by public health laboratories has increased detection of outbreaks among reported cases and improved the ability of public health agencies to identify the source of outbreaks (Jackson et al., 2016). In the US, molecular subtyping by PFGE was introduced with PulseNet, the National Molecular Surveillance Network coordinated by CDC in 1998. Prior to PulseNET, an average of 0.3 outbreaks of listeriosis per year were reported in the US, with an average of 69 cases per outbreak (Fig. 3). With the introduction of PulseNET, the number of outbreaks detected increased to 2.3 per year and the average size of the detected outbreaks decreased to 11.5 cases. In 2004, the *Listeria* Initiative was implemented to attempt to have every reported case interviewed to determine

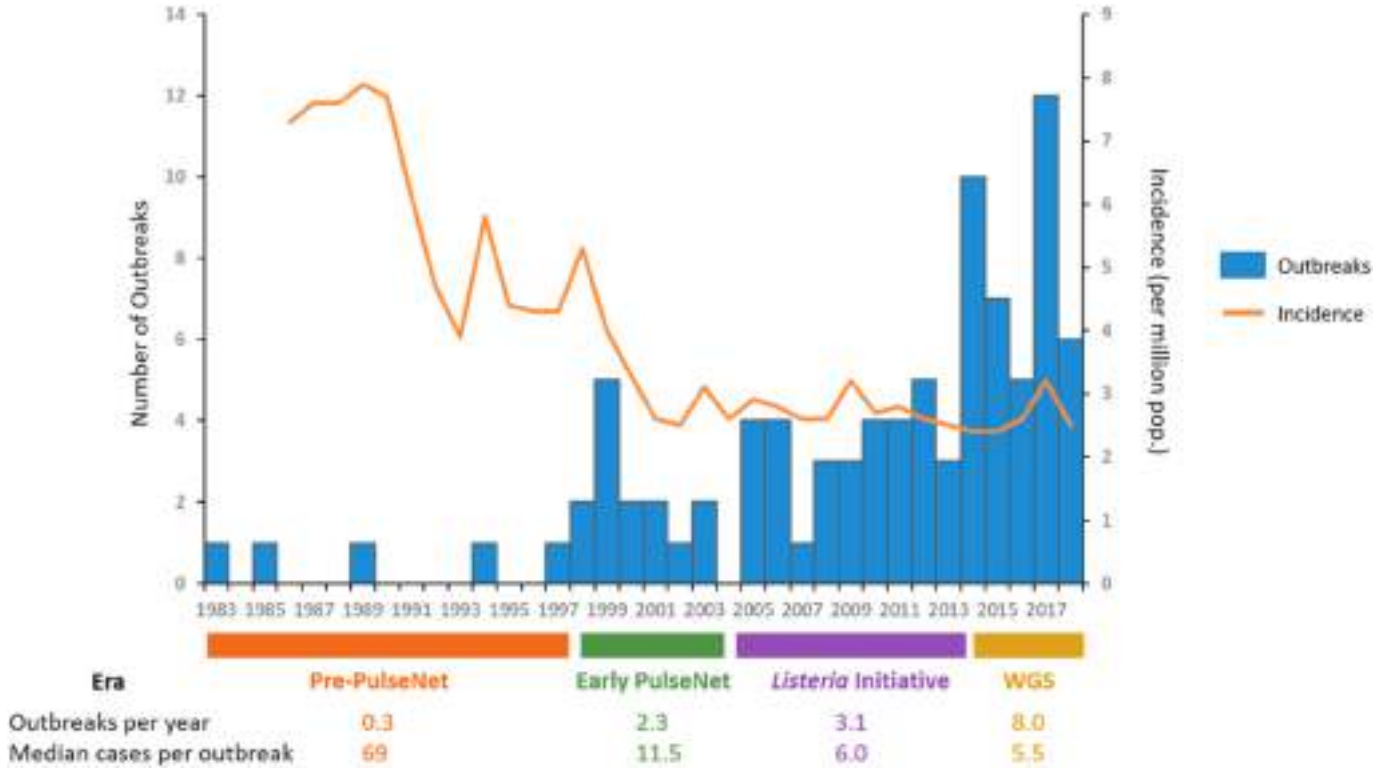

Fig. 3. Listeriosis outbreaks* and incidence in the USA: 1983–2018. (Modified from CDC-NORS, MMWR, FoodNet)
*Outbreaks reported to CDC, by year of detection. Data maintained as part of FDOSS, Foodborne Disease Outbreak Surveillance System, now part of NORS, National Outbreak Reporting System.

possible exposures and to have every case-associated isolate submitted to public health laboratories for subtyping by PFGE. With the *Listeria* Initiative, the number of reported outbreaks increased to 3.1 per year, and the average number of cases per outbreak dropped to six cases. Finally, the introduction of whole genome sequencing (WGS) increased outbreak detection to 8.0 per year, but the number of cases per outbreak dropped only marginally. Because WGS has allowed linkage of cases over time, the average size of detected outbreaks is being inflated by cases that occurred months before the outbreak was recognized. Of 30 outbreaks detected by WGS from 2015 to 2018 in the US, 9 (30%) included cases with onsets over 24 months before the outbreak was detected (see Fig. 3).

The distribution of multistate outbreaks reported in the US from 2011 through 2019 highlight the range of conventional (e.g., raw milk, deli meat) and novel food vehicles (e.g., enoki mushrooms, frozen vegetables, cantaloupes, caramel apples) detected in recent years (Table 3). Interestingly, outbreaks associated with novel vehicles such as cantaloupes or caramel apples were larger than outbreaks caused by more commonly identified vehicles. This likely reflects the impact that awareness of a potential vehicle has on the ability of public health agencies to identify the vehicle as the source for an outbreak. Increased awareness leads to more effective investigations.

Improved surveillance for listeriosis resulting in more outbreak investigations identifying food vehicles, also results in increased disclosure of these investigations (Desai et al., 2019). One measure of this increased awareness of listeriosis is the number of events reported through ProMED, a global outbreak reporting system that is operated by 50 subject matter experts in 35 countries who monitor news media and professional networks. From 1996 through 2016, ProMED identified 81 outbreak events (Desai et al., 2019). Events associated with novel food vehicles and international events increased over the study period.

Three recent outbreaks have significance for evaluating the public health impact of listeriosis and regulatory oversight of food production. The first outbreak associated with polony was recognized due to a marked increase in hospitalizations due to listeriosis in one province of South Africa. Overall, 43% of cases occurred among neonates <28 days of age, with 32% occurring among adults aged 15–44 years (Smith et al., 2019). This outbreak highlights the importance of having effective public health surveillance and effective regulatory oversight of food production facilities.

The second notable recent outbreak involved frozen corn and mixed vegetables produced in Hungary and distributed throughout the EU (European Food Safety Authority, 2018a). A total of 47 outbreak-associated illnesses from 2015 to 2018 were linked by WGS and epidemiologic investigation. WGS analysis of the *L. monocytogenes* strains demonstrated that the outbreak isolates were closely related to isolates from frozen corn, other frozen vegetable mixes and environmental samples from the processing facility. Enumeration studies of contaminated frozen vegetables demonstrated multiple samples in the range of 10–100 *L. monocytogenes* per gram (European Food Safety Authority, 2018b). Although cases were not systematically interviewed about consumption of frozen vegetables, many of those who were, noted consuming vegetables that were not frozen, but not cooked. Persistent environmental contamination of the vegetable freezing facility over a period of at least three years most likely led to the occurrence of this international outbreak. Although observed levels of contamination were <100 cfu/g, the potential for amplification post-thawing was noted. Exposure assessments of cases did not permit evaluation of this possibility. A recent expert scientific opinion published by EFSA (Koutsoumanis et al., 2020) in response to the Hungary frozen vegetables outbreak looked at the distribution and mean prevalence of *L. monocytogenes* in these products. Data was modeled to represent baseline (mean) best- (2.5th percentile) and worst- (97.5th percentile) case uncertainty scenarios pertaining to the consumption of frozen vegetables and likelihood of illness. The estimate even in the worst-case scenario shows that the number of listeriosis cases resulting from the

Table 3
Selected multi-state (US) and international outbreaks of listeriosis between 2011 and 2020.

Year	Product(s)	No. of cases	Country/ Region	Total US States	Reference(s)
2020	Enoki Mushrooms	36	US	17	Centers for Disease Control and Prevention, 2020a
	Hard-boiled Eggs	8	US	5	Centers for Disease Control and Prevention, 2020b
2019	RTE Meat Products	19 Belgium (1) Netherlands (2)	EU		European Centre for Disease Prevention and Control, 2019
	RTE Sandwiches	6	United Kingdom		Food Standards Agency, 2019
	Chilled Roaster Pork Meat	222	Spain		World Health Organization, 2019
	Cooked Diced Chicken	24	US/Canada	13	Centers for Disease Control and Prevention, 2019b
	Deli Sliced Meats and Cheeses	10	US	5	Centers for Disease Control and Prevention, 2019a
2018	Liver Pate	13	Austria		Cabal et al., 2019
	Pork Products	4	US	4	Centers for Disease Control and Prevention, 2018b
	Deli Ham	4	US	2	Centers for Disease Control and Prevention, 2018a
	Frozen Vegetables	47	EU		European Centre for Disease Prevention and Control, 2019
2017	Raw Soft Milk Cheese	8	US	4	Centers for Disease Control and Prevention, 2017
	RTE Meats Polony	1060	South Africa		World Health Organization, 2018; Thomas et al., 2020
2016	Frozen Vegetables	9	US	4	Centers for Disease Control and Prevention, 2016a
	Raw Milk	2	US	2	Centers for Disease Control and Prevention, 2016b
	Packaged Leafy Green Salads	19	US	9	Centers for Disease Control and Prevention, 2016c; Self et al., 2019
2015	Soft Cheeses	30	US	10	Centers for Disease Control and Prevention, 2015c
	Ice Cream	10	US	4	Centers for Disease Control and Prevention, 2015a
	Commercial Bean Sprouts	5	US	2	Centers for Disease Control and Prevention, 2015e
	Hispanic Style Soft Cheese	5	US	4	Centers for Disease Control and Prevention, 2015d
2014	Hispanic Style Soft Cheese	8	US	2	Centers for Disease Control and Prevention, 2014
	Caramel Apples	35	US	12	Centers for Disease Control and Prevention, 2015b
	Stone Fruits (Pluots, Peaches, Nectarines, Plums)	4	US	4	Chen, Burall, Luo, et al., 2016; Chen, Burall, Macarisin, et al., 2016
2013	Soft Cheeses	6	US	5	Centers for Disease Control and Prevention, 2013
2012	Ricotta Salata Cheese	22	US	14	Centers for Disease Control and Prevention, 2012
2011	Cantaloupe	147	US	28	Chen, Burall, Luo, et al., 2016; Chen, Burall, Macarisin, et al., 2016

consumption of uncooked frozen vegetables is 2600 cases per 10^{12} servings in elderly women and 3800 cases per 10^{12} servings in elderly men (Ages 65–74). The analysis demonstrated the probability of illness per serving is also 3600 times greater when consumed uncooked versus cooked. Based on a rough calculation using annual frozen vegetable production for the top five frozen vegetables consumed in the US (USDA, 2019), the recommended amounts customarily consumed (serving size; Food & Drug Administration, 2017), and the US population (US Census Bureau, 2019), the total number of frozen vegetable servings consumed annually in the US can be estimated. Using this rough estimate and applying the worst-case and best-case scenarios for uncooked frozen vegetables based on EU data for elderly men aged 65–74 (Koutsoumanis et al., 2020), there is likely a very low risk of listeriosis resulting from the consumption of uncooked frozen vegetables (see Supplemental Material).

The final outbreak with important implications for public health and food regulatory activity was an outbreak of *L. monocytogenes* linked to commercial ice cream production in the US (Chen, Burall, Macarisin, et al., 2016). An initial cluster of five cases was linked to a single hospital. All the cases with available exposure information had consumed milkshakes, while hospitalized for other conditions, and subsequently developed invasive *Listeria* infections. The implicated ice cream products were linked to a common production line. In order to investigate the relationship between exposure dose and risk of illness, 2320 samples of ice cream from seven different production dates were tested (Chen, Burall, Macarisin, et al., 2016). Remarkably, *L. monocytogenes* was isolated from 99.4% of the samples. The geometric mean MPN/g of different production dates ranged from 0.15 to 7.12, with an overall mean MPN of 3.57 *L. monocytogenes* per gram. Only four samples contained more than 100 MPN/g. The uniform and low-level contamination of these ice cream products suggests that virtually all the consumers who consumed the products had exposure to the outbreak-associated strain. An estimated 151,000 to 1,356,000 servings of ice cream contaminated by 10,000 *L. monocytogenes* organisms were consumed, including 4000 to 39,000 servings consumed by pregnant women (Pouillot et al., 2016; see Table 4). The fact that the only cases linked to the Kansas outbreak were hospitalized patients who consumed multiple milkshakes made with the product, suggests the possibility of an amplifying event related to the milkshakes. While environmental assessment at the hospital did not identify any problems with the milkshake machine, previous outbreaks have been attributed to persistent contamination of milkshake machines in hospital settings (Li et al., 2017).

The ice cream "outbreak" detailed above is complicated because although it is often referred to as a single outbreak, it represents two separate events, one associated with the Texas production facility and the second one with the Oklahoma (OK) production facility.

The Texas (TX) production facility was associated with the cluster of cases from the Kansas (KS) hospital. This was the facility from which the FDA did extensive sampling of products to identify the high rate of prevalence at very low levels of contamination (Pouillot et al., 2016).

There were 5 cases linked to the hospital. All had previously been hospitalized before developing listeriosis, and for the 4 cases with information, all had eaten milkshakes made with the contaminated ice cream. There appears to be one case for which specific exposure information could not be determined. Thus, all known exposures were to the milkshake rather than to the original ice cream product. One of these 5 cases had a strain of *L. monocytogenes* that differed from the ice cream isolate. However, CDC included this case in its case count because that case also drank milkshakes, but Pouillot et al. (2016) excluded that case from their dose response paper.

There was a second event linked to ice cream produced at an OK facility. This event was originally identified because of samples taken from ice cream cups collected during the investigation of the KS hospital outbreak. The strains from the OK facility were different from strains

isolated from the TX facility by PFGE and WGS. There were no OK facility linked cases in KS, but a search of PulseNET identified 6 human isolates that matched by PFGE: 4 in TX, 1 in Arizona and 1 in OK. One TX case differed by WGS and was excluded. Thus, 5 human cases were identified that matched the OK ice cream isolate. There were 3 TX cases which occurred in people who had previously been hospitalized at a hospital that had received ice cream cups, however, only 1 of these had a history of possibly eating the ice cream. In total, there is very little known about exposures for these OK facilities linked cases, other than that they were all retrospectively linked by PFGE/WGS. Although the CDC combined both the TX and OK events into a single multi-state outbreak, there was good case exposure information and product sampling information from the TX-product cluster, but very limited information from the OK-product cluster. Thus, we cannot definitively say any of these cases had exposure only to ice cream products as they were originally distributed.

Finally, the outbreak of listeriosis associated with ice cream offers some interesting similarities and contrasts to the 2011 outbreak associated with cantaloupe. In the 2011 cantaloupe outbreak, 94% of implicated cantaloupes collected from grocery stores were contaminated with an outbreak strain (McCollum et al., 2013). Most cases reported purchasing whole cantaloupes and had multiple cantaloupe exposures eaten over several occasions, suggesting the possible amplification of contamination over time. Although 7 pregnancy-associated cases were reported, the risk of illness was estimated to be approximately 1 per 10,000 exposed pregnant women (Imanishi et al., 2015).

Improvements in surveillance will continue to identify new food vehicles for outbreaks of listeriosis and help better distinguish the relative importance of raw commodities from contaminated food processing environments as major risk factors for human illness. Root cause analyses from these outbreak investigations will provide better evidence to improve *Listeria* prevention activities.

10. Specifics of the *Listeria monocytogenes* dose-response

The elucidation of dose-response relations for *L. monocytogenes* has been a work in progress for over 20 years. It has involved efforts by multiple research groups employing different approaches and different data sources. In each of these cases, investigators have attempted to take into account the epidemiology of *L. monocytogenes* infections which clearly demonstrates that invasive listeriosis is predominantly a disease of pregnant women, neonates, and those with a compromised immune system. The methods used have involved evaluations of the epidemiology of listeriosis outbreaks, the combination of annual disease statistics and *L. monocytogenes* contamination levels (Buchanan et al., 1997; FAO/WHO, 2004; Pouillot et al., 2016), animal modeling data (Roulo et al., 2014; Smith et al., 2008; Williams et al., 2007), and mechanistic models based on the bacterium's mode of infection (Buchanan et al., 2000, 2009). The method employed in the Food & Drug Administration (2003) risk assessment combined data from animal testing, epidemiological observations and annual disease statistics.

Table 4
Estimated attack rates from Pouillot et al. (2016).

Exposure scenario/ model	Number of Servings (Maximum Theoretical Attack Rate[a]), by Population				
	All	Highly susceptible	Pregnant	Age > 65	Age > 75
Lower	151,468 (0.3)	724 (69)	4363 (11)	23,024 (2.2)	11,664 (4.3)
Medium	618,448 (0.1)	1500 (33)	17,812 (2.8)	94,004 (0.5)	47,622 (1.0)
High	1,356,612 (0.04)	3264 (15)	39,071 (1.3)	206,208 (0.2)	104,460 (0.5)

[a] Maximum theoretical attack rate calculated as cases per 100,000 servings in the population group based on 0.5 cases occurring in that population group. In the absence of cases (other than the hospital cluster) attributed to these products, the actual attack rate is undefined.

One of the requirements for a non-threshold model for an infectious agent such as *L. monocytogenes* is that the decrease in the probability of disease from a specific dose becomes linear as the concentrations enter low dose extrapolations (FAO/WHO, 2003). This restricts the number of mathematical models that can be used to describe dose-response relations for *L. monocytogenes*. Some of the models used include the exponential, beta-Poisson, lognormal-Poisson, Hypergeometric, Weibull-gamma, and Gompertz models (Buchanan et al., 1997; FAO/WHO, 2003; 2004; Pouillot, Gallagher et al., 2015, Pouillot, Hoelzer et al., 2015 2016). Since the Weibull-gamma and Gomperz models do not have a slope of 1 at low doses, these models may be less appropriate. However, the specific model that is most effective is, in part, dependent on the underlying distribution of *L. monocytogenes* strains' ability to cause disease, the likelihood that they will be isolated from foods, their levels in the foods, and the likelihood and frequency that these foods would be eaten by consumers, particularly those consumers that are at increased risk due to underlying conditions or diseases. Thus, the diversity in the relative virulence of *L. monocytogenes* strains, the relative frequency and extent of food contamination, and the relative susceptibility among humans leads to substantial variability and uncertainty.

The simplest of the dose-response models that has been successfully used to describe the behavior of *L. monocytogenes* is the exponential model. It is a single parameter model that assumes that for any specific strain of the pathogen, there is no variability among the bacterial population. The dose parameter is referred to as the r-value, which can be viewed as the probability that a single cell of the isolate can cause a case of invasive listeriosis. The underlying assumption in this model is that each cell has the same probability of causing a disease, so that the probability of an adverse effect increases with an increasing number of cells ingested. The FAO/WHO *L. monocytogenes* risk assessment (2004) simplified the more complex dose-response model used in the FDA/FSIS risk assessment after observing that the exponential model accounted for the majority of the fit in that model. Typically, a dose-response model for the general population has a very broad confidence interval due to the variability in human susceptibility. However, the exponential model in combination with disease incidence data developed by French researchers allowed the FAO/WHO risk assessment team to develop a series of dose-response curves specific for various high-risk subpopulations, confirming that such subpopulations have a 10- to 10,000-fold increased susceptibility compared to the baseline population of healthy adults who are under 60 years of age. This technique has been used by several other groups to better define the risks associated with specific subpopulations and thereby decrease the uncertainty associated with *L. monocytogenes* dose-response modeling (FAO/WHO, 2004; Pouillot et al., 2009; Pouillot, Hoelzer et al., 2015, 2016).

The r-value approach above has also been used to develop dose-response relations for individual strains of *L. monocytogenes*. Differences in the association of invasive listeriosis with various *L. monocytogenes* serotypes have long been noted, with serotypes 1/2a and 4b being most commonly associated with listeriosis outbreaks (Pine et al., 1990; Food & Drug Administration, 2003; FAO/WHO, 2004; Orsi et al., 2011). In addition, differences in virulence are associated with specific genomic lineages. For example, the presence of "premature stop codons" (PMSC) in serotype 1/2c isolates of *L. monocytogenes* has been hypothesized to be responsible for the decreased incidence of listeriosis cases attributable to this serotype (Nightingale et al., 2005). Examining lineages I and II, it is estimated that their average Log (r-value) was −7.88 and −10.3, which would equate to the likelihood that a person would acquire invasive listeriosis from eating a single *L. monocytogenes* cell once in 75,857,758 times and once in 19,952,623,150 times, respectively (Chen et al., 2006). The ingestion of 100 g of food product containing 100 cfu/g of *L. monocytogenes* (100% prevalence) would result in a likelihood of a person acquiring invasive listeriosis of once per

7586 and 1,995,263, respectively, i.e., a factor 10,000 higher. The use of the r-value concept to establish individual dose-response estimates for individual strains of *L. monocytogenes* was expanded upon by comparing the r-values for strains with and without PMSC (Chen et al., 2011). The r-value for a set of *L. monocytogenes* isolates without PMSCs had an r-value of log (−8.13), equivalent to once in 134,896,288 times, while the r-value for strains with PMSCs was log (−10.68), equivalent to once in 47,863,009,232 times for a one cell exposure or a 10,000 fold greater factor for an exposure of 100 g of a food product containing 100 cfu/g of *L. monocytogenes*. These probabilities reinforce the fact that invasive listeriosis is a rare disease, despite it being a common low-level contaminant in foods. Pouillot, Hoelzer, et al. (2015) calculated r-values for invasive listeriosis based on data from the 2015 ice cream outbreak for four risk groups: highly susceptible, pregnant, age > 65 or > 75 years old and three exposure levels (low, medium and high), corresponding to the different numbers of contaminated ice cream products and exposure times. Logarithms of the reported r-parameter values ranged from −6.92 (high exposure, highly susceptible) to −8.72 (high exposure, > 65 or 75 years old). These correspond to a risk of invasive listeriosis from eating a single *L. monocytogenes* cell once in 8,333,333 times and once in 526,315,789 times, respectively. The decision about the "best" value to use to protect susceptible populations is ultimately the responsibility of risk managers, but the range of values in the paragraph above encompasses reasonable possibilities.

11. *Listeria* sampling and environmental monitoring

The prevalence, movement, and harborage of both *L. monocytogenes* and *Listeria* spp. in food production environments are complex phenomena. Environmental sampling and testing schemes to monitor the contamination are complicated to design, can be extremely expensive involving high numbers of samples, and difficult to scientifically validate. For these reasons, while new modeling tools are available (Zoellner et al., 2019), environmental monitoring efforts across the world are limited to very elementary practices directed towards indicator *Listeria* spp. findings. The most proactive form of this approach is colloquially termed as 'Seek and Destroy' and remains a significant component in a facility's toolkit to combat *L. monocytogenes* persistence (Malley et al., 2015; North American Meat Institute (NAMI), 2003).

Regulatory guidance to address environmental monitoring has pursued multiple approaches in different parts of the world and encompasses varied sampling and testing recommendations (e.g., FDA *L. monocytogenes* guidance, FSIS, *Listeria* rule, Canada, Codex, EFSA). Routine monitoring, for example, is applied as a means of verifying the effectiveness of sanitation procedures, hygienic design and practices, and the overall food safety system targeting the presence of *L. monocytogenes* in facilities. Over the years, a crucial movement in regulatory thinking has been an emphasis on the identification of *Listeria* spp. in the production environment, rather than on the direct identification of the pathogen. Most recently, the US FDA re-drafted its *L. monocytogenes* industry guidance, specifically recommending that positive *Listeria* spp. findings on food contact surfaces trigger re-testing and corrective actions be used following any repeat positives. This proposal provides flexibility to manufacturers by allowing them to evaluate and address the potential risk of *L. monocytogenes* in their production environments by testing only for the indicator species (i.e., *Listeria* spp.), while taking appropriate and timely corrective measures commensurate with a potential *L. monocytogenes* finding, thereby precluding the risks of regulatory non-compliance.

An active and successful environmental monitoring program targeting *L. monocytogenes* is difficult to define and it is an evolving process of continuous learning and improvement. However, it can be rooted in core microbiological principles of scientifically valid procedures for swabbing (suitable tools, methods and trained personnel), sampling (appropriate locations, timing, frequency, compositing), testing (accurate, timely, and cost-effective), and data and trend analysis (American Frozen Food Institute, 2019). Robust programs reflect not only the ubiquity, repeated introduction and movement of *L. monocytogenes* in the production environment, but also ongoing internal risk assessments relative to ingredients, processes, and the finished food products. The approaches used are intended to periodically identify positive findings and, combined with trend analysis, should provide facilities the needed knowledge to conduct root cause analysis and undertake timely corrective actions.

Environmental monitoring remains a significant defense to prevent the transfer of *L. monocytogenes* to food and manufacturers should rely on developing robust monitoring verification programs. However, they should also invest in more sustainable structural assessment and modifications. These may include, but not limited to, facility infrastructure such as air flow, hygienic zoning and movement of vehicular traffic and personnel, equipment hygienic design, personnel training and management engagement, all aimed at building awareness of the risks associated with the presence of *L. monocytogenes* and address its ability to persist and find harborage in food facilities (American Frozen Food Institute, 2019).

Robust environmental monitoring programs are consistently evolving paradigms specific to the facility, processes and foods, but manufacturers should incorporate reliable recordkeeping to inform both their deficiencies and improvements in the prevention and control of *L. monocytogenes*. The FSIS regulatory model mirroring the 'seek and destroy' approach applied in the US meat industry has demonstrated significant gains in the ability to manage the prevalence of *L. monocytogenes* in RTE meats, and serves as an excellent success story to be replicated in other areas of the food industry. While RTE foods can pose specific and direct risks to consumers relative to *L. monocytogenes*, the design and implementation of effective environmental monitoring programs should be recognized as crucial to the control of *L. monocytogenes* by the food industry.

More specific details on *Listeria* Sampling and Environmental Monitoring can be seen in the Supplemental Material.

12. Alternative approaches to current two-class sampling plans

The performance of sampling plans is dependent on the number of samples taken (e.g., $n = 1$, 5 or 60), and on the microbiological limit m (e.g., absence in 25 g, absence in 10 g, ≤ 100 cfu/g). Furthermore, a sampling plan can either not allow any sample to be above the limit m ($c = 0$) or accept a certain number of samples to be above the limit m ($c \neq 0$). The advantage of a non-zero-tolerance plan that has either a quantitative limit (e.g., $m = 100$ cfu/g) or $c \neq 0$, is that trend analysis can be performed, and an early warning can be provided, i.e., action can be taken before the process is not compliant. However, in order to have the same performance as a zero-tolerance sampling plan, more samples would need to be analyzed.

12.1. The performance of sampling plans

Various sampling plans were investigated to quantitatively compare their performance. For this, the International Commission on Microbiological Specifications for Foods (ICMSF), 2009 spreadsheet was used, and the performance was defined as the arithmetic mean concentration above which a sampling plan would reject a batch with more than 95% confidence, when the distribution of the organisms is log-normal with a standard deviation of 0.80 log cfu/g (Table 5). Other outcomes like the geometric mean and the performance for other standard deviations can be found in the Supplementary Material.

The performance of the US sampling schemes for the FSIS and FDA ("zero-tolerance" with 1 or 2 samples of 25 g) are between the two Codex limits. The Codex criterion for products supporting *L. monocytogenes* growth (5 samples) is much more stringent than the US criteria, while the criterion of Codex for products not permitting *L. monocytogenes* growth (100 cfu/g) is more lenient than the US criteria.

Therefore, one could say that the Codex plan with $n = 5$ for products permitting growth is stricter than the current US "zero-tolerance" criterion. In fact, the EU criterion for foods for infants and special medical purpose is even more stringent ($n = 10$) parallel to its increased risk.

The outcome of these performance calculations also depends on the standard deviation assumed. In general, homogeneous well-mixed food products have a low standard deviation, and less mixed products have a large standard deviation. Therefore, the performance for several standard deviations has also been calculated (Table 6). For very homogeneous products (SD = 0.25), the arithmetic mean concentrations are lower than for non-homogeneous products (SD = 1.2). However, for all standard deviations, when comparing the Codex criteria to the US criteria, the plan for products permitting growth is more stringent, while the plan for products not permitting growth is less stringent than the US criteria.

The number of samples with an equal total sample volume also influences the performance of the plan (Table 6). A plan with more samples with an equal total sample weight performs better, and even more so at a higher standard deviation (e.g., compare 5*25 g and 1*125 g, as well as 1*375 g and 15*25 g).

Ideally, microbiological criteria should be risk-based, but this is not always the case. For example, in the EU legislation, certain criteria do not seem to logically follow the level of risk (Zwietering, 2015). It is clear from many risk assessments for *L. monocytogenes*, that the risks in products permitting growth is much higher than products in which growth is not possible. The Codex criteria vary greatly (a factor of 4350, 3.6 logs, Table 5) between products permitting growth ($n = 5$; absence in 25 g) and not permitting growth ($n = 5$; levels below 100 cfu/g). The criteria in the US are equal for both types of products. The disadvantage of having a "zero-tolerance" for low-risk and/or foods not supporting growth of *L. monocytogenes* is that all positive outcomes result in a recall (red light), therefore potentially limiting the willingness to frequently sample. Additionally, no warning management indicator is available (yellow light). The Codex criteria for no growth products (having a quantitative limit $m = 100$ cfu/g) is more informative, as numbers are available, and warnings are observable and trend analysis can be performed.

Table 5
Performance of various sampling plans for *L. monocytogenes* defined as the concentration *C*, which is the arithmetic mean of a lognormal distribution with a standard deviation of 0.8, that is detected with a 95% probability.

	n	m	M	c	*C* (cfu/g)
EU: food for infants and special medical purpose[a]	10	0/25 g	–	0	0.031
Codex/EU foods supporting *L. monocytogenes* growth[b]	5	0/25 g	–	0	0.10
Codex/EU foods not supporting *L. monocytogenes* growth	5	100 cfu/g	–	0	434
FSIS[c]	1	0/25 g	–	0	4.3
FDA[d]	2	0/25 g	–	0	0.68

[a] Commission Regulation (EC) No 2073/2005 of November 15, 2005 on microbiological criteria for foodstuffs (http://data.europa.eu/eli/reg/2005/2073/2014-06-01).

[b] Codex Alimentarius Commission. 2007. Guidelines on the application of general principles of food hygiene to the control of *Listeria monocytogenes* in foods. CAC/GL 61–2007. Food and Agriculture Organization and World Health Organization, Rome.

[c] FSIS Routine Lm Risk-Based (RLm) product samples are 5 composited 25g samples from 5 individual product samples making a single 125g sample. Food Safety Inspection Service Compliance Guideline: Controlling *Listeria monocytogenes* in Post-Lethality Exposed Ready-to-Eat Meat and Poultry Products. 2014.

[d] FDA takes two 125g samples, blends or stomachs the samples, and then takes the equivalent of two 25g analytical units for analysis (https://www.fda.gov/media/92979/download).

The 3-class sampling plan can be very effective in providing a "warning signal." To illustrate this, several scenarios can be observed where *n* samples are taken and one sample is accepted to be positive ($c = 1$), for which a limit of 100 cfu/g is accepted. In Table 7, the number of samples to be tested can be seen for sampling plans with 5 samples and the number of samples which are needed to have a similar performance to the FDA or FSIS sampling schemes.

A rejection is defined as:

1. For a two-class qualitative plan: more than *c* samples positive in an enrichment of *x* g material. For example, more than zero out of 10 samples of 25 g positive for *L. monocytogenes* for foods for infants or special medical purpose (Table 5), or more than zero of 5 samples of 25 g positive for *L. monocytogenes* for a product supporting growth (Table 5), or more than two of 10 samples positive for the presence of Enterobacteriaceae in 10 g of powdered infant formula (Codex microbiological criteria for powdered infant formula).
2. For a two-class quantitative plan: more than *c* samples above the *m* value. For example, more than zero out of five samples >100 cfu/g of *L. monocytogenes* (Table 5), or more than 15 out of 50 samples with >1000 cfu/g of *Campylobacter* (EU criteria for broiler carcasses)
3. For a 3-class plan, more than *c* samples in the marginal region (between *m* and *M*) or 1 or more samples above *M*). For example, i) more than 1 out of 5 samples contain *L. monocytogenes* in 0.1 g, or one or more samples contain >100 cfu/g of *L. monocytogenes* (Table 7) or, ii) more than 2 out of 5 samples with >500 cfu/g of mesophilic bacteria

Table 6
Performance of various sampling plans for *L. monocytogenes* defined as the concentration *C* (cfu/g), which is the arithmetic mean of a lognormal distribution that is detected with a 95% probability for various standard deviations.

	n	*m*	S.D.			
			0.25	0.4	0.8	1.2
EU: food for infants and special medical purpose[a]	10	0/25 g	0.013	0.014	0.031	0.15
Codex/EU foods supporting *L. monocytogenes* growth[b]	5	0/25 g	0.027	0.033	0.10	0.73
Codex/EU foods not supporting *L. monocytogenes* growth[b]	5	100 cfu/g	110	136	434	3621
FSIS[c]	1	0/25 g	0.19	0.35	4.3	143
FDA[d]	2	0/25 g	0.077	0.11	0.68	10
1*125g[e]	1	0/125 g	0.038	0.071	0.86	28.5
1*375g	1	0/375 g	0.013	0.024	0.29	9.5
15*25g (= 375g in total)	15	0/25 g	0.008	0.009	0.017	0.065

[a] Commission Regulation (EC) No 2073/2005 of November 15, 2005 on microbiological criteria for foodstuffs (http://data.europa.eu/eli/reg/2005/2073/2014-06-01).

[b] Codex Alimentarius Commission. 2007. Guidelines on the application of general principles of food hygiene to the control of *Listeria monocytogenes* in foods. CAC/GL 61–2007. Food and Agriculture Organization and World Health Organization, Rome.

[c] FSIS Food Safety Inspection Service Compliance Guideline: Controlling *Listeria monocytogenes* in Post-Lethality Exposed Ready-to-Eat Meat and Poultry Products. 2014.

[d] FDA takes two 125g samples, blends or stomachs the samples, and then takes the equivalent of two 25g analytical units for analysis (https://www.fda.gov/media/92979/download).

[e] FSIS RTE Sampling Program (larger sample) - Protocol in Routine Lm Risk-Based (RLm) product samples are 5 composited 25g samples from 5 individual product samples making a single 125g sample. Food Safety Inspection Service Compliance Guideline: Controlling *Listeria monocytogenes* in Post-Lethality Exposed Ready-to-Eat Meat and Poultry Products. 2014.

or more than zero samples containing > 5000 cfu/g (Codex microbiological criteria for powdered infant formula).

For a 3-class plan, the limits *m* and *M* are often quantitative (e.g., 500 cfu/g; 5000 cfu/g), but they could also be partly qualitative like in Table 7 (e.g., *m* = 0/25 g and *M* = 100 cfu/g), or both be qualitative (e.g., *m* = 0/25 g, *M* = 0/0.1 g), although these last two types are currently not being used.

These 3-three class sampling plans in Table 7 have as microbiological limits a mixture of a qualitative limit (e.g. 0/25 g) and a quantitative limit (100 cfu/g). Practically one could, for example, enrich 25 g of product in 225 ml of enrichment broth, and, in parallel, count one sample for each of the *n* samples. Alternatively, one could also freeze 1 ml of product for each of the *n* samples and enumerate only those samples that are positive after enrichment.

Such a sampling plan has strength in that it can distinguish between a low frequency, low level accidental contamination (that can happen) and either a higher frequency or a higher-level contamination (both of which, one would like to prevent). The test detects the higher frequency by detecting more than one positive in, for example, the 3rd, 4th, or 5th samples which results in non-acceptance. For example, in the US ice cream outbreak, the *L. monocytogenes* levels were not high, but there was consistent contamination indicating inadequate processing and environmental control. On the other hand, such a 3-class plan can also signal an alarm if an infrequent point contamination is detected to be very high. For example, if only 1/100 samples contain a million *L. monocytogenes* per gram, many illnesses can follow from a large batch of food. For evaluation of the potential level of the contamination, a positive sample can also be enumerated. This would only need to be done for the generally infrequent positives, but would also require one to withhold all of the additional (frozen) stored samples, and an additional holding time before product release. Testing could also be done in parallel to get immediate results, however, in this case, both qualitative and quantitative testing would need to be done at the same time for all of the samples.

In order to be able to calculate the performance of this type of mixed qualitative/quantitative plan, the ICMSF spreadsheet was adapted (see Supplementary Material).

To have 3-class sampling plans with a similar performance to the FSIS/FDA criteria, (4.3 and 0.68 cfu/g, respectively) with an *m* value of absence of *L. monocytogenes* in 0.1 g, sample numbers would need to be very high (24–94 samples). However, for a 25 g enriched sample (c = 1), 3 and 4 samples would give slightly better performance than the USDA and FDA sampling plans, respectively. The performances of additional sampling schemes which have been developed, can be seen in Table 8.

The value of *M* (20, 50, 100 cfu/g) does not have a large impact on the performance of the plan; it only has an impact at very low sample weights (i.e., a small *m* of absence in 0.1 g). The *c*-value and the *m* value do have a relevant effect on the performance, e.g., increasing *c* from 1 to 2 gives about a factor 2.5 lower performance; the effect of sample weight on the performance is approximately proportional (see Supplemental Material).

Table 7
Performance of various 3-class sampling plans for *L. monocytogenes* defined as the concentration *C*, which is the arithmetic mean of a lognormal distribution with a standard deviation of 0.8 that is detected with a 95% probability.

	n	m	M	c	*C* (cfu/g)
3-class	5	0/0.1 g	100 cfu/g	1	70.4
3-class	24	0/0.1 g	100 cfu/g	1	4.2
3-class	94	0/0.1 g	100 cfu/g	1	0.68
3-class	5	0/g	100 cfu/g	1	7.9
3-class	7	0/g	100 cfu/g	1	3.7
3-class	18	0/g	100 cfu/g	1	0.66
3-class	3	0/25 g	100 cfu/g	1	1.4
3-class	4	0/25 g	100 cfu/g	1	0.57
3-class	5	0/25 g	100 cfu/g	1	0.32

Table 8
The performance of various 3-class sampling plans for *L. monocytogenes* defined as the concentration *C* in cfu/g, which is the arithmetic mean of a lognormal distribution with a standard deviation 0.8 that is detected with a 95% probability.

m	*M*	*c*	(*n* = 3)	*C* (*n* = 4)	(*n* = 5)
0/25 g	100 cfu/g	1	1.4	0.57	0.32
0/25 g	100 cfu/g	2	11.2	2.1	0.87
0/10 g	100 cfu/g	1	3.45	1.4	0.79
0/10 g	100 cfu/g	2	26.4	5.2	2.2
0/1 g	100 cfu/g	1	33.1	14.0	7.9
0/1 g	100 cfu/g	2	167	45.8	20.8
0/0.1 g	100 cfu/g	1	247	118	70.4
0/0.1 g	100 cfu/g	2	597	261	145
0/25 g	50 cfu/g	1	1.4	0.57	0.32
0/25 g	50 cfu/g	2	10.8	2.1	0.87
0/10 g	50 cfu/g	1	3.45	1.4	0.79
0/10 g	50 cfu/g	2	24.3	5.1	2.2
0/1 g	50 cfu/g	1	31.5	13.7	7.8
0/1 g	50 cfu/g	2	130	41.2	19.6
0/0.1 g	50 cfu/g	1	206	104	63.9
0/0.1 g	50 cfu/g	2	385	191	115
0/25 g	20 cfu/g	1	1.4	0.57	0.32
0/25 g	20 cfu/g	2	9.7	2.1	0.87
0/10 g	20 cfu/g	1	3.4	1.4	0.79
0/10 g	20 cfu/g	2	20.3	4.9	2.1
0/1 g	20 cfu/g	1	28.2	12.9	7.5
0/1 g	20 cfu/g	2	86.8	33.1	17.2
0/0.1 g	20 cfu/g	1	145	79.4	51.2
0/0.1 g	20 cfu/g	2	191	109	71.7

12.2. Compositing

For qualitative sampling plans with *c* = 0, theoretically, there should be no effect on the outcome of the test when compositing a sample (and the whole sample is enriched). However, practically there can be an effect, since the initial level of one positive sample "diluted" in the composite starts at a lower concentration, so it might take longer to get to the detection level. Additionally, it could be that a separate enriched sample would turn positive, but if mixed with another sample with a heavy background flora, would give a false-negative reaction due to inhibition by the background microorganisms. Practically, these effects will not occur often, and compositing could be accepted.

For quantitative sampling plans there is a difference in the results after composting. For example, for a plan with *m* = 100 cfu/g, the outcome of the test could be positive when doing separate testing of the 5 samples (e.g., 160, 10, 10, 10, 10 cfu/g), but the composite would show 40 cfu/g as an outcome (≤100 cfu/g). Due to inhomogeneity these effects are expected, so compositing should generally not be used in quantitative sampling plans (unless these criteria are addressed).

Compositing should also not be used for plans where *c* is not equal to zero, since the number of samples that are positive cannot be determined and compared with *c*.

In the supplementary material, calculations are provided which were obtained using Excel software. Results are also presented assuming other standard deviations (0.25, 0.4 and 1.2). Plan performances are also expressed as the geometric mean. The general conclusions are similar, regardless of whether the geometric or arithmetic means are used. There is also some discussion on the effects of high background levels of *L. innocua* on the recovery of *L. monocytogenes*, as well as on the frequency of sampling.

12.3. Implications of performance standards and extensive sampling plans for regulators and industry

The application of performance standards and sampling plans that use a sample size of n > 1 will have time, cost and resource implications for both regulatory agencies and the food industry. However, this should not stop regulators from pursuing these performance standards and

sampling plans, if they are equal in performance and of added benefit to all stakeholders in the food chain.

1. From a regulatory perspective, inspectors would be advised to implement a finished product sampling plan consistent with the recommended performance standards. Depending on the performance standard chosen, this may involve additional steps to detect and enumerate *L. monocytogenes*. Regulatory agencies may need increased budgets to sustain performance standard level testing, however, it would facilitate science and risk-based decision making.
2. At the food processing facility level, manufacturers may implement periodic product testing as a part of their broader food safety program verification; while these costs may be incremental, the benefits derived from verification of the system would result in a more robust food safety program.
3. Across the broader industry, performance standards are likely to be used as supply chain controls with specified lot and batch testing requirements. This may result in an increase in the time to report, as well as increased costs and needed resources.

13. Risk-benefit assessment

Risk-benefit assessment (RBA) is a process aimed to support risk management decisions that maximize the "net good" per unit of limiting resources expended by explicitly considering not only the risks to the population being considered, but also the benefits that may also be realized by any strategies that may be imposed. In RBA, risk is the probability of an adverse effect in response to exposure to an agent, and benefit is the probability of a positive health effect and/or the probability of a reduction of an adverse health effect in reaction to exposure to an agent. Note that when a reduction in risk is the benefit being explored, this can also be referred to as a risk-risk trade-off process. Cost-benefit assessment (CBA) is another form of RBA where the risks and/or the benefits are described in terms of financial value (European Food Safety Authority Scientific Committee, 2010).

Historically, risk assessment and benefit assessment were generally separate activities (as a result of distinct methodologies). As a result of this separation, policies were based on a detailed safety assessment, but sometimes a less extensive (if any) exploration of the risk-benefit relationship (Fransen et al., 2010). Risk-benefit assessment frameworks have a history in diverse risk domains, for example, in drug approval processes where regulators (e.g., FDA) aim to determine that the drug is not only effective, but that its expected benefits outweigh its potential risks to patients (Guo et al., 2010), and in transportation, where the cost of fatalities/injuries is balanced against the cost of the regulation; see Thompson et al. (2002) for a discussion on the importance of validating potential risk and benefit assessments as it relates to health, safety, and environmental regulations. Specifically, the authors caution that regulatory analysis tools seldom produce findings that are biased against these types of regulations.

In the last two decades, the application of RBA for food issues has been increasing. In food, risk-benefit assessments are generally focused on the risk-benefits from a singular food and are aimed at identifying optimal intake of that food by exploring the "trade-off'. Food issues where RBA has been applied include chemical hazards in food, nutritional questions of optimal intake, and more recently, microbiological contamination issues. For example, the risk-benefit trade-off associated with fish consumption has received much attention (Mozaffarian & Rimm, 2006; Ponce et al., 2000). Fish consumption is associated with beneficial fatty acids which have many health benefits, including promoting normal nervous system development and reducing heart disease risk. It is also recognized that some species of fish are contaminated with heavy metals including mercury, which is a neurotoxicant which can lead to developmental delays in children when exposed *in-utero*, making this an issue of importance in women of child-bearing age. Increased intake of fish leads to increased benefits from the fatty acids, but also increased risk from increased mercury intake. Other risk-benefit assessments have focused on nutritional components of food, for example, essential elements that have a u-shaped dose-response curve. If an individual consumption level is insufficient there may be adverse health effects; equally if consumption exceeds a safe upper limit, there may also be adverse health effects, but between the two limits is a range of intakes conferring benefit over risk (Renwick et al., 2004). More recently, Berjia and colleagues examined the risks posed by *L. monocytogenes* in smoked fish (Berjia et al., 2012), again considering the benefits from the intake of omega-3 fatty acids in fish, but comparing to the risks posed by infection with *L. monocytogenes* that may contaminate the product.

13.1. Risk tolerability

When considering the risk-benefit trade-off, a key concept is that of risk tolerability. Risk tolerability is a public risk management principle that is concerned with a judgement of the appropriate level of risk to the public from an activity managed by government or an institution. Risk tolerability is a system or regime-level evaluation that is based on the acknowledgement that society cannot afford to reduce all risks and the reality that costs matter to the system and to society, and that risks vary in the ease with which they may be reduced. The UK Health and Safety Executive (HSE, 2001) developed and elaborated guidance on a Tolerability of Risk Framework as part of the implementation of the legal requirement that public risks be As Low As Reasonably Practicable (ALARP) with social and economic factors being taken into account. The Framework begins with the assumption that many societal risks are often not unconditionally or universally accepted but are worth taking in view of their careful management and the benefits that are gained from the activity. This is a risk-based approach that views risk tolerability as a problem of trade-offs.

There are 3 levels of risk under the ALARP framework (summarized in Fig. 4): **Acceptable risk**: the region where the risk is low enough that it requires no further reduction, and/or further effort to reduce the risk is not reasonably practicable. Risks in this zone should be monitored and reduced if risk increases or if reduction measures become more practicable. **Tolerable risk** is the region that begins at the threshold of acceptability and meets a defined safety objective and there is no need to reduce further. This region extends to the lower safety limit. The UK HSE defines a tolerable risk as a managed risk at a level that is appropriate in view of benefits gained and other contextual and ethical factors (HSE, 2001). **Unacceptable risk** is the region where risk is greater than the basic safety limit. Risks in this area are unlikely to ever be considered acceptable without a dramatic change in circumstances.

Risk tolerability guidelines or limits are often relatively crude and are usually expressed as the risk of death to an individual in a year. Different individual risk criteria have been adopted as guidelines or as legal requirements in various countries. Some common risk aversions are built into some of the levels, with public risk limits being stricter than those for workers, and societal risk criteria reflecting a presumed societal aversion to events that involve multiple fatalities. When determining land use and risks to the population in the surrounding area, the following risk limits have been defined (Duijm, 2009):

- *De minimis* risk: agreement in the EU on individual fatality risk of 10^{-6}/year for the general population
- Flemish, Dutch & British define a fatality risk of 10^{-5}/year for small non-vulnerable groups
- UK and Flemish define a lower limit of 10^{-7}/year fatality risk for some vulnerable groups

13.2. Application of risk-benefit assessment in food

Risk-benefit Assessment should generally follow the paradigm of risk assessment, and should include (1) hazard and positive health effect identification, (2) hazard and positive health effect characterization

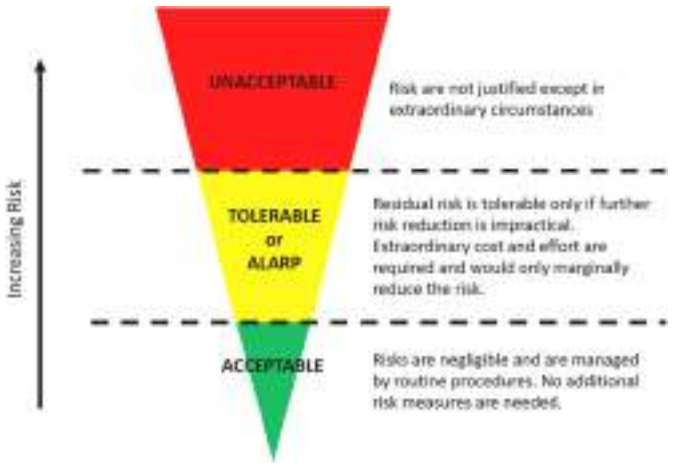

Fig. 4. Levels of risk under the "As Low as Reasonably Practicable" (ALARP) Triangle (Neilson et al., 2017).

through dose-response functions, (3) exposure assessment, and (4) risk and benefit characterization including risk-benefit comparison (Fransen et al., 2010). The risks and benefits that are relevant to exposure will vary by situation, and the complexity with which they can be measured and predicted. To enable risk-benefit comparison, the assessment should provide a semi-quantitative or quantitative estimate of risks and benefits at relevant exposures using common metrics. The comparison of risks and benefits using a composite metric enables expression of the outcome of the risk-benefit assessment as a single net health impact value. Examples of common metrics include population health metrics such as Health-Adjusted Life Years (HALYs), Disability-Adjusted Life Years (DALYs), and Quality-Adjusted Life Years (QALYs). Using a population health metric allows diverse health outcomes to be combined into a single net impact value.

The identification of the risks and benefits to be included in the risk-benefit comparison for a specific scenario should be a consultative process ensuring the extent of risk-benefit consideration is appropriate for the specific risk to be managed in terms of the stakeholder need. In reality, not all aspects of risk and benefit can be included in a timely analysis, and may not all fall under the mandate of the risk manager conducting the exercise, e.g., the results of a risk-benefit assessment for *L. monocytogenes* in fish could have implications for the fishing industry, but the risks to the industry (for example industry decline, job losses) may (or may not) be considered secondary to the consideration of the health risks and therefore not included in the assessment process.

Readily measured risks and benefits would include:

- **Reduction in the risk of illness and death**, including either or both sporadic cases and outbreak cases. The complementary benefit would be a reduction in those risks. A direct follow-on from risk of illness is cost per illness (if it can be directly quantified).
- **Avoiding economic losses** from outbreaks including industry losses and other economic impacts such as health care costs, societal costs (days of lost work, Value of Statistical Life (VSL)). The benefit would be loss avoidance. Outbreaks incur significant costs. A listeriosis outbreak in Ontario (Canada) in 2008 was estimated to have resulted in direct and indirect costs to the implicated processing facility of CAN $23–100 million (not including wider industry losses). The cost of illness was estimated to be $200 million in case costs, including both health care costs and societal costs (Thomas et al., 2015).
- **Avoiding unnecessary recalls.** A survey (Grocery Manufacturers Association, 2011) found that 5% of companies incurred over US $100 million in direct and indirect costs. These costs are in-turn passed on to the consumer through increasing food costs. In the US, salmonellosis incorrectly linked to tomatoes by the FDA cost the tomato industry more than an estimated US $100 million in related losses in 2008 (Gurtler et al., 2018). (Contamination was eventually traced to jalapeño and serrano peppers from Mexico).

There are more complex risks and benefits that can and should be considered. These include:

- **Consumer confidence.** With the increase in access to information about food recalls and food-related outbreaks, consumer confidence in food is an important component of the food system. A study reported that 83% of consumers can name a product recalled because of safety concerns in the previous two years, and 57% have stopped eating (temporarily or permanently) a particular food because of a recall (Berjia et al., 2012).
- **Food security.** Foods may be replaced by less (or more) nutritious foods as a result of availability (recall), accessibility (cost), or confidence (trust).
- **Food waste.** Consumers are shifting toward the desire to avoid food waste where possible. Food recalls lead to increased food waste, potentially of food that had minimal risk. This impact is economically less tangible but is an issue of increasing concern to consumers.
- **Environmental effects.** Shifts in food preference and food use (as a result of food risks/benefits either perceived or demonstrated) might change land use and impact natural resources use. These impacts could be transient or irreversible. For example, livestock production compared to plant-based agriculture impacts land use choices and green-house gas emission levels (Röös et al., 2017).

13.3. Challenges

Conducting RBA poses many fundamental challenges and requires coordination across the risk-management team (which includes assessors and stakeholders) to determine which risks and benefits should be explored and how they should be measured (lives lost, HALY, VSL, etc.). Ideally, the RBA would be accompanied by a cost-effectiveness analysis, with the aim of pairing a desirable risk-benefit profile with a practicable cost-effectiveness and consideration of who bears that cost, i.e., is it industry, society, government (e.g., centralized health care, oversight inspection costs), or a combination, and can that cost be tolerated?

14. Consumer food handling and communication related to *Listeria monocytogenes*

Consumers play a role in risk reduction associated with *L. monocytogenes* as individuals make food handling decisions in purchasing, storage and cooking practices in their homes. Although most consumers claim to have knowledge and understanding of food safety related to food preparation and handling, observational research conflicts with the self-reported practices when observing meal preparation (Redmond & Griffith, 2003, 2004, 2005; Byrd-Bredbenner et al., 2008; Cates et al., 2019; Clayton et al., 2003, 2018; Fischer et al., 2007; Worsfold & Griffith, 1995). Two of the most common consumer food safety behaviors that increase *L. monocytogenes* risks are not using proper refrigeration storage conditions and undercooking foods (Anderson et al., 2004; Clayton & Griffith, 2004; James et al., 2017; Redmond et al., 2004; Scott, 2003). The reasons for the disconnect between recommendations and behavior are unclear, but lack of perceived importance or risk control benefit may be contributing factors (Clayton & Griffith, 2004; Levine et al., 2017).

While there is a lack of *L. monocytogenes*-focused consumer food safety behavior research in the literature, other studies stemming from the domestic kitchen, suggest that consumers fail to handle and prepare their food safely. Phang and Bruhn (2011) investigated consumers; preparation of hamburgers in their homes and found that 22% of participants (N = 199) did not cook them to a safe internal temperature. Additionally, only 4% of participants checked endpoint temperature

with a meat thermometer (Phang & Bruhn, 2011). Another study (Dedonder et al., 2009) observed the preparation of frozen, uncooked, breaded chicken products, which have been linked to outbreaks associated with consumer mishandling. Only 7% (N = 41) of participants were observed adhering to the product labeling instructions that were provided, with five participants using a meat thermometer to determine the doneness of the chicken product.

Further insights into the challenges related to changing consumer *L. monocytogenes* thinking and behaviors in relation to *L. monocytogenes* control measures can be gleaned from Meah (2014) who undertook an ethnographic study of home kitchen practices in the UK to evaluate people's food handling and explore their cultural constructs in the context of food safety. Study participants presented perfectly 'good' reasons for engaging in what food authorities might consider 'bad' behavior. Food handling behaviors were often formed through reasoned and practical logics in which food safety was considered in combination with other factors such as experiential knowledge and beliefs, established habits and routines, concern for the environment and minimizing food waste. For example, consuming food past its best-before-date could be considered a food safety risk, but beneficial for reducing food waste. Study participants considered themselves as being responsible not only for themselves, but also to others in the wider sense (Meah, 2014). Many time-temperature measurement indicators and packaging sensors aimed at ensuring safe consumption have the potential to mitigate food safety risks associated with poor storage, mishandling, and improper food preparation behaviors. However, these technologies are likely to be extremely expensive and difficult to commercialize, particularly for multi-component foods.

Depending on who is asked, one concept that is important to tackle is overcoming consumer perceptions of who holds responsibility for ensuring consumers eat safe food in light of increasing risks. In a poll of American adults conducted in January 2014, 50% of respondents felt that food processors and packagers were to blame, 19% assigned the blame to the federal government, and 16% cited those who grow or raise food as being responsible (Shannon-Missal, 2014). However, the public's views on risk and responsibility are likely to differ from those of others in the farm-to-fork food chain (Kher et al., 2011; Levine et al., 2017). A 2014 survey on consumer perceptions found that 67% of Americans are confident in the safety of their food supply, and only 18% were concerned about food contamination and related illnesses (International Food Information Council, 2014).

It is paramount to not discount the role of consumers in making decisions and practicing safe behaviors related to reducing pathogenic *Listeria* risks. Rather, consumers should be engaged and not patronized and unduly blamed for failing to recognize risk reduction steps. Food safety as a shared responsibility, including consumers, and impacting *L. monocytogenes* risks requires an open discussion with consumers of risky foods, how they become contaminated, and control measures that can reduce risks in a home kitchen.

14.1. Consumer insights: lessons from outbreaks with NRTE foods

One of the biggest situations that can impact consumer exposure to *L. monocytogenes* is the confusing nature of what foods are ready-to-eat and which are not. While this difference may seem obvious to those close to the food safety system, in multiple outbreaks this confusion has led to illnesses. In outbreaks linked to frozen poultry, consumers indicated that they considered the product to be fully cooked, had prepared the product in a microwave, and failed to measure the internal temperature of the product prior to consumption—each element serving as a potential contributing factor to contracting a foodborne illness (Kenny et al., 1999; Smith et al., 2019; MacDougall et al., 2004; Medus, 2006a, 2006b). In a 1998 outbreak linked to frozen foods, investigators identified consumer confusion about the raw nature of the product as the primary reason consumers failed to fully cook. Sickened individuals believed the product was fully cooked and only needed to be reheated and prepared in a microwave oven. Furthermore, when questioned, most individuals claimed to have prepared the entrée per the manufacturer's instructions. An additional outbreak was identified from August 2005 to February 2006 involving 41 cases of salmonellosis associated with raw, frozen breaded stuffed chicken entrées. As a result, the processor of the implicated entrée voluntarily recalled approximately 75,800 pounds of product. Dr. Robert Post, USDA FSIS Director of Labeling and Consumer Protection, released the following statement; "It is likely, that by improving the cooking instructions as well as documenting that cooking methods are validated as part of the official labeling record, a situation like the one that led to the recall could be avoided" (Post, 2006). Despite the public health interventions attempted after each outbreak, at least 15 additional outbreaks with frozen entrees, pizzas or vegetables have identified the same risk factors as the index outbreak in 1998—failure to follow label instructions, preparation of the raw product in a microwave oven, and failure to use a food thermometer.

14.2. Consumer handling risk factors identified in outbreaks associated with NRTE foods

The process for manufacturing some NRTE products can sometimes include steps that make the product appear to be fully cooked, which can confuse consumers. Frozen kale for instance, due to blanching has the appearance of a frozen cooked green. Another example is NRTE frozen breaded poultry entrées which incorporate a short frying or baking step to set the surface batter and breading. This short heating process (pre-browning) causes the NRTE product to appear fully cooked to many consumers.

The potential exists for consumers to buy NRTE foods in bulk and discard the packaging, with the accompanying cooking instructions and precautionary statements, to save freezer space. A case-control study completed in Canada reported that one quarter (n = 82) of participants repackaged large boxes of frozen products into smaller freezer portions most of the time (MacDougall et al., 2004). Furthermore, 32% did not retain the cooking instructions from the original packaging. Consumers then relied on their memory of how to properly prepare the entrée.

14.3. Consumer insights: lessons from outbreaks linked to ready to eat (RTE) foods: high-risk populations, food choice

Listeriosis outbreaks and illnesses have been linked to both RTE foods and NTRE foods, and consumers' responsibility and influences on the safety of each of these types of products are different. In situations where consumers have been linked to *L. monocytogenes* illnesses from RTE foods, there are usually at least one of these factors involved: at-risk individuals consuming foods known to be high risk for *L. monocytogenes* contamination (deli salads, deli meats), individuals unsafely storing foods that support the growth of *L. monocytogenes* (cut cantaloupe, deli meats), or individuals provided foods by health care institutions where *L. monocytogenes* risks are not being adequately controlled (ice cream, sandwiches).

Outbreaks associated with RTE foods highlight the need for better instructions on home refrigerator temperature displays and better temperature control, cooking/heating as an alternative for specific types of foods or avoiding high risk foods altogether.

14.4. What about cooking instructions, safe handling instructions and labels as measures to control L. monocytogenes in consumer homes?

Practical instructions must be available to consumers, as overly complex instructions may be difficult for them to follow. Most consumers do not cook with a food thermometer when preparing convenience products. Therefore, manufacturers must develop products using the worst-case scenario: a segment of the population will not see, read or follow manufacturer's cooking instructions, or see them as not needed or

too confusing. To combat the lack of compliance with instructions, the information presented on food labels should be accurate and simple. Ariely and Levav (2000) determined that too much information may be overwhelming to consumers or target audience. Similarly, Carter-Young et al. (2007) reported that overly complicated information might deter consumers from making a food purchase. In addition to complex instructions, there are multiple factors that may also limit the effectiveness of a label. These include, consumers not taking the time to read product labels, the size of the print, consumers' concerns about accuracy, and a lack of understanding due to language barriers. Nayga et al. (1998) reported that time restraints experienced by working consumers may limit the time spent reading food labels prior to preparation. Several studies have found that consumers believe the print size used on labels is too small (Harper et al., 2007). Sloan (2003) suggests that manufacturers should create larger labels, catering to older individuals such as aging baby boomers and older generations who currently account for 30% of the U.S. population. According to the US Census, in 2018, there were 52 million people aged 65 and older, and this age group's share of the population grew from 12.4% in 2000 to 16.0% in 2018 (US Census Bureau, 2018). Buzby and Ready (1996), through surveys, found 55.9% of consumers used food labels; however, only 10.2% fully trusted the information being presented. Furthermore, McIlveen and Semple (2002) reported that 19% found labels difficult to understand. According to Rothman et al. (2006), approximately 90 million Americans do not have the necessary skill set to read and understand product labels. When designing new product labels, manufacturers should consider such factors to increase the effectiveness of the information being presented to consumers.

Certain high-risk groups may benefit more from having cooking instructions with more specific food safety guidance. Food-safe recipe interventions should focus on targeting those who write recipes for groups who are at a greater risk for *L. monocytogenes* illness, including those who are or who prepare recipes for pregnant women, older adults, and those with compromised immune systems. Targeting food-safe recipe interventions toward those who write recipes for male audiences may also be beneficial, since men tend to demonstrate poorer food safety behaviors as compared to women (Byrd-Bredbenner et al., 2008; Patil et al., 2005).

14.5. Social media as a vehicle for communication related to Listeria monocytogenes risks

Social media provides many opportunities for food safety and health risk communications, including the ability to respond quickly and to reach a wide variety of people with tailored messages. However, exclusive reliance on social media is exclusionary for some groups at high risk for listeriosis (Overbey et al., 2017). In addition, while social media can be an asset, it has its limitations, specifically the lack of control on accurate messages and information overload. (Rutsaert et al., 2014; Overbey et al., 2017).

14.6. Where do we go with consumer messages related to listeria in foods? A risk communication approach

Risk communication is intended to provide people with the information they require, to enable their decision-making about the acceptability of a hazard (Morgan, Fischhoff, Bostrom, & Atman, 2002). Cultural and social factors need to be considered in designing messages (FAO, 1999), so that individuals have the information they need to determine the personal relevance of potential risks (Jacob et al., 2010). To be meaningful, food safety information must be able to be integrated into the complex purposes and routines of consumers' everyday food practices, and the broader societal constructs in which these take place (Evans, 2011; Meah, 2014).

Verbeke et al. (2007) reported that experts in food risk management tend to view the general public as deficient in understanding food hazards and associated risks; they display behavioral patterns and make choices that seem irrational or illogical or at least inconsistent with expert opinions and scientific knowledge. As noted by Bob Lalasz, the director of science communication for the Nature Conservancy, there is the assumption that "the public isn't getting the gravity of the problem – because if they did, how could they fail to act?" (Contractor & DeChurch, 2014). In other words, if people had more knowledge or a different attitude about *L. monocytogenes* risks, their food safety practices would improve. However, this deficit-of-knowledge premise has been criticized for its lack of appreciation of the social, cultural and practical complexities in which consumers' everyday practices are embedded (Halkier & Jensen, 2011) and is not supported by evidence.

So-called teachable moments need to be carefully selected for communication about risks and often those who are declaring these moments to be ideal for messages are not basing their decisions on risk communication literature. To be effective, messages about *L. monocytogenes* should be rapidly distributed at appropriate times, tailored to the target audience, and contain reliable information (Frewer et al., 1998; Jacob et al., 2010). Statements providing direction and to which the audience members could personally relate, are considered, to be particularly persuasive. Consumers are motivated if they perceive a personal ability to control risk (Mullan & Wong, 2009). Messages need to come from trusted sources as well, and for many groups at risk for *L. monocytogenes*, this means addressing message delivery through primary or specialized healthcare providers.

Communications efforts will be wasted if people already know the information or consider it irrelevant (Fischhoff & Downs, 1997). Providing generalized risk messages will be ineffective, unless the risk affects everyone equally (Cope et al., 2010). Messages about risks should be clear and specific, and tailored for the audience's estimated level of comprehension (Lundgren & McMakin, 2013; Covello, 2003). Galarce and Viswanath (2012) recommended that communication planners be mindful of factors related to the communication process, such as culture, gender, age, language, race/ethnicity, and income and education levels of the target audience, as well as factors that might impact implementation of desired behaviors, including financial resources, location, transportation and healthcare access. Combining written, verbal, and visual formats can also improve effectiveness (Durant, 2002). Important points should be highlighted throughout the material. Information presented should be concise and in plain language. Research suggests that many people misunderstand quantitative information, leading to a misinterpretation of risk (Cunningham & Boom, 2013). Providing too much information is a common problem (Foster & Käferstein, 1985) and should be avoided; messages that are difficult to decipher or burdensome to receive are easily ignored (Verbeke, 2008). Research indicates that people can have difficulty remembering more than three messages and recall of technical messages may also be poor (Sugerman et al., 2012).

15. Conclusions

It should be noted that in all the global risk-based strategies implemented or considered, none absolutely assures the elimination of listeriosis. Regulatory efforts should primarily be directed at RTE foods that support the growth of *L. monocytogenes*. Furthermore, recommendations for regulatory compliance actions such as a product recall should not be made upon finding low levels (<100 cfu/g) of the organism in a food not supporting *L. monocytogenes* growth or in a NRTE food unless: i) the GMP status of the plant is in question; ii) the plant has a prior history of violations, recalls, etc., iii) there is evidence of an illness(es) linked to the product; iv) there are repeat findings of *L. monocytogenes* in the product and/or v) the product is known to be targeted to at-risk individuals.

From a public health standpoint, there is little to be gained from using government resources to test and recall low-risk RTE or NRTE products that do not support the growth of the organism, e.g., sunflower seeds; frozen NRTE foods bearing validated on-package cooking

instructions that ensure safe consumption. As evidenced by many years of studying *L. monocytogenes*, a multi-pronged approach to the control of *L. monocytogenes* in RTE foods is needed. The following are recommendations for best practices in the control of *L. monocytogenes* in RTE foods.

1) Following good manufacturing practices (GMPs) as a key foundational piece in terms of *L. monocytogenes* control in RTE food facilities.
2) Using Hygienic Zoning - Designing and managing the flow of traffic as it relates to personnel, supplies, product and equipment, can significantly reduce the potential for *L. monocytogenes* cross-contamination.
3) Hygienic Design - The hygienic design of equipment and facilities in food facilities is one of the most important *L. monocytogenes* control components.
4) A well designed and executed sanitation program that includes detailed written procedures (i.e., SSOPs), master sanitation schedules, as well as appropriate validation and verification procedures (e.g., environmental monitoring). SSOPs also need to include detailed instructions on equipment disassembly required as part of sanitation procedures.
5) A comprehensive and well-designed *Listeria* spp. environmental monitoring program that includes root cause analysis, trend analysis and does not treat positive results as a failure in the system, but rather as a sign that the program is running effectively.
6) i) End product verification testing. Strong consideration should be given to alternate sampling approaches to the current 2-class presence-absence sampling plans that are being used in some countries for low risk foods that do not support the growth of the organism. So called "zero-tolerance" approaches actually discourage companies from doing aggressive sampling to find positives. In addition, there is no "warning management indicator" (see 6 ii below). If the industry were to more widely adopt zone 1 testing and/or finished product testing without being immediately penalized, this would very likely lead to better overall control of *L. monocytogenes*. In fact, regulatory policies that incentivize aggressive environmental monitoring and elimination of *L. monocytogenes* on food contact surfaces, offer an effective approach towards public health protection.
   ii) The disadvantage of having a "zero-tolerance" approach for low risk foods that do not support the growth of *L. monocytogenes* is that all positive outcomes inevitably result in regulatory compliance action such as a product recall, therefore potentially limiting the willingness of manufacturers to frequently sample and test finished products. Additionally, there is no "warning management indicator" available. In contrast, if one were to use a 3-class sampling plan, e.g., with an $n = 4$; an analytical unit of 25 g (m), and have maximally one sample out of 4 ($c = 1$) positive, but not being over the limit of 100 cfu/g (M), the performance of this 3-class sampling plan for *L. monocytogenes* (defined as the concentration C in cfu/g, which is the arithmetic mean of a lognormal distribution with a standard deviation 0.8, that is detected with a 95% probability), would be better than the FDA's zero-tolerance 2-class sampling plan of 2×25 g. Thus, if one sample of the four is found to be positive, but is below 100 cfu/g, this is still acceptable, and gives a warning signal/heads-up to the company or regulatory agency taking the sample, before a potential recall has to be performed. Furthermore, this result indicates that the contamination is i) not widespread (only one positive) and ii) not at a very high level ($M = 100$ cfu/g). These 3-class sampling plans are unique in that they are a mixture of a qualitative limit (e.g., 0/25 g) and a quantitative microbiological limit (100 cfu/g). Additionally, in the current monitoring dynamic, a large volume of *L. monocytogenes* testing proceeds without the benefit of subsequent enumeration – thereby potentially losing data that would help to improve risk assessments related to the presence of *L. monocytogenes* in foods.
7) Future efforts in the area of risk assessments should include using big data to better inform the assessments. In addition, risk-benefit assessments should be strongly considered as an additional tool to help regulators decide when and if a recall is warranted. The substantial benefits of not doing a recall on low-risk foods that do not support the growth of *L. monocytogenes* include i) not losing consumer confidence, ii) maintaining a secure and sufficient food supply, iii) decreased food waste, iv) avoiding negative effects on the environment, and v) avoiding unnecessary and costly food recalls.
8) Consumer food handling/communication approaches that place an emphasis on simple and practical labelling instructions should be adopted. Appropriate on-package, focus-tested, simple and practical messaging combined with effective consumer education campaigns, used to positively influence consumer behavior in at-risk populations, can be very effective in reducing the risk of acquiring foodborne listeriosis.
9) Effective and consistent science-based education of all health care workers and the public in terms of avoidance of high-risk foods for at-risk populations, selecting lower risk options for common foods, i.e., making wise food choices, handling and preparing food safely, and ordering "smart" when ordering in or eating out should be developed and implemented.

In summary, using all of the above best practices, along with a risk-based policy that treats foods not supporting growth from foods supporting growth differently, i.e., does not use a zero-tolerance approach for RTE foods not supporting growth of the organism, currently offers overall the best evidence-based scientific approach to the control of *L. monocytogenes* in RTE foods. We recommend that, in general, frozen foods labeled with cooking instructions should be considered as NRTE foods and must be cooked prior to consumption, and food safety education and guidance to at-risk consumers regarding cooking instructions should be a priority. What is needed is an evidence-based, globally harmonized public health approach to the definitions of RTE and NRTE foods along with guidance on how these definitions should be applied in any regulatory policy on *L. monocytogenes*.

Declaration of competing interest

The authors have no competing interests to declare.

Acknowledgements

The authors thank Dr. Robert Buchanan (University of Maryland, College Park), Dr. Phil Voysey (Campden BRI), Dr. Lory Reveil and Dr. Donna Garren (American Frozen Food Institute for assistance with technical discussion, industry perspectives and preparing and formatting the manuscript. The authors also thank the American Frozen Food Institute for providing meeting and administrative support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodcont.2020.107601.

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