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REVIEW

Human Listeriosis

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SUMMARY *Listeria monocytogenes* is a Gram-positive facultative intracellular pathogen that can cause severe invasive infections upon ingestion with contaminated food. Clinically, listerial disease, or listeriosis, most often presents as bacteremia,

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meningitis or meningoencephalitis, and pregnancy-associated infections manifesting as miscarriage or neonatal sepsis. Invasive listeriosis is life-threatening and a main cause of foodborne illness leading to hospital admissions in Western countries. Sources of contamination can be identified through international surveillance systems for foodborne bacteria and strains' genetic data sharing. Large-scale whole genome studies have increased our knowledge on the diversity and evolution of *L. monocytogenes*, while recent pathophysiological investigations have improved our mechanistic understanding of listeriosis. In this article, we present an overview of human listeriosis with particular focus on relevant features of the causative bacterium, epidemiology, risk groups, pathogenesis, clinical manifestations, and treatment and prevention.

KEYWORDS epidemiology, histopathology, *Listeria monocytogenes*, listeriosis, neurolisteriosis, pathophysiology, pregnancy-related listeriosis, bacterial genetics

INTRODUCTION

Listeria monocytogenes is a Gram-positive rod-shaped facultative intracellular pathogen that is widespread in the environment and can be isolated from soil, ground water, and feces of animals and humans (1–3). *L. monocytogenes* is a tenacious organism that easily adapts to fluctuating environments and survives harsh conditions including cold temperatures, acidity and high salt concentrations (4–7). The bacterium uses seven percent of its genome for adaptive regulation to engage specific environmental conditions (8).

L. monocytogenes infection, also known as listeriosis, is mainly foodborne, contracted through the ingestion of contaminated food products such as processed meat, dairy products, pre-packed sandwiches, cold-smoked fish, prepared vegetables, salads and fruits (9–11). Many listeriosis cases are classified as sporadic, but foodborne outbreaks are frequently observed (12–15). Human listeriosis ranges from subclinical and uncomplicated febrile gastro-enteritis to severe invasive disease (16). Invasive *Listeria* infections can be categorized into 3 main clinical forms: (i) pregnancy-associated and neonatal listeriosis, (ii) bacteremia or septicemic listeriosis, and (iii) central nervous system (CNS) infection, such as meningitis or meningoencephalitis (in this review, generically referred to as neurolisteriosis), with each respectively accounting for 14%, 52%, and 31% of human listeriosis cases (12, 16). Less common infection sites include the peritoneal cavity, arthroskeletal tissue, lung and pleural cavity, cardiovascular system, urinary tract, biliary tract, and the eye; each typically accounting for less than 1% of the total number of listeriosis cases (16, 17). There is also an unusual form of cutaneous listeriosis, a pyogranulomatous rash seen in farmers or veterinarians, contracted by direct exposure to infected lochia, placenta or aborted fetuses from materno-fetal cases of *L. monocytogenes* infection in ruminants (18).

The identification of *L. monocytogenes* as a foodborne pathogen in the 1980s led to the establishment of extensive food safety programs at national and international level (10). While implementation of these programs contributed to reducing the number of outbreaks (19–22), listeriosis remains one of the main 3 causes of foodborne disease leading to hospital admissions in North America and Europe (12, 23–25). In North America, health care and food safety costs associated with human listeriosis have been estimated at 2.3 billion to 22 billion dollars per year (26). The worldwide burden of the disease amounted in 2010 to 23,150 cases, 5,463 deaths and 172,823 disability-adjusted life-years (DALY) (27). With these figures, human listeriosis ranks among the 5 most important foodborne illnesses (25, 27, 28). In this review, we provide an update on human listeriosis, focusing on the epidemiology and risk groups for infection, bacterial characteristics and typing methods, pathogenesis and pathophysiology, and clinical presentation, outcome, treatment and prevention.

LISTERIA MONOCYTOGENES

L. monocytogenes is the only *Listeria* species that is recognized as a human

pathogen (29). Phylogenetically it belongs to the *Listeria sensu strictu* division (29). A second pathogenic species, *Listeria ivanovii*, causes abortion, septicemia and enteritis in ruminants (30, 31), but is very rarely isolated from humans (32). Nonpathogenic species in the *sensu strictu* division are *Listeria innocua*, *Listeria welshimeri*, *Listeria seeligeri*, and *Listeria marthii* (29). At earlier bifurcations of the genus, there is a more diverse group of *Listeria*-related organisms collectively known as "*Listeria sensu lato*" species, all of which are nonpathogenic (29). Evidence from comparative genomic studies indicates that the *Listeria sensu strictu* clade evolved from a common ancestor that had acquired the *Listeria* pathogenicity island 1 (LIPI-1), with repeated loss of this central virulence locus (and the other members of the PrfA virulence regulon) (see below) resulting in the nonpathogenic species (33). The *Listeria sensu strictu* genome has a size of 2.8–3.2 Mb and is rather stable, with limited gene gain and loss. It comprises 2,032 core genes and approximately 4,500 accessory genes (in *L. monocytogenes*, 2,360 and 3,109 genes, respectively) (33, 34). Seventeen percent of the genome is described as involved in nucleic acid synthesis and metabolism, 14% in cellular macromolecular metabolism and, 10% in protein metabolism (33). During the last decade, a number of new *Listeria* species have been discovered (35), and the Pasteur Institute has developed an interactive web platform for phylogenomic analysis and systems biology of *Listeria* (36).

Whole genome single nucleotide polymorphism (SNP) analyses show that *L. monocytogenes* is an ancient species that diversified into 4 different lineages designated I to IV (37, 38). These can be subdivided into 13 sublineage-related serotypes and more than 1,500 (registered) sequence types grouped into clonal complexes (CCs) or core-genome multi-locus sequence typing (MLST) types (CT) and sublineages (SL) (39, 40). While all *L. monocytogenes* strains are potentially pathogenic, epidemiological and experimental evidence indicates it is heterogeneous in terms of virulence. For example, only 3 of the 13 serotypes - 4b, 1/2a and 1/2b - represent 92% to 95% of the clinical isolates (41–45). Phylogenetic studies of *L. monocytogenes* lineage I and II showed that serogroup 4 (sublineage I) was most likely ancestral in *L. monocytogenes* and horizontal gene transfer events introduced serotype 1/2-related O-antigen genes and gene clusters (46). There is also a lower rate of homologous recombination in lineage I compared to lineage II (47, 48). The majority of genomic differences involve insertion/deletion events and include phage insertions, transposable elements, scattered unique genes, and genomic islands encoding mostly unknown functions (37).

Core Virulence Determinants

All *L. monocytogenes* isolates have a core set of virulence determinants responsible for the basic features of the listerial intracellular infection cycle, namely, (i) host cell invasion, (ii) escape from the phagocytic vacuole, (iii) rapid intracellular proliferation, and (iv) actin-based motility and cell-to-cell spread (Fig. 1) (49–53). These virulence functions are encoded by 10 key virulence genes arranged in 5 transcriptional units, all coordinately expressed under the control of the PrfA transcriptional regulator (54, 55). For this reason, these 10 virulence genes are collectively designated as the PrfA regulon (55). Two of the transcriptional units lie in a discrete 10-kb chromosomal region called LIPI-1 (51). These include *hly* encoding the pore-forming toxin listeriolysin O (LLO), which mediates vacuole escape (56); the *plcA* and *plcB* encoding 2 phospholipases C (phosphatidylinositol-specific and broad-substrate range, respectively), which act in concert with LLO to promote bacterial release from the phagocytic vacuole (57, 58); *mpl* encoding a metalloprotease required for the post-secretional processing of pro-PlcB into an active phospholipase (59); and the surface protein ActA, required for actin-based intracellular motility and cell-to-cell spread (60). Given the important role of the LIPI-1 products in the establishment of listerial intracellular infection, LIPI-1 is also referred to as the "*Listeria* intracellular survival cassette" (61).

Three other PrfA-regulated transcriptional units are at different chromosomal locations. Two of them encode members of the internalin (*inl*) multigene family of *Listeria*. The *inlAB* operon encodes 2 surface-associated internalins, InlA and InlB, required for entry into normally non-phagocytic cells (62). Together with the actin-based cell-to-cell

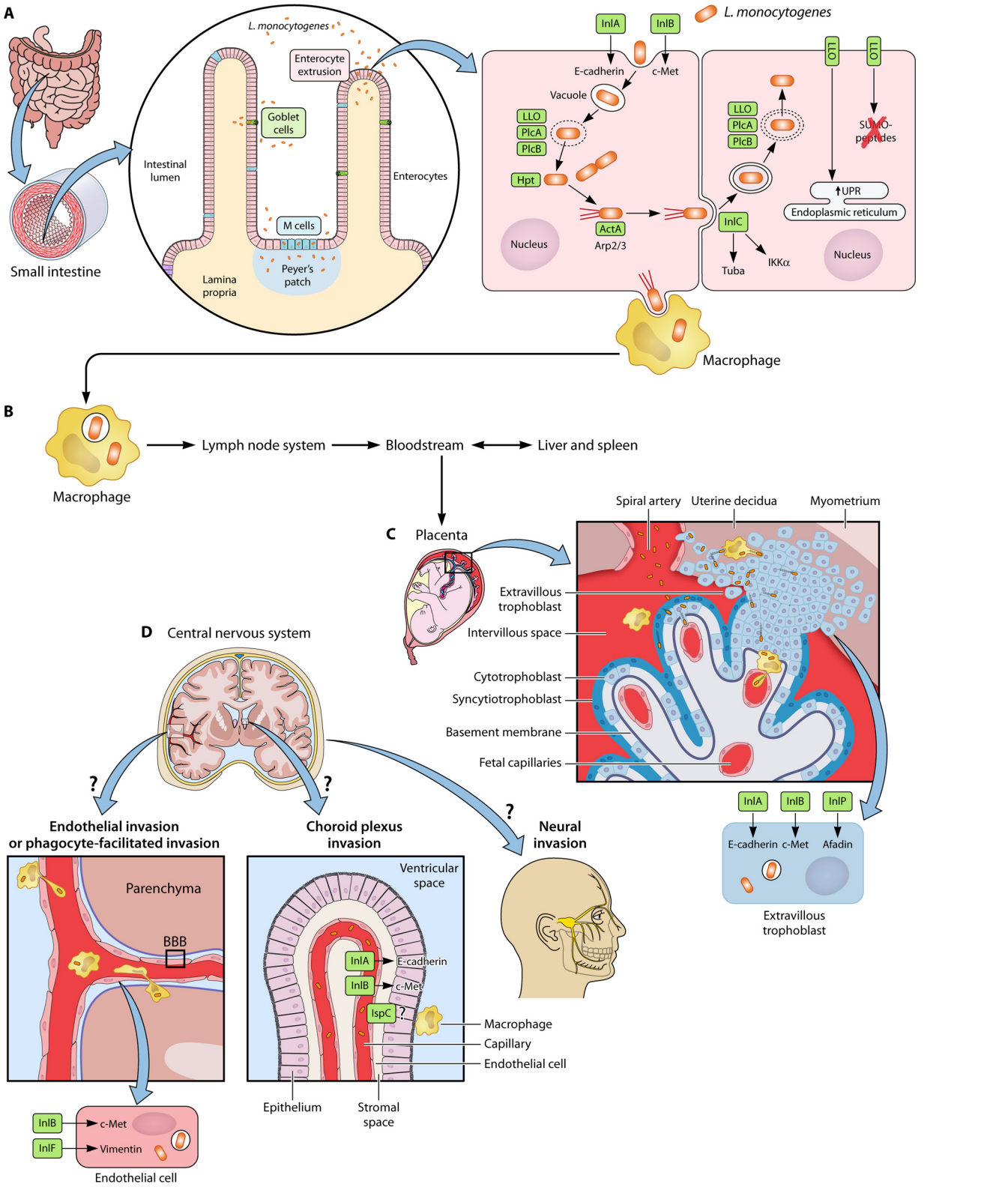

FIG 1 Pathogenesis of *L. monocytogenes* infection. (A) Invasion of the intestine through intestinal villi enterocytes, goblet cells and M cells. Entry into non-phagocytic cells is mediated by expression of bacterial surface-associated internalins A and B (InlA and InlB), which use as host ligands the adherens junction protein E-cadherin and the Met tyrosine kinase receptor, respectively. After host cell internalization, the listerial pore-forming toxin listeriolysin O (LLO) and phospholipases A and B (PlcA and PlcB) lyse the phagocytic vacuole membrane. The released bacteria replicate in the cytosol aided by the listerial virulence factor Hpt, which promotes rapid intracellular proliferation by allowing utilization of host-cell hexose phosphates. Then, the listerial actin-polymerizing protein ActA recruits host cell Arp2/3 complexes

(Continued on next page)

spread mechanism mediated by ActA, InlA and InlB are responsible for the invasive character of *L. monocytogenes* infections. Another member of the internalin multigene family, the *inlC* monocistron, encodes a small, secreted protein, which is predominant in the *L. monocytogenes* culture supernatant (63) and aids in the ActA-mediated cell-to-cell passage process (see below) (63). Finally, another monocistronic unit, the *hpt* gene, encodes an organophosphate transporter that promotes rapid replication in the cytosol by allowing *Listeria* bacteria to access host cell-derived glucose metabolic intermediates (glucose-6-phosphate, glucose-1-phosphate and fructose-6-phosphate) as a carbon source (64). At the time of its discovery, Hpt was the first nutritional virulence factor to be identified in a bacterial pathogen.

As is the case for many bacterial virulence factors, individual members of the PrfA virulence regulon may have several critical roles in listerial infection. Thus, besides its key role in vacuole escape, the pore-forming toxin LLO promotes host cell invasion by inducing Ca^{2+} influx, suppresses the macrophage oxidative burst, reduces the transcriptional activity of a subset of host genes –including key innate immunity genes– by inducing histone modifications, dysregulates protein small ubiquitin-related modifiers (SUMO)ylation altering key host cell processes, silences the adaptive immune responses by promoting the expression of negative regulators of T cell receptor signaling, and prevents plasma membrane damage and premature host cell killing by interacting with the endocytic adaptor protein Ap2a2 (65, 66). ActA also allows *L. monocytogenes* to avoid autophagy in the host cell cytosol in addition to its critical role in cell-to-cell spread (67). Another example is InlC, which not only promotes membrane protrusion formation during cell-to-cell spread by binding to the host protein Tuba, inhibiting N-Wasp and reducing actin cortical cytoskeleton rigidity (68), but also dampens innate immune responses by targeting the IκB kinase subunit IKKα, reducing NF-κB activation (69).

Regulation of *Listeria* Virulence

The central regulator of *Listeria* virulence is the LIPI-1-encoded PrfA protein, an allosterically controlled transcription factor of the Crp/CAP family. PrfA binds to a 14-bp palindromic sequence TTAACANNTGTTAA, called the "PrfA-box," located in the -35 region of the regulated promoters, recruiting RNA polymerase and activating transcription (49, 55). PrfA acts as a master switch that turns on and off virulence gene expression when *L. monocytogenes* senses its presence in a mammalian host (specifically its cytosolic compartment, see below) or the environmental habitat, respectively (49, 52). As such, PrfA is not only essential for the coordinated activation of the listerial virulence program during infection, but also for ensuring maximum bacterial fitness outside the host by preventing the metabolically costly production of virulence factors when these are not needed (70). In addition to the "core" set of 10 directly regulated genes, transcriptomic studies indicated that PrfA exerts a more global role in listerial homeostasis, influencing the expression of as many as 145 genes of the *L. monocytogenes* EGD genome (55).

The mechanism underlying PrfA's allosteric on-off switching remained elusive for a long time but has recently been elucidated. PrfA activity levels are antagonistically regulated by activating and inhibitory nutritional peptides imported via the listerial Opp oligopeptide transporter (71). Activating peptides provide cysteine, which *Listeria* cannot synthesize, and

FIG 1 Legend (Continued)
and induces actin-based motility, which propels the bacteria through the cytosol and into neighbouring cells, where the infection cycle starts again. InlC, another listerial virulence factor, assists in the process of cell-to-cell spread by targeting the cytoskeletal protein Tuba, and also interacts with IκB kinase (IKKα) dampening the innate immune response. (B) *L. monocytogenes* is taken up by macrophages which transport the bacteria to the lymph node system, and via the bloodstream to the primary target organs (liver and spleen), and from there to the secondary target organs (placenta or brain). See Fig. 3. (C) *L. monocytogenes* can colonize the placenta via cell-to-cell spread from infected macrophages to extravillous cytotrophoblasts, or via direct invasion of the trophoblast through InlA and InlB. Another internalin family protein, InlP, has been reported to facilitate placental invasion involving interaction with the cell junction-associated host protein afadin. (D) *L. monocytogenes* can gain access into the central nervous system in different ways: via cell-to-cell spread from infected phagocytes, or via direct (InlA/B-mediated) invasion of endothelial cells of brain microcapillaries, the basolateral side of the choroid plexus, or nerve cells of trigeminal nerve terminals (followed by intra-axonal ascension to the rhombencephalon). Invasion of brain endothelial cells is further facilitated by interaction of the listerial internalin family protein InlF with the host intermediate filament protein vimentin. See text for details.

is the rate-limiting precursor of the redox buffer tripeptide glutathione (GSH), required for PrfA function (71). GSH (γ-L-glutamyl-L-cysteinylglycine) is endogenously synthesized by the listerial GshF enzyme and stabilizes PrfA in active ("on") conformation by binding with low affinity in a large tunnel between the N- and C-terminal domains of the PrfA monomer (72, 73). On the other hand, exogenous peptides that lack cysteine directly inhibit virulence gene expression via promiscuous (sequence-independent), high-affinity competitive binding to PrfA's GSH binding site (71). Through this clever mechanism, PrfA acts as a sensor of the surrounding habitat via the sensitive detection of changes in the composition of available peptides, the main N source for microbes, to adjust listerial virulence gene expression levels accordingly.

A number of other mechanisms, involving environmental, metabolic, or stress signals and their processing pathways, contribute to modulate PrfA-dependent expression (74–82). Particularly important among them is an RNA thermoswitch that inhibits *prfA* gene translation below 30° C (83), a signal indicative of presence outside a warm-blooded host. The multiplicity of redundant mechanisms converging on PrfA, specifically those aimed at repressing its activity, indicates that preventing any fitness loss due to untimely virulence factor expression (e.g., outside the host) is critically important for *L. monocytogenes* (70).

Spontaneous inactivation of PrfA function due either to nonsense, missense, frameshift or truncation mutations in the *prfA* gene, or mutations in the *gshF* gene encoding the listerial GSH synthase, may occur and result in complete loss of virulence in *L. monocytogenes* (84, 85). Although relatively infrequent (0.1% of isolates), the PrfA-disabling mutations have considerable evolutionary significance as they convert *L. monocytogenes* in an obligate saprophyte. These mutations are probably at the origin of the emergence of the nonpathogenic species within the *Listeria* spp. "sensu strictu" clade (*L. innocua*, *L. seeligeri*, *L. welshimeri* and *L. marthii*) (33, 53, 85–87).

Other Virulence-Associated Factors

The PrfA virulence regulon is at the basis of *Listeria* pathogenicity and facultative intracellular parasitism and is present in all strains of the pathogenic *Listeria* spp, *L. monocytogenes* and *L. ivanovii* (30, 33). In addition, species- or genogroup-specific virulence determinants have also been identified. Unique to *L. ivanovii*, LIPI-2, a large, spontaneously deletable pathogenicity island, encodes multiple PrfA-regulated internalins and SmcL, a sphingomyelinase that contributes to vacuole escape (88). In *L. monocytogenes*, LIPI-3 is present in 88% of lineage I strains which are most often associated with epidemic outbreaks, but is absent from lineage II isolates. LIPI-3 encodes listeriolysin S (LLS), initially described as a peptide hemolysin but later identified as a bacteriocin that displays bactericidal activity and modifies the host microbiota during infection. This highlights the importance of *L. monocytogenes* interactions with gut microbes in foodborne listeriosis (89–91). A cellobiose phosphoenolpyruvate:sugar phosphotransferase system (PTS) designated LIPI-4, unique to the *L. monocytogenes* "hypervirulent" clonal complex CC4, was associated with the capacity to cause invasive (maternofetal and neuromeningeal) listeriosis, yet through (an) unknown mechamism(s) (92).

Additional listerial components have been reported to be involved in infection. These include surface-associated determinants, secreted proteins, secretion mechanisms, metabolic pathways, and stress tolerance or detoxification factors. Among the latter, bile salt resistance mechanisms have been shown to promote listerial survival in the intestine. Regulators other than PrfA, such as SigB, CodY, DegU, VirR, Agr, the SreA/SreB S-adenosylmethionine (SAM) riboswitches, and various others including a number of small RNAs, have also been reported to have a role in *L. monocytogenes* virulence. We refer the reader to other publications and references therein for more information about these additional virulence-associated factors (93–97). A caveat is that while these additional mechanisms are explicitly or implicitly described as virulence factors, many are present in the nonpathogenic *Listeria* species. In contrast to the PrfA regulon, most of these factors have therefore probably not primarily evolved to support a parasitic lifestyle but instead fulfill housekeeping functions generally important for optimal bacterial survival in diverse conditions, including infection.

Subtyping

Historically, many different methods have been used for *Listeria* subtyping. These include serotyping, phage typing, isoenzyme typing, pulse-field gel electrophoresis, ribotyping, multilocus tandem-repeat sequence analysis (MLSTA), different variations of MLST (e.g., multi-virulence-locus sequence typing (MVLST)), 10-gene multilocus sequence typing (98), PCR serogroup-sequence typing, and single nucleotide polymorphism (SNP) analysis (99). Because of the diversity of typing methods, comparison between studies over time has often been difficult. Such was the case of the most common subtypes associated with human listeriosis in Asia as determined by PCR serogroup-sequence typing (IIb-ST87, followed by IIa-ST378, I ST8 and IIa-ST155) (100–102), which could not be compared to the corresponding European and North-American data where MLST was more frequently used (92, 103).

Since the introduction of next-generation sequencing, whole genome MLST has enabled the rapid comparative analysis of *L. monocytogenes* isolates (104–108). This has been aided by a number of initiatives in different countries aimed at harmonizing *Listeria* subtyping, such as the Pasteur Institute's *Listeria* MLST database which allows interlaboratory comparison of data (39), the PulseNet network organized by the Centers for Disease Control (CDC) in the United States (US) focusing on foodborne outbreak investigation (https://www.cdc.gov/pulsenet/index.html), or 'GenomeGraphR', a web application for foodborne pathogen whole genome sequencing (WGS) data integration and analysis (109).

WGS-enhanced surveillance changed the landscape of listeriosis outbreak detection. A study showed that WGS in combination with epidemiologic and food product tracing data detected more listeriosis clusters and outbreaks compared to the pre-WGS era (107). WGS has also improved listeriosis outbreak investigation (110) and the sensitive, early detection of clusters of cases through accurate whole genome phylogenetic relatedness, potentially resulting in fewer cases per outbreak (107). This is particularly important given the often wide (often international) distribution of processed retail food and the low attack rates of listeriosis. Without the level of resolution afforded by WGS, related isolates from low incidence common source outbreaks could be easily missed and wrongly interpreted as unrelated sporadic cases (111–116).

EPIDEMIOLOGY

Surveillance

Human listeriosis has an estimated incidence ranging between 0.1 and 11.3 cases per million population per year, depending on geographical location and surveillance system (117). *L. monocytogenes* emerged as a human foodborne pathogen in 1981 following its identification as the cause of a listeriosis outbreak in Nova Scotia, Canada, involving 7 adults and 34 perinatal cases, associated with consumption of contaminated coleslaw (10). A coleslaw sample from the refrigerator of one of the patients yielded a *L. monocytogenes* strain of the same serotype (4b) as that isolated from the blood of the same patient. This landmark study was soon followed by additional publications linking human listeriosis outbreaks to the consumption of food, paving the way for the introduction of *Listeria*-targeted food safety measures (10). Subsequently, strict regulations were introduced in the food industry aimed to decrease the number of human listeriosis cases (118, 119).

Pioneering work in this area was developed in the 1980s by the French *Listeria* reference laboratory, initially established by Audurier et al. based on phage typing of the isolates (120). In the USA, the Foodborne Disease Active Surveillance Network (FoodNet) is implementing laboratory-based surveillance in *Listeria* epidemiology since 1996 (20, 121). FoodNet involves the CDC, the US Department of Agriculture's Food Safety and Inspection Service (USDA-FSIS) and the US Food and Drug administration (FDA). USDA-FSIS and FDA are responsible for improvement of food safety through regulations in food processing to prevent *Listeria* contamination (20). Reports from the FDA showed a stable incidence rate in the US over the period 2004–2013 (21, 22).

In 2002, the European Union (EU) established the European Food Safety Authority

(EFSA), which among others assesses the risks posed by *L. monocytogenes* by monitoring prevalence and levels of the pathogen in food, and advises on control measures (122). Control and safety criteria have been regulated by EU legislation (123–125). A steady increase of human listeriosis was detected in Europe over the period 2010–2014 at European level (13), probably driven by the increased use of ready-to-eat food products and relative rise of the susceptible population - particularly the immunocompromised and the elderly (116, 126, 127).

L. monocytogenes Diversity and Distribution

Large-scale genotyping studies of clinical, food, and environmental isolates have provided key insight into the structure and distribution of *L. monocytogenes* populations (115). While all *L. monocytogenes* isolates are considered to be potentially pathogenic by regulatory authorities, epidemiological evidence indicates that the species is heterogeneous in terms of virulence. Indeed, there is an unequal distribution of genotypes among clinical strains of *L. monocytogenes*, with two-thirds belonging to lineage I and only one-third to lineage II. Also, only 3 of the 13 serovars of the species (1/2b and 4b within lineage I and 1/2a within lineage II) cause >95% human listeriosis cases. In addition, although lineage II predominates among isolates recovered in food surveys (chiefly serovars 1/2a and 1/2c) or the environment, the majority of listeriosis cases is caused by lineage I serovar 4b strains (40, 47, 115, 128–136).

A detailed population genomic study in France based on the analysis of 6,633 strains found that certain serovar 4b lineages, specifically CC1, CC2, CC4, and CC6, were overrepresented among clinical isolates from invasive (neuromeningeal and placental-fetal) listeriosis cases, and tended to be found in patients with fewer or no debilitating comorbidities (92). These serovar 4b CCs were considered to be "hypervirulent". This was as opposed to lineage II CCs such as CC9 or CC121, which were mostly found in food or, if causing infection, in immunocompromised patients (associated with bacteremia rather than invasive maternofetal or neuromeningeal listeriosis), and were considered "hypovirulent" (92). Other studies point in the same direction and confirm the predominance of certain serovar 4b CCs among human listeriosis cases. A study involving 1143 *L. monocytogenes* strains from 22 European countries found that CC1 and CC6 were most commonly isolated from clinical cases and CC121 and CC9 from food products (137). Among neurolisteriosis cases, the most common MLST sequence types in strains collected from the cerebrospinal fluid (CSF) in The Netherlands between 1985 and 2014 were ST2 (CC2) (24%), ST1 (CC1) (16%), and ST6 (CC6) (12%) (118). The reason for the predominance of serovar 4b isolates, and specifically certain clones thereof, in invasive listeriosis cases remains unknown. Based on preliminary data in mice, it has been recently suggested, however, that this predominance might be related to a previously unrecognized capacity of the "hypervirulent" *L. monocytogenes* serovar 4b clones to survive *in vivo* (138).

L. monocytogenes clonal complexes can be associated with different food product sources (139). Hypovirulent CC121 and CC9 strains were associated with meat products and food processing environments, and were rarely isolated in dairy products. In contrast, hypervirulent clonal complexes, in particular CC1, were most commonly found in dairy products. These findings seem to suggest that the adaptation of certain *L. monocytogenes* genotypes to specific ecological niches impacts their distribution in food products (139).

Over time, *Listeria* population genetics trends evolve, with absolute and relative changes in the predominance of CCs (140). This has been recently observed, for example, in the Netherlands among CNS infections, with an increase of CC6 and CC155 and a decrease of CC1, CC2, and CC3 (118). Regional population structure trends are also noted, with CC6 being most commonly found in Europe and North America and less in other continents (92, 115, 141, 142). However, in 2017–2018, an extensive listeriosis outbreak in South Africa was caused by an ST6 (CC6) strain (lineage I, sublineage 6, sequence type 6, and core genome multilocus sequence type 4148) detected both in patients and the food source (polony, a ready-to-eat processed meat, see below)

(143, 144). Of note, in 2017, the European Centre for Disease Prevention and Control also identified an ongoing ST6 outbreak affecting several European countries (114, 145, 146).

Outbreaks

A substantial proportion of human listeriosis cases has been linked to outbreaks. A retrospective study using WGS-enhanced surveillance of human listeriosis in Europe over the period 2010 to 2015 concluded that up to 50% of 2,726 cases had a high likelihood to have occurred within an outbreak (147). Focusing on the last 4 decades, we identified more than 80 outbreaks worldwide affecting 5 or more patients with a known source of contamination (Fig. 2) (10, 107, 112–114, 117, 146, 148–215). The number of cases associated with these outbreaks varied between 5 and 1566, and the 2 largest occurred in Italy (in 1997) and South Africa (period 2017 to 2018) (Table 1).

The Italian outbreak stressed the significance of human listeriosis in immunocompetent patients. The clinical features in the infected patients were mainly limited to fever and gastrointestinal complaints (155). The food sources identified were corn and tuna salad served in a school cafeteria. Samples taken at the catering plant were positive for *L. monocytogenes* serotype 4b. A total of 292 patients (all children) were hospitalized for a median duration of 3 days; 123 of 141 stool specimens (87%) were positive in contrast to only 1 blood sample. All patients affected survived.

The source of the South African outbreak was identified as processed meat sausage (polony) (189). The total number of laboratory-confirmed cases in this outbreak was 937, including over 400 neonates (39%) and 193 fatal cases (27%) (189). It was a nationwide outbreak, and it took several months before the source of contamination was identified using whole genome-sequencing of the isolates and systematic use of questionnaires (189). In this outbreak, HIV infection was associated with 53% increased odds for death (144).

Another interesting well-documented outbreak took place in 2000 in British Colombia, Canada. Here, 84 patients were infected with a serotype 4b *L. monocytogenes* acquired through consumption of a soft ripened cheese (166). The pasteurized milk and pasteurization process were ruled out as contamination source. Instead, wild swallows defecating in the dairy plant's open cistern water reservoir and thereby contaminating the water supply used during the curd-washing step of the cheese making process, were identified as the infection source (166). This finding led to enhanced inspection of plants and improved plant design.

Serotypes were identified for 66 of the 87 outbreaks (76%) listed in Fig. 2 (10, 107, 112–114, 117, 146, 148–155, 157–218): of these, 4b and 1/2a were the most common, accounting for 62% and 29%, respectively, of the outbreaks (Table 1). One outbreak was caused by serotype 3b (158). The median number of cases per outbreak was 22 (interquartile range [IQR] from 11 to 38) and median number of deaths was 3 (IQR 1 to 6) (10, 107, 112–114, 117, 146, 148–155, 157–218). Unpasteurized milk products and ready-to-eat products were the cause in 54 of 87 outbreaks (62%) (112–114, 117, 146, 148–152, 154, 155, 157, 159–163, 165, 167–169, 171, 172, 182, 183, 188, 189, 191–193, 195–208, 210, 211, 216–218). A meta-analysis of *L. monocytogenes* contamination in deli meat, soft cheese, and packaged salads based on review of studies with a sample size $\geq$100 showed prevalences of 2,9%, 2,4%, and 2%, respectively (219). *Listeria* contamination of meat products is higher in deli counters compared to deli meat factories (220). This is probably explained by cross-contamination at retail level due to insufficient cleaning and sanitisation of the slicing equipment (220, 221). Another concerning source of *L. monocytogenes* contamination are frozen foods, such as ice cream (156, 222). In 2014–2015, an ice cream-associated listeriosis outbreak in the USA affected 10 patients (222). Four of the affected individuals had consumed the contaminated ice cream in the same Kansas hospital where they were treated during a previous unrelated admission $\leq$28 days before listeriosis onset (223). A multistate listeriosis outbreak in the USA also caused by contaminated ice cream and affecting 25 patients was ongoing at the time of writing (191). Although official outbreak reports are not yet

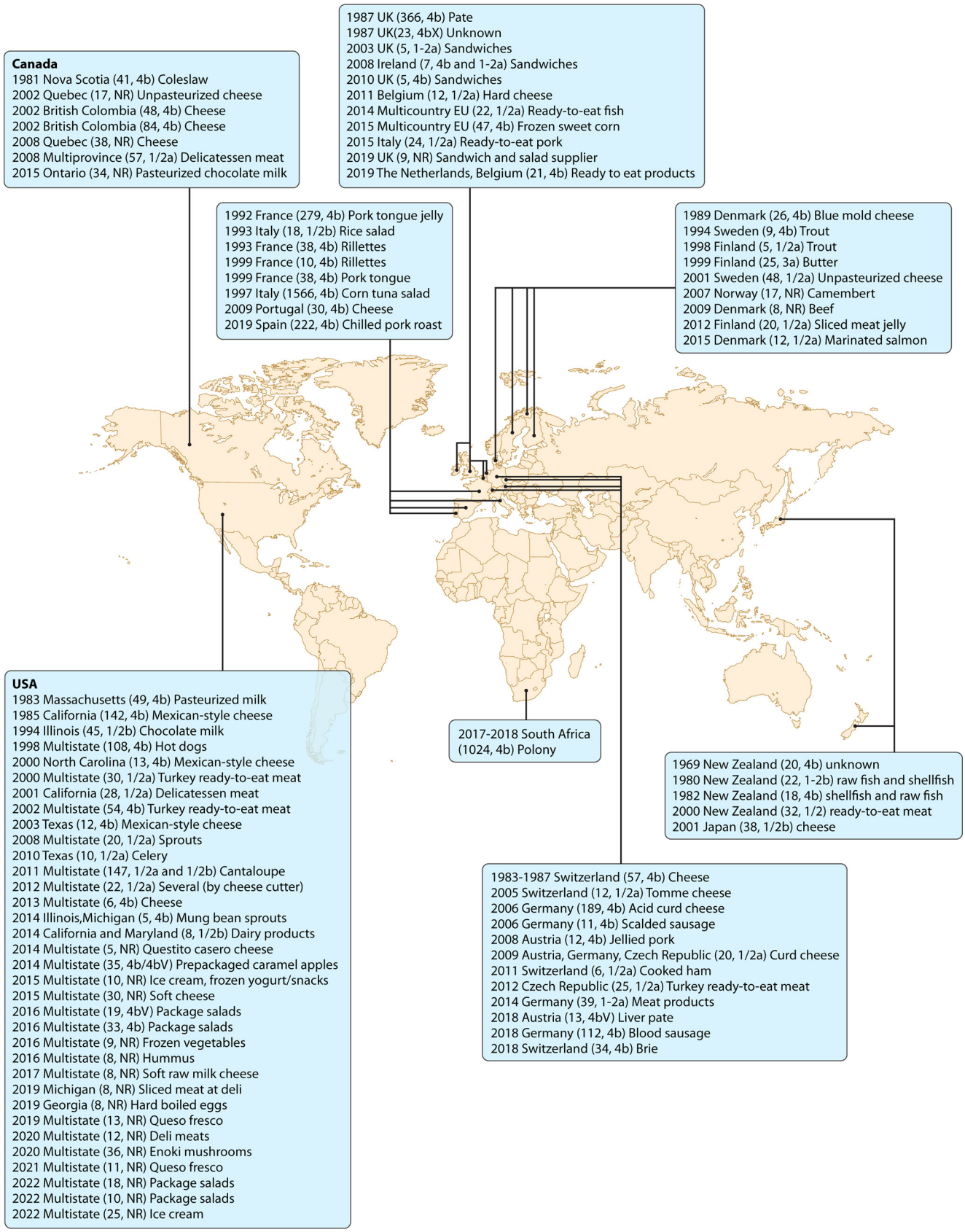

FIG 2 Outbreaks of *Listeria* between 1969 and 2022. Described by year, location, number of patients, serotype and source of infection. NR = not reported.

TABLE 1 Outbreaks in human listeriosis between 1969 and 2022[a]

Author and yr of publication	Period	Country	Cases	Perinatal cases	Death	Suspect vehicle	Serotype
Flight et al. 1971 (541)	1969	Auckland, New Zealand	20	14	NA[b]	Not yet known if food borne	4b
Lennon et al. 1984 (197)	1980	Auckland, New Zealand	22	22	5	Raw fish and shellfish	1/2b
Schlech et al. 1983 (10)	1981	Nova Scotia, Canada	41	34	18	Coleslaw	4b
Faoagali et al. 1985 (198)	1982	Christchurch, New Zealand	18	NA	NA	Shellfish and raw fish suspected	4b
Fleming et al. 1985 (199)	1983	Massachusetts, USA	49	7	14	Pasteurized milk	4b
Bula et al. 1995 (148)	1983	Switzerland	57	NA	18	Vacherin Mont d'Or cheese	4b
Linnan et al. 1988 (149)	1985	California, USA	142	94	48	Mexican-style cheese	4b
McLauchlin et al. 1989 (200)	1987	United Kingdom	366	NA	NA	Pate	4b
McLauchlin et al. 1989 (200)	1987	United Kingdom	23	NA	NA	Unknown	4bX
Jensen et al. 1994 (201)	1989	Denmark	26	3	7	Blue mold cheese	4b
Jacquet et al. 1995 (194)	1992	France	279	0	85	Pork tongue in jelly	4b
Salamina et al. 1996 (152)	1993	Italy (North)	18	0	0	Rice salad	1/2b
Goulet et al. 1998 (151)	1993	France	38	31	10	Rillettes	4b
Dalton et al. 1997 (153)	1994	Illinois, USA	45	0	0	Chocolate milk	1/2b
Ericsson et al. 1997 (154)	1994	Sweden	9	3	1	Cold-smoked rainbow trout	4b
Aureli et al. 2000 (155)	1997	Italy (North)	1566	NA	0	Cold corn and tuna salad	4b
Miettinen et al. 1999 (157)	1998	Finland	5	0	0	Vacuum-packed cold-smoked trout	1/2a
CDC[c] website (191)	1998	Multistate, USA, 22 states	108	NA	14	Hot dogs	4b
Valk et al. 2001 (159)	1999	France	10	3	3	Rillettes	4b
Lyytikainen et al. 2000 (158)	1999	Finland	25	0	6	Butter	3a
Valk et al. 2001 (159)	1999	France	32	9	10	Pork tongue	4b
MacDonald et al. 2005 (161)	2000	North Carolina, USA	13	11	5	Mexican-style cheese	4b
Olsen et al. 2005 (162)	2000	Multistate, USA	30	8	7	Turkey ready-to-eat meat	1/2a
Sim et al. 2002 (160)	2000	New Zealand	32	NA	NA	Ready-to-eat meats	1/2
Frye et al. 2002 (163)	2001	California, USA	28	0	0	Delicatessen meat	1/2a
Carrique et al. 2003 (165)	2001	Sweden	48	0	0	Unpasteurized cheese	1/2a
Makino et al. 2005 (164)	2001	Japan	38	NA	NA	Cheese	1/2b
Gaulin et al. 2003 (203)	2002	Quebec, Canada	17	3	0	Unpasteurized cheese	unknown
Gottlieb et al. 2006 (167)	2002	Multistate, USA	54	12	8	Turkey ready-to-eat meat	4b
McIntyre et al. 2015 (166)	2002	British Colombia, Canada	48	2	NA	Cheese production	4b
McIntyre et al. 2015 (166)	2002	British Colombia, Canada	86	NA	NA	Cheese (contaminated by swallows)	4b
Little et al. 2012 (204)	2003	United Kingdom	5	0	0	Prepacked sandwiches	1/2a
Swaminathan et al. 2007 (117)	2003	Texas, USA	12	NA	NA	Mexican-style cheese	4b
Bille et al. 2006 (168)	2005	Switzerland	12	3	2	Tomme cheese	1/2a
Winter et al. 2009 (169)	2006	Germany	11	NA	5	Scalded sausage	4b
Koch et al. 2010 (170)	2006	Germany	189	11	26	Acid curd commercial cheese (made from pasteurized milk)	4b
Johnsen et al. 2010 (205)	2007	Norway	17	0	3	Camembert cheese from pasteurized milk	unknown
Pichler et al. 2009 (171)	2008	Austria	12	0	0	Jellied pork	4b
Gaulin et al. 2012 (206)	2008	Quebec, Canada	38	16	2	Pasteurized milk cheese	unknown
Little et al. 2012 (204)	2008	Ireland	7	0	3	Sandwiches with sliced meat	4b and 1/2a
Cartwright et al. 2013/Jackson et al. 2016 (107, 173)	2008	Multistate, USA	20	0	5	Sprouts	1/2a
Currie et al. 2015 (172)	2008	Canada	57	0	24	Delicatessen meat	1/2a
Smith et al. 2011 (207)	2009	Denmark	8	0	2	Beef from the same meals-on-wheels delivery catering company	unknown
Fretz et al. 2010/Rychli et al. 2014/Schoder et al. 2014 (174–176)	2009	Austria, Germany, Czech Republic	20	0	3	Traditional Austrian curd cheese (Quargel)	1/2a
Magalhaes et al. 2015 (177)	2009	Portugal	30	2	11	Cheese	4b
GaμL et al. 2013 (178)	2010	Texas, USA	10	5	0	Celery	1/2a
Little et al. 2012 (204)	2010	United Kingdom	5	0	1	Sandwiches with salmon and cress	4b
Yde et al. 2012 (179)	2011	Belgium	12	0	4	Hard cheese (pasteurized milk)	1/2a
McCollum et al. 2013/ Laksanalamai et al. 2012 (180, 181)	2011	Multistate, USA	147	33	4	Cantaloupe	1/2a en 1/2b
Hachler et al. 2013 (193)	2011	Switzerland	6	NA	NA	Cooked ham	1/2a
Gelbicova et al. 2018 (182)	2012	Czech Republic	25	2	0	Turkey ready-to-eat meat	1/2a

(Continued on next page)

TABLE 1 (Continued)

Author and yr of publication	Period	Country	Cases	Perinatal cases	Death	Suspect vehicle	Serotype
Acciari et al. 2015/Heiman et al. 2015 (184, 185)	2012	Multistate, USA	22	4	1	6 from ricotta salad from pasteurized sheep milk (from Italy) and others from cross-contamination of cheese cut with the same equipment	1/2a
Jacks et al. 2016 (183)	2012	Finland	20	0	2	Ready sliced meat jelly	unknown
CDC Website (191)	2013	Multistate, USA	6	1	1	Cheese	4b
CDC Website (191)	2014	Illinois and Michigan, USA	5	2	0	Mung bean sprouts	4b
Chen et al. 2017 (222)	2014	California and Maryland, USA	8	NA	0	Dairy products	1/2b
CDC Website (191)	2014	Multistate, USA	5	1	1	Quesito casero cheese	*[d]
Lachmann et al. 2020/Adler et al. 2020 (209, 210)	2014	Germany	39	0	3	Meat products (sold in healthcare facilities)	1/2a
CDC Website (191)	2014	Multistate, USA	35	NA	7	Prepackaged caramel apples	4b, 4bV
Maesaar et al. 2021 (212, 228)	2014	European Union (Denmark, Estonia, Finland, France, Sweden)	22	NA	5	Ready-to-eat fish	1/2a
Duranti et al. 2018 (213)	2015	Italy	24	NA	4	Pork ready-to-eat products	1/2a
McLauchlin et al. 2021 (113, 214)	2015	Multicountry, Europe	47	0	9	Frozen sweet corn	4b
CDC Website (191)	2015	Multistate, USA	10	NA	3	Ice cream/frozen yogurt/frozen snacks	*
CDC Website (191)	2015	Multistate, USA	30	NA	3	Soft cheeses from a dairy company	*
Hanson et al. 2019 (187)	2015	Ontario, Canada	34	1	4	Pasteurized chocolate milk	Unknown
Schjorring et al. 2017 (188)	2015	Denmark, Germany, France	12	NA	4	Marinated salmon	1/2a
CDC Website (191)	2016	Multistate, USA	19	NA	1	Package salads	4bV
Self et al. 2019 (195)	2016	USA and Canada	33	0	1	Package salads	4b
Marshall et al. 2020 (211)	2016	Multistate, USA	9	NA	3	Frozen vegetables	*
Marshall et al. 2020 (211)	2016	Multistate, USA	8	NA	0	Hummus	*
CDC Website (191)	2017	Multistate, USA	8	NA	2	Soft raw milk cheese	*
National Institute for Communicable diseases (542)	2017	South Africa	1024	410	200	Polony	4b
Cabal et al. 2019a/Cabal et al. 2019b (112, 196)	2018	Austria	13	0	0	Liver pate	4bV
Halbedel et al. 2020 (146)	2018	Germany	112	0	1	Blood sausage	4b
Inderbinden et al. 2021 (114)	2018	Switzerland	34	1	10	Brie	4b
CDC Website (191)	2019	Michigan, USA	8	NA	1	Sliced meat at a deli	*
CDC Website (191)	2019	Georgia, USA	8	NA	1	Hard boiled eggs	*
Palacios et al. 2022 (215)	2019	Multistate, USA	13	4	1	Queso fresco (pasteurized)	*
Regional Health Authorities in Andalucía (543)	2019	Spain	222	NA	3	Chilled pork roast	4b
ECDC[e] Website (217)	2019	The Netherlands and Belgium	21	1	3	Ready to eat products	4b
Government Website UK (218)	2019	United Kingdom	9	NA	6	Sandwich and salad supplier	Unknown
CDC Website (191)	2020	Multistate, USA	12	NA	1	Deli meats	*
CDC Website (191)	2020	Multistate, USA	36	6	4	Enoki mushrooms	*
CDC Website (191)	2021	Multistate, USA	13	NA	1	Queso fresco	*
CDC Website (191)	2022	Multistate, USA	18	NA	3	Packaged salads	*
CDC Website (191)	2022	Multistate, USA	10	NA	1	Packaged salads	*
CDC Website (191)	2022	Multistate, USA	25	NA	1	Ice cream	*

[a]Outbreaks were included in this table if they included 5 or more cases.
[b]NA; Not available.
[c]CDC; Centre for Disease Control.
[d]Typing known according to CDC but not published.
[e]ECDC; European Center for Disease Control.

available, a number of listeriosis outbreaks have been recently reported across Europe. In Spain, the source was Andalusian chilled pork roast containing a serotype 4b *L. monocytogenes*; 222 cases were linked to this outbreak including 3 deaths (216). In the Netherlands and Belgium, a total of 21 listeriosis cases including three deaths (14%) were traced back to a serotype 4b strain linked to a ready-to-eat meat product-manufacturing company (217). In England, a nosocomial outbreak which affected 9 patients of whom 6 died (67%), was linked to a sandwiches and salads supplier of several UK hospitals; the serotype has not been published (218). In Germany, a retrospective WGS and questionnaire study identified 22 outbreaks between 2010 and 2021 (with 18 outbreaks $\geq$5 clinical cases) in which smoked and graved salmon products were the most likely source based on genetically closely related isolates from clinical cases and fish processing plants (224).

The role of public health in tracing outbreaks. High-income Western countries have a well-established track record of listeriosis surveillance, resulting in more but smaller outbreaks being described than in other geographic areas (10, 107, 112–114, 117, 146, 148–155, 157–215, 225). National and international disease prevention and control centers collaborate to connect (multi-country) outbreaks spanning over longer periods of time, and to identify contamination sources via WGS typing based epidemiological tracing (112–114, 122, 146, 147, 226, 227). For example, in 2019 a rapid outbreak assessment traced *L. monocytogenes* sequence type 1247 (CC8) originating from an Estonian fish procesing company as the cause of 22 listeriosis cases (212, 228, 229). Outbreak analyses and food testing have helped to focus and enhance national and international hygiene regulations (230–234). In 2018, a 7-step strategy was introduced to intensify sampling routes (214). The WGS source tracking program in the US suggested that each additional 1,000 WGS isolate added to the public National Center for Biotechnology Information (NCBI) database resulted in a decrease of approximately 2.31 human listeriosis cases per year (i.e., 13% reduction). Annual health benefits of WGS for *E. coli*, *L. monocytogenes* and *Salmonella* together are estimated at nearly $500 million, compared to an approximately $22 million investment by public health agencies (235).

Risk Groups

L. monocytogenes infection can manifest in young and healthy patients (16, 236, 237), but well-known risk groups are pregnant women/neonates, the elderly, and immunocompromised people (16, 236). A major role is played by the host immune system in the susceptibility to invasive *Listeria* disease (12, 16, 238–240).

The elderly. Listeriosis incidence in patients $\geq$65 years old is 1.3 cases per 100,000 population compared to an annual average of 1.3 for the general population (relative rate, 4.4) (12). Aging of the immune system involves functional and structural alterations in host defense mechanisms. Next to a decreased ability to fight infections and an impaired ability to effectively respond to antigens, elderly have a diminished response to vaccines, a higher rate of cancer and auto-immune diseases and persistent low-grade inflammation (241). Cell-intrinsic changes are found in both innate and adaptive immune cells (241). Age-associated decline of the adaptive immune response manifests in naive $CD4^+$ T cells deficits, and their response to type I interferon signaling and cytokines (242–244). A mouse study showed older *Listeria*-infected animals lost body weight dose dependently and had higher bacterial colony forming unit (CHU) counts (245). Older mice tend to have higher baseline of T helper type 2 (Th2) cell and regulatory T cells (Treg) responses (245). This response increases during *Listeria* infection thereby counteracting the protective pro-inflammatory responses, resulting in less effective pathogen removal from the host (245). Due to their diminished immune response, the elderly could be considered as a specific category of immunocompromised patients.

Immunocompromised adults. Patients with a malfunctioning immune system are more susceptible to a low-grade infection, such as listeriosis. The prospective MONALISA study (16) showed that 93% of all patients with listeriosis had at least 1 underlying

immunosuppressive comorbidity (16). Most frequent among these were solid tumors (31%) and diabetes mellitus (22%). Immunosuppressive therapy was given to 43% of listeriosis patients over a 5-year period prior admission. Another prospective study showed that patients with active cancer, both solid and hematological malignancies, were more likely to develop listerial CNS infection (21%) compared to patients without cancer (5%) (246, 247). Other vulnerable groups in neurolisteriosis are alcoholics (248). Patients with a history of chronic liver disease have a 5-fold increased risk of brain infection caused by *L. monocytogenes* compared to other pathogens, whereas the risk is 8-fold increased in patients with a history of immunosuppressive therapy (249).

Pregnant women. Compared to the overall population, pregnant women have a 10 to 18-fold higher risk for listeriosis in relation to the overall population (incidence 3 to 12 per 100.000) (12, 255), and a >100-fold increased risk compared to non-pregnant women of reproductive age (256). During pregnancy, cellular immunity is diminished due to the elevated progesterone levels, increasing the susceptibility to *L. monocytogenes* invasive infection (257, 258). Between the 1980s and 2015, the number of neonatal *Listeria* infections decreased 12-fold in France, and a 17-fold reduction in listerial meningitis cases in neonates was observed in the Netherlands (118, 119). The incidence in women in childbearing years has been slowly increasing in Europe over the period 2008 to 2015, but a relation with pregnancy has not been confirmed (231).

Within the pregnancy risk group, ethnic minorities were found to have a higher incidence of perinatal listeriosis in the US (Hispanics), France (Maghreb or Sub-Saharan Africa origin), UK and Australia. This unequal distribution was suggested to be linked to dietary habits and insufficient education on listeriosis during pregnancy (16, 21, 250, 256, 259, 260). US studies in the periods 2004 to 2009 and 2008 to 2016 also suggested a higher relative risk for listeriosis in non-pregnant Hispanics (256), Afro-American, and Asian populations as well (261).

Neonates. The reported incidence of neonatal listeriosis is between 1.3 and 25 per 100.000 live births (260, 262–266). Neonatal listeriosis can have severe manifestations such as meningitis, sepsis, or pneumonia (264, 267, 268). CNS infection as the main manifestation occurs in 13 to 18% of neonatal cases (16, 264, 265). Surveillance data in the USA placed *L. monocytogenes* as the second leading cause of bacterial meningitis in patients younger than 1 month (22%) in the 1990s (269). Twenty years later, this pattern appears to have changed. Bacterial meningitis cases were caused by *L. monocytogenes* in 5% of children <90 days old admitted in 7 tertiary centers in Canada (270), in 4% of infant cases in England (271), and 1.5% of neonatal (<28 days) bacterial meningitis cases in France (272). This suggests that the relative importance of *L. monocytogenes* in neonatal meningitis has decreased (273).

Nosocomial and iatrogenic risk. Listeriosis is infrequently reported as nosocomial infection. However, hospitalized patients are considered to be a vulnerable group, and a number of hospital-acquired listeriosis outbreaks have taken place. Outbreaks were foodborne in origin, caused by prepacked sandwiches (274), sliced-meat-jelly (183), or other contaminated food (110, 178, 191, 275–277) and linked to products supplied by hospital caterers (278). Furthermore, cases and small outbreaks of nosocomial listeriosis due to cross-infection in neonatal wards have been reported (279–285). One example is an outbreak occurred in 1989 in Costa Rica involving 9 neonates between 4 and 8 days old where the proven source was a mineral oil from a multidose container applied to the infants (286).

As iatrogenic risks, in addition to immunosuppressive therapy, 3 nationwide observational studies, in Australia, Denmark, and Germany, showed that use of proton pump inhibitors (PPI) was associated with increased likelihood of developing listeriosis (250, 251, 252). The precise pathophysiological mechanisms are unknown, but, in general, the use of proton pump inhibitors raises the gastric pH, potentially increasing the survival of the ingested *Listeria* when crossing the stomach (253, 254).

PATHOGENESIS

Listeria Intracellular Parasitism

Host cell invasion. The invasive nature of *Listeria* infection is primarily determined by the action of 3 surface proteins of the PrfA virulence regulon, the invasins InlA and InlB from the internalin multigene family, and the actin-polymerising protein ActA. The former are used by the pathogen to invade different normally non-phagocytic cells such as enterocytes, fibroblasts, hepatocytes or endothelial cells. InlA binds to E-cadherin, a junctional protein expressed by a variety of cell types (287). InlB recognizes the tyrosine kinase receptor Met, the natural ligand for hepatocyte growth factor (HGF) (288). It also uses the gC1qR complement component C1q receptor and host cell surface glycosaminoglycans as co-receptors (289). InlA and InlB hijack the endocytic recycling machinery of these receptors, inducing signaling events which, in the case of InlB, involve activation of class I phosphoinositide 3-kinase (PI3-K) (290–292), ultimately triggering cytoskeletal remodeling and bacterial internalization (94, 287, 293). Both InlA and InlB are needed for efficient host cell entry, while the relative importance of InlA and InlB varies depending on the cell type or the receptor isoform produced by a particular animal species, potentially influencing cell and host tropism (62, 287, 290–292, 294–297). ActA, in addition to mediating a key direct cell-to-cell invasion pathway (discussed below), has been shown to also contribute to host cell invasion from the extracellular space, presumably via recognition of heparan-sulfate proteoglycan receptors (298). Other *Listeria* proteins may aid in the interaction with non-phagocytic host cells, such as LAP (*Listeria* adhesion protein), a 104 kDA alcohol acetaldehyde dehydrogenase that promotes adhesion to gastrointestinal cells in an InlA-independent manner (299–303). Additionally, *L. monocytogenes* gains access to the intracellular compartment via the normal phagocytic function of macrophages and other antigen presenting cells. This internalization pathway is independent of the InlA/InlB invasins and involves the immunoglobulin Fc receptor I (FCGR1A) and other phagocytic receptors (304).

Vacuole escape and cytosolic replication. After internalization, whether by a professional phagocyte or a normally non-phagocytic cell, other PrfA-regulated virulence factors promote listerial intracellular survival and replication. As mentioned above, 3 secreted membrane-damaging proteins, LLO (56) and the PlcA and PlcB phospholipases, the latter assisted by its activating metalloprotease, Mpl, lyse the membrane of the phagosome and cause bacterial release to the cytosol (61, 65, 305). LLO is a key virulence factor, as shown by the severely attenuated phenotype of *L. monocytogenes hly* mutants (56, 65). LLO is the only member of the cholesterol-dependent cytolysins (CDC, a family of pore-forming toxins widespread among Gram-positive bacteria) that has evolved as a phagosome-specific lysin.

Once *Listeria* reach the cytosol, bacterial growth ensues at comparable rates to those in rich medium. Rapid intracytosolic replication is fueled by utilization of the first intermediates of host cell glucose metabolism, glucose-6-phosphate, gluclose-1-phosphate or fructose-5-phosphate, as a carbon source. Uptake of these sugars is mediated by the Hpt transporter, a hexose phosphate permease related to the enterobacterial UhpT. Hpt expression is controlled by PrfA and thus selectively activated in the cytosol (64). Cytosolic peptides rather than free amino acids are the primary N source as demonstrated by recent experiments with mutants with a disabled Opp oligopeptide transporter (71), also supported by the lack of significant defects in intracellular proliferation of *L. monocytogenes* auxotrophic mutants requiring specific amino acids (306). The available evidence indicates that both the Hpt-transported sugar phosphates and the Opp-transported peptides allow *L. monocytogenes* to sense the cytosolic compartment and induce the strong PrfA activation that takes place during intracellular infection (49). On the one hand, uptake of sugar phosphates by Hpt bypasses a catabolite repression-like response that causes PrfA downregulation, by as of yet unclear mechanisms. Sugars that repress PrfA are those transported via the phosphotransferase (PTS) system, such as free glucose or, particularly, β-glucosides such as cellobiose abundantly present in the environment (307). On the other hand, data using *L. monocytogenes* bacteria with disabled

Opp-mediated oligopeptide transport indicate that uptake of cysteine in peptide form from the host cytosol is essential for the early activation of PrfA and PrfA-dependent gene expression upon host cell infection (71). The regulation of the *prfA* gene by the global regulator CodY (308) may provide additional layers of regulation linking listerial virulence and metabolism upon CodY sensing intracellular levels of branched-chain amino acids (BCAAs), such as leucine (81), or GTP pools, which become depleted during the starvation-induced stringent response (78, 309).

L. monocytogenes intracellular replication (but not extracellular growth in culture media) requires the bacterial lipoate ligase enzyme LplA1 (310). Lipoic acid (LA) is a disulfide-containing antioxidant that, via ligation of its lipoyl moiety, acts as a cofactor in target enzyme complexes, of which the most well-known is pyruvate dehydrogenase (PDH). Accordingly, LplA1, exogenously sourced by *Listeria* in the form of lipoyl peptides (311), was shown to mediate lipoylation of the listerial E2 subunit of PDH to produce E2 lipoamide (310), which plays a pivotal role in the aerobic metabolism of glucose in most organisms. This observation is intriguing because *L. monocytogenes* has a bifurcated tricarboxylic acid cycle and its metabolism is essentially fermentative, so the virulence-specific role of LplA1-mediated lipoate ligation may be related to the modification of other listerial proteins specifically required for intracellular survival.

Direct (intracellular) cell-to-cell spread. Another key feature of the *Listeria* intracellular parasitic lifestyle is the ability of these bacteria to directly spread cell-to-cell. This is mediated by a surface protein encoded by the first gene of LIPI-1's *actA-plcB-orfX* operon (57), ActA, which accumulates at the older pole of each of the 2 daughter bacteria after cell division (312, 313). The *actA-plcB-orfX* operon is expressed from a PrfA-regulated promoter with nucleotide mismatches and thus requiring full activation of the PrfA system, which takes place once listerial cells are actively replicating in the host cytosol (55, 314). The polarly distributed ActA protein triggers actin polymerization at the surface of *L. monocytogenes*, involving mimicry of host proteins of the WASP family by the N-terminal region of ActA (315), thus bypassing the control of upstream Rho-family small GTPases on the actin nucleation activity of the Arp2/3 complex (312, 316). In their movement across the cytosol, the bacteria eventually reach the cell periphery, and push outwards in pseudopod-like protrusions with a bacterium at a tip, know as "listeriopods". These structures are eventually phagocytized by neighboring cells, resulting in double-membrane secondary vacuoles, from which *Listeria* escape again by the concerted action of LLO, PlcA and, particularly, PlcB (57, 317, 318), reinitiating the infection cycle. Listeriopod formation is aided by the PrfA-regulated small-secreted internalin InlC, which locally reduces membrane tension by inhibiting recruitment of the cortical actin regulator N-WASP and the host endoplasmic reticulum (ER) coat protein complex II (COPII proteins) via interaction with the protein adaptor Tuba (68, 319). Internalization of listeriopod protrusions by neighboring macrophages involves efferocytosis (the process by which phagocytes remove dead cells by phagocytosis) via recognition of exofacial phosphatidylserine (PS) by the PS-binding receptor T cell membrane protein 4 (TIM-4) upon LLO-mediated plasma membrane damage (320).

Implications for pathogenesis and immunity. The mode of spread of pathogenic *Listeria* across host tissues, directly from cytosol to cytosol largely avoiding exposure to the extracellular space, has a pivotal impact on the immune response and the type of immune effectors that mediate infection resolution. Since extracellular host defenses, such as antibodies, complement and the highly listericidal neutrophils, do not have access to the intracellularly spreading *Listeria* bacteria, infection clearance depends on cytosolic innate immunity and the correct mounting of a cell-mediated immune response involving tumor necrosis factor α (TNF-α), interferon γ (IFNγ), M1 (classically) activated macrophages, and major histocompatibility complex (MHC)-class-Ia-restricted $CD8^+$ T cells (61). A detailed review of the immune mechanisms in *Listeria* infection is beyond this review and the reader is referred to other publications (321, 322).

The listerial virulence factors and, in particular, the intrusion of *Listeria* bacteria into the intracellular compartment, can modulate or interfere with a number of cellular

functions and responses, with potentially significant impact on the host-pathogen interaction. For example, ActA-mediated actin-based motility and the PlcA and PlcB phospholipases help *L. monocytogenes* avoiding intracellular destruction by autophagy (323–326), while the actin cloud at the listerial surface itself prevents ubiquitin deposition and accumulation of signaling molecules involved in autophagosome formation (327, 328). Inlc, also highly expressed in (and secreted into) the cytosol, interacts with the IκB kinase subunit IKKα, preventing nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, thus dampening the innate immune response (68, 69). The major vacuole disrupting factor, LLO, induces histone H3 dephosphorylation and histone H4 deacetylation by promoting efflux of potassium ions (329). It also causes a decrease in SUMO-conjugated host proteins by inducing proteasome-independent degradation of Ubc9, a critical component of the SUMOylation machinery which plays a critical role in the post-translation control of a wide range of cellular processes (330, 331). Additional examples include the secretion of nucleomodulins, such as the listeria-nuclear-targeted protein A (LntA) protein (332) or the LIPI-1 encoded OrfX (57, 333). Via these and other mechanisms, *Listeria* can manipulate host cell transcription and gene expression to diminish the innate immune response and depress specific interferon stimulated genes, or induce the upregulation of the unfolded protein response (UPR) in the endoplasmic reticulum (ER) (334) and the induction of mitochondrial fragmentation (335), among others (94, 336).

Pathophysiology of Infection: Early Stages

Pathophysiologically, *Listeria* infection can be subdivided into 3 distinct phases, as extrapolated from experimental data in laboratory animals, clinical observations, and logical interpretation of the natural history of listeriosis (61). The first 2 involve the traversal of the intestinal barrier and translocation to mesenteric lymph nodes and the "primary target organs," i.e., liver and spleen (61, 138). These early stages are subclinical in most patients but could manifest as a nonspecific febrile syndrome and, in some cases, gastroenteritis. Whether *Listeria* infection is halted at its early stages or progresses to clinical invasive listeriosis through systemic dissemination and colonization of the "secondary target organs," i.e., brain or placenta, is likely determined by 3 main factors: (i) the number of bacteria ingested with food, (ii) the virulence properties of the strain, and (iii) the immunological status of the host (61). The following sections discuss the different stages of the physiopathogenesis of listeriosis. Figure 3 summarizes the key steps of the process.

Survival in gastrointestinal tract. To reach the portal of entry in the small intestine, ingested *Listeria* bacteria are confronted to significant environmental stresses starting with the harsh conditions of the acidic stomach (337). The glutamic acid decarboxylases (GAD) (338) and induction of the adaptive acid tolerance response (ATR) assist as a defense mechanism for *L. monocytogenes* survival to the high gastric acidity (6, 8). *In vitro* studies have shown that pre-exposure to a pH of 5.5 results in an increased resistance of *L. monocytogenes* down to a pH of 3.5 (339). Moreover, acid-adapted *L. monocytogenes* has an increased tolerance toward other environmental stressors such as heat and osmotic stress (339). Bile salts are another important gastrointestinal stressor encountered by *L. monocytogenes*. To counter their toxic effect, the bacterium uses a bile salt hydrolase (*bsh* gene product) to deconjugate the bile acid (254, 340), and a bile exclusion (*bilE*) exclusion pump (*lmo1421-1422* gene products) (341). Furthermore, transcriptomic analyses showed upregulation of 2 multidrug efflux pump genes, *mdrM* and *mdrT*, following contact with bile acid (342). A key part of *L. monocytogenes* adaptation to the gastrointestinal tract is the activation of the general stress response sigma factor, SigB, as demonstrated by transcriptomic studies which show a strong induction of its controlled regulon in the intestine (343). Members of the SigB regulon include systems for bile, acid, and salt adaptation (343). SigB regulon activation is specific to the intestine as is observed neither once the pathogen has invaded host tissues nor in the intracellular compartment (76, 344–346). In addition to resisting the above stresses, *L. monocytogenes* needs to overcome competition by the intestinal microbiota. A mechanism involved in

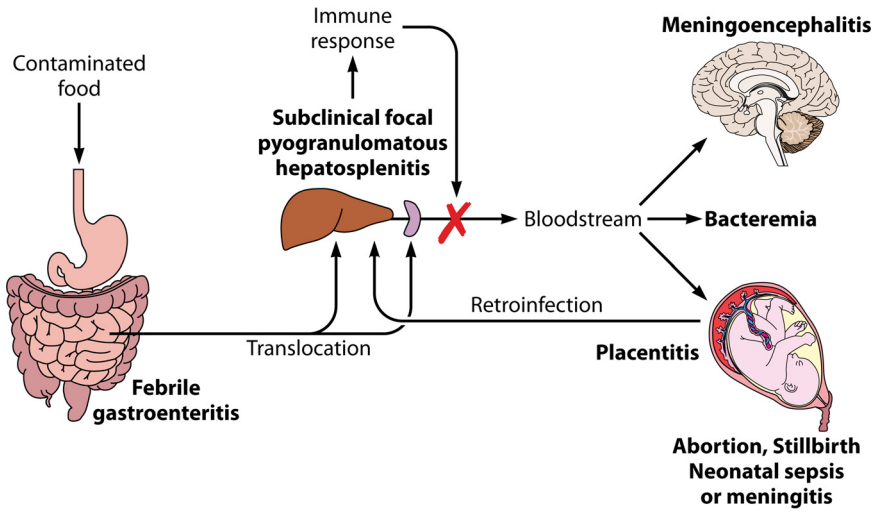

FIG 3 Pathophysiology of foodborne listeriosis. *L. monocytogenes* bacteria cross the epithelial barrier of the intestine, translocate to the mesenteric lymph nodes, and reach their primary target organs, i.e., liver and spleen. There they establish infectious foci that in an immunocompetent individual are efficiently cleared by cell-mediated immunity. In adult people with no predisposing conditions, the process is largely subclinical. In this population, exposure to larger infective doses may cause febrile gastroenteritis and, in rare cases, invasive disease. In immunocompromised adults and elderly people who are unable to mount an efficient T-cell-mediated immune response, the primary infectious foci are inadequately resolved and *Listeria* bacteria may be released to the bloodstream. This results in febrile bacteremia and, eventually, invasive infection of the brain. In pregnant women, *L. monocytogenes* colonizes the uterus in addition to the liver and spleen. While the infection is controlled in the latter organs, the placental immune tolerance mechanisms provide a permissive niche for the proliferation of *L. monocytogenes*. Bacteria from the placental reservoir released to the bloodstream may reinfect the mother's liver and spleen, contributing to infection maintenance and amplification (395). Transplacental dissemination to the fetus results in abortion, stillbirth, or neonatal sepsis. A late-onset congenital form is also observed in neonates, often accompanied by meningitis. Reproduced from reference 410, based on an earlier depiction in reference 61.

this aspect is the above-mentioned bacteriocin listeriolysin S encoded by LIPI-3, present in lineage I epidemic strains of *L. monocytogenes* (90, 91).

Traversal of intestinal barrier. *L. monocytogenes* uses 2 pathways for intestinal crossing. One is InlA/B-independent and inefficient, involving penetration through the M-cells lining the Peyer's patches. The other involves the active invasion of the intestinal epithelium mediated by the InlA/B internalins (294, 347–349). InlA/B-mediated invasion of the enterocytes lining the intestinal villi and crossing of this epithelium can occur within 15 min (296, 297, 350, 351). The InlA receptor, E-cadherin (E-cad) accumulates in the basolateral membrane of the enterocytes and is difficult to reach from the intestinal lumen, but can be accessed by *L. monocytogenes* around goblet cells, extruding enterocytes at the tips of intestinal villi, and in the epithelial folds of the villi (297). After intestinal barrier traversal, *L. monocytogenes* spreads to the draining mesenteric lymph nodes, followed by lymphohematogenous dissemination to the liver and spleen.

Infection of primary target organs (liver and spleen). In systemically infected mice, 60% of the intravenously injected *L. monocytogenes* bacteria are cleared within 10 min by the liver (352). A fraction of the bacteria are found in the spleen but most (90%) of the inoculum accumulates in the liver (353) upon uptake by Kupffer cells, the resident macrophages that line the hepatic sinusoids. Kupffer cells possess a complement C3b receptor called 'complement receptor for immunoglobulin superfamily' (CRIg) (354), which facilitates phagocytosis of circulating *Listeria* opsonized with C3b (355). After a drop in the bacterial load during the first 6 h after infection, likely reflecting killing by resident macrophages, *L. monocytogenes* numbers rise in both liver and spleen. Hepatocytes are the principal site of listerial multiplication in the liver (356–359). Initial control of the infectious foci in the liver is the result of the coordinated action of Kupffer cells, neutrophils, migrating macrophages

and (lymphokine-activated) natural killer cells (357). Influx of neutrophils into the liver within hours after infection kills extracellular bacteria and destroy *Listeria*-infected hepatocytes (352, 360, 361). Neutrophil-Kupffer cell interaction is promoted by adhesion molecules expressed by Kupffer cells such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (362). Liver and spleen macrophages elicit a pro-inflammatory response by producing interleukin (IL)-6, IL-12, IL-1β, tumor necrosis factor α (TNF-α) and nitric oxide (363). Modulated by IL-2 and IL-12, local natural killer (NK) cells produce interferon γ (IFN-γ) leading to an early innate immune response triggering macrophage activation (364–366). This is followed by an adaptive immune response that in naive mice typically clears the *L. monocytogenes* foci in liver and spleen by day 7 to 10 postinfection. Resolution of the infection is promoted by IFN-γ-secreting Th1 $CD4^+$ T cells, which stimulate the bactericidal capabilities of macrophages, and ultimately mediated by $CD8^+$ T cells which destroy infected cells by cytolysis (321, 367). During this process, the neutrophils that initially surround the infectious foci are gradually replaced by activated mononuclear cells and lymphocytes, forming characteristic granulomas (368).

Central Nervous System Invasion

The key events in the pathogenesis of CNS infections is the interaction with the blood-brain or blood-choroid plexus barriers (Fig. 1). Neuro-invasion by *L. monocytogenes* occurs in the context of a systemic disease and typically results from bacterial dissemination via the bloodstream (369). Evidence indicates that *L. monocytogenes* may invade brain endothelial cells either directly or by cell-to-cell spread from infected phagocytes (369–371).

The exact preferential site of brain invasion by *L. monocytogenes* remains unclear. Studies have indicated either the choroid plexus, ventricles, or the brain microvasculature as entry sites (372–374). Recently, entry via the trigeminus nerve has been suggested in a case series of *Listeria* rhombencephalitis (375). Neuroimaging analyses showed involvement of the trigeminal nerve and nucleus in the early stage of disease but remained inconclusive (375). Animal studies have documented axonal entry and spread while neuropathological studies showed bacteria in axons, Schwann cells, satellite cells, and ganglionic neurons (376, 377). Studies in ruminants suggested that the neuropathogenesis process involves interaction between *Listeria* bacteria and E-cad expressed in satellite cells and myelinating Schwann cells (378). A study in neonatal mice hypothesized that listerial invasion of the central nervous system can take place via nasal spread. By colonization of the mucosa in the nasopharynx, listeriae ascended via the olfactory epithelium and the sensory neurons to the cribriform plate, resulting in infection of the frontal segment of the brain (379).

In vitro data support that *L. monocytogenes* may gain access to the CNS by InlA/B-mediated direct invasion of endothelial cells, with a possible major role for InlB (370, 371, 380, 381). Alternatively, brain infection may proceed through InlA/B-mediated invasion of epithelial papilloma cells in the choroid plexus from the basolateral side (382, 383). *In vitro* studies using sheep choroid plexus epithelial cells and *in vivo* studies using intravenously inoculated mice suggested that *L. monocytogenes* may use a surface-associated autolysin, IspC (a novel peptidoglycan hydrolase), to breach the choroid plexus (382). Invasion is interrupted locally by inflammatory cells and phagocytes from the bloodstream. *In vitro* experiments show low endothelial infiltration grade when host inflammatory cells are present and activated (384). *L. monocytogenes* colonization of the endothelial layer is supported by the pore-forming toxin LLO (385). A recent *in vivo* mouse study showed that infected monocytes are protected by InlB from $CD8^+$ T cell-induced cell death, resulting in increased transfer of infected phagocytes into the brain (380). Experiments in mice also suggested that vimentin, an intermediate filament protein present in the cytosol and localized to the cell surface, plays a role in the uptake of *L. monocytogenes* into brain endothelial cells via interaction with the internalin InlF (386, 387).

Once bacteria have been detected in the CSF by the immune system (372, 373, 388), macrophages and neutrophils are attracted into the CNS resulting in further pro-

inflammatory cytokine production (389). The macrophage inflammatory proteins MIP-1α, MIP-1β and MIP-2 attract neutrophils and monocytes into the CSF (390). Studies in gerbils showed that after invasion of the CNS, the majority of *Listeria* are observed in the brain parenchyma rather than in the CSF (391). Macrophages, neutrophils, choroid plexus epithelial cells, ependymal cells of the ventricular wall, and periventricular neurons are all target cells for murine listerial meningoencephalitis (388). During listerial meningoencephalitis, a severe inflammatory response occurs in a normally immune privileged site (392). *In vivo* and *in vitro* studies indicated that extracellular traps (ETs) released from microglial vesicles and composed of extracellular DNA, matrix metallopeptidases MMP9 and MMP12, and citrullinated histone H3, could arrest or kill *Listeria* bacteria in the brain (393). Co-localization in human CSF was confirmed by marking the microglia and staining the extracellular DNA of CSF samples from 9 listerial CNS infection patients (393). A study of CSF samples from neurolisteriosis patients revealed elevated concentrations of 51 cytokines and chemokines compared to controls (394). In this study, 101 cytokines, chemokines and complement factors were analyzed, showing that inflammatory markers involved in T cell activation (sIL-2Rα, sCD40L and IL-12p40), complement activation (C3a), immunoregulatory responses (IFN-α2, IL-18, CX3CL1, CCL20), and endothelial growth factor production (VEGF, CXCL7), were associated with poor outcome (394). It remains unclear whether these pro-inflammatory markers are causatively linked to the outcome of are merely a reflection of severe disease (394).

Invasion of Placenta and Fetus

Like the major invasion pathway of the brain by *L. monocytogenes*, listerial colonization of the placenta is hematogenous (Fig. 1 and 3). Studies in animal models, and specifically, competitive infection experiments in guinea pigs (which have a placental structure similar to humans) have shown that small numbers of *L. monocytogenes* bacteria that traffic from primary infectious foci in the maternal organs are sufficient to establish a placental infection, most often as a clonal expansion of a single bacterial cell (395). This fits well with a hypothetical scenario in which invasive listeriosis is caused by blood-borne *L. monocytogenes* released from primary infectious foci in the liver and spleen and which, secondarily, seed the placenta in pregnant women (or the brain in at-risk non-pregnant adults; see above). The time required for the initial subclinical expansion of the bacterial population in the primary target organs, and secondary expansion of a small inoculum reaching the placental-fetal unit until onset of obstetric signs, is consistent with the relatively prolonged incubation period of pregnancy-associated listeriosis (median 27.5 days, range 17 to 67 and up to 90 days) (396).

The available experimental evidence supports a key role for the fetally-derived trophoblast in placental barrier penetration by *L. monocytogenes* (397–400). Studies with human placental explants or primary cells indicated that the syncytiotrophoblast lining the villi, which forms most of the maternal-fetal interface and is extensively exposed to maternal blood, is relatively resistant to *L. monocytogenes* infection (399, 401) (Fig. 1). The extravillous cytotrophoblast (EVT), which anchors the placenta in the uterine decidua and line the maternal arteries (Fig. 1), was more permissible and the preferential entry site. While still capable of eliminating approximately 80% of the intracellular *Listeria* in 24 h, bacteria surviving this bottleneck can successfully colonize the placenta (402) (see below). The *Listeria*-restricting capacity of EVTs may be linked to the intriguing ability of decidual killer lymphocytes (NK cells) to transfer the antimicrobial peptide granulysin via nanotubes to the trophoblast cells without killing them (403). *L. monocytogenes* triggers inflammasome signaling in human trophoblasts with enhanced secretion of IL-1β and IL-18, driving the innate immune defense against placental infection (404). In addition to a pro-inflammatory response, signature genes associated with poor pregnancy outcomes and production of tolerogenic factors are also upregulated in *Listeria*-infected trophoblasts, which on the other hand could facilitate placental infection (401). Evidence also indicates that early

immune signaling events during *Listeria* infection even prior to transplacental invasion blunts maternal regulatory T cell (Treg)-mediated suppression, disrupting fetal tolerance and precipitating fetal demise (405). These observations illustrate that the immune response to *Listeria* infection in the human placenta is a double-edge sword, and how it is regulated or affected by the pathogen may be critical in determining the fetal outcome.

The mechanism by which *L. monocytogenes* invades the trophoblast remains unclear. While in *in vitro* cell culture systems the internalins InlA and InlB (required for entry into non-phagocytic cells, see above) promoted listerial internalization into trophoblast cells, *in vivo* in animal models –either mice (including transgenic mice expressing the human isoform of the InlA receptor E-cad), gerbils, or guinea pigs– these listerial invasins had only a contributing yet dispensable (or even negligible) role (400, 406, 407). It therefore appears that listerial placental invasion *in vivo* primarily takes place via cell-to-cell spread from infected phagocytes trafficking to the maternal-fetal interface rather than via blood-borne free extracellular bacteria (395, 408, 409). This is supported by experiments in mice showing that the actin polymerizing protein ActA consistently facilitated the colonization of the fetoplacental unit whereas InlA and InlB were dispensable (407). However, in guinea pigs, an *actA* mutant was only minimally affected in placental invasion, although spread to the fetuses was significantly reduced (398). The relative contribution of each of these 2 invasion pathways may vary according to the specificities of the experimental host system, in particular the species-specificity of the InlA/B-host receptor interactions (400). It may also critically depend on the intensity of the blood-borne exposure of the placenta to *L. monocytogenes*, in turn determined by the infection dose and extent and dynamics of the primary infection in maternal organs (410). Additional listerial factors could also contribute to the colonization of the placenta, as recently reported for InlP. This secreted internalin family protein has been reported to promote placental invasion in mice and guinea pigs (presumably by favoring *L. monocytogenes* transcytosis via interaction with the cell junction-associated host protein afadin) as well as listerial proliferation in human placental organ cultures and trophoblasts (408, 411).

A critical role of the inoculum size in the outcome of maternal-fetal listeriosis has been experimentally confirmed in nonhuman primates. Cumulative analysis of trials where pregnant macaques received single oral or intragastric *L. monocytogenes* inocula shows a stillbirth rate of 6 out of 26 mothers (23.1%) when the infection dose was between 10^2 and 10^6, and of 8 out of 11 (72.7%) with 10^7 to 10^{10} doses (412–414). The incubation periods were also shorter with the larger doses (average of 20 versus 59 days). The more acute course observed with the latter correlated with an extensive neutrophilic inflammatory response and disruption of the macaques' maternal-fetal barrier, with necrotic thrombovasculitis of the decidual spiral arteries and presence of bacteria in the intervillous maternal circulation, villous capillaries, and umbilical cord (414), obviously facilitating listerial spread to the fetus. In all the experiments with macaques, no outward signs of maternal illness were observed until fetal demise, confirming the eminently subclinical nature of *L. monocytogenes* systemic infection in the pregnant mother (412–414).

Once the placenta is invaded by *L. monocytogenes*, active bacterial proliferation ensues, leading to colonization of the fetus involving ActA-mediated cell-to-cell spread (397, 398). Experimental infections in pregnant guinea pigs showed rapid listerial growth in the placenta ($>10^3$-fold at 24 h, 10^7-fold at 72 h), equalizing or even surpassing the bacterial population in the maternal organs from an initial ratio of $1{:}10^3$-10^4 (395, 398, 406). Collectively, the experimental observations indicate that the placenta offers a permissive "sanctuary" for *L. monocytogenes* survival and proliferation. This has been linked to the fetal trophoblast lacking class I human leukocyte antigen (HLA) -A and -B antigens and class II antigens while expressing nonclassical HLA class I molecule, which dampens allorecognition by uterine NK cells and T cells. Together with other placental immune tolerance mechanisms, this may prevent rejection of the

semiallogenic fetus (415–417) while, at the same time, allowing the proliferation of intracellular pathogens like *L. monocytogenes*, which depend on T cell-mediated immunity for clearance (321, 322). Hofbauer cells (villous macrophages of fetal origin) may play an important role as an intracellular amplification niche in the chorionic villi from which *L. monocytogenes* can spread to other placental and fetal cells (418). While Hofbauer cells undergo the typical M1 (pro-inflammatory) polarization observed in infected macrophages, they maintain the expression of tolerogenic factors known to prevent maternal anti-fetal adaptive immunity (418).

HISTOPATHOLOGY

Brain

Although often referred to as listerial meningitis, in human patients the infection often involves the brain tissue and pathologically is therefore more accurately described as meningoencephalitis. A study of 4 brains from neurolisteriosis patients showed that the pathogen was found intra- and extracellularly in the brain parenchyma, the blood vessels, and the meninges (419). The intracellular listeriae are often present within phagocytes while extracellularly they are often found in necrotic areas (420, 421). In neuropathological studies, monocytes and macrophages appeared to be the primary host defense cells. Efferocytosis, a clearance mechanism in which apoptotic cells are engulfed by macrophages, forming a large fluid-filled vesicle around the dead cell, is also observed. It has been shown that *L. monocytogenes* takes advantage of efferocytosis to facilitate cell-to-cell spread (320) and this mechanism could contribute to the dissemination of the pathogen in the brain tissue. Other characteristic neuropathological findings in listerial CNS infection are ventriculitis and small periventricular abscesses (419). Abscesses are also found in the basal ganglia, brainstem, or cerebral white matter (237, 421–423). It has been hypothesized *L. monocytogenes* enters the CNS through the choroid plexus and ventricles, and subsequently spreads via meningeal blood vessels and perivascular structures, contributing to abscess formation and extensive ventricular inflammation (372, 374, 422–424).

Placenta

In a series of 7 histopathologically examined second and third trimester placentas from pregnancy-associated listeriosis, macro abscesses and inflammation of the decidua and septum were found in all cases. Abscesses had a median size of 1.7 cm (range 0.5 to 3.0 cm), and showed necrosis and neutrophil infiltration (425). Chorioamnionitis, villitis, and funisitis were also consistently present. Remarkably, 4 of the placentas described in the study had an incorrect initial diagnosis (placental infarction) based on a macroscopical examination, stressing the need for histological analysis to accurately visualize microabscesses (425). Early gestational listeriosis experiments performed in macaques showed extensive infiltration of the endometrium and placenta, while pathological changes in the decidual arteries included severe vasculitis, thrombosis, and necrosis consistent with a hematogenous infection. Neutrophils infiltrated into the cytotrophoblastic shell and multifocal necrosis and multiple micro-abscesses were present. In the intervillous maternal circulation, the capillaries showed inflammation with necrosis and intralesional bacteria. In the fetuses, there was inflammation and edema of the chorion and amnion, neutrophil infiltration, vasculitis, and necrosis in the umbilical cord (414). The abundant presence of neutrophils in the macaque study indicated a strong inflammatory response which could have contributed to the spread of the bacteria to the fetus (414). Observations in human patients indicates that if the amnion is infected (culture positive in 10% of cases) (267), high concentrations of *Listeria* bacteria can be found in fetal lung and gut due to ingress of infected amniotic fluid (426, 427). In stillbirth cases, histopathological analyses may reveal a disseminated form of listerial infection known as granulomatosis infantiseptica, characterized by the widespread presence of microabscesses and granulomas, reflecting milliary dissemination across the fetus (426, 427).

CLINICAL PRESENTATION AND OUTCOME OF LISTERIOSIS

This section focuses on the 3 most common forms of invasive listeriosis, i.e., neurolisteriosis, bacteremia, and pregnancy-related infection including neonatal listeriosis, which respectively represent 31%, 52%, and 14% of cases (12, 16). There are only few prospective cohort studies on the clinical presentation and outcome of human listeriosis (16, 428–430), but many retrospective cohort studies are available (15, 102, 236, 250, 261, 267, 251–253, 431–433).

Brain Infection (Neurolisteriosis)

Most patients with neurolisteriosis are of older age and/or immunosuppressed (236, 430, 432, 434, 435). In a recent cohort study of 2140 patients with community-acquired bacterial meningitis, *L. monocytogenes* was identified as the causative pathogen in 16% of >80 years old patients (436). Cancer and diabetes mellitus were described as the most common debilitating comorbidities (437, 16). A recent study identified inflammatory bowel disease as risk factor for neurolisteriosis, which was linked to TNF inhibitors usage (438). About 4% of patients are young (≤ 40 years) non-immunosuppressed adults without relevant medical history, typically presenting with brainstem symptoms (16). It has been suggested these patients may have a genetic predisposition to *Listeria* infections, but data are lacking to substantiate this hypothesis (16). Subclinical immunodefiencies might also increase the risk for listerial infection. A Danish long-term follow-up study showed that following a diagnosis of neurolisteriosis, the risk of death from cancer within 5 years was 3-fold higher compared to controls (437). Patients with listerial CNS infections typically present with a slower onset of symptoms compared to patients with bacterial meningitis due to other pathogens such as pneumococci or meningococci (428). Median time of presentation of symptoms in patients with neurolisteriosis is 2 days before hospital admission (428, 432). While fever is consistently reported (85 to 90% of cases) (16, 428, 430), the classical triad of bacterial meningitis consisting of fever, neck stiffness, and a change in mental status, was found in a relatively low proportion of patients (36 to 68%) (428, 430, 432). One in five patients present in a coma while seizures are observed in 10% of cases (430, 432). CSF leukocyte counts in listerial meningitis are elevated but to a lesser extent than as seen in meningitis due to other bacteria (16, 428, 432, 439). CSF protein level is typically high and CSF to blood glucose ratio low (16, 428, 430).

Focal cerebral lesions detected by computed tomography (CT) or magnetic resonance imaging (MRI) have been reported in 23 to 26% of cases (428, 432). Ventriculitis is seen on neuroimaging in about 10% of cases and may be associated with hydrocephalus, which is seen in 10 to 15% of adult neurolisteriosis patients (428, 440). *Listeria* infection has been identified as an independent risk factor for hydrocephalus in community-acquired bacterial meningitis (441). The frequency of cerebral hemorrhage is 15% (428, 440). It is hypothesized that dysregulation of coagulation and fibrinolytic pathways, vascular endothelial cell swelling, and vasculitis, play a role in the pathophysiology of hemorrhages in bacterial meningitis (442–446). Brain abscesses are rare in neurolisteriosis, being reported in only 2% of cases (16), mostly in immunocompromised patients (447, 448). A meta-analysis of brain abscess cohort studies showed *L. monocytogenes* was cultured from the abscess aspirate in only 13 (0.4%) of 5894 cases (449).

The reported case fatality rate of listerial CNS infection ranges from 13% to 36% (16, 45, 118, 430, 432, 439, 450, 451) in Western countries, and 11%–73% in Asian studies (452, 453). Patients with a positive blood culture who received adjunctive dexamethasone had a higher risk of dying in the MONALISA study (16). However, in a Dutch prospective cohort study no harmful nor beneficial effect of adjunctive dexamethasone treatment was identified (428), and comparable results were found in a Danish study (454). In patients who survive *Listeria* CNS infections, neurological sequelae have been reported in 16% to 44% of cases (16, 432).

Bacteremia

Bacteremia, or systemic infection, is the most common invasive form of listeriosis, but can be difficult to recognize (16). In the above-mentioned MONALISA study, although the

mean time between symptom onset and hospital presentation was 2 days, in up to 25% of patients it was delayed until ≥6 days (16). Manifestations present in a continuum, ranging from nonspecific symptoms such as fever, diarrhea, chills, and muscle/joint pain, to septic shock leading to multiorgan failure and death (16). In systemic listeriosis, there is a slight male predominance (54-60%) (16, 453, 455) and patients have a higher age compared to neurolisteriosis patients (mean age 74 [SD 14] versus 67 [SD16] for neurolisteriosis) (16, 45). Almost all (97%) listerial bacteremia cases in the MONALISA study had an immunosuppressive condition, which included over 70 years of age (16). Other common immunosuppressive conditions linked to bacteremic listeriosis are cancer (31-62%), (16, 45, 455, 456), steroid use (39%) (453, 455) and diabetes mellitus (22-31%) (16, 455). Most commonly associated cancer forms are solid organ neoplasias (31%) (16). Patients present with fever or tachycardia in 94% of cases and diarrhea in 22% of cases (16). Elevated inflammatory parameters in blood are found in up to 96% of cases (16). The most common means of diagnosis for systemic listeriosis is a positive blood culture (61 to 79%) (16, 45). Twenty-one percent of patients with bacteremia needed intensive care, and half of them needed mechanical ventilation. Multiorgan failure has been reported in 18% of patients (16). Systemic listeriosis has been associated with high case fatality rates of 21 to 46% (12, 15, 45, 102, 250, 429, 451, 453, 455). Risk factors for death due to listerial bacteremia are advanced age, active malignancies, female sex, and disease characteristics such as weight loss, multiorgan failure, low monocyte count, and neutrophilia in blood (16, 45, 429, 455).

Pregnancy-Associated and Neonatal Infections

In most documented cases, maternal-fetal listeriosis manifests in the third term of gestation. Duration of symptoms prior to diagnosis is usually shorter compared to non-pregnancy-related listeriosis or neurolisteriosis (mean time before presentation is approximately 1 day) (457). Although maternal listeriosis may occur without clear symptoms before manifestation of obstetric signs, 20 to 34% of cases present with general malaise as well as symptoms such as abdominal pain, dry cough, fever, nausea, vomiting, headache, and dyspnea (16, 119, 250, 260, 261, 431, 453, 458). In cases where the mother experiences few symptoms, the only manifestation may be early labor, which may be accompanied by severe fetal distress (268, 457). In contrast to systemic listeriosis, immunosuppressive comorbidity is rare in pregnancy-associated listeriosis (128). In a Chinese retrospective study between 2008 and 2017, 89% of cases among pregnant women had an intrauterine *Listeria* infection (based on cervical swabs) (453). The diagnostic modality with the highest sensitivity for diagnosis of pregnancy-associated listeriosis are placental swabs and newborn gastric fluid swabs (both 78% positive) (16). Blood cultures positive for *L. monocytogenes* in mothers have been reported in 33 to 68% of cases (16, 119, 250, 260, 268, 459). Severe illness in *Literia*-infected pregnant women is uncommon, most cases recovering without impairment (102, 128, 268), even without antibiotic treatment (16).

Neonatal listeriosis is caused by transmission of the bacteria from the mother to the infant. Two forms of presentation can be distinguished: (i) early-onset, when symptoms present at or within 48 h of birth; and late-onset, when symptoms develop 48 h postpartum. Although it is commonly believed that early-onset cases result from transplacental transmission and late-onset ones from exposure to infected vaginal or certical fluids during labor (460), the primary cause of neonatal listeriosis is most likely a placental infection (see above). Neonates in pregnancy-associated listeriosis develop bacteremia in 62 to 72% of cases (453, 458), pneumonia in 9 to 13% of cases, and meningitis in 13 to 19% of cases (453, 458). Reported mortality rates for neonatal listeriosis are 9 to 50%, and up to 13% of surviving babies develop neurological sequelae (250, 260, 264, 267, 451, 453, 455, 458, 461, 462). Fetal and neonatal adverse effects are less common as gestational age increases or with higher gestational age at birth (265, 266, 431, 459, 463). In a recent study of 42 neonatal cases from the large South African polony outbreak 2017 to 2018, 81% were born preterm (median 32 weeks). Common clinical symptoms were respiratory depression or distress, often requiring respiratory support (69%). In 4 newborns (11%), listerial CNS infection was demonstrated by culture, although based on high CSF white cell counts or protein levels, 40% were defined

as listerial meningitis (462). In a retrospective study of listeriosis in China, miscarriage or fetal demise/stillbirth accounted for a fatality rate of 42% among maternofetal/neonatal cases (453). Early treatment of neonatal listeriosis improves the outcome and therefore early diagnosis and treatment is strived for (464).

TREATMENT

Antimicrobial Therapy

Fast administration of an adequate antimicrobial treatment is key to prevent complications, death, and long-lasting sequelae in human listeriosis (16, 249, 433, 465, 466). However, no controlled trials have been conducted so far to establish a drug of choice or optimal duration of therapy (467). The β-lactam antibiotics penicillin and aminopenicillins ampicillin or amoxicillin are the first-choice treatment despite they appear to be bacteriostatic against intracellular *L. monocytogenes* (467, 468). At subinhibitory concentrations, β-lactams have been reported to reduce the production of the essential virulence factor LLO (469), whereas they achieve full bacterial killing at high concentrations (e.g., from 16-fold above MIC) (470). Binding of β-lactams to key penicillin-binding-proteins (PBPs) is crucial for effective killing of *L. monocytogenes*. Several PBP's play a role in listerial susceptibility to β-lactams, albeit to different degrees, with PBP3 being a critical target (470). *L. monocytogenes* has a natural resistance to antibiotics that poorly bind PBP-3 such as cephalosporins, even if other PBP's (1, 2, and 4) are completely blocked (471). PBP3 is involved in the late stages of peptidoglycan synthesis and its blockade significantly hinders *Listeria* viability (472).

Cotrimoxazole (trimethoprim-sulfonamide) is the alternative choice in listerial infections (473, 474). Trimethoprim and sulfonamides are effective against intra- and extracellular *Listeria* and, while bacteriostatic on their own, in combination they achieve bactericidal activity. Cotrimoxazole enters mammalian cells via diffusion and therefore easily reaches intracellular *L. monocytogenes* (475, 476).

β-lactam antibiotics are usually combined with an aminoglycoside to treat listeriosis, although clear proof of improved efficacy is lacking (474). *In vitro* and *in vivo* studies show contradicting results on the added value of the aminoglycoside combination (477–480). The case for adding an aminoglycoside originates from an *in vitro* study where 7 *L. monocytogenes* strains from neonatal infections were tested (481). However, although aminoglycosides rapidly kill *L. monocytogenes* in broth culture (482), they have poor activity against intracellular bacteria (483). Aminoglycosides are taken up by mammalian cells via fluid-phase pinocytosis, resulting in varying concentrations per cell type and over time. Intracellularly, aminoglycosides are trapped in lysosomes and their functionality is diminished due to low pH values (484, 485). Nevertheless, 2 large cohort studies have suggested clinical beneficial effects of using the β-lactam-aminoglycoside combination (16, 236, 486), leading to an ongoing discussion on the added value of aminoglycosides in the treatment of human listeriosis (432, 466, 487–489). Other antibiotics used in the treatment of listeriosis are shown in Table 2.

A potential addition to the combination therapy of listeriosis is fosfomycin, a bactericidal antibiotic that inhibits peptidoglycan biosynthesis through covalent inactivation of UDP-*N*-acetylglucosamine-3-enolpyruvyl transferase (MurA). In addition to a well-established safety record and synergistic activity with many antimicrobials including β-lactams, intravenous fosfomycin has low plasma protein binding and excellent intracellular and tissue penetration, including the blood-brain barrier and placenta (490). Interestingly, *L. monocytogenes* is intrinsically resistant to fosfomycin *in vitro* (467, 491, 492) due to the presence of a *fosX* gene encoding a fosfomycin-hydrolyzing enzyme (493). However, the *fosX*-mediated resistance is overcome when expression of the PrfA-regulated sugar phosphate transporter Hpt, required for rapid cytosolic replication (64), and which also transports fosfomycin into the bacterial cell, is activated intracellularly (492). Consequently, most *L. monocytogenes* isolates are fully susceptible to fosfomycin *in vivo* during infection despite testing resistant *in vitro* (492, 494, 495). These findings represented the first molecular elucidation of an *in vitro-in vivo* paradox in

TABLE 2 Antibiotics and *L. monocytogenes* invasive disease

Antibiotic	Bactericidal/ bacteriostatic	Intracellular activity	Pass placental barrier	Pass blood-brain barrier	Synergetic effect with...
Aminoglycosides					
Gentamicin	Bacteriostatic (482)	Limited (482)	Limited (544)	No (236, 502)	Amoxicillin (16, 502, 505) imipenem (545)
Amoxicillin	Bacteriostatic intracellular, bactericidal extracellular (546)	Yes (480)	Yes (504)	Yes (502)	Gentamicin (16, 502, 505) cotrimoxazol (502)
Ampicillin	Bacteriostatic (546)	Yes (480)	Yes (504)	Yes (502)	
Chloramphenicol	Bacteriostatic (478)	Yes (547)	Yes (504)	Yes (501)	
Cotrimoxazole	Bactericidal (548)	Yes (549)	Yes (509)	Yes (502)	Amoxicillin or rifampicin (502)
Glycopeptides					
Vancomycin	Bactericidal (545)	No (480)	Limited (544)	No (502)	
Fosfomycin[a]	Bactericidal (495)	Yes (492)	Yes (544)	Yes (550)	
Imipenem	Bactericidal (548)	Yes (480)	Yes (551)	Yes (502)	Gentamicin (552)
Linezolid	Bacteriostatic (553)	Yes (553)	Yes (504)	Yes (499)	
Macrolides					
Erythromicin	Bacteriostatic (478)	Yes (480)	Limited (507)	Limited (477)	
Meropenem (273, 483, 497)	Bacteriocidal (483, 554)	Yes (554)	Limited (555)	Yes (556)	
Penicillin	Bacteriostatic (478)	Limited (478)	Yes (504)	Limited (501)	
Quinolones					
Moxifloxacin	Bactericidal (468, 483)	Limited (480)	Yes (557)	Yes (501)	
Rifampicin	Bacteriostatic (467)	Yes (480)		Yes (502)	Cotrimoxazole (502)
Tetracyclines	Bacteriostatic (467)	Limited	Yes (504)	Yes (501)	

[a]Sodium salt for intravenous use. It is important to note that *L. monocytogenes* tests resistant to fosfomycin *in vitro* whereas it is fully susceptible to this antibiotic *in vivo* during infection. The reason for this *in vitro-in vivo* paradox is that expression of the fosfomycin transporter, the virulence factor Hpt (a sugar/organophosphate permease homologous to enterobacterial UhpT), is tightly controlled by the *Listeria* virulence gene activator PrfA. As a result, Hpt-mediated fosfomycin uptake is fully activated within infected host cells whereas it is abolished *in vitro* in culture media (492, 493).

antimicrobial therapy (492), and of an epistatic interaction between virulence and resistance genes in a pathogen (493). They also illustrate how basic microbiological research can translate into direct clinical applications.

Treatment per age-group and indication. In neonates with listeriosis in the first week of life, ampicillin or amoxicillin (100-300 mg/kg/day during 14 days, parenterally) is the antimicrobial treatment of choice. If listeriosis occurs later (between day 8 and 28), a 21-day course is advised. Both regimens can be prescribed in combination with gentamicin (2 mg/kg during 7 days) (496).

According to the IDSA and ESCMID bacterial meningitis treatment guidelines, adult neurolisteriosis should be treated with 12 g β-lactam antibiotics a day during at least 21 days (273, 497). Because ampicillin and amoxicillin penetrate the blood-brain barrier relatively poorly, the dosages are higher than those used in non-CNS infections (498–501). Linezolid (499), rifampicin (502), moxifloxacin (479, 500, 503), meropenem (466), fosfomycin (501), cotrimoxazol (501), and chloramphenicol (501) are found in high concentrations in the cerebrospinal fluid and are able to penetrate the blood-brain barrier with both inflamed or uninflamed meninges; however, no superiority to β-lactam antibiotics has been proven (501). In patients with *Listeria* brain abscesses or rhombencephalitis, it is advised to prolong antibiotic treatment for at least 6 weeks with radiological monitoring (236).

During pregnancy, β-lactam antibiotics have a long history of use without significant harmful effects on the fetus and therefore are considered safe (504). Intravenous amoxicillin or ampicillin (6 to 12 g/day) both pass through the placental barrier quickly (457) and are the first-line drugs for pregnancy-related listeriosis. In France, amoxicillin 100 mg/kg/day for 2 weeks or until delivery, in combination with gentamicin 5 mg/kg/day for 3–5 days, is recommended (505). Erythromycin (4g/day) is suggested as second-line antibiotic in case of penicillin allergy in pregnant women (506), but transplacental passage is low and concentrations reached in the amniotic fluid and fetal serum are subtherapeutic (507). Recommendations on second-line antibiotic treatment of maternofetal listeriosis

vary through the literature. Cotrimoxazole can pass the placenta easily, and has a bactericidal effect on *L. monocytogenes* but is not commonly considered a safe second choice due to concerns that it might cause neural tube defects in the first trimester (267, 508). However, a large retrospective US study (2001 to 2008) involving 20,064 cases showed no increased risk of congenital anomalies in pregnant women treated with cotrimoxazole compared to β-lactams (509). Sulfamethoxazole has been contraindicated during the third trimester because of its ability to displace bilirubin from its albumin-binding sites in plasma, causing an elevation of plasma bilirubin potentially leading to kernicterus (496, 506). However, again a literature review (1940 to 2012) showed no reported cases of kernicterus in neonates treated with cotrimoxazole, so this risk also appears to be negligible (510).

Fetal complications in pregnancy-related listeriosis resulting in neonatal infection often occur in the absence of overt illness in the mother and symptoms can be nonspecific. In the absence of specific evidence, recommendations to start antibiotic treatment in mildly ill women with known or suspected exposure to *L. monocytogenes* vary. Expert opinions range from treating every febrile pregnant woman potentially infected with *L. monocytogenes* (263, 505), to only treating febrile and symptomatic pregnant women with known exposure to the pathogen (511).

The therapeutic approach also differs in bacteremic listeriosis. In an English study (2006 to 2015), 96% of cases in which treatment was documented received at least 1 antibiotic, 63% $\geq$ 2 antibiotics, 15% $\geq$ 3 antibiotics, and 3% $\geq$ 4 antibiotics (45). Amoxicillin or ampicillin are the most used antimicrobials to treat listerial bacteremia (71 to 82%), followed by (adjuvant) gentamicin (44 to 48%) (16, 45).

Antimicrobial resistance. The rate of antibiotic resistance in *L. monocytogenes* isolates causing human listeriosis is low (512–515). In a French study which examined strains recovered between 1926 and 2007, 23 antibiotics were tested and no clinically significant acquired resistance was found against any first-line drug. Only 1.27% of isolates showed resistance, in most cases to tetracycline or ciprofloxacin (516). More recent studies reported sporadic intermediate resistance to erythromycin, chloramphenicol (513), rifampin, gentamicin (517), and cotrimoxazole (512). Although antimicrobial resistance is rarely a clinical issue in listeriosis, surveillance of susceptibility is important to monitor transfer of resistance genes from other bacteria or MIC increases to penicillin/β-lactams (480, 516). Horizontal transfer of transposons and plasmids from other Gram-positive bacteria to *Listeria* has been observed and there is therefore a risk of resistance acquisition through these mechanisms (514).

Several *L. monocytogenes* genes have been associated or shown to protect against quaternary ammonium compounds, commonly used as disinfectants in the food industry and medical environments. One of these is the *emrE* gene encoding a small multidrug-resistant (SMR) protein family efflux pump (518), found in LGI1, a *Listeria* genomic island identified in isolates responsible for a deadly listeriosis outbreak in Canada in 2008 (519). The plasmid pLM80 (520), also found in *L. monocytogenes* strains from a human listeriosis outbreak, specifies resistance to benzalkonimum chloride (BC) via a 3-gene cassette *bcrABC*, 2 SMR efflux pumps, and cognate transcriptional regulator (520). Furthermore, a transposon (Tn*6188*) was identified in serovar 1/2a isolates from food and food processing environments which contains a *qacH* gene coding for a quaternary ammonium compound resistance protein (521). In addition to resistance to BC disinfectants, these genes may be associated to resistance to antimicrobials or even increased virulence (522, 523). An example of the latter is the efflux transporter gene *emrC* linked to the emergence of neurolisteriosis with an increased rate of poor outcome in patients, caused by an ST6-strain in the Netherlands (524). Disinfectant resistance genes are not equally represented in *L. monocytogenes,* and have specifically been associated with the food environment-adapted CC9 and CC121 genotypes while rarely found in CC1 and CC4 isolates (139).

Adjunctive Treatment

Clinical trials have shown that treatment of bacterial meningitis patients with dexamethasone associates with decreased mortality, from 30% to 20% (273, 525, 526).

These observations are consistent with experimental pnemococcal meningitis data showing a reduced inflammatory response in the subarachnoid space in rabbits and an improved outcome when treated with antibiotics and a corticosteroid (527, 528). However, when considering listerial CNS infection patients specifically, dexamethasone was found to have no beneficial effect on outcome in a nationwide cohort of 92 patients of whom 53% received dexamethasone (428). Moreover, in the MONALISA study, a deleterious effect of dexamethasone was suggested, but only 32 of 252 patients (13%) received dexamethasone and there may have been confounding by indication, meaning only the most severely ill patients received dexamethasone (16). Further investigation is needed to establish whether adjunctive treatment with corticoids has any significant clinical effect in invasive listeriosis.

PREVENTION

Being a foodborne infection caused by an environmental organism, control of human listeriosis revolves around reducing food chain contamination by *L. monocytogenes*. Substantial efforts have been made through food safety regulations and educational programs (529), and by the food industry via specific control measures and risk analysis models for listerial contamination 'from farm to fork' (230). Among the first interventions were those implemented in France in 1986 in production plants that exported cheese to the USA, subsequently expanded to all cheese production manufacturers by the government in 1988, and to ready-to-eat and meat products in 1992 (230). Control measures included systematic microbiological monitoring of raw and processed foods and sanitation plans in case of *L. monocytogenes* detection, complemented with food hygiene training programs for employees (230). Between 1987 and 1997 these measures reduced the incidence of human listeriosis in France by 68% to 72% (230), paving the way to modern *Listeria* control strategies and programs. A cornerstone of *Listeria* control is the monitoring of the environment in food processing plants to facilitate identification of bacterial harborage niches and subsequent enhanced sanitation efforts to eradicate the organism.

The importance of clear information and education on listeriosis to consumers and risk groups needs to be emphasized (230, 266, 530, 531). Educational efforts have traditionally focused on pregnant women (266, 530, 531), with positive results as noted for example in France with intensified education about prevalence and food-associated risk of human listeriosis (119). As a result, pregnant women are currently generally aware about the potential complications for the fetus caused by *Listeria* (530). Other areas potentially benefitting from education on listeriosis include collective canteens, nursing homes, and hospitals, in which food-related outbreaks among fragilized patients, or in neonatal units due to poor hygiene, have taken place (110, 178, 183, 191, 274–286). Targeted measures should also focus on the elderly, because they tend to store food beyond the 'best-before' date in their refrigerators (532). The domestic environment may be an unrecognized source of cross-contamination, as suggested by a sampling study in Dutch households which found *L. monocytogenes* in 21% of the 213 investigated houses, with particularly high CFU rates (10^4 CFU/object) in kitchen cloths and dish brushes (533).

CONCLUSIONS AND FUTURE DIRECTIONS

The impact of human listeriosis on society over the last 4 decades remains high (16, 428). Its identification as a foodborne disease has been fairly recent, as was the realization that robust continued action is needed to curb *Listeria* infections (10, 27). Although food regulatory measures are critical, there is no international consensus about the acceptable level of contamination by *L. monocytogenes*. European regulations established in 2000 a limit of $<$100 CFU/gram as acceptable (534), whereas in the US the Food and Drug Administration conducts a zero tolerance policy on the grounds that low contamination levels involves a risk to highly susceptible people (535). The latter is supported by risk assessments that indicated that consumption of 100 g food with $<$ 100 CFU *L. monocytogenes* was linked to 3.5% of human listeriosis cases (536), and implicitly by

epidemiological evidence from EFSA showing a slow but consistent increase of human listeriosis cases in Europe over the last 2 decades (231). The recent insight into the differential virulence of *L. monocytogenes* genotypes/clonal complexes (92) may help to clarify the debate and allow tailoring regulations to specifically target the application of zero tolerance criteria to those genotypes most likely to cause invasive listeriosis, thereby helping to reduce the economic burden of the control measures.

Given the crucial role of surveillance systems in *Listeria* control and the increasing internationalization of food production and retail distribution, transnational team-work and harmonization in WGS-based outbreak detection and identification of contamination sources is expected to develop further in the coming years.

Since listeriosis remains a difficult to treat infection with significant case fatality rates and frequency of sequelae, another area that will benefit from enhanced international collaboration is the clinical management of patients. Large, randomized trials (only possible through multi-center approaches given the relatively low incidence of listeriosis) will be important to test the therapeutic approaches and resolve controversies over the efficacy of gentamicin coadministration or the adjunctive treatment with corticoids. Among others, it would be important to ascertain the potential benefits of adding fosfomycin (492, 493) to the combination therapy of invasive listeriosis in terms of reducing the length of treatment and hospitalizations, and improving the clinical outcome.

Over the last 20 years, much has been learned about the genetic, molecular and cellular mechanisms underlying *Listeria* infection (336). In contrast to the many groundbreaking advances in these areas, the pathophysiological mechanisms of listeriosis have attracted less attention and remain less well characterized. Why does *L. monocytogenes* preferentially invade the placenta and the central nervous system, and why do pregnant women infrequently develop neurolisteriosis or bacteremia? (16) Why do some healthy young patients without risk factors contract neurolisteriosis (16, 428)? What is the significance and which mechanisms underlie the ascending neuroinvasion via the trigeminal nerve? These are examples of questions that require further investigation.

Since pioneering research discovered the basic molecular and cell biological features of its virulence in the late 1980s/early 1990s, *L. monocytogenes* is one of the best characterized models in bacterial intracellular parasitism (537). Its biomedical significance extends back to the 1960s, when the ability to survive inside macrophages and inability of antibodies to protect against intracellular infection established *L. monocytogenes* as a key research model in cellular immunity (321, 322, 538). Further research on this pathogen should not only help improving the clinical management of the severe infection it causes, but also deciphering the intricate mechanisms of microbial pathogenesis, and developing novel translational applications in medicine based on this knowledge (539, 540).

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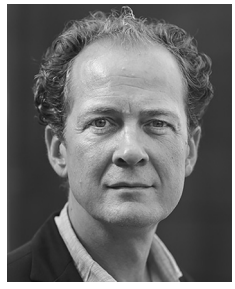

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