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The ECDC-EFSA molecular typing database for European Union public health protection

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§ Disclaimer: The positions and opinions presented in this paper are those of the authors alone and are not intended to represent the views or scientific works of their employers.

Abstract

Molecular typing or microbial DNA fingerprinting has developed rapidly in recent years. Data on the molecular typing of foodborne pathogens such as *Salmonella*, *Listeria monocytogenes* and Shiga toxin-producing *Escherichia coli* (STEC) could substantially contribute to the epidemiological investigations of foodborne outbreaks and to the identification of emerging health threats. Following the STEC O104:H4 outbreak in 2011, the European Commission asked EFSA and ECDC in January 2013 to provide technical support for the EU/EEA-wide collection of molecular typing data on foodborne pathogens from food, feed, animal, environmental and human samples. At that time point, ECDC had already been collecting equivalent data for human isolates since 2012. In addition, the European Commission asked EFSA and ECDC to perform regular joint analysis of these molecular typing data, which required the establishment of a joint database. This paper describes the architectural and procedural characteristics of the joint ECDC-EFSA molecular typing database. Rules regarding data sharing and confidentiality in the context of the data collection system are also presented. This database represents a firm basis that will, in the future, be upgraded to other typing methods such as whole genome sequencing.

Keywords

- Foodborne outbreak
- Foodborne pathogen
- Molecular typing
- Multiple Loci Variable-number tandem repeat Analysis (MLVA)
- Pulsed-Field Gel Electrophoresis (PFGE)

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Introduction

Molecular typing or microbial DNA fingerprinting has developed rapidly in recent years. Many typing methods, like polymerase chain reaction (PCR) techniques, pulsed-field gel electrophoresis (PFGE) and sequencing, have become part of routine strain characterisation in many laboratories. Molecular typing provides essential tools for different surveillance purposes such as monitoring spread of clones and strains, early detection of dispersed (international) outbreaks, and prediction of epidemic potential.

PFGE is the current standard method for *Salmonella*, *Listeria monocytogenes* (*L. monocytogenes*) and STEC typing. In addition, multiple loci variable-number tandem repeat (VNTR) analysis (MLVA) is the current standard method for further subtyping of *Salmonella* Typhimurium (*S.* Typhimurium) [Larsson *et al.*, 2013]. They are invaluable methods for routine surveillance of circulation of food and clinical strains.

Molecular typing data of foodborne pathogens such as *Salmonella*, *L. monocytogenes* and STEC could substantially contribute to the epidemiological investigations of foodborne outbreaks and to the identification of emerging health threats. For the three pathogens cited above, national and cross-border outbreak investigations in Europe are regularly supported by molecular typing information from Member States [*e.g.*, Fretz *et al.*, 2010; Friesema *et al.*, 2008; Inns *et al.*, 2015; Kinross *et al.*, 2014; Yde *et al.*, 2012]. In addition, molecular typing data make it possible to assess the molecular diversity and circulation of strains within the food chain and could be useful for source attribution studies when estimating the contributions of different food categories or animal species as sources of human infections.

At present, the circulation of food- and waterborne pathogens in the food chain and the occurrence of human clusters and outbreaks in the EU/EEA are monitored with various systems and tools. The European Food Safety Authority (EFSA) coordinates a network of nominated experts on zoonoses and zoonotic agents (Zoonoses Monitoring Data Network) and collects from Member States data on zoonoses, zoonotic agents, antimicrobial resistance and outbreaks according to the Directive 2003/99/EC on the monitoring of zoonoses and zoonotic agents (EC, 2003). The European Centre for Disease Prevention and Control (ECDC) manages a network of nominated epidemiologists and microbiologists, with special expertise in food- and waterborne diseases, under the Food- and Waterborne Diseases and Zoonoses Disease Programme (FWD DP). This network helps to provide human data to the European Surveillance System (TESSy), which is a highly flexible metadata-driven system for collection, validation, analysis and dissemination of human communicable disease data. The separately collected human and non-human data are analysed jointly by EFSA and ECDC and published annually in two European Union Summary Reports: one report on zoonoses, zoonotic agents and foodborne outbreaks, and another on antimicrobial resistance [EFSA and ECDC, 2015; 2016].

Three platforms exist for rapid and secure online exchange of information on detected foodborne threats in humans and hazards in food or feed: 1) the Epidemic Intelligence Information System for Food- and Waterborne Diseases (EPIS-FWD): an ECDC-hosted platform for communication and exchange of information about emerging clusters and outbreaks as well as unusual increases in human cases detected at the national level; 2) the Early Warning and Response System (EWRS): an official notification system of the European Commission (EC) and competent Public Health Authorities in Member States regarding events of cross-border relevance due to communicable diseases at the European Union (EU) level; and 3) the Rapid Alert System for Food and Feed (RASFF): an official system for sharing information on hazards found in food and feed and trade of (potentially) contaminated batches between Member States, and for tracing these batches back and forward.

The European Union Reference Laboratories (EURLs), established in accordance with Article 12 of Regulation (EC) No 882/2004 [EC, 2004], coordinate the implementation of the analytical methods in their respective networks of veterinary National Reference Laboratories

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(NRLs). In particular, they (i) provide NRLs with details of analytical methods, including reference methods, (ii) coordinate the application by the NRLs of the methods referred to in (1), in particular by organising comparative testing and by ensuring appropriate follow-up of such comparative testing in accordance with internationally accepted protocols, when available, (iii) coordinate, within their area of competence, practical arrangements needed to apply new analytical methods and inform NRLs of advances in this field, and (iv) conduct initial and further training courses for the benefit of staff from NRLs and of experts from developing countries. For this purpose, the EURLs conduct regular training sessions, annual workshops, and typing proficiency testing trials (PT trials).

The development of databases of molecular typing data represents a tool to support and enhance surveillance and monitoring of foodborne pathogens by allowing the linkage of genetic profiles of isolates from human cases of disease to similar genetic profiles of respective strains isolated from food, feed, animals and their environment. Being able to query such a repository makes it possible to improve preparedness for outbreak investigations. For the purpose of collecting usable typing data of pathogens isolated from food, feed, animals and the related environment as well as from humans, the standardisation of processes for typing data production, analysis and storage is essential.

Aim of the database

Following the outbreak of STEC O104:H4 infections in 2011 [EFSA, 2011; Frank *et al.*, 2011], a vision paper on the development of databases for molecular typing of foodborne pathogens with a view to outbreak preparedness was prepared by the EC [EC, 2012], in consultation with EFSA, ECDC and the EURLs for *Salmonella*, *L. monocytogenes* and *Escherichia coli*. The vision paper was endorsed by the Member States' food and veterinary competent authorities at the Standing Committee on Plants, Animals, Food and Feed (PAFF) (former Standing Committee on the Food Chain and Animal Health (SCFCAH)) meeting in December 2012. Soon after this, the EC asked EFSA and ECDC to provide technical support regarding the collection of molecular typing data on foodborne pathogens, namely *Salmonella*, *L. monocytogenes*, STEC and possibly others such as *Campylobacter*, from food, feed, animal, environmental and human samples. At that time point, the ECDC had already established an equivalent molecular typing data collection system for human isolates, which was operational since 2012. In addition, the EC asked EFSA and ECDC to perform regular joint analysis of the molecular typing data on these pathogens, which required the establishment of a joint database.

The purpose of the joint ECDC-EFSA molecular typing database (referred to as 'the joint database') is to share comparable typing data in a common repository so that microbiological data from humans can be linked to similar data from the food chain. This will enable and support early detection and investigation of cross-border foodborne outbreaks, will contribute to source attribution studies, and will enhance better understanding of the epidemiology of foodborne pathogens. At present, the molecular typing data collection covers PFGE for *Salmonella*, *L. monocytogenes* and STEC, together with MLVA for *S.* Typhimurium and *S.* Enteritidis. In addition, other typing data will be collected, including serotype and serogroup, when available.

Architecture of the database

The joint database is physically hosted at, developed and maintained by ECDC, and more specifically in the European Surveillance System (TESSy) [Van Walle, 2013]. Since 2012, typing data of strains isolated from human *Salmonella*, *L. monocytogenes*, and STEC infections are submitted to ECDC by public health authorities and laboratories of the Member States. Typing data on respective bacterial isolates from food/feed and animals and their environment (non-human data) are reported to EFSA (through the EFSA molecular typing data collection system) by the food and veterinary authorities and laboratories of the Member States. These

data are then submitted by EFSA to the joint database within 48 hours.

Figure 1 presents an overview of the overall logical architecture of the data collection system and describes the main entities (systems or user groups) involved in the context of the joint database, as well as the data flow of the shared information.

For each bacterial isolate from non-human samples, the data providers at Member State level generate the molecular typing results, PFGE and MLVA data [Caprioli *et al.*, 2014; Jacobs *et al.*, 2014; Peters *et al.*, 2017; Roussel *et al.*, 2014], and any other microbiological results together with the epidemiological data of the sample from which the isolate was obtained, according to EFSA requirements [EFSA, 2014]. In particular, data providers are required to structure their data according to a specific data model based on the Standard Sample Description ver. 2 (SSD2) [EFSA, 2013]. Data are then submitted to the EFSA's molecular typing database via machine-to-machine communication (*i.e.*, web service).

Data on human samples are collected through the TESSy that allows Member States to upload and analyse molecular typing data from isolates of *Salmonella*, *L. monocytogenes*, and STEC, including a minimum set of epidemiological data [Van Walle, 2013]. Standardisation of molecular typing results of *Salmonella*, *L. monocytogenes* and STEC across the participating laboratories is ensured by standard operating procedures (SOPs) developed by ECDC.

The whole process of non-human data collection, as well as the characteristics of EFSA's molecular typing database have been harmonised with the standards of the TESSy database, in order to support joint integrated analysis of molecular typing data from non-human and human isolates. The EFSA molecular typing data collection system interfaces with and submits data to the joint database through TESSy. To guarantee the confidentiality of non-human data for the respective data owners, the microbiological information (PFGE and MLVA typing data as well as serotype/serogroup) will be accompanied by a minimum subset of epidemiological data stored in the EFSA database for the purpose of sharing it in the joint database (Table 1). Additionally, the different user groups that are allowed to query the joint database have specific access rights, limiting their access to the information (Table 2). In particular, restrictions apply to 'sensitive' data that are visible only to the respective data providers and to all nominated authorised users from the same country. Data managers and data curators have access to all data present in the joint database.

Users and their role in the database

The actors involved in the process of molecular typing data collection and analysis in the joint database have different roles. Besides the responsibility of both ECDC and EFSA for the management of the database, two main roles are identified: data provider and curator.

The data providers (national public health reference laboratories for human data, and NRLs and other official laboratories in the Member States for non-human data):

- are nominated by the relevant Competent Authority at Member State level;

- are responsible for uploading microbiological data, including molecular typing data, and epidemiological data to ECDC and EFSA, respectively;

- can query the joint database for matching isolates for instance, and visualise and/or download the data depending on data accessibility rights.

The curators (*i.e.*, the relevant EURLs and ECDC's curators) have the responsibility to:

- assess the quality of data (when applicable) submitted by data providers;

- support data providers in correctly implementing the SOPs for molecular typing methods and provide suggestions for improving image quality in case of PFGE typing;

- assign molecular typing specific nomenclature (*e.g.*, reference types).

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In addition, EFSA, ECDC, EURLs and ECDC curators are in charge of the following tasks:

- perform regular scientific analyses of the data.

- provide technical support to internal and external users.

Curation

The integrated analysis of data stored in the joint database requires validation of the PFGE molecular typing data, namely the curation process, and assignment of reference types to the isolate profiles. This activity is carried out in the joint database by the EURLs (in their role as curators) for the non-human strains according to the relevant SOPs for curation [Caprioli *et al.*, 2014; Jacobs *et al.*, 2014; Roussel *et al.*, 2014], and by the laboratories specifically appointed for this task by ECDC (ECDC curators; currently Statens Serum Institute in Denmark for all three pathogens) for the human isolates. Briefly, the new PFGE profiles submitted are validated for their quality and are classified as either 'accepted' or 'rejected'. If the profile is accepted, a standardised sequential reference type is assigned to each indistinguishable PFGE pattern. The nomenclature of the reference types follows the TESSy nomenclature - short text codes analogous to *e.g.*, a serotype (*e.g.*, '*Asc*I.0001': *Asc*I for the restriction enzyme *Asc*I and the reference type number). The system offers the possibility for the data provider to consult, through the TESSy web interface, the joint database according to the differentiated access rights previously mentioned and which are described in a specific agreement. The system also offers data providers the possibility of downloading the results of the curation process, *i.e.*, whether their molecular typing data were accepted and what reference types were assigned and, in this way, to synchronise their database with the joint database at the EU level. This functionality is similar to what was set up in the EURL for the *L. monocytogenes* molecular database [Felix *et al.*, 2014].

The curation process forms an important quality step for PFGE so that any scientific analyses are performed (*i.e.*, cluster detection) on only those isolates meeting the minimum requirements for PFGE quality.

Analysis of data in the database

The joint analysis of human and non-human molecular typing data aims at finding joint microbiological clusters, based on the reference type, time, and geographical localisation of the strain profiles submitted, and identifying those that merit further attention and investigation at EU/EEA level because they may be part of a cross-border foodborne outbreak. This analysis is carried out in the joint database by ECDC and EFSA, with the support of the relevant curators, and the clusters are notified through the EPIS-FWD to the affected countries' public health and food safety and veterinary contact points. In case of specific public health threats, such as cross-border foodborne outbreaks or the emergence or re-emergence of specific clones of foodborne pathogens of particular concern, EFSA could search the EFSA molecular typing database to retrieve additional epidemiological information for the purpose of generating or testing hypotheses that could explain the clusters identified. The analysis of data and the investigation of an event are also supported by information shared by Member States through the EPIS-FWD, EWRS and RASFF.

Data confidentiality

Different rights for data accessibility are associated with each role. Moreover, to further protect the confidentiality of data, a collaboration agreement has been signed between the main actors in the database (ECDC, EFSA and EURLs). In addition, to avoid any improper or non-authorised use of the data, all data providers are asked to sign an agreement with EFSA or ECDC, based on their area of competence, before any data submission or access to the database.

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Participation in data collection

The Member States participate in data collection as data providers on a voluntary basis. The data providers are invited to upload their molecular typing data as soon as these become available, in order to maximise the usefulness of molecular typing data collection for disease prevention and control, and food and feed safety. The upload of historical data from the participating laboratories is also encouraged. This would support source-hypothesis generation when a multi-country outbreak is under investigation, but would also contribute to a better understanding of the epidemiology and transmission routes of foodborne pathogens.

Discussion

The joint ECDC-EFSA molecular typing database has been designed to allow the timely identification of microbiological clusters of public health relevance and support epidemiological investigation.

This represents the first attempt to implement a fully integrated enhanced surveillance/monitoring system for foodborne pathogens and related human infections according to the 'One Health' principle at the EU level. The system was designed to be compliant with the legal requirements and the official role of relevant institutions under the legislation of the public health and the food safety/veterinary area. In addition to the legal aspects and the technical challenges in developing a system able to support outbreak detection and investigation for public health purposes at the European level, major efforts were made to ensure that the system is attractive to data providers and in particular is able to support their surveillance activities at the national level, while respecting the sensitivity of the data. This is achieved by offering the data providers the possibility of retrieving the results of the curation process from the joint database and the assignment of the reference type. In addition, data providers have the possibility of searching, based on their access privileges, the joint database in order to perform their own analysis in the EU/EEA context, while respecting confidentiality of data.

Within the international community, the importance of sharing data is increasingly recognised. This provides numerous benefits including a more efficient and contextualised analysis of data and information. However, its adoption also entails overcoming a number of barriers with respect to legislation, data quality, data completeness, data timeliness and participation. In particular, there are concerns about the ultimate use of the data provided by data producers, generators and collectors without data owner's explicit permission. For these reasons, a compromise has been found between the policies for data accessibility and data protection, and this compromise has subsequently been agreed with both public health and food safety and veterinary Competent Authorities representing all Member States. The sharing of a limited set of descriptive data and the differentiated rules for data accessibility for the users of the joint database guarantee that the relevant scientific information is shared between all official actors in the process, but limits the possibility of tracing back restricted information, thereby ensuring compliance with the obligation to protect confidentiality.

The strength of the system itself is the clear definition of rules, procedures and actors involved in a cross-sectoral environment, increasing the potential for protection of public health from widely spread and dispersed foodborne infections across countries, which are otherwise hard for Member States to control in a sustainable manner. This approach guarantees the assignment of specific roles to the actors involved in the process, the clear understanding of what data will be shared and how data will be used, the harmonisation and high quality of the information received, and the comparability of results between the public health and food safety/veterinary sectors.

The data collection system, designed according to the mandate received, works based on the voluntary participation of the Member States. The data collection system will have real added value only if a substantial number of Member States submit a consistent volume of data. Real-

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time data will support the detection and investigation of ongoing foodborne outbreaks, and historical data will contribute to source attribution studies and will enhance better understanding of the epidemiology of foodborne pathogens.

The database can be extended to other pathogens and methods, following the agreement between the relevant actors. This database represents a firm basis that will, in the future, be upgraded to other typing methods such as whole genome sequencing (WGS) as the technology and capacity at the EU level improves, while at the same time benefitting from an existing structure of rights/responsibilities in line with EU regulations.

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APPENDIX

FIGURE 1 / Structure of the joint ECDC-EFSA database

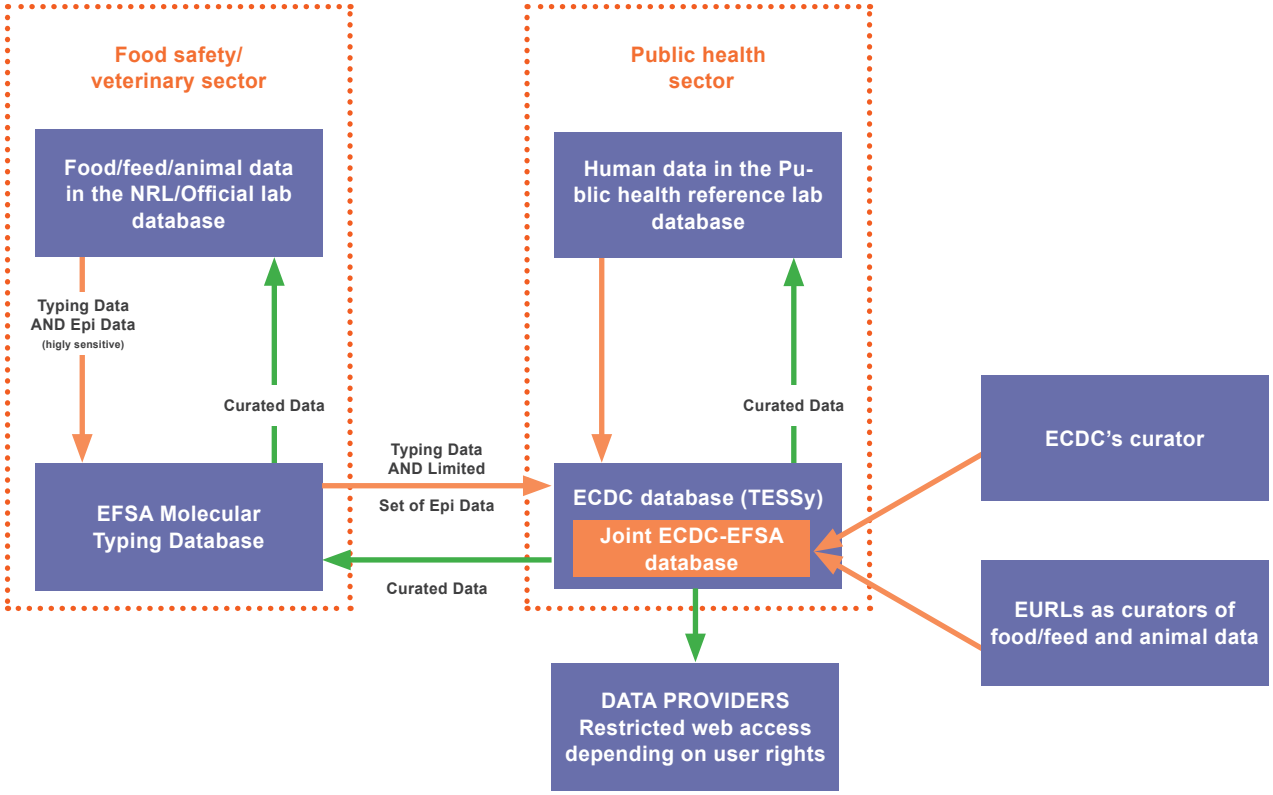

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TABLE 1 / Type of data stored in the Joint Database

Food safety/veterinary sector	
Non-sensitive data	Microbiological data, limited to • Molecular typing data: PFGE and MLVA. • Other typing data: *Salmonella* serotype, *Listeria* serotype and STEC serogroup. EFSA Isolate Id Date of sampling Date of receipt of isolate in the reference laboratory Type of sample: defines the source of the isolate, *e.g.*, 'animal', 'food', 'feed', 'environment'.
Sensitive data	Country of sampling Laboratory identification code
Human sector[1]	
Non-sensitive data	Microbiological data, limited to • Molecular typing data: PFGE and MLVA. • Other typing data: *Salmonella* serotype, *Listeria* serotype and STEC serogroup. ECDC Isolate Id Date of sampling Date of receipt of isolate in the reference laboratory
Sensitive data	Reporting country

1. All other human descriptive data such as age and gender are physically stored in the same system (TESSy) but are not part of the Joint Database.

TABLE 2 / Access to the Joint Database

User group[1]	**Non-human data (food, feed, animal, environmental data)**				**Human data**			
	Country of sampling, Laboratory identification code	**Date of sampling/ sample type**	**Microbiological data**[2]	**Food, feed, animal or environmental descriptive data**[3]	**Country of sampling**	**Date of sampling/ sample type**	**Microbiological data**[2]	**Human descriptive data**[4]
EFSA	Yes	Yes	Yes	No (not in Joint Database)	Yes	Yes	Yes	No
ECDC	Yes	Yes	Yes	No (not in Joint Database)	Yes	Yes	Yes	Yes[5]
Users from Member State food/ veterinary side	Only if isolate is from the same country as the user	Yes	Yes	No (not in Joint Database)	Only if isolate is from the same country as the user	Yes	Yes	No
Users from Member State human side	Only if isolate is from the same country as the user	Yes	Yes	No (not in Joint Database)	Yes	Yes	Yes	Yes[5]
Curators non-human data	Yes	Yes	Yes	No (not in Joint Database)	Yes	Yes	Yes	Yes
Curators human data	Yes	Yes	Yes	No (not in Joint Database)	Yes	Yes	Yes	Yes[5]

1. EC has the right upon request to receive any data related to a specific event.
2. PFGE and MLVA typing as well as serotype/serogroup
3. Detailed description of the sample, *e.g.*, food category/animal population, origin. These are considered sensitive data and are not part of the Joint Database.
4. More information on the patient, *e.g.*, age, gender. These are considered sensitive data.
5. These data are stored physically in the same system (TESSy), but are conceptually not part of the Joint Database.