

Molekulárně-biologické metody - jejich význam v surveillance a šetření ohniska infekčních onemocnění - podpora ECDC

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- Specifické místo mezi molekulárními metodami zaujímá sekvenace celého genomu infekčních agens **Whole Genome Sequencing (WGS)**, resp. **Next Generation Sequencing (NGS)**, která se neuvěřitelně rychle přesunula z uplatnění ve výzkumu do rutinního používání v surveillance infekčních onemocnění.
- V řadě zemí bylo již prokázáno, že kromě zpřesnění dat surveillance, přináší WGS i úsporu finanční a časovou.
- ECDC podporuje řadu projektů, které jsou zaměřeny na celoevropskou implementaci molekulární surveillance infekčních onemocnění.

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ECDC strategic framework for integration of molecular and genomic typing into European surveillance and multi-country outbreak investigations, 2019–21

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Summary:	<p>This document is a strategic framework for integration of molecular and genomic typing into European surveillance and multi-country outbreak investigations, revised after consultation with the National Focal Points for Microbiology and Surveillance in October 2018.</p> <p>In execution of ECDC's public health microbiology strategy 2022 and expert opinion on whole genome sequencing (WGS) for EU outbreak investigations and public health surveillance, this strategic framework presents the proposed priority list of pathogens/diseases and technical implementation options for the medium-term (2019–21) preparation and/or implementation of integration of molecular/genomic typing information into EU-level surveillance and multi-country outbreak investigations. In consideration of the evidence and partner consultations, ECDC proposes in this strategic framework that the priorities for 2019–2021 are to prepare for and/or implement the gradual integration of sequence-based typing data workflows in support for joint response and surveillance operations with EU/EEA Member States for the following applications and pathogens:</p> <ul style="list-style-type: none"> • Outbreak investigation objective: support to multi-country outbreak investigations through sequence-based typing: <i>Campylobacter</i> spp., <i>Clostridium difficile</i>, hepatitis A virus, <i>Legionella</i> spp., <i>Listeria monocytogenes</i>, multidrug-resistant <i>Mycobacterium tuberculosis</i> (MDR TB), <i>Neisseria meningitidis</i>, outbreaks of emerging multi- or extensively drug-resistant (MDR or XDR) bacteria, outbreaks of new pathogens or new modes of transmission of healthcare-associated or

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Priority ECDC 2019 - 2021



Outbreak investigation objective

Support to multi-country outbreak investigation through sequence-based typing

Control and strategy-oriented objectives

EU-wide sequence-based continuous surveillance

Strategy-oriented objective

Sentinel surveillance or surveys

Outbreak investigation objective

1. *Campylobacter spp.*
2. *Clostridium difficile*
3. hepatitis A virus
4. *Legionella spp.*
5. *Listeria monocytogenes*
6. multidrug-resistant *Mycobacterium tuberculosis* (MDR TB)
7. *Neisseria meningitidis*
8. emerging multi- or extensively drug-resistant (MDR or XDR) bacteria
9. new pathogens or new modes of transmission
10. *Salmonella enterica*
11. Shiga-toxin producing *E.coli*
12. West Nile virus

Control and strategy-oriented objectives

1. influenza virus
2. *Listeria monocytogenes*
3. MDR TB
4. *Neisseria meningitidis*
5. *Salmonella enterica*
6. Shiga-toxin producing *E.coli*

Strategy-oriented objective

1. antibiotic-resistant *Neisseria gonorrhoeae*
2. *Bordetella pertussis*
3. carbapenem- or colistin-resistant *Enterobacteriaceae*
4. carbapenem-resistant *Acinetobacter baumannii*
5. HIV transmitted drug resistance
6. *Streptococcus pneumoniae*

Implementation of ECDC/TESSy platform for sequence data sharing, integrative analysis and reporting

This chapter briefly describes envisioned technical solutions for sharing, storage, analysis, and visualisation of WGS typing data. The overall long term vision is to use a combination of solutions at ECDC and externally provided solutions such that:

- Data providers submit sequences and descriptive data about sequences and epidemiological data (Fig. 2) in a timely fashion using an easy to use solution for machine to machine communication.
- Based on Member States policies for public WGS data release, WGS data can be uploaded to a protected, access-controlled, and long-term reliable storage solution. The WGS data are made public after an initial embargo period if the data provider so desires.
- The WGS data submission process should ensure that every isolate submitted to the WGS solution has corresponding epidemiological data in TESSy.
- Data are analysed, signals detected and visualisations are produced with a high level of automation.

Současný systém ECDC má tyto komponenty

- Sharing: direct submission of assemblies or the European Nucleotide Archive (ENA) and the Short Read Archive (SRA) accession numbers, as well as epidemiological data and descriptive data about sequences to TESSy, SFTP for raw data, e-mail for assemblies.
- Storage: ENA/SRA is used for WGS data generated by an ECDC sequencing provider, data published in scientific articles, and for data that are already in ENA/SRA. Short term local storage is used for other WGS data.
- Analysis: BioNumerics cgMLST for cluster detection.
- Visualisation: BioNumerics trees, MicroReact.

Possible models for future EU WGS data sharing, storage, integrated epidemiological analysis and visualisation



A total of three models are proposed, which are represented in Figure 3.

Model 1, in-house solution: WGS data are submitted to TESSy through an ECDC FTP-server, or a WGS data repository that is either public or can be accessed by both the submitting institution and ECDC, with epidemiological data submitted to TESSy. ECDC performs analysis and visualisation, and possibly submits the WGS data for long-term storage in an externally provided WGS storage component such as ENA. TESSy is currently capable of receiving assemblies directly. TESSy can also import locally stored raw reads but further automation is required to make this method feasible for larger volumes. TESSy is currently also capable of importing raw reads that are publicly available in SRA/ENA, there is however no functionality for directly receiving data from databases restricted to a set of users.

Model 2, hybrid solution: WGS raw read data are submitted to an externally provided complete storage and analysis system, epidemiological data are submitted to TESSy. The WGS data are analysed in the external analysis system and derived data are retrieved into TESSy by ECDC. Visualisation, including generation of trees from allele identifiers, is performed by ECDC.

Model 3, external solution: Both WGS data and epidemiological data are submitted to an externally provided storage and analysis system, the epidemiological data are either provided by ECDC via TESSy or directly to the external solution. Analysis and visualisation is performed in the external system and visualisations are provided through a portal controlled by ECDC.

Table 4. Suggested operational models for managing molecular and genomic typing data proposed for priority pathogens for strategic framework implementation activities, 2019-2020.

Pathogen	Outbreak	Continuous surveillance	Sentinel surveillance or periodic surveys
Antimicrobial Resistance and Healthcare-associated Infections Programme (ARHAI)			
Carbapenem-resistant <i>Acinetobacter baumannii</i>	WGS (model 1)	NA	WGS (model 3)
Carbapenem-/colistin-resistant <i>Enterobacteriaceae</i>	WGS (model 1)	NA	WGS (model 3)
<i>Clostridium difficile</i>	WGS (model 1; TBC)	Postponed due to low Member State WGS capacity	NA
Outbreaks of emerging MDR or XDR pathogens including MRSA	WGS (model 1)	NA	NA
Outbreaks of healthcare-associated pathogens with new modes of transmission	WGS (model 1; TBC)	NA	NA
Emerging and Vector-borne Diseases Programme (EVD)			
West Nile virus	WGS (model 3)	NA	NA
Food- and waterborne diseases and zoonoses Programme (FWD)			
<i>Campylobacter jejuni/ C. coli</i>	Ad hoc WGS support in case of a suspected multi-country event	NA	NA
Hepatitis A virus	Gene-sequencing or WGS (model 3)	NA	NA
<i>Legionella</i> spp.	SBT, WGS (WGS (possibly model 2))	SBT continues as per agreed EU/EEA surveillance scheme; WGS currently not applicable	NA
<i>Listeria monocytogenes</i>	WGS (model 1)	WGS (model 1)	NA
<i>Salmonella enterica</i>	MLVA, WGS (model 1)	WGS (model 1)	NA
Shiga toxin-producing <i>E. coli</i> (STEC)	WGS (model 1)	WGS (model 1)	NA
HIV, AIDS, STIs and viral hepatitis Programme (HSH)			
Antibiotic-resistant <i>Neisseria gonorrhoeae</i>	NA	NA	WGS (model 3)

HIV	NA	NA	Gene sequencing or WGS (model 1, model 3) Interim solution: Aggregated interpreted data collection
<i>Influenza and other Respiratory Viruses Programme (IRV)</i>			
Influenza virus	NA	Gene-sequencing or WGS (model 1)	Gene-sequencing or WGS (model 1)
<i>Tuberculosis Programme</i>			
MDR/XDR TB	WGS (model 3; transition to model 2 aimed by 2020)	WGS (model 3; transition to model 2 aimed by 2020)	NA
<i>Vaccine-preventable Diseases Programme (VPD)</i>			
<i>Bordetella pertussis</i>	NA	NA	WGS (Model 3)
<i>Neisseria meningitidis</i>	WGS (model 2)	WGS (model 2)	NA
<i>Streptococcus pneumoniae</i>	NA	NA	WGS (Model 3)

Note: NA, not applicable; TBC, to be confirmed