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Genomic Characteristics of Listeria that Caused Invasive Listeriosis During the COVID-19 Pandemic

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Abstract

Index terms—

immunocompromised (patients undergoing treatment for cancer, AIDS and organ transplants), pregnant women and their unborn or newborn infants [4,5]. Defining the age limits of the elderly group, Mook et al. concluded that age >60 years was associated with an increased risk for listeriosis in England and Wales [5]. According to Goulet et al., the age of the high-risk group with no underlying conditions was >65 years in France [6]. Immunosenescence in the elderly is associated with declines in adaptive and innate immunity [7]. Immunocompromised persons have suppressed T-cell-mediated immunity as a consequence of the treatment [5]. The decrease in the number of helper T cells in the second and third trimesters of normal pregnancy is evidence of immunodeficiency in pregnant women [8]. In addition, in pregnancy, in the second and third trimesters, the gastrointestinal (GI) tract undergoes a series of changes, the root cause of which is a decrease in intestinal motility [9]. GI motility plays a key role in mucus renewal. The mucus is the first line of defense against the infiltration of microorganisms [10]. It coats the interior surface of the GI tract, lubricates luminal contents and physically entraps bacteria, sweeping ingested bacteria out of the small bowel into the colon [11]. Decreased GI motility results in the enrichment of the mucus with Proteobacteria and Actinobacteria (in October 2021, the valid names became Pseudomonadota and Actinomycetota [12]), and in the reduction in the health-related bacterial abundances [13]. Alterations in the mucus microbial community result in a decrease in the production of protective factors including short chain fatty acids (SCFAs), in particular, acetate and formate, which have antimicrobial properties against enteric pathogens [11], and butyrate, which has anti-inflammatory effects [13].

Neurological disorders, stress, and antibiotic treatment are also accompanied by a reduction in the mucus-associated gut microbiota layer and mucus secretion [10,14,15]. The damage to the GI mucosa could be caused by viral pathogens often having seasonal patterns [16,17]. ??chwartz et al. were the first to analyze the association of invasive listeriosis with the consequences of a viral infection in Philadelphia between 1 December and 1 April 1987, i.e., during the period of the epidemic rise in the incidence of influenza virus in the Northern Hemisphere [17]. The subsequent years of intensive study into the microbial communities in different environmental niches within human bodies demonstrated the effects of viral infections on both the gut and respiratory microbiome. Influenza infection, for instance, has been found to result in significant changes in the gut microbiome, despite the lack of detectable virions in the GI tract [18]. Furthermore, according to Bortel et al. pulmonary infection triggers the production of IL-10 by Ncr1+ cells, which could be a factor that increases the survival of invasive *L. monocytogenes* [19].

At the end of 2019, humanity faced a new virus, SARS-CoV-2, which caused severe respiratory coronavirus disease 2019 (COVID-19), reaching pandemic levels on March 11 2020 [20]. In 2020, Xiao et al. and other researchers provided evidence for the GI infection of SARS-CoV-2 [21,22,23]. A cell receptor for SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2) protein, was demonstrated to be abundantly expressed in the glandular cells of gastric, duodenal, and rectal epithelia, supporting the entry of SARS-CoV-2 into the host cells [21,23]. Among the hospitalized patients infected with SARS-CoV-2, 53.42% tested positive for SARS-CoV-2 RNA in their stool, and more than 20% of patients with SARS-CoV-2 remained positive for viral RNA in feces even after the test results for viral RNA in the respiratory tract became negative [21]. Furthermore, SARS-CoV-2 infection causes an alteration of intestinal permeability, resulting in enterocyte dysfunction [22]. These data suggest a direct effect of SARS-CoV-2 on the gut microbiota, in addition to in-direct effects via the gut-lung axis [24,25].

Previously, we showed the impact of respiratory viral infections on the incidence of invasive listeriosis in a metropolis in 2018/2019. *L. monocytogenes* of phylogenetic lineage (PL) II prevailed in the groups of cases that

2 THE ANALYSIS OF THE CHANGE IN SARS-COV-2 PANGOLINEAGES IN THE MOSCOW METROPOLIS.

49 occurred when the epidemic threshold for influenza was crossed during the 2018/2019 season. *Listeria pneumonia*
50 identified in the senior age group occurred during the season London Journal of Research in Science: Natural
51 and Formal of autumn acute respiratory viral infections and was primarily caused by *L. monocytogenes* of PLI
52 [26]. It is strains of PL I and II that cause the majority of human illness, despite the fact that the population of
53 *L. monocytogenes* consists of four divergent lineages (I-IV) [27].

54 The aim of this study was to research the impact of the COVID-19 pandemic on the incidence of invasive
55 listeriosis in the same metropolis, comparing the spectrum of the *Listeria* genotypes that previously caused the
56 disease with the spectrum of the *Listeria* pathogens identified during the COVID-19 pandemic.

1 II. RESULTS

58 The monitoring of the clinical and food-borne *L. monocytogenes* isolates started in November 2018 in a large
59 metropolis with a population of 20.4 million (<https://mosstat.gks.ru/folder/64634/> (accessed on 24 July 2022)).
60 The COVID-19 pandemic divided our study into two periods: before the pandemic (November 2018-October
61 2019) and during the pandemic (March 2020-January 2022). Since SARS-CoV-2 was constantly mutating during
62 the pandemic, we characterized the stages of the pandemic by the number of genotypes (pangolineages) circulating
63 at the same time.

2 The analysis of the change in SARS-CoV-2 pangolineages in the Moscow metropolis.

66 The large amount of data on SARS-CoV-2 sequences related to the Moscow region, presented in the GISAID
67 EpiFlu? Database (<http://gisaid.org/> (accessed on 24 July 2022)) including our own data (EPI_ISL_421275,
68 EPI_ISL_1708505, EPI_ISL_1708506, EPI_ISL_1708510 -EPI_ISL_1708519, EPI_ISL_1731043 -
69 EPI_ISL_1731045, EPI_ISL_2322757 -EPI_ISL_2322762, EPI_ISL_2356912, EPI_ISL_2356913,
70 EPI_ISL_3102159, EPI_ISL_9058873, EPI_ISL_9058988 -EPI_ISL_9058990, EPI_ISL_9058992), indicates
71 that the pandemic period included in our observation can be divided into two stages (Figure 1 In the period
72 before the pandemic, the autochthonous ST7 of PLII prevailed, while ST6 (PLI) was the second most prevalent
73 (Fig. 2a1,2b), (Table S1). If ST7 is typical in Russia (with the exception of the Far East Federal District
74 (FD)) for isolates from food and the environment [31,32], then the sources of ST6 have not yet been found.
75 *L. monocytogenes* of this genotype is absent in food from domestic production in the Moscow region [31]. In
76 perinatal listeriosis, only listeria of these two STs were found (Fig. 3a), while in invasive listeriosis in the older
77 age group (meningitis and sepsis), three more STs of PLII and two STs of PLI added diversity (Fig. 4a). In
78 general, during the period before the pandemic, *L. monocytogenes* of STs of PLII prevailed, which is typical
79 for the population of listeria in most of the territories of the Russian Federation. Only in the Far East FD did
80 listeria of PLI predominate both in the environment and among the clinical isolates [33,34]. From the eight
81 genotypes of PLII, only two STs (7 and 14) coincided with those identified in the period before the pandemic
82 (Figure 2b). From the STs that appeared during the pandemic (Figure 2a4), ST451 was attributed only to
83 perinatal listeriosis. ST451 was new in the Central FD in January 2021. In August 2021, the strain with the
84 same ST and internalin profile (IP), including inlA, inlB, inlC, and inlE, was isolated from a lightly salted salmon
85 fillet imported from the Faroe Islands. However, in 2016/2017, *L. monocytogenes* ST451 was also isolated in the
86 Northwestern FD in the case of perinatal listeriosis (ID 37701) [35], and from chilled beef of unknown origin (ID
87 42266) [35].

88 It should be noted that comparative analysis of the sequences of internalin A demonstrated that isolates of
89 ST451 had the same N187S substitution in the leucine-rich repeat (LRR) 5 domain as the strains of PLI. This
90 is important for internalin A-E-cadherin interaction, which is exploited by *L. monocytogenes* for the invasion of
91 enterocytes and to cross the placental barrier [36].

92 The two more STs, 21 and 8, were revealed not only in the perinatal listeriosis group (Figure 3b), but in the
93 meningitis and sepsis group too (Figure 4b). Previously, ST21 was not observed in human listeriosis. In 1975, an
94 isolate of this genotype was isolated from a goat in the North Caucasian FD of Russia [32], but it differed from
95 the human isolate by the locus of internalin C in the IP. The *L. monocytogenes* isolates of ST8 were previously
96 found in food (meat, fish, dairy) in Russia, but were absent in clinical cases of listeriosis. The isolates of Clonal
97 Complex (CC) 8 were detected in meat (ST16, ID 42269) [35] and in the environment (ST758) [34], and in cases
98 of meningitis (ST2096) before the COVID-19 pandemic [26]. All isolates of CC8 but one (ST758, IP34), had the
99 same IP53.

100 During the COVID-19 pandemic, *L. monocytogenes* ST8 was revealed in four clinical cases (Figures 3b and 4b),
101 and one of them had a fatal outcome.

102 The greatest diversity of the PLII genotypes was noted in the older age group (meningitis and sepsis) during
103 the pandemic (Figure 4b), and each of the genotypes was associated with a case of listeriosis with a fatal outcome
104 (Table S1). ST20 was first detected in human listeriosis in the Central FD, but in 2007 an isolate of this genotype
105 was isolated from the crucian carp (*Carassius carassius*) [34]. The IP of clinical and environmental isolates were
106 identical. However, in 2016 *L. monocytogenes* ST20 was isolated in the North-western FD in the case of perinatal
107 listeriosis (ID 42272), later, in 2017, a strain of this ST was isolated from chilled beef of unknown origin (ID
108 42270), and then, in 2018, it was isolated from wastewater (ID 42274) [35].

109 L. monocytogenes of ST425 is also new in human listeriosis in Russia but was isolated in the environment
110 (from red deer (*Cervus elaphus*) feces) in 2009 [34]. However, in this case, clinical and environmental isolates
111 differed in the internalin B locus of the IP. A single-nucleotide variant (SNV) in the same position of the inlB
112 alleles relative to the most common for the PLII allele 14 (A/T, A/C) leads to the same amino acid substitution
113 (Ile/Leu).

114 ST37, found in food and food processing environments (FPEs) in 2017 (ID 37695) [35], and in 2019-2021 (ID
115 49371, 49372, 76388) [31], was isolated for the first time in 2021 in a case of human listeriosis. Note that food
116 and clinical isolates had the same IP.

117 Finally, ST391 (CC89) was discovered for the first time, but it is a single locus variant (SLV) of ST1547 (CC89)
118 identified in human listeriosis in 1997 [32]. The internalin B locus distinguishes the IP of these genotypes.

119 Thus, we note a significant role of the PLII STs in the group of diseases "meningitis and septicemia". Evaluating
120 the L. monocytogenes genotypes in the older age group for the entire observation period (Fig. 4b), it should be
121 noted that the proportion of the PLI is low, but the diversity index is high, which is provided by the PLII STs.
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123 3 Comparison of L. monocytogenes of two stages of the COVID- 124 19 pandemic

125 Comparing the causative agents of invasive listeriosis in the two periods of time, before the pandemic and during
126 the pandemic, we saw a significant difference in the diversity of genotypes, in the representation of phylogenetic
127 lineages, and in the number of deaths (43.8% before the pandemic and 81.2% during the pandemic in the group
128 of the meningitis and septicemia [37]). Noteworthy is the sharp decrease in age in the group with meningitis and
129 septicemia: from 59 to 33 years (Figure 5). Since the pandemic period can be divided into two stages according to
130 the number of circulating pangolineages, we compared the diversity of the L. monocytogenes genotypes between
131 the pandemic stages (Figure 2a2,2a3). As can be seen from the data in Figure 2a2, the increase in the diversity of
132 the L. monocytogenes STs and in the proportion of the PLI genotypes occurred precisely at the first stage of the
133 pandemic. At the second stage of the COVID-19 pandemic (Figure 2a3), the diversity of the L. monocytogenes
134 STs was equal to the data for the period before the pandemic, and the proportion of the PLI genotypes was even
135 lower than before the pandemic. However, the list of STs changed dramatically: all genotypes revealed at the
136 second stage of the pandemic are new for clinical cases in the Central FD (Figure 2b).

137 4 Internalins' diversity in the different phylogenetic lineages

138 The internalins, as factors of the pathogenicity of listeria, are important for the bacteria-human cells interaction,
139 and listeria adaptation [36]. As a result, we note a large number of IP in the batch of Russian isolates, with the
140 new ones among them in recent times presented in Table 1. * IP57 ???; 13, 16, 6) was detected by Ermolaeva
141 S.A. and Psareva E.K. (not published); IP63-65 were published in [85]. For new alleles of the internalin genes,
142 the GenBank Accession Numbers are given in the parentheses.

143 Different internalins contribute to the diversity of IP of the clinical isolates in two phylogenetic lineages (Table
144 2). In the group of the clinical isolates of PLI, the inlA locus was the most diverse, according to the H value,
145 and inlC was the least diverse locus. At the same time, in PLII, both inlA and inlC were the most diverse loci.
146 It was the intC locus that distinguished isolates of ST21 when comparing the bacteria that caused human and
147 goat listeriosis.

148 5 Virulence factors

149 The virulence of L. monocytogenes depends on its ability to colonize the gut and disseminate within the host
150 [38]. The key genes and gene products involved in microbial virulence were named as virulence factors (VFs) [39].
151 A number of well-studied VFs are also known as pathogenicity factors, such as internalins, because virulence and
152 pathogenesis represent two sides of one coin. The former is viewed from the point of view of the microorganism and
153 the latter from its effect on the host [40]. The virulence factor database (VFDB) (<http://www.mgc.ac.cn/VFs/>
154 (accessed on 24 July 2022)), which is an extensive collection of VFs from the important bacterial pathogens [41],
155 was used for the VF analysis of L. monocytogenes, revealed during the monitoring.

156 Whole-genome sequencing (WGS) was performed for the isolates of the repeated genotypes and new genotypes
157 for the clinical cases or for the Listeria population in Russia. Thus, the cohort of the sequenced isolates included
158 L. monocytogenes of 12 STs, four of which belonged to PLI, and eight to PLII (Table S2). As a result, 45
159 virulence genes related to 12 VF classes were identified (Table 3). The VF classes "Adherence", "Invasion" and
160 "Regulators" were the most numerous: seven, seven and nine genes, respectively, were revealed in all analyzed
161 genomes. Only one VF of the "Invasion" class which was encoded by the vip gene (bold font in Table 3) was
162 absent in the genomes of ST7, 8, 21, and 37.

163 The vip protein (lmo0320) is an LPXTG surface protein, but does not contain LRRs, and thus does not belong
164 to the internalin family [42]. According to Cabanes et al., vip is required for entry into some eukaryotic cells via
165 the endoplasmic reticulum resident chaperone Gp96 [42]. Doumith et al. demonstrated the presence of lmo0320
166 in seven L. monocytogenes strains of the serovar 1/2a isolated in cases of human sporadic or epidemic listeriosis

[43]. London Journal of Research in Science: Natural and Formal In our cohort, the vip gene was absent in the genomes of the isolates (ST7, 8, 21, 37) that caused serious consequences or even the death of patients (Table S1). In the reference genome of *L. monocytogenes* EGD-e (serotype 1/2a), the vip gene (lmo0320) is flanked by lmo0319 (phospho-beta-glucosidase) and lmo0321 (a protein of unknown function). The size of the vip gene is 1200 bp. In the genomes of ST7, 8, 21, and 37, the intergenic region between the genes encoding phospho-beta-glucosidase and uncharacterized protein is 275 bp. These data suggest the absence of the ORF (open reading frame) for vip in the mentioned genomes.

6 Plasmids as source of genes essential for cellular survival

The plasmids can help *L. monocytogenes* in its adaptation to survive both in the environment as well as within the body of humans and other animals, mediating heavy metals, heat resistance and virulence [44,45]. However, as demonstrated by Lebrun et al., only 13% of strains from humans and animals with listeriosis harbored plasmids [46]. London Journal of Research in Science: Natural and Formal The blue ring-pLmcUH26 (*L. monocytogenes* GIMC2079: LmcUH26, ST425); the gene names highlighted in blue refer to the two regions of difference annotated by the RAST; the red ring-pLmcIH1-6 (*L. monocytogenes* GIMC2088:LmcIH1-6, ST20); and the green ring-pLmcC11 (*L. welshimeri* GIMC2049:LmcC11, ST2331). The position of the incomplete prophage is shown by an aqua-colored segment.

In our WGS research, 5 isolates from 35 of the PLI and the PLII bore plasmids: four isolates were ST425, CC90, PLII and one isolate was ST20, CC20, PLII. These plasmids (accession numbers MZ869810, MZ869811, OM867528 -OM867530) were 72,763 bp in length (Table 4). We designate them here as pLm. The plasmids contained the incomplete prophage 10 Kb, a part of the *Listeria* phage A006 (Figure 6). Sixteen ORFs of prophage included the post-segregational killing system, encoded by a co-transcriptional gene pair of Phd antitoxin (prevent host death protein) and Doc (death on curing protein) toxin, which is involved in maintaining the plasmid in host cells [47,48]. This set of *Listeria* adaptive genes is known also as the mazEF-like toxin-antitoxin system, which modulates the growth in the response to specific stress factors [49]. Another pair of genes encoding CadA and CadC proteins constituted the cadmium efflux system. One more interesting gene encoded the CRISPR-associated protein Cas5.

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The same incomplete prophage we revealed earlier in a plasmid 57,530 bp in length (Accession Number MZ869809) was from the *L. welshimeri* strain of ST2331 isolated in the meat processing plant (Table 4). We will designate it here as pLw.

The alignment percentage (AP) of the six plasmids was more than 89% and the average nucleotide identity (ANI) was more than 99%. The GC content of identified plasmids was 36%. The number of coding sequences (CDS) varied from 67 in pLw to 86/88 in pLm.

The main region of differences between pLm and pLw was a pathogenicity island including 17 ORFs (Figure 6). First of all, these ORFs encoded proteins for the copper homeostasis, which is particularly acute during infections (copper-translocating ATPase and copper chaperone). The levels of copper fluctuate in the host from high in the gallbladder to low in the liver and spleen [50]. Thus, the plasmid coding the copper homeostasis proteins helps in adapting to these different niches, which is important for a successful infection.

The second group of genes encode the proteins contributing to the regulation of the iron concentration: the complex of the ABC transporters and the permease responsible for the iron export, and the Dps protein (DNA protection during starvation). The Dps, a ferritin-like protein, forms dodecamers that can bind approximately 500 iron molecules [51]. Moreover, Dps has a dual role in protecting the cells against oxidative stress, either by binding directly to DNA, or by sequestering iron, thus avoiding oxidative damage [87], because in the presence of iron, superoxide and hydrogen peroxide can be transformed into the highly reactive hydroxyl radical [52].

One more gene of this region encoded deoxythymidine diphosphates (dTDP)-4-dehydro rhamnose 3,5-epimerase, or cupin RmlC. This protein's synthesis is the precursor of L-rhamnose, which is used by the *L. monocytogenes* serogroup 1/2 for the modification of the peptidoglycan-attached teichoic acids (wall teichoic acids). Such modification is significant for *L. monocytogenes* virulence [53].

The smaller region deleted in pLmcC11 is represented by three genes encoding transposase, site-specific DNA recombinase and AraC family transcriptional regulator.

The comparison of pLm with the *Listeria* plasmids deposited in GenBank showed high similarity to the pLIS19 (MZ089999), pLIS38 (MZ127847), and pLIS43 (MZ147615) plasmids of *L. innocua* strains, isolated from food and city environments in 2003-2017 in Poland [54] (Table 4). The ANI and AP among these plasmids are more than 99%.

The pLw showed more than 99% similarity to the plasmids of *L. innocua* strains isolated from food [55] and to the plasmids of *L. monocytogenes* strains isolated from food and from clinical sources in different years and different geographical locations [56][57][58][59] (Table 4). The *L. monocytogenes* strains belonged to ST3 of PLI and to different STs of PLII. The oldest clinical strain was isolated in 1967 in Germany [58]. The 13 plasmid replicons mentioned above (Table 4) were included in the analysis. The neighbor-joining tree (Figure 7) was built on the basis of the ANI of whole-genome alignment and revealed two closely related groups of plasmid replicons.

227 Group I, which is located at the top of the figure, includes smaller plasmids, which are distributed according to
228 the source of isolation. In group II, in the lower part of the figure, there are larger plasmids, and the most
229 different among them is the plasmid of the strain isolated from the environment.

230 London Journal of Research in Science: Natural and Formal Listeria plasmids have been classified into two
231 groups based on their replication protein RepA sequences [58]. According to this classification, all of the analyzed
232 plasmids belong to the repA_G1-Replication system group, which is the most common group [54]. All of the
233 analyzed plasmids also carried two loci involved in the active partitioning of plasmid molecules (PAR_1 and
234 additional parA), and the loci coding Y-family polymerase components (UvrX and YodD) representing London
235 Journal of Research in Science: Natural and Formal the POL_1 group. A whole conjugative transfer module is
236 absent in the studied plasmids, except for the relaxase component of the mobL_1a type.

237 Of the functional genes that promote adaptation and are present in all plasmids, mention should be made
238 of a region encoding a glycine betaine ABC transport system substrate-binding protein and an oxidoreductase
239 (NADH peroxidase), and the gene for the ATP-dependent protease ClpL. The first group of the genes may play
240 a role in responses to high osmolarity and oxidative stress, and was shown to be upregulated under high-salt
241 conditions [60]. The ATP-dependent protease ClpL was shown to be involved in the increased heat resistance of
242 *L. monocytogenes* strains [45], and was also found to be upregulated in response to low pH [60].

243 No other additional genes, such as arsenic resistance loci, fluoride efflux transporters, or antibiotics resistance
244 loci, or virulence factors, have been found in plasmids.

245 8 Core genome comparison

246 During the monitoring, especially in the pandemic period, we observed repeated genotypes among clinical isolates.
247 To determine the epidemic relationship between isolates of the same genotype, we used the approach of cgMLST
248 genotyping, developed by Moura et al. and having the discriminatory power required for epidemiological
249 surveillance [39]. The criteria for assignment to an epidemic outbreak was seven or fewer allelic mismatches
250 between cgMLST profiles, including 1748 loci.

251 London Journal of Research in Science: Natural and Formal The results of the comparison are shown in Figure
252 8. Among the isolates of PLI (Figure 8a), complete coincidence of the profiles was observed for isolates of ST219
253 attributed to perinatal listeriosis. Both strains were isolated in March 2021. One strain was isolated from a
254 newborn, and a second strain was from a woman in the seventh week of pregnancy. The second group of isolates
255 of PLI with minimal differences in cgMLST profiles belongs to ST4. The isolate from July 2020 (fatal) differs
256 from the isolate from October 2020 (newborn) and the isolate from March 2021 (fatal) in three loci. The last two
257 isolates have the same cgMLST profiles. The two isolates of ST6 (August 2019 and September 2020, both from
258 newborns) have only two allelic mismatches, but the earlier isolate (March 2019, newborn) differs in 13-15 loci.

259 In PLII (Figure 8b), the isolates of ST8 (December 2021 (newborn) and January 2022 (meningitis, alive)), and
260 ST21 (September 2021 (pregnant women) and December 2021 (septicemia, fatal)) had the same cgMLST profiles.
261 Attention is drawn to strains of ST425. The four isolates shown in the figure are divided into two pairs according
262 to the places of hospitalization. The isolates from April 2021 (septicemia, fatal) and June 2021 (meningitis, alive)
263 were isolated from COVID-19 patients in one hospital with an interval of one and a half months, and had identical
264 cgMLST profiles. The same profile is seen in the isolate from September 2021 (meningitis, fatal) from the second
265 pair of the patients, which were from another hospital. The second isolate from this pair, from August 2021
266 (meningitis, alive), has one difference in the cgMLST profile from the three previous isolates of ST425. Thus,
267 the isolates of ST219, 4, and two isolates of ST6 from the PLI, and the isolates of ST21, 8 and 425 from PLII
268 can be attributed to epidemic outbreaks. London Journal of Research in Science: Natural and Formal However,
269 the isolates of ST37, often revealed during the COVID-19 pandemic in the group with meningitis and sepsis,
270 had more than seven mismatches in the cgMLST profile (Figure 8b). The presented isolates, from March 2020
271 (meningitis, fatal), July 2021 (meningitis), and July 2021 (meningitis, fatal), were from three different hospitals.
272 The isolates from July 2021 had fewer distinct loci (23) compared to the isolate at the start of the pandemic,
273 March 2020, ST34 and 37). As such, the three patients had different sources of the infection.

274 Previously, we obtained similar results for the isolates of the autochthonous ST7, which also belongs to PLII
275 and was the most common in the pre-COVID-19 period (Figure 2a1) [26]. We compared the following isolates of
276 ST7: the clinical isolates from June 2020 and February 2019 and a food isolate from May 2018. *L. monocytogenes*
277 "February 2019" caused premature birth and pneumonia in a newborn, and listeria "June 2020" caused the death
278 of an elderly patient recovering from COVID-19. The clinical isolates differed in 20 loci of cgMLST profiles, and
279 both had 23 allelic mismatches with the food isolate. As such, three isolates of ST7 had no epidemiological link,
280 but were closely related. The most considerable common mutation of the three isolates was the nine-nucleotide
281 deletion in the MFS transporter gene (lmo2172) sequence, which distinguished this group of isolates from other
282 food isolates and from the clinical *L. monocytogenes* ST7 previously isolated in Russia [26].

283 9 Possible functional role of mutated genes

284 The comparison of ST7 clinical isolates revealed 20 distinct loci coding for the proteins required for the metabolism
285 of bacteria parasitizing in the human body. First of all, there were two virulence factors: listeriolysin O (lmo0202)
286 and hexose phosphate transporter (lmo0838). According to the classification of pathways and functional systems

287 using categories of the Clusters of Orthologous Genes (COG) [61], 20 loci can be classified into 12 COG categories
 288 (Figure 9); note that a quarter were related to the category "Carbohydrate transport and metabolism". Four genes
 289 belonging to this category were transporters of two types: secondary and ATP-dependent transporters, as follows
 290 from the analysis using the TransportDB 2.0 [62]. Secondary active transporters, lmo0831 and lmo0838, have
 291 malonate/malate and hexose phosphate as a substrate, respectively, and couple the transport of substrates against
 292 their concentration gradients with the London Journal of Research in Science: Natural and Formal transport
 293 of other solutes down their concentration gradients [63]. Two other transporters, lmo0980 and lmo2123 (ATP-
 294 dependent), belonged to the ABC family most represented (89.7%) among the transporters of *L. monocytogenes*
 295 (<http://www.membranetransport.org/> (accessed on 24 July 2022)). If lmo2130 was responsible for the transport
 296 of maltose/maltodextrin, then lmo0980 was classified as a multidrug resistance transporter.

297 The fifth gene of this COG category was glucosamine-fructose-6-phosphate aminotransferase (lmo0727), an
 298 important point in the biosynthesis of amino sugar-containing macromolecules. It has been marked by Zhou et
 299 al. as the gene encoding the bile-induced protein of *L. monocytogenes* wild-type strain EGD [64].

300 It is interesting that in the COG category "Translation, ribosomal structure and biogenesis", there were two
 301 tRNA synthetases (RS), PheRS (lmo1222) and AlaRS (lmo1504), included in the Class IIc, showing distinctive
 302 quaternary features. These enzymes are hetero- and homo-tetramers [64]. Moreover, Phe-RS is indispensable for
 303 growth in all organisms [65].

304 The third gene in this category is lmo2620, encoding 50S ribosomal protein L5. Prokaryotic 5S rRNA interacts
 305 with the ribosomal protein L5, forming 5S ribonucleoprotein particles, and enhances protein synthesis by the
 306 stabilization of the ribosome structure [66].

307 In the category "Replication, recombination and repair", the delta subunit of DNA polymerase III (lmo1481) is
 308 remarkable. It is present in 5-7-fold excess over the gamma complex, and probably performs the clamp unloading
 309 function, sparing the limited number of gamma complex and polymerase III molecules in the cell for other
 310 important functions such as processive DNA replication. Additionally, the delta subunit does not require ATP
 311 for its activity, so the delta-catalyzed unloading reaction cannot be quenched with hexokinase and glucose as
 312 described for the gamma complex and polymerase III [67].

313 The next gene, lmo1646 (exonuclease SbcD), is part of the heterotetrameric SbcCD complex, which cleaves
 314 DNA hairpin structures. SbcC might constantly check the replication fork for misfolded DNA and associate with
 315 SbcD only when DNA repair is necessary, so a small amount of protein SbcD is required for the complex activity
 316 [68].

317 In the category "Signal transduction mechanisms", two loci distinguish clinical strains of ST7.

318 Response regulator LiaR (lmo1022) is a component of the LiaFSR system, including membrane-bound inhibitor
 319 protein LiaF, sensor histidine kinase and a cognate response regulator. Additionally, LiaR is the less abundant
 320 component of this system. The LiaFSR system strongly responds to the presence of a number of cell wall
 321 antibiotics, such as bacitracin, daptomycin, nisin, ramoplanin and vancomycin, and is weakly induced by other
 322 more unspecific stresses that interfere with envelope integrity, such as alkaline shock and secretion stress [69].

323 The arginine phosphatase (lmo2540) is the next important protein for bacteria stress response. It modulates the
 324 arginine phosphorylation states of regulators such as the stress response regulator CtsR and the global regulator
 325 MgrA, particularly in response to oxidative stress [70]. Thus, using the example of the most represented categories
 326 of COG, we have shown the importance of genes affected by mutations for the vital activity of *L. monocytogenes*
 327 ST7.

328 Two loci distinguishing isolates of ST6 (August 2019 and September 2020, both from newborns) also belonged
 329 to the category "Carbohydrate transport and metabolism": lmo1728-cellobiose phosphorylase, and lmo2761-
 330 beta-glucosidase. These enzymes catalyze anaerobic (phosphorolytic) and aerobic (hydrolytic) pathways of the
 331 cellobiose catabolism, respectively. The phosphorolytic London Journal of Research in Science: Natural and
 332 Formal pathway requires one less ATP for each molecule of cellobiose to be metabolized by glycolysis, so it
 333 performs better than the hydrolytic pathway in terms of product yield in stressful conditions [71].

334 Three loci distinguishing the isolates of ST4 "October 2020 (newborn)" and "March 2021 (fatal)" from the
 335 isolate "July 2020 (fatal)" belonged to the three COG categories: "Transcription" (lmo0520-NagC transcriptional
 336 regulator), "General function prediction only" (lmo2049-nucleotidyltransferase), and "Translation, ribosomal
 337 structure and biogenesis" (lmo2596-30S ribosomal protein S9). Consider the most impressive locus lmo0520.
 338 In *E. coli*, as demonstrated Bréchemier-Baey et al., NagC is the transcriptional repressor of the catabolism of
 339 the mucin-derived sugars N-acetylglucosamine, and the activator of the locus of enterocyte effacement, which is
 340 critical regulator for the colonization of the intestine by bacteria [72].

341 10 The genotypes of *L. monocytogenes* isolated from food

342 The search for the source of infection that caused the cases of invasive listeriosis prompted us to analyze *L.*
 343 *monocytogenes* isolated from food in the metropolis during the monitoring period (Table S3). London Journal
 344 of Research in Science: Natural and Formal *L. monocytogenes* was most commonly isolated from fish, followed
 345 by chicken and meat (Figure 10c). All food isolates were subdivided into two groups according to the isolation
 346 data: before the pandemic and during the pandemic (Figure 10).

347 The proportion of genotypes that coincided in the two periods of observation, namely ST7, 9, 37, 121, and
 348 155, was 69% and 68%, respectively. The differing genotypes were more diverse during the COVID-19 period

(5ST vs. 3ST), which led to a slight increase in the Shannon diversity index from 2.8 to 3.1 (Figures 10a,10b). The proportion of PLI increased insignificantly during the pandemic, and ST288 of PLI was replaced by ST3, which had not previously been found in Russia. As such, the genotypes of *L. monocytogenes* infecting foods did not change significantly during the COVID-19 pandemic. In the final list of the genotypes of the clinical isolates of the second stage of the COVID-19 pandemic, only ST8 and ST37 coincide with the list of the food isolates' genotypes.

11 III. DISCUSSION

Listeriosis is relatively rare, but is one of the deadliest food-borne infections. In Russia in 2020, clinical diagnosis of listeriosis was laboratory-confirmed in 42 patients, and six cases were fatal (<https://rospotrebnadzor.ru/> (accessed on 24 July 2022)). In Moscow, 18 cases of listeriosis were registered in 2020, and 21 cases in 2021 (<https://77.rospotrebnadzor.ru/> (accessed on 24 July 2022)). The analysis of food included 6883 samples subjected to laboratory control in the departments of Rospotrebnadzor in Moscow in 2020, and 0.6% of samples were positive for *L. monocytogenes* (<https://77.rospotrebnadzor.ru/> (accessed on 24 July 2022)). However, persons with recognized underlying diseases such as liver disease, cancer, diabetes and COVID-19 in the case of listeriosis can be counted as having an underlying disease in the clinical report. In perinatal listeriosis, neonatal complications (respiratory failure and heart failure in newborns, cerebral ischemia, etc.) can also be registered as the main diagnosis. Therefore, cases of listeriosis may be underreported in statistics.

Our study included 50 clinical and 37 food *L. monocytogenes* isolates revealed from November 2018 to January 2022 in the metropolis. The obtained results clearly indicate a change in the spectrum of the *Listeria* genotypes causing invasive listeriosis during the COVID-19 pandemic.

L. monocytogenes ST7 (PLII) and ST6 (PLI), which previously typically prevailed among the clinical isolates in the metropolis (Figure 2a1), were changed by the variety of the PLI genotypes (ST1, ST4, ST194, ST219) and the PLII genotypes (ST8, ST20, ST21, ST37, ST391, ST425, ST451) (Figure 2a4). *L. monocytogenes* of ST8 and ST425 were previously found in food and in the environment, but during the pandemic, *L. monocytogenes* of these genotypes were isolated for the first time in cases of human listeriosis in Russia along with ST21, ST37, and ST391. In addition, we observed an increase in the number of fatal cases of invasive listeriosis in the group with meningitis and sepsis (43.8% vs. 81.2%), as well as a sharp decrease in age in this listeriosis group: from 59 to 33 years.

Previously, we showed the impact of respiratory viral infections on the incidence of invasive listeriosis in a metropolis in 2018/2019 [26]. The consequences of SARS-CoV-2 on gastrointestinal tract conditions and sensitivity to food-borne pathogens have yet to be fully characterized. The available evidence suggests that SARS-CoV-2 infection alters the gut barrier, leading to the systemic spread of bacteria, endotoxins, and microbial metabolites [73]. Gut disorders during SARS-CoV-2 infection might also participate in concomitant or secondary bacterial infections, which develop in severely ill COVID-19 patients [73]. According to our observations, infection with SARS-CoV-2 not only contributed to an increase in the incidence of invasive listeriosis even among younger patients, but London Journal of Research in Science: Natural and Formal also increased the sensitivity to a range of previously non-human *L. monocytogenes* genotypes: ST8, 20, 21, 37, 391, and 425.

Almost all new genotypes of the clinical isolates revealed during the COVID-19 pandemic in the metropolis were previously described in the works of European researchers. The *L. monocytogenes* diversity which related to 1185 cattle abortion cases in Latvia during the period of 2013-2018 included 27 different ST overall [74]. Four of them, ST29, 37, 451 and 7, covered more than half of the *L. monocytogenes* isolates; ST8, 20, 21, 391, and 425 were also detected [74]. Šubicová et al. (Slovakia, 2010-2020) described ST451 as the most prevalent in the cohort (15.3%) as a whole, and especially in food (14.8%) and animal isolates (17.5%) [75]. In food, CC11-ST451, followed by CC7, CC14, and CC37, were the most prevalent CCs in the milk sector, and CC9 and CC8 were most prevalent in the meat sector [75]. In the Czech Republic, ST29, 37, and 451 were the most frequent genotypes of *L. monocytogenes*, isolated from vacuum-packed steak tartare in 2013-2016 [76]. In 2019, as non-human isolates, *L. monocytogenes* ST8, ST21, and ST451 were mentioned in the work of researchers from Austria [77]. They found ST21 to be more associated with vegetables, and ST451 with dairy products [77]. Finally, during the COVID-19 pandemic in Italy (September and October 2020), a nosocomial outbreak of listeriosis caused by an ST451 strain of *L. monocytogenes* was recorded [78]. This outbreak involved one immunocompromised patient and three cancer patients hospitalized in different units of the same hospital. The source of contamination was identified in the hospital kitchen, where a meat slicer used to prepare meals tested positive for the same ST of *L. monocytogenes*. This was the first report of an outbreak of listeriosis caused by ST451 in Italy [78].

In our study, the epidemic connections were shown for the PLI isolates (ST219, ST4, ST6), and also for new clinical isolates of ST21, 8 and 425 (PLII), which can be attributed to epidemic outbreaks because of similar cgMLST profiles (0-3 allelic mismatches of cgMLST). The strains of ST425 were isolated from four COVID-19 patients in two hospitals with an interval of 5.0 months. The sources of outbreaks have not been identified.

L. monocytogenes of all genotypes revealed in the clinical cases were analyzed for the presence of 42 VFs. All VFs but one (vip) were observed in all of the analyzed isolates. The vip involved in cell invasion [42] was absent in the isolates of ST7, 8, 21, and 37, which were associated with clinical cases (perinatal listeriosis, septicemia, meningitis), including fatal ones. We found confirmation of our results in the works of a number of researchers. The lack of the vip gene in FPE *L. monocytogenes* isolates of ST8 and ST37 was noted by Alvarez-Molina et

17 MULTILOCUS SEQUENCE TYPING (MLST) AND MULTI-VIRULENT-LOCUS SEQUENCE TYPING (MVLST)

411 al. from Spain [79]. In the research into the isolates obtained from cattle abortion cases by ?teingolde et al.
412 (Latvia), the list of vip-missing genotypes was expanded and additionally included ST29, 120, 226, 391, 403, 573
413 (PL II) and even ST 2, 4, and 6 (PL I) [74]. Thus, the thesis about the obligatory presence of the vip gene in
414 the genomes of isolates of the PLI and PLII [42,43] needs to be revised.

415 In addition to the main 42 virulence factors, Maury et al. noted the following features of the PLI isolates
416 with high clinical frequency (CC1, CC2, CC4, and CC6), which were named as hypervirulent: 1) the over-
417 representation of genes involved in replication, recombination, and repair, which may indicate a higher exposure
418 to genotoxic conditions; and 2) the over-representation of genes involved in cell wall and membrane biogenesis,
419 which may reflect the selection of genes involved in interactions with the host [80]. In our investigation, the cases
420 of perinatal listeriosis were associated with hypervirulent *L. monocytogenes* of ST6 during the pre-COVID-19
421 period. *Listeria* belonging to the additional genotypes of CC1 (ST1) and CC4 (ST4 and ST219) caused the
422 perinatal listeriosis during the COVID-19 pandemic. According to Charlier et al., *L. monocytogenes* of CC1,
423 CC2, CC4, are overrepresented in maternal-neonatal (MN) infections in France, with more than two-thirds of
424 cases London Journal of Research in Science: Natural and Formal being due to one of these CCs. [81]. Among
425 them, CC4 is the most associated with MN infections, with 20% of CC4 isolates being of MN origin [81].

426 The plasmids can become an additional source of virulence factors. The presence of plasmid replicons in the
427 clinical *L. monocytogenes* isolates is not a frequent phenomenon [46]. In our study, the plasmids were found in five
428 isolates: four isolates of ST425 and one of ST20. All of them were new in clinical cases. More often, the discussion
429 of *Listeria* plasmids takes place in the context of the ability of *Listeria* spp. to colonize various environments,
430 especially the FPE, with a focus on the genes that provide resistance to sanitizers [82], heavy metals [58] or
431 elevated temperatures [45]. However, according to Chmielowska et al., there is evidence that the presence of
432 some cadAC resistance cassettes in *Listeria* can influence other phenotypic traits, such as virulence and biofilm
433 formation, which suggests that these heavy metal resistance determinants may have additional functions [54].

434 Other genes encoding the proteins contributing to copper homeostasis, the regulation of iron concentration,
435 the modification of wall teichoic acids and even in-creased heat resistance may facilitate the increase in virulence
436 and the spread and survival of *Listeria* in the human body. Thus, on the one hand, if, during the COVID-19
437 period, invasive listeriosis is caused by *Listeria* of genotypes previously typical of food isolates, in addition to
438 containing plasmids, then we can confirm that SARS-CoV-2 has a serious damaging effect on the defense system
439 of the gastrointestinal tract. On the other hand, *L. monocytogenes* of ST425 (of one epidemic cluster, according
440 to cgMLST analysis) caused disease not only in people in the older age category, but also in younger people (36
441 and 47 years old); therefore, isolates of this genotype can hardly be classified as hypovirulent, and their virulence
442 factors, including those introduced by plasmids, are subject to further study.

443 12 IV. CONCLUSIONS

444 The COVID-19 pandemic has had a significant impact on the health of the human population, promoting bacterial
445 infections in weakened organisms. Listeriosis, as one of the deadliest foodborne infections, completely changed
446 the portrait of those *L. monocytogenes* genotypes that caused invasive listeriosis both in the perinatal group and
447 in the group with meningitis and sepsis, according to monitoring in a metropolis with a population of 20.4 million.
448 The rejuvenation of listeriosis and increase in mortality in the group with meningitis and sepsis, the emergence of
449 new genotypes of PLII, previously classified as food and hypovirulent, and new genotypes of *L. monocytogenes* of
450 PLI in the perinatal group indicate the need for the even more stringent control of food products for the high-risk
451 groups regarding invasive listeriosis. S2).

452 13 V. MATERIALS AND METHODS

453 14 1 Bacterial isolates

454 15 Methods

455 16 DNA isolation

456 For genotyping, *Listeria* isolates were grown on BHI agar overnight at 37 °C. One loopful of cells was suspended
457 in 20 µL of the lysis buffer (0.25% SDS and 0.05 M NaOH), warmed up for 15 min at 95 °C, and 180 µL of
458 the bidistilled water was added. The resulting lysate was stored at temperature 4 °C. For the whole-genome
459 sequencing, *Listeria* isolates grown on BHI agar overnight at 37 °C were suspended in the BHI broth and grown
460 overnight at the same temperature. The cells were centrifuged, and the washed pellet was used for DNA isolation
461 according to the Monarch Kit instructions (New England Biolabs, Ipswich, Massachusetts, USA).

462 17 MultiLocus Sequence Typing (MLST) and Multi-Virulent- 463 Locus Sequence Typing (MvLST)

464 For MLST, we used a combination of primers [83] and [84], laboratory-designed *ldh* primers, and our modification
465 of PCR and sequencing protocols [31]. New alleles and new sequence types (ST) for MLST genes were controlled
466 by the team of curators of the Institut Pasteur MLST system (Paris, France).

467 The MvLST scheme including four internalin genes (inlABCE) chosen earlier by [33] was used with our
468 modification [30]. The alleles of the internalin genes were numbered in the order of the detection, submitted
469 in GenBank and published in [26, 31-33, 85, 86]. For each *L. monocytogenes* isolate, the combination of four
470 detected alleles (in order inlABCE) received an internalin profile (IP) number. New alleles and IP from this
471 research are presented in Table 1.

472 18 Whole genome sequencing (WGS)

473 The genomes of the strains with ST6, ST7, ST451, and new ST for the Russian listeria population (ST4, 194, 219),
474 and new ST for clinical listeria isolates (8,21, [25]), were sequenced on the Illumina platform. The Nextera DNA
475 Flex Library Prep (Illumina, San Diego, CA, USA) protocol was used for the library's preparation. Sequencing
476 was performed on MiSeq and NextSeq 500/550 (Illumina, San Diego, CA, USA).

477 19 Data analysis

478 CLC Genomic Workbench v.20.0.4 (QIAGEN, Germantown, MD, USA) and SPAdes v.3.13.0 (St. Petersburg
479 genome assembler, Russia, URL: <http://cab.spbu.ru/software/spades/> (accessed on 24 July 2022)) were used
480 for genome assembling. CGView Server (http://stothard.afns.ualberta.ca/cgview_server/ (accessed on 24
481 July 2022)) was applied for the visualization of assembling results and for the genome comparison [87]. The
482 software Rapid Annotations Subsystems Technology (RAST) and SEED were used for genome annotation
483 [88,89]. Prophage sequences were revealed with the help of PHASTER (PHAge Search Tool Enhanced Release,
484 <https://phaster.ca/> (accessed on 24 July 2022)) [90].

485 WGS data are available in GenBank: Bio Project PRJNA605697. Previously published ST7 genomes
486 (GenBank Accession Numbers CP060433-CP060435) were used for the comparison. The plasmid sequences of the
487 strains GIMC 2079:Lmc UH26, GIMC2080:Lmc UH27, GIMC2090:LmcH67_6, London Journal of Research in
488 Science: Natural and Formal GIMC2095:LmcH67_8 (ST425) and GIMC2088:LmcIH1-6 (ST20) were submitted
489 to GenBank (Accession Numbers MZ869810, MZ869811, OM867528 -OM867530).

490 The core genome MLST scheme of 1748 loci (cgMLST) was used for *L. monocytogenes* genome characterization
491 [91] on the basis of an open bioinformatics platform (<https://bigsd.pasteur.fr/listeria/>(accessed on 24 July
492 2022)). Alleles which were not characterized by the computational tool due to their difference from the registered
493 sequences were searched by comparing genomic data with alleles of the reference EGD-e strain using BLAST
494 NCBI. The identified sequences of the corresponding alleles of the isolates of the same ST were compared by
495 the number of differences with the closest match. New alleles were considered identical if there were the same
496 substitutions.

497 The assignment of genes to different Clusters of Orthologous Genes (COG) categories was carried out with
498 NCBI Blastp and the COG database/Conserved Protein Domain Family database [61].

499 The comparison of the plasmids pLmcIH1-6 and pLmcC11 with the reference pLm-cUH26 was performed by
500 using BLAST Ring Image Generator (BRIG) with blast-2.7.1+ [92].

501 CLC Genomics Workbench v. 21.0.1 with the Whole Genome Alignment 21.0 plugin was used for plasmid
502 alignment and tree building. The Whole Genome Alignment 21.0 plugin works by identifying seeds (short stretches
503 of nucleotide sequence that are shared between multiple genomes but not present multiple times on the same
504 genome) in the plasmid. This option determines the number of nucleotides required for a seed to be included
505 in the later stages of the alignment. The minimum initial seed length was 15 bp. From the initial extended
506 seed matches, a distance matrix between the input plasmid was calculated. This distance matrix was used for
507 the subsequent pairwise processing, where the most similar plasmid sequences were processed first. Proceeding
508 iteratively on the most similar pair of plasmids, the tool extended and merged seed matches to create longer
509 alignment blocks. The minimum alignment block length was 100 bp.

510 The Create Average Nucleotide Identity Comparison tool was useful for obtaining a quantitative measure of the
511 similarity between plasmids. This tool took whole-genome alignment as input, and for each pair of plasmids, the
512 regions aligned between the two plasmids were identified. The tool was launched using the following parameters:
513 the minimum similarity fraction-0.8 and the minimum length fraction-0.8. On the basis of Create Average
514 Nucleotide Identity Comparison tool data, the neighbor-joining tree was constructed.

515 The analysis of virulence factors was performed using the Virulence Factors Database (VFDB,
516 <http://www.mgc.ac.cn/VFs/> (accessed on 24 July 2022)) and VF analyzer ([http://www.mgc.ac.cn/cgi-
517 bin/VFs/v5/main.cgi?func=VFanalyzer/](http://www.mgc.ac.cn/cgi-bin/VFs/v5/main.cgi?func=VFanalyzer/) (accessed on 24 July 2022)) [41].

518 The Shannon diversity index (H) was used to characterize *L. monocytogenes* diversity and was calculated by
519 the formula:



Figure 1:

1

Figure 2: Figure 1 :



2

Figure 3: Figure 2 :

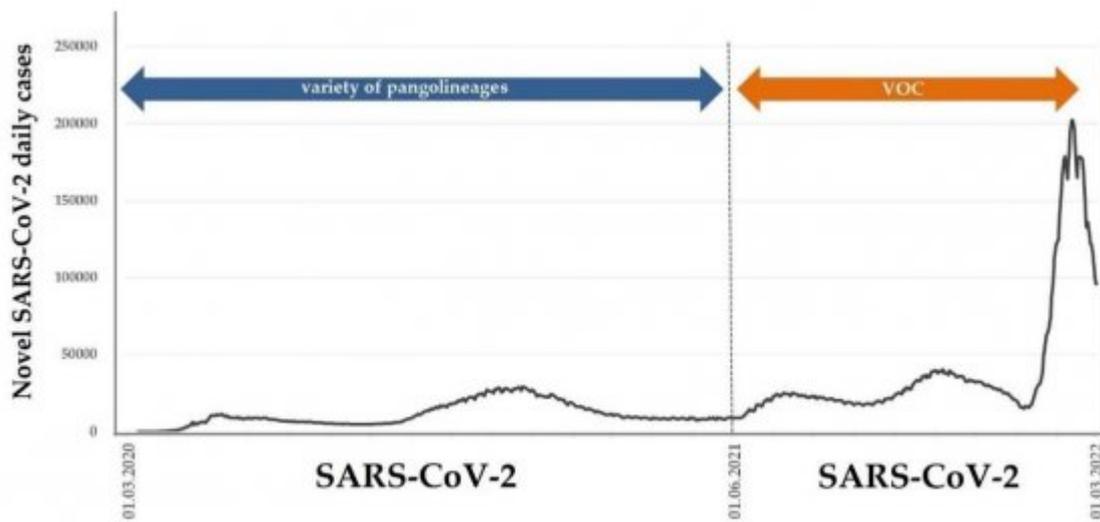
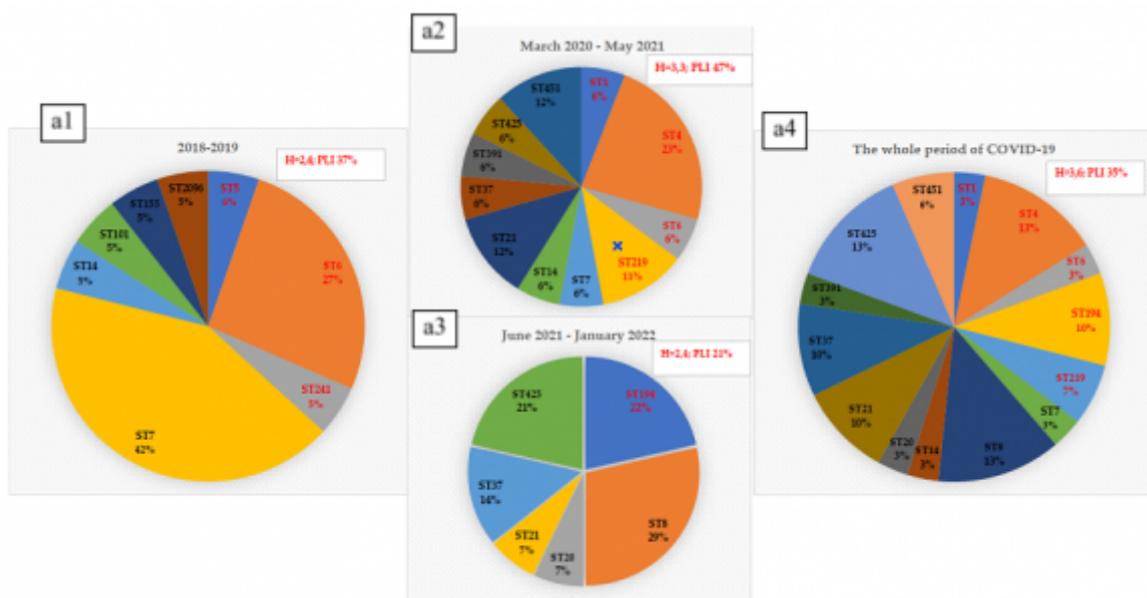
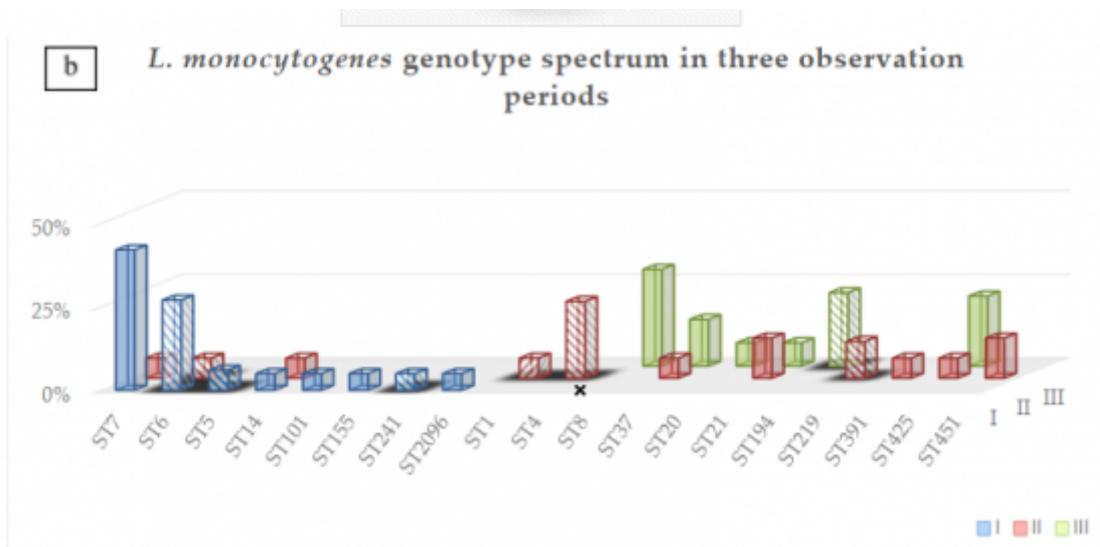


Figure 4:



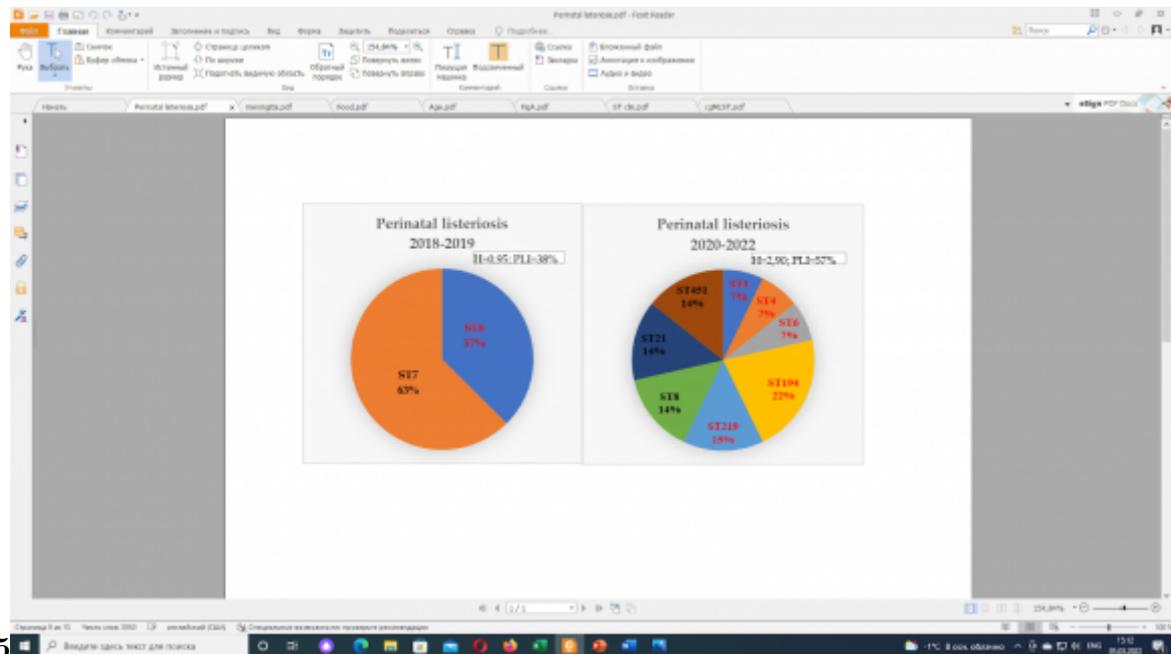
3

Figure 5: Figure 3 :



4

Figure 6: Figure 4 :



5

Figure 7: Figure 5 :

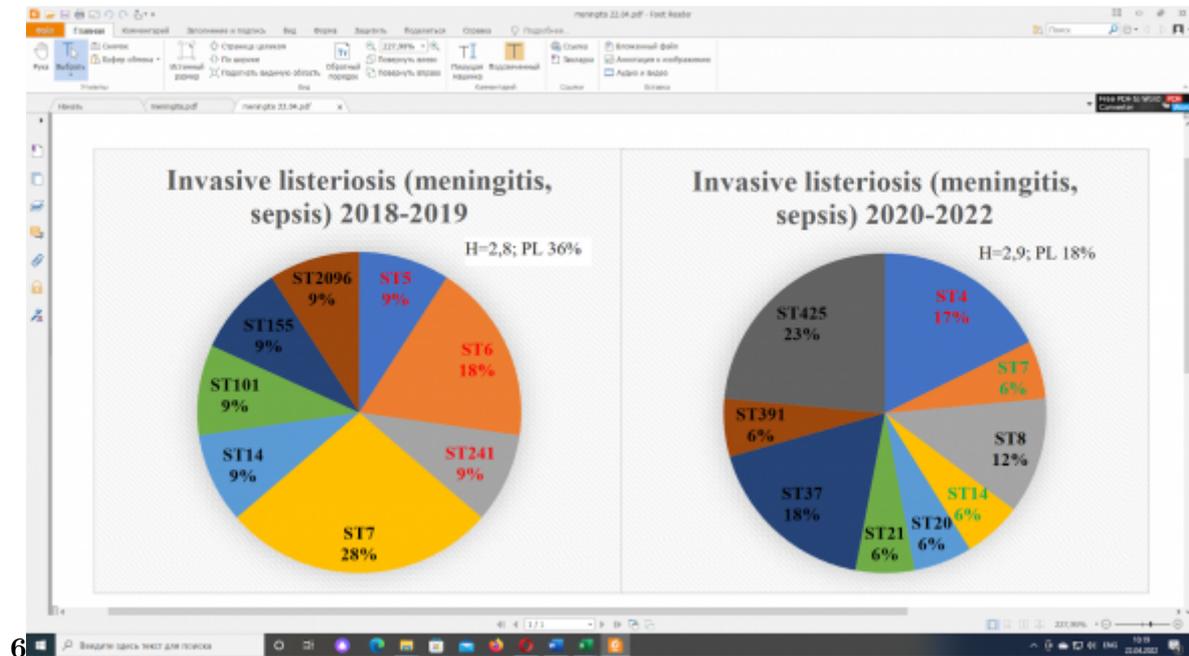


Figure 8: Figure 6 :

7 b

Figure 9: Figure 7 :

8 a

Figure 10: Figure 8 :

9 b

Figure 11: Figure 9 :

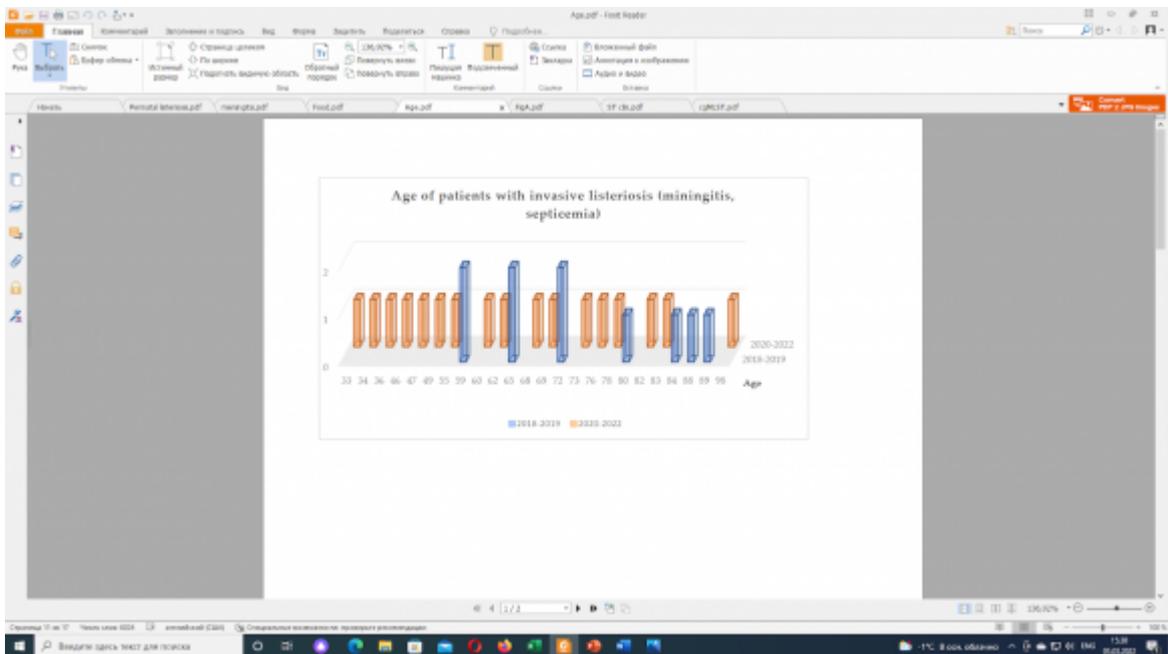
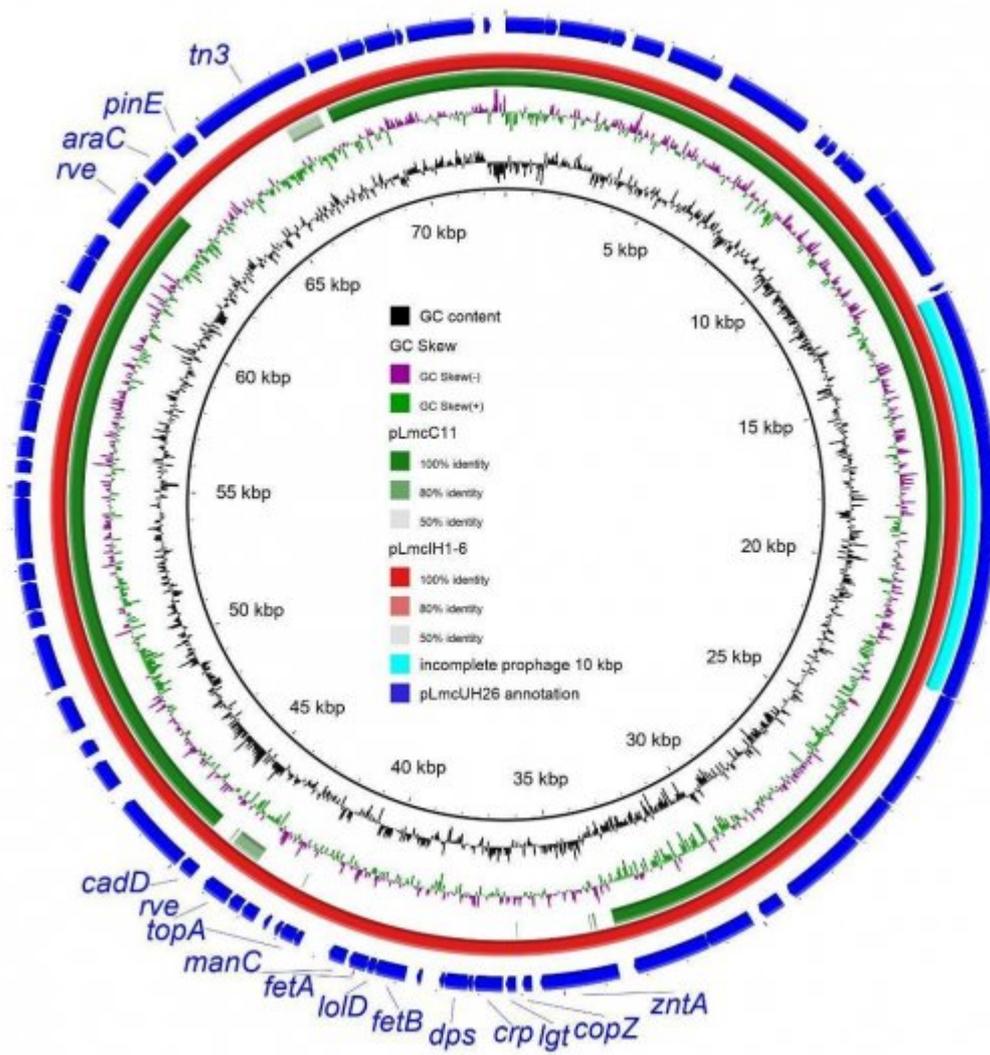


Figure 12:



10

Figure 13: Figure 10 :

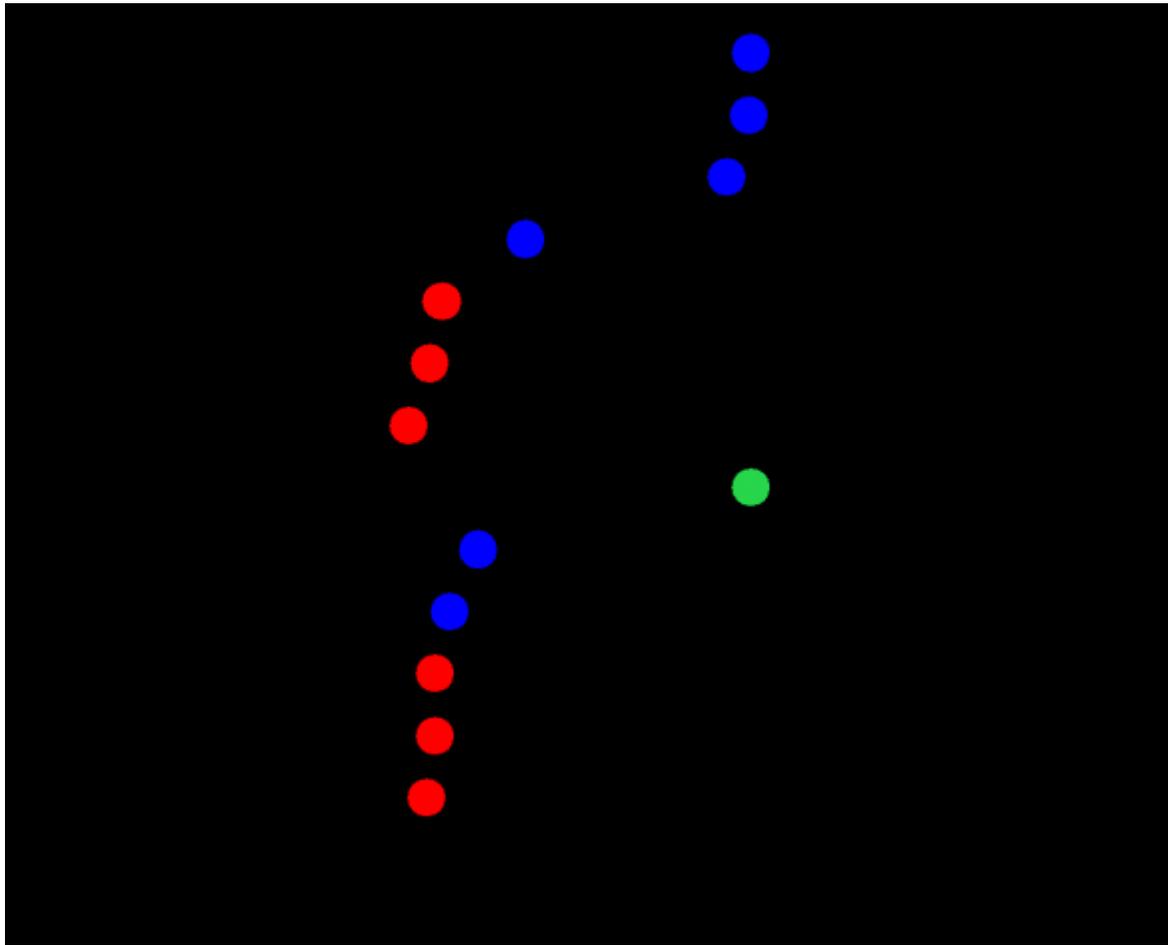


Figure 14:

1

CC	ST	inlA	inlB	inlC	inlE	IP	Phylogenetic Lineage
CC21	21	12	14	7	8	56	II
CC11	451 22 (MW538938)		23 (MW538939)	6	6	58	II
CC26	26	7	14	6	6	59	II

London Journal of Research in Science: Natural and Formal 15 39 © 2023 London Journals Press Volume 23 | Issue 5 | Compilation 1.0 Genomic Characteristics of listeria that Caused Invasive listeriosis During the COVID-19 Pandemic

Figure 15: Table 1 :

2

Phylogenetic lineage	Shannon's diversity index (H)			
	inlA	inlB	inlC	inlE
I	2,5			

Figure 16: Table 2 :

4

Size	Plasmid name	GenBank ID	Strain	Species	ST	CC	Phylogenetic lineage date	Isolation Source	Country	Reference
	pLmcUH26	MZ869810	GIMC2079:Lm cUH26	L. monocytogenes	425	90 II	2021	Homo sapiens (blood)	Russia	this research
	pLmcUH27	MZ869811	GIMC2080:Lm cUH27	L. monocytogenes	425	90 II	2021	Homo sapiens (blood)	Russia	this research
	pLmcH67_6	OM867530	GIMC2090:Lm cH67_6	L. monocytogenes	425	90 II	2021	Homo sapiens (cerebrospinal fluid)	Russia	this research
	pLmcH67_8	OM867529	GIMC2095:Lm cH67_8	L. monocytogenes	425	90 II	2021	Homo sapiens (blood)	Russia	this research
7276 3 bp	pLmcIH1-6	OM867528	GIMC2088:Lm cIH1-6	L. monocytogenes	20	20 II	2021	Homo sapiens (cerebrospinal fluid)	Russia	this research
	pLIS19	MZ089999	297/05	L. innocua	nd	nd	innocua 2005	L. innocua (ice cream) food	Poland	[54]
	pLIS38	MZ127847	10/03	L. innocua	nd	nd	innocua 2003	L. innocua (contact surface swab) environ	Poland	[54]
	pLIS43	MZ147615	Sr108	L. innocua	nd	nd	innocua 2017	L. innocua (city) meat	Poland	[54]
			GIMC2040:Lm	L. innocua	222	222	Listeri			this

Fifty clinical *L. monocytogenes* isolates (19 isolates from the first time period: November 2018-October 2019; 31 isolates from the second time period: March 2020-January 2022) were obtained from microbiological laboratories of the Moscow laboratory diagnostic centers. All *L. monocytogenes* were isolated from the samples of the patients with invasive listeriosis: perinatal listeriosis-44%, meningitis and listeria septicemia-56%. Isolates were submitted in the Bacterial Isolate Genomic Database (BIGSdb) (<https://bigbdb.pasteur.fr/listeria/> (accessed on 24 July 2022)), ID: 42973-42983, 45724-45730, 49373-49375, 75929, 75931, 75932, 76308-76311, 76389, 77384-77386, 78377, 78378, 78657-78660, 78714, 82478-82480, 82484-82486, 82489-82492, 82494 (Table S1).

Figure 19:

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525 [RU-TW9zY293IENpdHk](https://outbreak.info/location-reports?xmin=2021-02-26&xmax=2021-08-09&loc=RUS_RU-TW9zY293IENpdHk) 18 July 2022. Center for Viral Systems Biology. Moscow City (Russia Variant Report)
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