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A review on the characteristics, taxanomy and prevalence of *Listeria monocytogenes*

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Abstract : *Listeria monocytogenes* is a Gram-positive bacterium that is commonly isolated from food sources. This opportunistic human pathogen is the causative agent of listeriosis, an illness that mainly effects immunocompromised, the elderly, infants, and pregnant women. Ever since its detection, listeriosis cases has been very prevalent and commonly associated with food sources such as dairy products, ready-to-eat food, and poultry. The prevalence of listeriosis is of public health concern and proper management is required to control this illness from spreading widely. Thus, this review seeks to elucidate a better understanding on the characteristics, taxanomy, prevalence and their associated food sources, as well as management methods in order to devise proper control actions to reduce listeriosis incidence worldwide.

Keywords: *Listeria monocytogenes*; Gram-positive; listeriosis; dairy products; characteristics; prevalence

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Introduction

The bacterium *Listeria monocytogenes* is an ubiquitous facultative saprotroph which present widely in the soil, plants, ground water and vegetation[(1;2)]. Animals, such as cattles, sheeps, goats and poultry which fed on these silages are also identified as a host of this pathogen. As the causative agent of listeriosis, *L. monocytogenes* has been identified as animal pathogen since 1920s [(3)]. Over the last two decades, *L. monocytogenes* has been associated with many foodborne diseseas in humans[(3;4;5)]. Humans who consume contaminated food, especially ready-to-eat (RTE) food, dairy products, meat and poultry, will later develop listeriosis[(6;7;8)]. Despite the advancements in food preparations, healthcare system, and public awareness, this pathogen remains as a major cause of foodborne illness.

This bacterium was first identified by Murray in 1926 from unusual sudden death of laboratory rabbits in Department of Pathology of Cambridge. Due to its striking characteristic of mononuclear leukocytosis, the isolated microorganism was named *Bacterium monocytogenes*[(9;10)]. Prior to 1926, this pathogen was actually

encountered in 1891 by Hayem in France, 1893 by Henle in Germany and 1911 by Hulphers (which he named the organism as *Bacillus hepatis*)[11]. In 1927, Pirie discovered a unique microorganism which was responsive for "Tiger River disease" (later also known as listeriosis) in South Africa from gerbilles and named it *Listerella hepatolytica*, devoting it in honour of Lord Lister. Both the strains discovered by Murray and Pirie were found to be similar by the National Type Collection at the Lister Institute in London, and it was named *Listeria monocytogenes*[10].

Initially, *L. monocytogenes* was known to cause veterinary illness till Nyfeldt isolated this bacterium from 3 patients who succumbed from infectious mononucleosis-like disease in 1929. Nonetheless, its route of transmission was obscured until 1980 when a series of outbreaks associated with food occurred[11;12]. Listeriosis first well-documented foodborne outbreak was reported in Canada in 1983 after consumption of contaiminated coleslaw [4]. Ever since then, many reported outbreaks happened in high-income countries including United States of America, Japan and Europe, predominantly attributed to meat and poultry products, dairy products, seafood and vegetables[13]. Fish and fish products are known to be frequently contaminated with *L. monocytogenes*. For instance, this microorganism was isolated from 44% of fresh prawns in Malaysia[14], 10.5% of fish patties in Malaysia[15], 7.5% and 13.6% of crab and smoked fish samples in the US, respectively[1], and 5.5 to 12.1% of minced tuna and fish roe products in Japan. In 2011, a severe and deadliest listeriosis outbreak occurred in United States of America (USA). The outbreak was associated with cantaloupe and caused 146 illneses with 30 deaths and one miscarriage[16].

The high case fatality rate of listeriosis has demanded a need for scrutined identification and surveillance of *L. monocytogenes*. This bacterium is able to infect the human food chain directly or via animal farms[17]. A contaimination level above 10^4 CFU/g is professed as a high level of contaimination and responsible for listeriosis[18;19]. Anything below 10^2 CFU/g of *L. monocytogenes* contaimination in food unlikely to cause clinical illness[20], however there is reported levels of 10^2-10^4 CFU/g of *L. monocytogenes* causing illness in immuno-comromised people[19;21]. According to WHO, pregnant women, the elderly or individuals with a weakened immune system, such as people with immuno-compromised status due to HIV/AIDS, leukaemia, cancer, kidney transplant and steroid therapy, are at greatest risk of severe listeriosis and should avoid high risk foods[22].

L. monocytogenes has spread widely in the environments and management of Listeria in food production sector requires constant surveillance. Hence, better understanding on the characteristics, taxanomy, prevalence and their associated food sources, as well as management methods is necessary in order to devise proper control actions to reduce listeriosis incidence worldwide.

2. Characteristic of *Listeria monocytogenes*

L. monocytogenes is characterized as a short, Gram positive, non-spore forming and facultative anaerobe. It is a bacillus that may sometimes appear singly or in short chains resembling Streptococci[1;6;23]. It is a non-fastidious bacillus with low G+C % DNA content[1;24]. In addition, it is a facultative intracellular microorganism in which its expression of flagellum-based motility is dependent on the growth temperature, with the desirable temperatures being less than 30 ^oC[25].

This bacterium occurs naturally in environments and often reported to be isolated from human, animals, food products and food processing plants including abattoirs and smokehouses[26]. *L. monocytogenes* grows rapidly on most of the commonly used bacteriological media. On nutrient agar, bluish grey, smooth and slightly raised colonies of the diameter 0.2-0.8mm are generally observed after 24 hours of incubation[6]. A characteristic blue-green iridescence is demonstrated under obliquely transmitted light, making the colonies readily discriminated, even among high numbers of contaminants[6;27]. Furthermore, it displays a characteristic of end-over-end tumbling motility at room temperature and this can be seen by an umbrella-shaped pattern that develops overnight incubation in a semisolid agar[27;28].

As a psychotropic foodborne pathogen, *L. monocytogenes* is capable of multiplying at a range of temperatures 1-45^oC and remains moderately inactivated at temperatures below 0 ^oC, thus making RTE foods with a relatively long shelf-life of particular concern[1;6]. Temperatures above 50^oC can completely inactivate the microorganism[1]. This thermo-related characteristic allowed WHO to ensure high-temperature short-time pasteurization (71.7^oC/15 sec) is sufficient to completely inactivate normally populating *L. monocytogenes* in raw milk [6]. Besides, its resiliency is proven by the ability to tolerant acid (pH range 4.4 to 9.6) and high salt concentration (up to 10% NaCl), and the propensity of forming biofilms in order to thrive in food-processing environments[1;6;29].

3. Taxanomy

Listeria genus consists of 17 species: *L. monocytogenes*, *L. ivanovii*, *L. seeligeri*, *L. innocua*, *L. welshimeri*, *L. martii*, *L. rocourtiae*, *L. grayi*, and recently discovered *L. weihenstephanensis*[30], *L. fleischmannii*[31], *L. floridensis*, *L. aquatica*, *L. cornellensis*, *L. riparia*, *L. grandensis*[32], *L. booriae* and *L. newyorkensis*[33]. Among these species, *L. grayi* is the most distantly related species[1;23]. Both *L. ivanovii* and *L. monocytogenes* are known to cause listeriosis primarily in ruminants and human, respectively[1;34].

Although all species are phenotypically very similar, they can be easily differentiated by the following 5 tests: acid production from mannitol, D-xylose, L-rhamnose and α-methly-D-mannoside, and hemolysin production[6]. *L. monocytogenes* is catalase positive, urease test positive, Voges-Proskauer test positive and oxidase test negative[6;27;28]. It hydrolyses esculin and sodium hippurate, and shows beta-hemolysis on blood agar. Other characteristics include CAMP test positive with *Staphylococcus aureus* and negative with *Rhodococcus equi*, production

of acid but not gas from D-glucose, production of acid from D-salicin, L-rhamnose and α-methyl-D-mannoside, no production of acid from D-mannitol or D-xylose, no reduction of nitrates to nitrites, methyl red positive, negative reactions for hydrogen sulphide production and ammonia production from arginine[6;28]. However, since identification using biochemical methods are laborious, time-consuming and of greater chance inaccuracy, molecular typing procedures are commonly employed[35]. The high sensitive and discriminatory genotypic approach, such as pulsed-field gel electrophoresis (PFGE) and multi-virulence-locus sequence typing (MVLST) are frequently used recently to identify an outbreak.

L. monocytogenes is one of the human foodborne pathogens of great public concern. It can be classified into 12 serotypes (1/2a, 1/2b, 1/2c, 3a, 3b, 3c, 4a, 4b, 4c, 4d, 4e and 7), which is designated based on the immunoreactivity of the cell surfaces antigens, O and H. 1/2a, 1/2b and 4b were identified to cause most (95%) human listeriosis, with 4b serotype most frequently (98%) associated with outbreaks[23;34]. 1/2a and 1/2b serotypes were commonly related to sporadic cases[23].

L. monocytogenes isolates can also be categorized into at least 4 evolutionary lineages, with different but overlapping ecological niches[26]. Lineage I which consists of serotypes 1/2b, 4b, 3b and 3c, are associated with most human listeriosis outbreak due to their high pathogenecity. It contains 2 epidemic clones (ECs) of serotype 4b (ECI and ECII) that have been associated to multiple listeriosis epidemics globally and also significantly overrepresented among sporadic cases[36]. Isolates in this subgroup carry listeriolysin S hemolysin that is not present in others[26]. Evidences of low prevelance of plasmids and insertion sequence elements in these isolates, suggesting the existence of mechanisms that limit the acquisition of foreign DNA by horizontal gene transfer. Lineage II which consists of serotypes 1/2a, 1/2c and 3c, are commonly isolated from food, nature and farms. It is often associated to animal listeriosis and sporadic human cases. Most are virulence-attenuated due to premature stop codon mutations (PMSC) in *inlA* and *prfA*. The isolate are more resistant to bacteriocins and have higher genetic recombination rates than that from lineage I, thus probably confers an advantage for their survival in environment. They have better ability to be recovered in certain enrichment media, indicating their enhanced ability to survive environmental stress and hence related to their genuine overrepresentation in foods. Lineage III and lineage IV are less clinically important as they had low incidence among human listeriosis, suggesting of reduced human virulence.

4. Prevalence of *Listeria monocytogenes*

The World Health Organization (WHO) has estimated around 600 million people are infected with foodborne disease yearly[37]. Foodborne diseases effect the socioeconomic development by straining the healthcare system, as well as harms the country's economic, tourism and trade[37]. The identified foodborne pathogens are such as *Salmonella* sp.[38;39;40;41], *Listeria* sp.[42;43] and *Vibrio* sp.[44;45;46] are often associated with foodborne gastroenteritis cases worldwide. *L. monocytogenes*, the causative agent of Listeriosis is known to cause sporadic cases, which a specific food source is rarely identified. The occurrence of ≥ 3 listeriosis cases of the same pulsovar strain over a period is defined as cluster[47]. An outbreak is considered when the clusters of cases caused by a source strain are greater than expected during a specified period of time and place. It is challenging to investigate the origin of an outbreak as listeriosis has long and variable incubation period (3 to 70 days), which can lead to recall bias and difficulty in establishing an appropriate exposure period for food histories, and it will be much difficulty to identify rapidly foods that are not typically known to be a source of contamination in humans[48;49].

4.1 United States

The US Centers for Disease Control and Prevention (CDC) has reported listeriosis was responsible for an approximately 1,600 illnesses and 260 deaths annually in the US. In 2013, the annual incidence was 0.26 cases per 100,000 individuals, with a total number of 123 cases, 112 hospitalizations and 24 deaths were reported[50;51]. The incidence had declined by approximately 42% in 2012 as compared to that of in 1996-1998. The signification declines in the number of outbreaks in ready-to-eat (RTE) red meats and poultry is due to the regulatory initiatives and industry actions that was implemented between 1998 and 2008. In contrast, listeriosis outbreaks is more prevalent from dairy products[52]. The US has identified a number of listeriosis attributed food sources including fruit and vegetables (e.g., celery, lettuce, cantaloupe, sprouts, stone fruit and caramel apples), as well as ice cream.

There were no significant changes observed in incidence between 2006-2008 and 2012. In Texas, machine cut diced celery which was served in 5 different hospitals caused listeriosis[53]. The infected patients were over 55 years old, with mean age of 80 and had underlying health illnesses. 5/10 of the patients died and listeriosis was attributed as the cause of death. All 10 patients had one or more immunocompromising conditions or were receiving corticosteroid or acid-reducing treatments that could have increased their susceptibility to invasive listeriosis. The largest multistate outbreaks in the US history took place in 2011 since 1998, associated with cantaloupe consumption from Jensen Farms in Colorado[50;54]. 147 cases were reported among residents of 28 states, resulting in 33 deaths and 1 miscarriage. The median patient age was 78 years; most ill people were over 60, and 99% of the patients were hospitalized. Seven of the cases were related to pregnancy or were newborns. With the nationwide implementation of Listeria Initiative (LI) since 2005, the strong association of outbreaks to cantaloupe was rapidly identified and its transmission was efficiently halted in less than 2 weeks as compared to the one-month delay between outbreak detection and product recall during 1985 outbreak associated with Mexican-style cheese[50;55]. This outbreak is extraordinary because it is associated with melon and comprising of widely differing PFGE pattern combinations and 2 serotypes (1/2a and 1/2b).

In 2011, another multistate outbreak associated with the consumption of Mexican-style cheese among the Hispanic, pregnant women was reported[56]. 7 pregnancy-related cases were identified and all reported to have consumed Mexican-style cheese during the month before the onset of illness. 2 out of 7 cases experienced stillbirths and 5 neonates were affected. Investigation had suggested post-pasteurization contamination as the pasteurization procedure of the milk was properly done.

Recently, five significant outbreaks were announced by CDC. During the period of September 2013 to October 2014, 5 cases related to Hispanic-style soft cheese (quesito casero) consumption were reported. 4 were hospitalized and 1 death was announced, and among these cases, 3 were identified to be pregnancy-related and a newborn was diagnosed with listeriosis[57]. In February 2014, 8 people were infected with 1 succumbed from the listeriosis, due to consumption of fresh cheese curd (Cuajada en Terron) produced by Roos Food[58]. In June and August 2014, 5 cases suggestive of consumption of mung bean sprouts from Wholesome Soy Products, Inc, were reported from two US states. All were hospitalized and 2 deaths had occurred[59]. A multistate outbreak associated to commercially produced, prepackaged caramel apples was later reported in December 2014. As of January 2015, 32 cases were reported from 11 states - 31 hospitalization cases and 7 deaths cases have been reported. 31 were hospitalized and 7 deaths have been reported. Among these deaths, at least 3 were resulted from listeriosis. 10 cases were pregnancy-related, with resulting in abortion. 3 cases of meningitis were diagnosed among otherwise healthy children aged 5-15 years. 25 of 28 (89%) patients have a history of eating commercially produced, prepackaged caramel apples. The outbreak strain was identified in the Californian packing plants. On 6th January 2015, Bidart Bros of Bakersfield voluntarily recalled all Granny Smith and Gala from this processing plant[60]. Lately in February 2015, *L. monocytogenes* was isolated from single-serving ice-cream during a routine sampling, and it was believed to cause 10 cases and 3 deaths[61].

4.2 Europe

In the European countries, there is an increase in incidence from year 2000 (4.7 cases/million persons) to 2006 (6.3 cases/millions person)[47;62]. Total of 1554 cases were confirmed in 26 EU members in 2007, with an average notification rate of 0.3 per 100, 000 population[62]. A increasing pattern of incidences were seen in France, Finland, Denmark, England, Belgium and Wales, whereas a decrease pattern was observed in Sweden. However, the reason of the increase number of incidence cases remains unclear. In France, it was proposed that the reduction of salt content in food products as a preventive measure for hypertension recommended by the French Food Safety Agency in 2002, has result in foods, such as RTE meat products, to be more frequently and heavily contaminated in 2006-2007[47;62]. The trend continues to demonstrate increment statistically, along with seasonal pattern over the period 2008-2012. In 2012, a total of 1642 confirmed cases were reported with a high fatality rate of 17.8% (198 deaths), which was the highest number of fatal cases reported since 2006. Most of these cases were believed to be contributed from fishery products as most often *L. monocytogenes* sampling from these products were found beyond the safety limit[63].

During January 2013-February 2014, 27 cases were reported which was significantly higher than the reported annual incidence of 7-12 cases during 2009-2012 in Northern Spain. 11 cases were pregnancy-related and a total of 6 deaths had occurred. Sequence type (ST) 87 serotype 1/2b strain, a rare *L. monocytogenes* type that had not been shown to cause human illnesses, was isolated from 15 cases in two epidemiologically unrelated outbreaks. First cluster involving 5 cases was identified during August-September 2013 and out of 3 were pregnancy-related. Specific food as source of outbreak was failed to be identified. In the early November 2013 till late February 2014, 10 cases were reported to be possibly linked to the consumption of foie gras[64].

It is also important to note that the prevalence of *L. monocytogenes* was much lower in fish products caught from tropical water as compared to that of in the Western countries[65]. Interestingly, serotype 4b isolates were commonly associated to summer and their existence in surface water was corresponded to higher air temperatures and the existence of bacterial indicators of fecal contamination such as *Escherichia coli* and enterococci[26]. Conversely, serotype 1/2a strains were more prevalent in water during fall and winter. It is difficult to deduce the effect of natural environment on the *L. monocytogenes* strains due to limited studies available; however, 1/2a strains may be typical inhabitants of natural environment while 4b strains may be from the cattle's excreta into water during summer. Thus, it somehow explained why listeriosis outbreaks are more prevalent in summer[7].

In a short, *L. monocytogenes* was commonly isolated from dairy and poultry products. Due to various factors like dietary habits, methods of processing food and health surveillance system, listeriosis was more prevalent in the US and Europe (as shown in Figure 1). It is important to keep in mind that the uncommon food sources can also be a source of transmission as shown in the recent outbreaks, thus with rapid detection allow effective interruption of the route of transmission.

4.3 Asia

Unlike United States and Europe where health surveillance system was efficient, data collection of listeriosis was not appropriately done in Asia. Perhaps, also because of different diet habits and prevalence of infectious illnesses, detailed investigations were focused on the commonly affected illnesses such as tuberculosis and dengue fever. In Japan, an estimation of 83 cases occurred annually (equivalent to 0.65 per million individuals) and it was deduced that raw RTE seafood products might have contributed to some of the cases, though the most probable number (MPN) of *the L. monocytogenes* detected was low[66]. In China, the average recovery rate of *L. monocytogenes* was deduced to be 3.7% in all food categories, with raw meat as the leading source, in 13

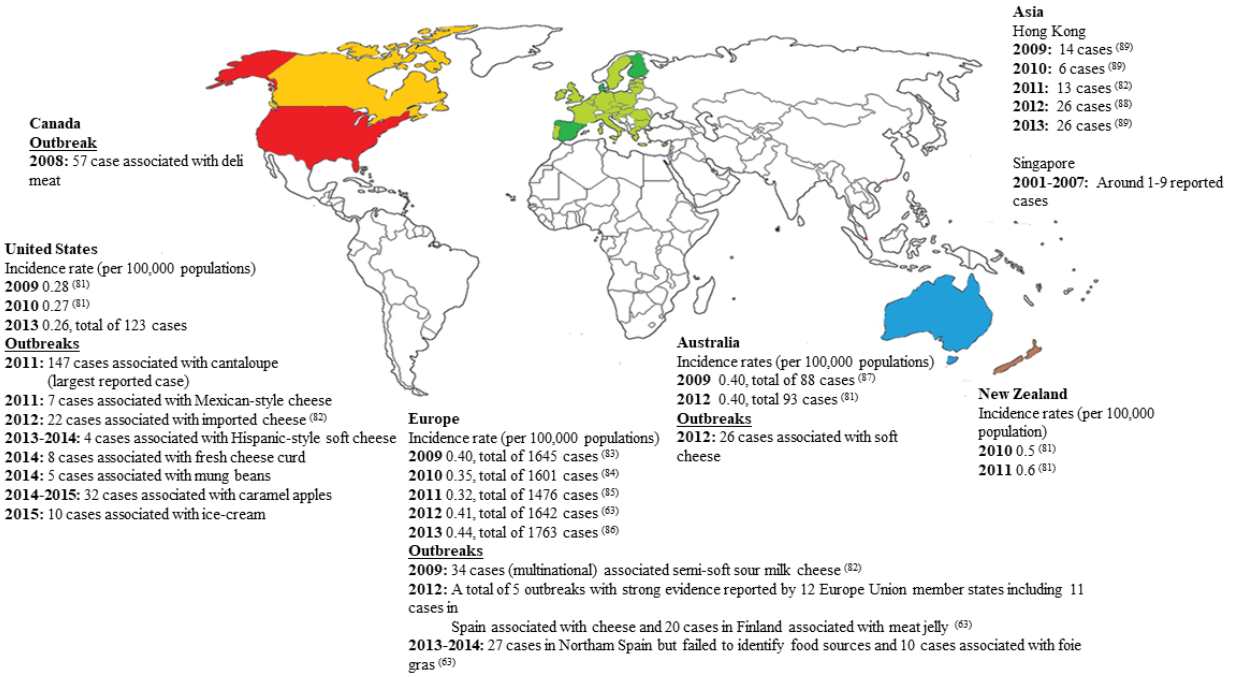

Figure 1. Incidence rate and outbreak of listeriosis in different regions global. Listerosis have effected around the world from USA to the Asia counties

provinces. However, there was no surveillance data due to limited identification techniques and insufficient attention to *L. monocytogenes* contamination. The only record was about the veterinary and human outbreaks happened in Yunan province in 1997[13].

4.4 Antibiotic resistant *L.monocytogenes*

Statistical analysis showed that *L. monocytogenes* was responsible for 23150 illnesses (0.337 per 100,000 population incidence rate) with 5463 death globally in 2010. Among all the cases, septicemia was the most common outcome, followed by central nervous system (CNS) infection. However, data from only 52% of world population was available and also due to differences in health surveillance system, the incidence and disease burden could not be extrapolated confidently[67].

Over the years, the food sector has witnessed the occurrence of antimicrobial resistant bacteria such as *Salmonella, Stapylococcus aureus, Escherichia coli* and *L. monocytogenes*[68;69;70;71]. In 1988, the first antibiotic resistant *L. monocytogenes* was identified in France. Since then, more and more strains from food sources are identified as antimicrobial resistant and human sporadic Listeriosis cases[72;73;74]. As a precaution measure and to control the increasing number of antibiotic resistant strains, the European Union has banned the usage of antibiotic as animal feed additives as of January 2006[75].

The indiscriminate use of antimicrobials in community and farms has led to increasing cases of antimicrobial resistant *L. monocytogenes* in the environments. A study reported *L. monocytogenes* strains from dairy farm exhibiting multidrug resistance towards phenotype towards cephalosporin C, streptomycin, and trimethoprim[76]. In addition in 2008, a another study found that *L. monocytogenes* strains from a turkey processing plant were multidrug resistant namely to ceftriaxone, ciprofloxacin, and oxacillin[77]. Antimicrobial resistant *L. monocytogenes* strains has also been isolated from ready-to-eat foods. The strains exhibited antibiotic resistance towards ampicillin, gentamycin and methicillin[78].

Given the increasing number of antibiotic-resistant *L. monocytogenes* strains being isolated around the world, it is imperative that we gain a better understanding of the extent of antibiotic resistance in *L. monocytogenes*, the antibiotic resistance gene patterns of this pathogen, and the ability of this pathogen to acquire resistance from other bacterial species. In addition, the range of antibiotics to which *L. monocytogenes* has acquired resistance is broad. Within this range of antibiotics are several that are traditionally used to treat listeriosis, such as penicillin and gentamicin. Multi-resistant strains are not common, but evidence for emergence is available[76]. Overall, the use of antibiotic in the aquaculture and agriculture should be control and managed in order to reduce the emergence of antibiotic resistant strains of *L. monocytogenes*.

Conclusion

Listeriosis is a rare but serious illness that predominantly affects the high risk population. Especially in recent years where there was increase in outbreaks and cases especially in the developed countries eg. the United States, Finland and Denmark, which mostly related to consumption of contaminated processed food. Majority of the affected individuals are pregnant or immunocompromised, and develop severe illnesses which result in abortion, long-term neurological complications and

even death. The severity of this illness alarmed the community about the importance of surveillance and prevention of *L. monocytogenes*. Besides the "zero tolerance" policy for RTE foods in US, most of the countries do not take any essential actions to counteract this problem. It is yet unclear about the causes of the significant low prevalence of cases in the developing countries which might perhaps due to dietary habit or inefficient health surveillance system. To understand the listeriosis better and future therapeutic regimen development, it is crucial to have a detailed understanding about the pathogenesis of *L. monocytogenes*. PrfA and the sigma factors are the main regulators of the expression of downstream virulence genes and also for the bacteria adaptation to the stress conditions. For mammalian cells invasion, InlA and InlB play critical for adhesion and internalization. Once within the cell, LLO and PLC aid in escaping from the phagosome, and subsequently together with actin assembly, allow intercellular spread. To treat the infection, the first-line treatment is penicillin with or without aminoglycosides, and TMP-SMZ is used in patients who are allergic to penicillin. In the current situation, antibiotics should be administrated wisely in aquaculture, agriculture and health care sectors to control the occurrence of antimicrobial resistance among pathogens. A non-antibiotic approach of utilizing bacteriophages in the aquaculture and agriculture fields may help to manage the increasing antimicrobial resistance problem. Bacteriophages have great advantages such as having host specificity, environmental friendly, readily discovered and isolated from the environment, and cost effective compared to antibiotics[79]. In addition, hactery farmers may adapt the method of switching antibiotics used in the aquatic field from time to time in order to allow withdrawal of antibiotic resistance profile in strains[80]. In summary, antibiotic resistance is a public health worry that effects millions of healthcare treatment worldwide. It is very important to educate the public on this issue through awareness campaigns or electronic media to prevent the over use of antibiotics and ensure the effectiveness of clinical antibiotics for treatments. In line with the campaigns, the Food and Agriculture Organization (FAO) had campaigns worldwide to increase awareness and promote the use of antimicrobials among the public [90; 91].

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Conflict of Interest

The authors declared that there is no conflict of interest.

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