



Multi-country outbreak of *Listeria monocytogenes* PCR serogroup IVb, MLST ST6

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Main conclusions and options for response

A multi-country outbreak of *Listeria monocytogenes* PCR serogroup IVb, MLST ST6 has been ongoing in the EU/EEA since at least 2015. Twenty-six cases from Austria, Denmark, Finland, Sweden and the United Kingdom have been classified as a confirmed microbiological cluster on the basis of whole genome sequencing (WGS) analysis, including core genome multi-locus sequence typing (cgMLST) and single nucleotide polymorphism (SNP)-based analysis, depending on the country. Four cases have died (case fatality 15.4%).

WGS analysis has demonstrated a close genetic match between the human isolates, supporting the hypothesis of a continuous common source outbreak. As yet, there is no definitive evidence as to the source of the outbreak and the potential risk of further cases remains.

To identify the source of the outbreak, Member States should consider collecting information by interviewing recent and new listeriosis patients using a standard questionnaire. ECDC recommends that interviews are not delayed to wait for WGS results from the human isolates.

In order to monitor the circulation of this strain and to assess the spread of the strain across countries, Member States should consider enhancing surveillance of invasive listeriosis. More specifically, whole genome sequencing should be performed on *L. monocytogenes* isolates and cgMLST or SNP analysis should be considered for confirmation of cases. ECDC will continue to offer sequencing support for human *L. monocytogenes* isolates with the outbreak PFGE profile or an epidemiological link in order to confirm whether these isolates are part of the outbreak. ECDC will also offer bioinformatics support if needed.

Countries are encouraged to report new cases and/or critical developments in the Epidemic Intelligence Information System for Food- and Waterborne Diseases and Zoonoses (EPIS-FWD).

Source and date of request

ECDC Internal Decision, 29 November 2017.

Public health issue

A multi-country outbreak of *Listeria monocytogenes* PCR serogroup IVb, MLST ST6 in five EU Member States (Austria, Denmark, Finland, Sweden and the United Kingdom)

Consulted experts

ECDC experts (in alphabetical order): Denis Coulombier, Josep Jansa, Saara Kotila, Taina Niskanen, Daniel Palm, Ettore Severi, Johanna Takkinen, Ivo Van Walle.

External experts representing national authorities (in alphabetical order of countries):

Austria: Franz Allerberger, Steliana Huhulescu, Ariane Pietzka, Christian Kornschöber (Austrian Agency for Health and Food Safety);

Denmark: Susanne Schjørring, Sofie Gillesberg Raiser (Statens Serum Institut);

Finland: Saara Salmenlinna, Ruska Rimhanen-Finne (National Institute for Health and Welfare);

France: Alexandre Leclercq, Alexandra Moura (Pasteur Institute);

Sweden: Cecilia Jernberg, Marie Jansson Mörk (Public Health Agency of Sweden);

United Kingdom: Sanch Kanagarajah, Lisa Byrne, Kathie Grant, Corinne Amar, Anais Painset (Public Health England).

Disclaimer

ECDC issued this rapid risk assessment document in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 853/2004 establishing a European Centre for Disease Prevention and Control (ECDC).

In the framework of ECDC's mandate, the specific purpose of an ECDC rapid risk assessment is to present different options on a certain matter with their respective advantages and disadvantages. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written under coordination of an internal response team at ECDC. All data published in this rapid risk assessment are correct to the best of our knowledge on 4 December 2017. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

The information provided in this confidential rapid risk assessment has not been verified and confirmed by the food safety and veterinary authorities.

Disease background information

Background information about listeriosis can be found in ECDC, CDC and WHO disease fact sheets [1-3].

During the period 2012–2016, between 1 754 and 2 555 *Listeria monocytogenes* cases were reported annually to the European Surveillance System (TESSy) by 30 EU/EEA countries [4]. PCR serogroup IVb is the most commonly reported PCR serogroup (44% of all cases with information on serogroup), with between 332 and 403 notifications reported annually by 13 EU/EEA countries. France, Germany and the United Kingdom accounted for 45%, 23% and 17% respectively of the reported *L. monocytogenes* PCR serogroup IVb cases during this period. Cases of PCR serogroup IVb did not differ significantly in gender distribution (52% in males) and were more common among persons over 65 years (61% of cases) for both genders. The majority (99%) of the PCR serogroup IVb cases were of domestic origin [5].

Event background information

On 3 November 2017, Finland reported in EPIS-FWD an urgent inquiry describing a cluster of *L. monocytogenes* PCR serogroup IVb, MLST ST6 confirmed by WGS (in-house cgMLST scheme), with 13 cases detected from different parts of Finland between January 2016 and September 2017.

As of 29 November 2017, nine EU/EEA countries had replied to the urgent inquiry. Four countries reported cases that could be linked microbiologically to the Finnish cluster based on the WGS data using either cgMLST [6,7] or SNP analysis (in-house pipelines).

In collaboration with the affected countries, ECDC has formed an international outbreak investigation team. ECDC and Member States have prepared an EU/EEA outbreak case definition. An EU/EEA questionnaire is under preparation to gather information on cases associated with this event. The WGS data from Denmark, Finland and the United Kingdom are being collated for a multi-country analysis.

Epidemiological and microbiological investigation

EU/EEA outbreak case definition

Confirmed outbreak case

A patient with laboratory-confirmed invasive listeriosis with symptoms onset on or after 1 January 2015 (date of sampling or date of receipt by the reference laboratory if date of onset is not available)

AND

Fulfilling the additional laboratory criterion: with *Listeria monocytogenes* having ≤ 7 cgMLST allelic differences from the outbreak reference isolate FI 122265 based on cgMLST analysis (assembly uploaded to EPIS UI-444 as IVb_MLST6_122265_S3_L001_R_q30w20.fasta). The cgMLST scheme should be either that of Moura et al. (2016), Ruppitsch et al. (2015) or a country respective cgMLST scheme [6,7].

OR

Fulfilling the additional laboratory criterion: with *Listeria monocytogenes* ≤ 5 SNP (single nucleotide polymorphism) cluster from an outbreak reference isolate FI 122265 based on SNP analysis (assembly uploaded to EPIS UI-444 as IVb_MLST6_122265_S3_L001_R_q30w20.fasta).

Probable outbreak case

A patient with laboratory-confirmed invasive listeriosis with symptoms onset on or after 1 January 2015 (date of sampling or date of receipt by the reference laboratory if date of onset is not available)

AND

Fulfilling the additional laboratory criteria: an isolate of *Listeria monocytogenes* PCR serogroup IVb or serotype 4b, 4d or 4e, and with PFGE (pulsed field gel electrophoresis) *AscI/ApaI* indistinguishable from the profile AscI.0003-ApaI.0070 (TESSy) (uploaded to EPIS as UI-444: BioNumerics.PFGE.AscI.0003-ApaI.00070.zip).

Exclusion criteria

Cases with travel history outside of the EU/EEA in the 30 days before disease onset.

Molecular typing data in TESSy

ECDC has collected a set of whole genome sequencing (WGS) data for *L. monocytogenes* human isolates from 2009 onwards including data from 27 EU/EEA Member States. The completeness of data in relation to reported listeriosis patients varies per country and per year. Of 2 969 isolates with validated WGS quality, 308 (10.4%) are ST6, spanning the years 2009–2017. Classical serotype is available for 263 of these isolates, with 247 (93.9%) being defined as serotype 4b. PFGE *AscI/ApaI* of validated quality is available for 65 of these ST6 isolates, including 26 unique PFGE profiles. Two isolates reported by two different countries in 2013 and 2015, for which both WGS and PFGE results were available, had indistinguishable PFGE profiles (*AscI.0003-ApaI.0070*) with 10 and 20 allelic differences respectively from the Finnish outbreak strain [6].

Joint investigation

As of 29 November 2017, four Member States have reported human isolates with close genetic matches to the Finnish cluster (zero to one allelic differences based on cgMLST or zero to one SNP difference). As such, a multi-country foodborne outbreak has been verified in five countries, involving 26 confirmed cases and four deaths (Table 1). Of 25 cases with available information on gender, 17 were females, two of whom were pregnant. Patients were interviewed using different national questionnaires and no common exposures were identified at country level.

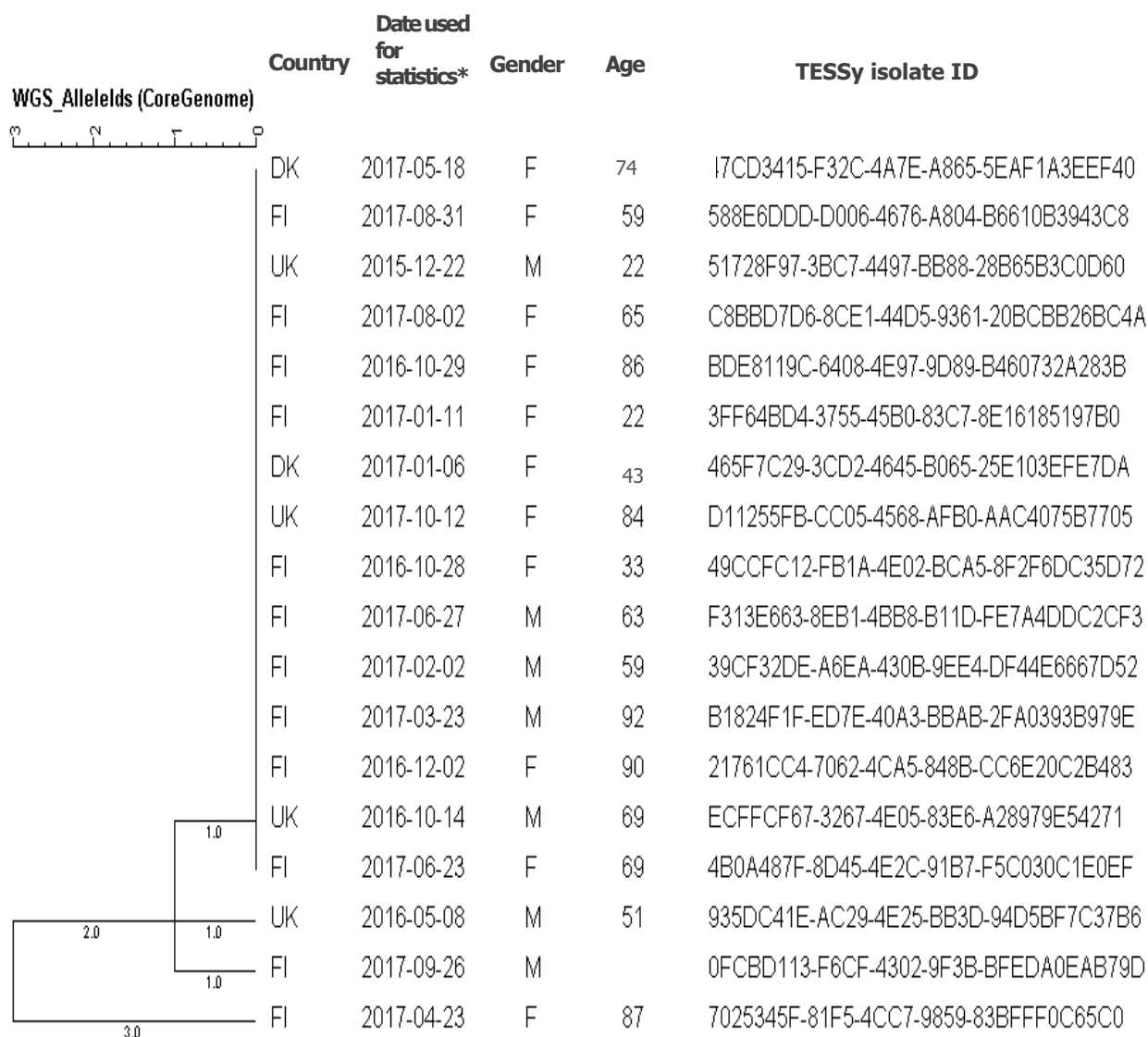
Austria has reported two human isolates from 2016 with zero and one allelic difference from the Finnish outbreak reference strain (using the cgMLST scheme of Ruppitsch et al [7]). Denmark has reported two human isolates with sampling dates in January and May 2017 with one allelic difference to the reference strain (by cgMLST scheme by Moura et al [6]). Sweden has reported a cluster of five human isolates matching the Finnish outbreak reference strain with zero SNP difference. Between 2015 and 2017 the United Kingdom reported four human isolates with zero or one SNP difference from the Finnish outbreak reference strain (Figure 1).

Table 1. Number of *Listeria monocytogenes* IVb, ST6 confirmed outbreak cases by country and year, 2015-2017 (n=26), as of 30 November 2017

Country	Confirmed cases (No. of deaths)			Total number of cases	Total number of deaths
	2015	2016	2017		
Austria	0	2 (1)	0	2	1
Denmark	0	0	2	2	0
Finland	0	4	9 (2)	13	2
Sweden	0	3 (1)	2	5	1
United Kingdom	1	2	1	4	0
Total	1	11 (2)	14 (2)	26	4

Germany, Luxembourg, the Netherlands and Portugal report no matches to the outbreak reference strain reported by Finland.

Figure 1. A single-linkage tree based on cgMLST (Moura et al. scheme) including sequences from human *Listeria monocytogenes* isolates from Denmark, Finland and the United Kingdom, 2015–2017 (n=18, one Finnish confirmed case missing), as of 30 November 2017



* Date of sampling (or date received at the reference laboratory if the former not available)

ECDC threat assessment for the EU

While still relatively rare, human invasive listeriosis is one of the most serious foodborne diseases under EU-wide surveillance, requiring hospitalisation and often causing deaths, particularly among the elderly [8]. The main risk groups are elderly and immunocompromised persons as well as pregnant women and infants.

In 2017, Finland reported a cluster of cases with infection of *L. monocytogenes* PCR serogroup IVb, ST6, identified by WGS. Between 2015 and 2017, Austria, Denmark, Sweden and the United Kingdom reported human isolates with close genetic matches (zero to one allelic differences based on cgMLST or zero to one SNP difference) to the Finnish outbreak reference strain. The microbiological evidence by WGS indicates an on-going multi-country outbreak dating back to 2015, and involving 26 cases from five countries. Four patients have died, one in Austria, one in Sweden and two in Finland.

WGS analyses have confirmed that the isolates from human cases are genetically related, and very probably associated with a common source of infection. Should one or more food items be the vehicle of infection for this outbreak, it could prove difficult to identify the suspected food vehicle(s) using traditional analytical epidemiological methods due to lack of statistical power and cross-contamination events with other food items. Therefore, an EU-wide analytical epidemiological study could increase the study power.

As there is no definitive evidence to implicate a food source(s), the source(s) may still be active and new cases associated with this outbreak may continue to occur. ECDC and the affected countries are preparing an EU/EEA questionnaire to gather epidemiological information from the different investigations.

Since only a minority of EU Member States use WGS to characterise isolates for invasive listeriosis or routinely perform and report PFGE data, it is possible that more countries are affected by the outbreak. In order to monitor circulation of this strain and to assess the spread of the outbreak strain across countries, Member States should consider enhancing surveillance of invasive listeriosis. More specifically, WGS should be performed on *L. monocytogenes* isolates and cgMLST or SNP analysis should be considered for confirmation of cases. ECDC will continue to offer sequencing support for human *L. monocytogenes* isolates with the outbreak PFGE profile or an epidemiological link in order to confirm whether these isolates are part of the outbreak. ECDC will also offer bioinformatics support if needed.

To identify the source of the outbreak, Member States should consider interviewing recent and new listeriosis patients using a standard questionnaire. ECDC recommends that interviews are not delayed to wait for WGS results from the isolates. ECDC has compiled a specific questionnaire for interviewing cases associated with this outbreak.

Countries are encouraged to report new cases and/or critical developments in the Epidemic Intelligence Information System for Food- and Waterborne Diseases and Zoonoses (EPIS-FWD).

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