EURL-PH-LEGI

EU Reference Laboratory for public health in the field of Legionella

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LIST OF ACRONYMS

CALD	Community Associated Legionnaires' Disease
CGMLST	Core Genome Multilocus Sequence Typing
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
ELDSNet	European Legionnaires' Disease Surveillance Network
EQA	External Quality Assessment
ESCMID	European Society of Clinical Microbiology and Infectious Disease
ESGLI	ESCMID Study Group for Legionella Infections
EU	European Union
EURL-PH-LEGI	European Reference Laboratory for public health on Legionella
HALD	Healthcare Associated Legionnaires' Disease
HaDEA	European Health and Digital Executive Agency
ISO	International Organization for Standardization
IVD	In Vitro Diagnostic
LD	Legionnaires' Disease
MIC	Minimum Inhibitory Concentration(s)
MTT	Molecular Typing Tool
NFP	National Focal Point
NGS	Next Generation Sequencing
NRL	National Reference Laboratory
OCPs	Operational Contact Points (for Microbiology for Legionnaires' disease)
PCR	Polymerase Chain Reaction
TALD	Travel Associated Legionnaires' Disease
TESSy	The European Surveillance System
UAT	Urinary Antigen Test
WGS	Whole Genome Sequencing
WHO	World Health Organization
WHO CC	WHO Collaborating Centre

1. Executive summary

Legionnaires' disease (LD) is a severe pneumonia with significant mortality, requiring robust surveillance and harmonization of diagnostic practices across Europe. The European Legionnaires' Disease Surveillance Network (ELDSNet) plays a critical role in monitoring cases, fostering laboratory collaboration, and promoting the use of Whole Genome Sequencing (WGS) for outbreak investigations. Despite advancements, disparities in diagnostic methods, limited culture-based confirmations, and underutilization of PCR-based diagnostics hinder effective surveillance. The European Reference Laboratory for public health on *Legionella* (EURL-PH-LEGI), established under EU Regulation 2022/2371, aims to address these challenges by supporting national laboratories through quality assurance programs, standardized protocols, expertise and training initiatives. Priorities include harmonizing diagnostic and typing methods, enhancing laboratory capacity, and ensuring comparability of data. The EURLs will coordinate efforts for improved outbreak detection and response, promote genomic surveillance, and facilitate knowledge sharing among EU/EEA laboratories. Long-term goals include advancing genomic-based epidemiology, addressing antimicrobial resistance, and identifying contamination sources, ultimately reducing LD incidence. By promoting collaborative training, reference diagnostics, and technical support, the EURL-PH-LEGI will strengthen Europe's preparedness for cross-border outbreaks and improve public health protection. These initiatives will also guide policy development, enhance preventive measures, and ensure harmonized surveillance to meet the evolving challenges posed by LD. This document is intended for public health laboratories, microbiologists, epidemiologists and policy makers involved in LD surveillance across EU/EEA. It aims to outline the current challenges and strategic priorities in the laboratory surveillance and diagnosis of LD in Europe.

2. Introduction

LD is an uncommon form of pneumonia with an average of 10 % mortality among notified cases in the EU/EEA. Cases are mainly reported in persons of older age groups, especially in males. Cases may present sporadically or in geographically limited outbreaks and may be classified as infected in the general community (community associated Legionnaires' disease, CALD), healthcare associated infections (healthcare associated Legionnaires' disease, HALD) or cases of travel associated Legionnaires' disease (TALD).

2.1. Description of the existing network for surveillance: ELDSNet

The ELDSNet consists of National Focal Points (NFP) for Legionnaires' disease and Operation Contact Points (OCP) for Epidemiology and Microbiology for Legionellosis. Epidemiological and microbiological surveillance data on *Legionella* related to surveillance activities for Legionnaires' disease are collected through the European Surveillance System (TESSy) and EpiPulse at European Centre for Disease Prevention and Control (ECDC).

There are currently four EU/EEA surveillance schemes coordinated at ECDC that include reporting of LD cases. Two of these are annual schemes covering all retrospective case notifications by EU/EEA countries and outbreak events. A further two involve case or events: i) reporting in 'near real-time' TALD cases to detect clusters, and ii) reporting through EpiPulse Events of any other possible cluster events that may indicate a cross-border community outbreak. In all these schemes, the added value of international collaboration in detecting and investigating clusters including microbiological findings

from clinical and environmental samples is evident. A fifth scheme on genomic surveillance of *Legionella* in the EU/EEA is under pilot in 2025.

One of the objectives of ELDSNet is to support a laboratory network for LD providing quality assurance and capacity-building opportunities to foster harmonized methodologies across Member States and finally contribute to good quality surveillance data for action. In an outbreak situation of LD, timely source identification depends on epidemiological and environmental investigations, with a central role for laboratories in both clinical and environmental sample testing. In order to relate clinical and/or environmental specimens, microbiological investigations are conducted, including sequencing and typing of the isolates. Identification of a likely common source is important to reassure that implemented public health actions will prevent further cases and to monitor the impact of implemented measures.

An enhanced LD genomic surveillance program utilizing highly discriminatory WGS data to identify genomic cluster of isolates and support outbreak investigations, and its integration into EU/EEA surveillance reporting and outputs has been developed and has been tested by ELDSNet members. The Molecular Typing Tool (MTT) provides ELDSNet members with a solution to explore microbiological, demographic, and epidemiological data.

Thus, laboratory diagnosis and molecular characterization of LD infection plays a crucial role not only in the timely initiation of adequate treatment, prevention, and control measures but supports surveillance activities as well. This is why strengthening the ELDSNet members' capacity for laboratory diagnosis and characterization of Legionnaires' disease infections and ensuring harmonized and well-established laboratory methodology is crucial.

2.2. EURL implementation

Article 15 of the Regulation of the European Parliament and of the Council on serious cross-border threats to health and repealing Decision No 1082/2013/EU provides that the Commission may designate EU reference laboratories to provide support to national reference laboratories to promote good practice and alignment by Member States on a voluntary basis on diagnostics, testing methods, use of certain tests for the uniform surveillance, notification and reporting of diseases by Member States. Coordinated EURLs strengthen preparedness, crisis management and outbreak response capacities in the Member States thereby representing an area with clear added value at EU level. Sustainable EU reference networks of microbiology laboratories also ensure an adequate response to biological threats, such as intentional release and bioterrorism, thus contributing to a high level of protection to biological agents and health security in Europe.

The EURL-PH-LEGI implements Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health, in particular relating to *Legionella*.

The EURL-PH-LEGI is part of the EURL for Public Health network coordinated by ECDC and is implemented and monitored by the European Health and Digital Executive Agency (HaDEA). The EURL-PH-LEGI has complementary actions with World Health Organization, ESCMID Study Group for Legionella Infection (ESGLI), EURL of Food Safety and Animal Health and EURL of In Vitro Diagnostics (IVD).

The main role of the EURL-PH-LEGI is to promote good practices and provide support to EU/EEA Member States on diagnostic, testing and typing methods, to ensure reliability and comparability of data and capacity strengthening, aiming for a high-quality surveillance, notification and reporting of cases. The EURL-PH-LEGI is aiming to be an essential player in the protection of public health, particularly in the context of multi-country LD outbreaks, providing a platform for coordinated investigation, mitigation and prevention of LD.

3. Vision: needs and challenges

The overall vision of the EURL-PH-LEGI is to foster a robust, harmonized, and science-driven diagnostic and surveillance network for Legionnaires' disease across the EU/EEA. This vision encompasses accurate and timely detection, comprehensive laboratory characterization, and coordinated outbreak response. The overarching goal is to minimize diagnostic disparities and build laboratory excellence across the network to effectively respond to both routine cases and emerging threats.

3.1. The need for harmonization of detection and characterization methods

In their last epidemiological report, the ECDC showed that the majority of cases in 2021 (9 566/10 723; 89 %) were reported to be diagnosed with a urinary antigen test (UAT) [1]. The last ECDC external quality assessment (EQA) from 2022-2023 showed an excellent concordance for urinary antigen reporting [2]. However, a lower concordance was obtained when a negative specimen was included. False positive results with enzyme immunoassays on urine samples were firstly described in the early 80s. Boiling (100°C) liberates bacterial polysaccharides from antibody complexes and eliminates the nonspecific interferences in enzyme-linked immunosorbent assays [3]. Therefore, the EURL-PH-LEGI will aim to establish boiling as a best practice for urinary testing to decrease reporting of false positive results.

In addition, in 2021, only 11 % of cases were reported as culture-confirmed [1], the percentage of culture-positive LD varies between countries, and for TALD only 3.5 % of isolates were cultured. While the reasons for the low proportion of cultured isolates are multi-faceted, the limited access to culture-based *L. pneumophila* isolates is a major hurdle for typing method, especially WGS. Therefore, there is an urgent need to train network laboratories on culture methods showing the best isolation success rates on upper respiratory tract samples. In addition, the EURL-PH-LEGI will compile standard operating procedures based on scientific evidence in a laboratory handbook to build capacity in all EU/EEA countries and increase reporting of culture-confirmed cases.

There is also increasing evidence that the introduction of real-time polymerase chain reaction (PCR) as a routine diagnostic method improves the diagnosis of LD. The use of PCR method tests was reported for 12 % of cases in Europe [1]. In addition, the use of PCR, and especially those targeting the pneumonia syndromic panel, revealed an obvious under-detection of *L. pneumophila* sg 2-15 cases and low specificity in several European countries. This induced an open discussion on a new LD surveillance case definition that proposes to include PCR test to define a confirmed case. It is therefore necessary to carry out a study that will establish the capacity of the network laboratories to perform PCR on clinical samples (kits used, home-made PCRs, PCR instruments, number of PCRs performed, type of samples analyzed...). In addition, given the various PCR methods available it is necessary to evaluate several real-time PCR kits marketed in Europe for LD diagnosis to determine the performance and ability of these kits to detect *L. pneumophila* and *Legionella spp*. This is not only needed to

motivate the introduction of PCR as a diagnostic surveillance criterion for LD confirmed cases but also to promote the use of the best-performing PCR methods in National Reference laboratories (NRLs).

The efforts in improving urinary antigen testing, culture and PCR methods will not only enhance diagnostic accuracy and surveillance quality, but also pave the way for a European laboratory network that can adapt to future technological advances in *Legionella* diagnostics but also to emerging epidemiological trends.

3.2. The need for quality insurance for diagnostic and genomic methods

The EQA programs are crucial for identifying testing errors and their causes at an early stage, which allows prompt corrective action to ensure future testing accuracy. In addition to promote surveillance data quality, they are necessary to assess the ability of participating laboratories to perform correctly routine diagnostic tests and typing for outbreak investigation. Furthermore, ISO 15189 (in its current version) accreditation requires participation in EQA programs. With the end of the ECDC Legionella EQA scheme framework contract, laboratories indicated that EQA should continue as they considered it of value in support to surveillance and outbreak investigation. Therefore, an EQA *Legionella* scheme needs to be provided to the ELDSNet members and should continue to assess the entire process involved in outbreak investigation, including PCR-based diagnostic. This EQA shall complement existing EQA programs, which are organized at national or international levels. In addition, considering the increased use of WGS for source attribution and outbreak investigation, a separate EQA based on whole genome sequences is also needed to evaluate typing capacities. Finally, even though acquired antimicrobial resistance in *L. pneumophila* is rare [4–9], resistant isolate to ciprofloxacin [10], fluoroquinolone [11]and elevated MICs for azithromycin [9] have already been observed. Therefore, it is also necessary to evaluate laboratory capacity to test and report on antimicrobial resistant isolates.

EQA may be complemented with technical support provided through country visits to review, evaluate and improve laboratory surveillance. The list of the ECDC disease network members to visit will be based on requests of interested laboratories and recent EQA results may be useful in consideration. A pre-visit call will be implemented to evaluate the status and needs for improvement and provide pre-visit recommendations. The visits will be opportunities for *in situ* evaluation and assistance in the implementation of recommendations. Post-visit meetings will collect participants' feedback and assess the impact of the visits.

Sustained and harmonized EQA participation together with country visits will ensure continuous improvement, facilitate adoption of novel technologies, and build the foundation for a quality-assured laboratory network prepared for future cross-border health threats.

3.3. The need for expertise on *Legionella* related subjects

The EURL-PH-LEGI will operate as a centralized technical support to ECDC and the ELDSNet members on laboratory topics related to the diagnostics and characterization of *Legionella spp*., method developments including genomic typing, reference material availability, and other topics related to laboratory aspects of LD. In case of multi-country outbreak or unusual events, support could also be provided on microbiology-related matters relevant to the outbreak/event.

Similarly, the EURL-PH-LEGI will upon request provide reference diagnostic services for the ELDSNet laboratory network where equivalent NRL for *Legionella* may not exist or where such reference

services are not available. In the context of outbreaks, a centralized laboratory support should be envisioned to validate diagnostic test results, provide advice and support, investigate atypical specimens, and assist in the characterization of new *Legionella* species. A complementary service could be provided upon requests to assist and support network laboratories with implementation, optimization, and troubleshooting.

By positioning itself as a centralized hub of *Legionella* expertise, the EURL-PH-LEGI aims to support knowledge transfer, foster scientific collaboration, and enable rapid mobilization of technical resources during public health emergencies.

3.4. The need for training on *Legionella* diagnostics

A coherent training program on both technical and scientific aspects of *Legionella* diagnostics and microbiological characterization needs to be created to build capacity in the member states. This program will be complementary to the content offered by ESGLI. All training activities should be aligned with and fall under the overall training program on prevention, preparedness, and response to serious cross-border health threats, that is currently developed to implement Article 11 of the Regulation 2022/2371.

The training plan should be developed to identify the skills and needs of the ELDSNet laboratories. it should rely on a specific survey and the results of the EQAs offered by the EURL-PH-LEGI. Gaps in the field of LD diagnosis, environmental investigation and typing could be covered through wet lab training or specific webinars animated by experts in the field. The wet lab trainings should aim to reduce disparities among European countries by both strengthening the diagnosis and monitoring of LD cases and providing support for typing and outbreak investigations. Topics for webinars should focus on general diagnosis of *Legionella spp*. including typing, new molecular surveillance methods and laboratory outbreak analysis tools. These training opportunities should be conducted in relation to the methods described in a laboratory handbook (see above).

This comprehensive training approach will reduce disparities, promote sustainability of laboratory capabilities, and ensure that all EU/EEA member states are equally equipped to detect, characterize, and respond to Legionella infections.

4. Priority actions

The implementation of the EURL-PH-LEGI is envisioned to meet the needs identified in the section above. The EURL-PH-LEGI will prioritize the following areas:

- reference diagnostics, including test protocols;
- reference material resources;
- external quality assessments;
- scientific advice and technical assistance;
- support in outbreak response, including monitoring, alert, investigation and laboratory capacities;
- training;
- assistance to implement the EU laboratory and surveillance strategies.

The EURL-PH-LEGI shall interact with ECDC and the laboratory members of ELDSNet consisting of the NFP for Legionnaires' disease and the OCPs for Microbiology for Legionellosis to implement its actions.

5. Expected outcomes

The EURL-PH-LEGI will provide support to the EU/EEA network laboratories to ensure quality, reliability and comparability of data and strengthen their technical capacity to better contribute to LD diagnosis and typing. These improvements will support investigation of multi-country and travel-associated outbreaks and EU surveillance. In addition to the laboratory network members and ECDC, all stakeholders (all ELDSNet members, WHO Collaborating Centers, ESGLI, policy makers, etc.) will benefit from the EURL-PH-LEGI activities.

5.1. Short-term effect: promote LD diagnosis

A first outcome of the EURL-PH-LEGI actions will be the development and harmonization of practices for LD diagnosis among European network laboratories, notably those reporting a low incidence. The aim is to promote the combination of PCR assays, culture and UAT for LD diagnosis. The lessons learnt from routine use of PCR in EU/EEA laboratories could later inform on the potential impact of the current ECDC/ELDSNet technical proposal for a revised LD surveillance case definition that would include *Legionella* PCR-positive patients as confirmed cases. Harmonizing PCR protocols and enhancing PCR assays as first-line diagnostic tests will enable to reinforce LD surveillance.

This short-term impact will be achieved in particular through developing a laboratory handbook, studying the performance of several PCR kits, proving laboratory advice and technical support to ELDSNet members on diagnostic techniques, evaluating PCR result reporting through EQA scheme as well as organizing country visits and wet laboratory trainings.

EURL-PH-LEGI actions, news and achievements can be consulted on the EURL-PH-LEGI website which is updated regularly.

5.2. Medium-term effect: promote *Legionella* identification, typing and sequencing

Legionella identification and typing will be promoted at different levels in each NRL according to their technical capacity. The EU/EEA laboratories that had previously a low capacity for molecular analyses should extend their diagnosis and genotyping abilities, by traditional approaches (e.g. Sequence-based typing) and WGS. The impact on environmental and outbreak investigations for these EU/EEA laboratories will be important and could lead to an improvement of LD prevention in certain countries. Capacity building in these countries should also improve TALD and multi-country outbreak investigations in the EU overall.

ELDSNet members, which already have access to a sequencing platform and bioinformatics departments, will benefit from a common database proposed by the ECDC, allowing for a more accurate LD genomic surveillance at European level, through cgMLST typing. The EURL-PH-LEGI by organizing specific bioinformatics EQA scheme, country visits to develop sequencing capacity, trainings on genomic surveillance but also by sharing and developing expertise on new typing approaches will support the ECDC surveillance. In the context of outbreaks, the ECDC will benefit from technical support to help the laboratories that do not have access to sequencing platforms. The EURL-PH-LEGI will also have a crucial role in the investigation of challenging LD cases at European level.

Thus, in the medium term, EURL activities should have an impact on increasing the number of network laboratories using molecular/genomic epidemiology, in particular WGS, at multiple levels (i) to support cluster/outbreak detection, (ii) to support event/outbreak investigation including for source attribution, (iii) to prevent and monitor of risk sources on the long-term, and (iv) to establish geographical distribution of genomic clones. By promoting WGS tools, the proposed EURL-PH-LEGI actions will also boost the characterization of new or atypical *Legionella* species and mixed infections, as well as the investigation of atypical environmental samples.

5.3. Long-term effect: improve European collaboration, investigation of emerging issues and prevention

The first long-term objective is to increase the isolation rate of *Legionella* from clinical samples. The EURL-PH-LEGI target is to achieve an average of 25 % of cases reported as culture-confirmed in all EU/EAA countries within the project period (7 years), a percentage achieved by only a few countries, such as in France, Denmark and The Netherlands. Promoting culture and supporting the isolation of clinical strains through scientific advice and technical support will improve the EU surveillance of LD and support the investigation of outbreaks and TALD by more likely identification of infectious sources.

The increasing number of clinical strains available will have several important long-term effects: (i) it will allow a better understanding of the epidemiology, including the characterization of the main European clones associated with the disease; (ii) it will allow better monitoring of the antimicrobial susceptibility of *Legionella* and the detection of rare events (antimicrobial resistance, identification of unusual environmental sources of contamination and epidemics). In the future, a strain collection could be established to allow large-scale evaluations of new kits, tools and practices in the NRLs and contribute to a better understanding of LD. Furthermore, a more diverse set of strains will improve current knowledge on *Legionella* spp. biology and epidemiology.

The consortium will also bring significant expertise in the investigation of LD cases where clinical strains are unavailable. Sequence-based typing (SBT) which targets seven specific genes of *L. pneumophila* remains a powerful method for source attribution. While Nested-PCR has been demonstrated to enhance epidemiological typing in the absence of isolates [12], it is not routinely performed by all network laboratories. To address this gap, the EURL-PH-LEGI will provide training on the use of nested PCR to support indirect typing approaches. This capacity building effort will improve the identification of infection sources that would otherwise remain unconfirmed, thereby enhancing outbreak detection and response. In the long term, more accurate source attribution will contribute to a reduction in high-risk environments and help prevent future LD clusters or outbreaks.

Finally, by improving the diagnosis of LD and identifying the sources of infection, the EURL-PH-LEGI actions should foster the prompt implementation of measures of prevention as closely as possible to the needs of the population in each member state and, ultimately, the reduction of LD numbers. The EURL-PH-LEGI may also have an advisory role for policy makers providing a sound framework for proposals in the area of LD prevention and emerging issues.

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7. EURL-PH-LEGI CONCEPTUAL FRAMEWORK

SCOPE AND PURPOSE OF THE FRAMEWORK						
The present framework aims at guiding the network laboratories to implement harmonized diagnostic methods including whole genome sequence-based typing and to improve quality of laboratory surveillance through the expertise and training provided by the EURL-PH-LEGI						
EXPECTED OUTCOME						
Better understanding and prevention of Legionnaires' disease cases and outbreaks and improved laboratory data reporting through increased laboratory capacity						
GOAL OF THE EURL-PH-LEGI						
To promote good practices and provide support to EU/EEA Member States on diagnostic, testing and typing methods, to ensure reliability and comparability of data and capacity strengthening, aiming for a high-quality detection and reporting of cases.						
TARGETS FOR NRLs						
PREVENTION AND SURVEILLANCE	**CAPACITY BUILDING**	**STRENGTHENING LABORATORY PRACTICES**	**QUALITY OF LABORATORY SURVEILLANCE**	**TECHNICAL SUPPORT**	**NETWORK INTERACTION**	**SUSTAINABILITY OF THE ACTION**
Better use of the ECDC platforms for coordinated investigation, mitigation and prevention of LD and improve surveillance in Europe **Increased contribution to the common molecular typing database** allowing for a more accurate LD surveillance at European level	**Follow the training plan** on Legionnaire disease diagnostic and laboratory surveillance	Use of all relevant diagnostic methods described in a laboratory handbook enabling **common laboratory practices**	**Participation to external quality assessments**, which are mandatory for accreditation purposes **Promote the improvement of the services** Self-evaluation of their approaches, methods and personnel	Reception of **scientific advice and technical support** Reception of support in situation where EU/EEA laboratories that have a low capacity for molecular analyses	**Efficient coordination** among the laboratory members of the ELDSNet Achieving **efficient and effective visibility, awareness, and acceptance** from internal and external stakeholders	Monitor the impact of training and capacity building activities Changes in national and international **legislation** that builds on the increased expertise of network laboratories on TALD and outbreak investigation

PRIORITY FOR EURL's ACTIONS						
Priority 1	**Priority 2**	**Priority 3**	**Priority 4**	**Priority 5**	**Priority 6**	**Priority 7**
PREVENTION AND SURVEILLANCE	**CAPACITY BUILDING**	**STRENGTHENING LABORATORY PRACTICES**	**QUALITY OF LABORATORY SURVEILLANCE**	**TECHNICAL SUPPORT**	**NETWORK INTERACTION**	**SUSTAINABILITY OF THE ACTION**
Supporting Member States in outbreak investigation and response, and in the investigation of travel-associated LD cases (TALD) Supporting future revisions of the EU surveillance **case definition** Better understanding of LD epidemiology	Development of a **training curriculum** based on LD diagnostic Training of representatives of network laboratories with wet-lab exercises Webinars on diagnostic methods and outbreak investigations Evaluating the **impact of training and capacity building activities** by pre- and post-training surveys	**Developing a laboratory handbook** with recommendations of well-established and approved methods **Assessing laboratory capacity to perform PCR methods** **Production of quality-assessed monoclonal antibody** for Legionella serogrouping	Providing and promoting harmonized multi-country **External quality assessments** Organizing **country visits** for *in situ* evaluation and assistance Evaluating testing capacities for **antimicrobial susceptibility** of LD **Characterisation of new or atypical Legionella species**, mixed infections, and better investigation atypical environmental samples	Provision of **reference diagnostic services** for network laboratories **Advice and technical support** to network laboratories, including genomic typing **Scientific advice and technical support** to ECDC Provide **information, guidance and/or support** to ECDC in outbreak responses	Promoting joint investigations of cross-border outbreaks by supporting the laboratory investigation Facilitating **networking** opportunities between **ELDSNet members** through laboratory network meetings	Providing guidance on novel or key developments or findings in the field of *Legionella* laboratory diagnosis or characterization **for consideration by national and/or EU policy maker** **Establishing collaboration** with international organizations such as WHO collaboration centers, ESGLI, EURL for IVD **Promote accessibility to the outcomes** of the EURL by disseminating documents to national experts.