ECDC Roadmap for integration of molecular and genomic typing into European level surveillance, 2016-19

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Rapid Microbial NGS and Bioinformatics: Translation into Practice
Hamburg, June 9-11 2016
Concept to integrate molecular typing data into EU-level surveillance. Stockholm

Roadmap - V1, 2012-16 for integration of molecular typing into European level surveillance and epidemic preparedness

ECDC WGS Strategy and Roadmap - V2, 2016-19 integration of molecular and genomic typing into European level surveillance and epidemic preparedness
The ECDC roadmap for integration of molecular typing in EU surveillance

Five year ECDC plan (2012-2016)* to integrate typing into surveillance development and implementation including:

- Shortlist of priority disease/pathogen and typing method(s)
- Systematic process for refining public health objectives and defining technical aspects before agreeing implementation
- Plan to revise and update content on bi-annual basis based on review of needs, technology advances and evaluation of operations through performance indicators

* Source: AF33 ECDC strategy and roadmap for integration of molecular typing into European level surveillance and epidemic preparedness – 2013 version
Guiding principles in selecting disease and typing methods priorities for EU surveillance

- **Public health need**: Disease or health issue for which EU molecular surveillance is necessary to inform public health policies and coordinated public health actions of Member States.

- **Fit for purpose tool**: Validated, standardised and portable typing system is in operation for surveillance and/or outbreak investigation in a substantial proportion of Member States.

- **Proof of concept EU added value**: pilot feasibility study (2012-14) on foodborne pathogens and MDR-TB followed up by performance and outcome indicators.
Implementation of Typing roadmap V1: 2013- date

<table>
<thead>
<tr>
<th>Pathogens/ AMR issue proposed for implementation</th>
<th>Typing method</th>
<th>EU public health objective/sampling design</th>
<th>Disease specific roadmap step/year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Surveillance, continuous</td>
<td>Surveillance, prevalence surveys</td>
</tr>
<tr>
<td>Salmonella enterica</td>
<td>PFGE, MLVA</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Shiga-Toxin producing E. coli (STEC)</td>
<td>PFGE</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>PFGE</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>MDR Mycobacterium tuberculosis</td>
<td>MIRU-VNTR, spoligotyping</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Performance and output evaluations 2014-15:
- Need for increased MS participation/ capacity
- More timely FWD reporting and epidemiological follow-up
Multi-country outbreak of *Salmonella* Stanley infections

Update

20 September 2012
EULabCAP survey tool: 60 indicators

1. Primary diagnostic testing
   - 1.1 Provisions and regulation of clinical microbiology services
   - 1.2 Diagnostic testing guidelines
   - 1.3 Diagnostic testing and utilisation
   - 1.4 Antimicrobial drug susceptibility testing

2. NRL services
   - 2.1 Provision and regulation of reference microbiology services
   - 2.2 Reference diagnostic confirmation and pathogen identification
   - 2.3 Molecular typing for surveillance
   - 2.4 Antimicrobial drug resistance characterisation and monitoring

3. Surveillance/Response support
   - 3.1 National surveillance networks
   - 3.2 Active participation in EU disease networks
   - 3.3 National outbreak response support
   - 3.4 Emerging diseases laboratory preparedness and response support

3 dimensions

12 targets
(5 indicators/target = 60 indicators)
Median EULabCap index scores by target (N=30 EU/EEA countries), 2013 and 2014

3 DIMENSIONS
1. Primary diagnostic testing
2. NRL services
3. Surveillance/epidemic response support

12 TARGETS
- EU/EEA median 2014
- EU/EEA median 2013
EULabCap molecular typing capacity level in 2014 by country

## Roadmap V1 priority disease specific typing strategies, 2014

<table>
<thead>
<tr>
<th>Disease</th>
<th>Surveillance design</th>
<th>Typing method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Influenza</td>
<td>Continuous, sentinel</td>
<td>Gene sequence/ WGS</td>
</tr>
<tr>
<td>HIV – resistance</td>
<td>Continuous, TBD</td>
<td>Gene sequence/ WGS</td>
</tr>
<tr>
<td>Invasive <em>Neisseria meningitidis</em></td>
<td>Continuous</td>
<td>Gene sequence/ WGS</td>
</tr>
<tr>
<td>MDR – <em>Neisseria gonorrhoeae</em></td>
<td>Repeat surveys</td>
<td>Gene sequence/ WGS</td>
</tr>
<tr>
<td>Carbapenem-resistant <em>Enterobacteriaceae</em></td>
<td>Repeat surveys</td>
<td>WGS/ resistome</td>
</tr>
<tr>
<td>Meticillin-resistant <em>Staphylococcus aureus</em></td>
<td>Repeat surveys</td>
<td>WGS/ resistome</td>
</tr>
</tbody>
</table>
Gonococcal antimicrobial susceptibility surveillance in Europe – 2010

Map 2: Geographical distribution of gonococcal isolates with respect to susceptibility to cefixime, 2010

Countries with no strains that exhibit decreased susceptibility to cefixime

Countries with strains that exhibit decreased susceptibility to cefixime (<5%)

Countries with strains that exhibit decreased susceptibility to cefixime (≥5%)
Molecular epidemiologic survey of *Neisseria gonorrhoeae* MAST genotypes in EU/EEA

- Genotype G-1407: strong association with decreased susceptibility to cefixime.

*Low numbers of isolates tested*
Molecular epidemiology of human pathogens: how to translate breakthroughs into public health practice, Stockholm, November 2011

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2. University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands
3. Statens Serum Institut, Copenhagen, Denmark

ECDC technical consultation on harnessing genomics for epidemiological surveillance

Paris, 1–2 October 2013
ECDC Joint Strategic Meeting September 2015 – conclusions on molecular typing

• ECDC to consolidate ongoing molecular typing for surveillance and prioritise those pathogens/diseases where it is possible to demonstrate EU public health benefits.

• Molecular typing for EU surveillance should undergo a stepwise transition to WGS, based on continuous update on cost, performance and assessment of public health value.

• Take into account both ECDC resources and mapping of national capacities. ECDC should continue supporting traditional typing methods.
ECDC support to WGS for public health, 2014-15

- Participation in EFSA scientific colloquium on WGS
- FWD-Next expert opinion on WGS-based surveillance
- Advice to projects on WGS analysis and data exchange (Global Microbial Identifier, PathNGenTrace project, COMPARE project, Pulsenet International,...)
- WGS-based surveillance pilot projects with Disease Networks on *N. meningitidis*, *N. gonorrhoeae* and *L. monocytogenes*
- Survey of MS capacity for WGS-based surveillance
- ECDC WGS Strategy: consultation of scientific experts and Molecular typing for Surveillance Task Force
Expert Opinion on the introduction of next-generation typing methods for food- and waterborne diseases in the EU and EEA

ECDC (October, 2015).
ECDC Vision
Whole genome sequencing for public health

• In five years’ time, ECDC will have contributed to establish standards and manage systems enabling the EU wide use of whole genome sequencing (WGS) as the method of choice for typing of microbial pathogens, replacing other methods.

• This will improve the accuracy and effectiveness of disease surveillance, outbreak investigation and evaluation of prevention policies by enhanced assessment of disease and drug resistance transmission dynamics.

Source: ECDC Strategy to harness whole genome sequencing for strengthening EU outbreak investigations and public health surveillance, 2016 – in press.
WGS data production, analysis and integration with epidemiological data for public health surveillance.
Technical requirements for multicentre sharing of genomic information for public health use

- Quality assurance standards
- WGS analysis strategy and genotype nomenclature
- WGS data storage and exchange resources.
- Integration of WGS data with epidemiological data
- Epidemiological concordance validation
- Resource investment and expertise diffusion.
ECDC WGS support strategy

1. Map the various WGS-based public health initiatives and engage partnership.
2. Lead on the integrated analysis of the epidemiological and WGS data.
3. Provide guidance and validation of WGS-based methods.
4. Support the Member States in performing the transition to appropriate use of WGS.
5. Develop and run pilot implementation studies with disease networks.
Survey of EU/EEA countries use of WGS for public health application for one or more diseases, 2015.

<table>
<thead>
<tr>
<th>Application for:</th>
<th>Current application July 2015 (# countries)</th>
<th>Plan for application in the next 3 years (# countries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outbreak investigations</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Surveillance programmes</td>
<td>10</td>
<td>18</td>
</tr>
</tbody>
</table>

Source: NMFP survey September 2015, N=28 respondents
Number of EU/EEA countries using WGS (or planning to) for surveillance by target

A  Surveillance application

B  Outbreak investigation

Pathogen target

Application
Plan

number of countries
Sampling frame used for NGS for surveillance programmes
- WGS strategy
- **Roadmap 2.1**

**STRATEGY**

- Disease objectives
- Performance indicators
- Surveillance system
- MS capacity

**EVALUATION**

- Pilot studies
- Routine operation

**OPERATIONS**

- Work plan (annual)
- Business cases (multiannual)

**CONSULTATION**

- REVISION
Role of the Molecular Typing for Surveillance Task Force (MSTF)

Composed of multi-disciplinary public health experts from the National Focal Points for Microbiology and for Surveillance.

Support the revision of the ECDC strategy and roadmap for integration of molecular/WGS typing into EU level surveillance:

a) Evaluate the added value of molecular typing proposals prepared by ECDC Disease Programmes.

b) Participate in Delphi process meeting in the process of ranking the roadmap disease priorities.

c) Review the final draft of updated strategy and roadmap.
ECDC candidate targets for molecular typing integration in EU surveillance, by disease, under revision in 2015.

<table>
<thead>
<tr>
<th>Disease target</th>
<th>Sampling</th>
<th>Typing method(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salmonellosis</strong></td>
<td>Continuous</td>
<td>PFGE, MLVA</td>
</tr>
<tr>
<td><strong>Listeriosis</strong></td>
<td>Continuous</td>
<td>PFGE</td>
</tr>
<tr>
<td><strong>Shiga toxin/producing E.coli infection</strong></td>
<td>Continuous</td>
<td>PFGE</td>
</tr>
<tr>
<td><strong>Multidrug-resistant tuberculosis</strong></td>
<td>Continuous</td>
<td>MIRU-VNTR</td>
</tr>
<tr>
<td><strong>Invasive meningococcal disease</strong></td>
<td>Continuous</td>
<td>Serogroup; 10 loci sequence; WGS/cgMLST</td>
</tr>
<tr>
<td><strong>Antibiotic-resistant gonococcal infection</strong></td>
<td>Repeat surveys</td>
<td>NG-MAST two loci sequence</td>
</tr>
<tr>
<td><strong>Carpapenemase-producing Enterobacteriaceae</strong></td>
<td>Repeat surveys</td>
<td>WGS/cgMLST / resistome/ virulome</td>
</tr>
<tr>
<td><strong>Meticillin-resistant Staphylococcus aureus (MRSA)</strong></td>
<td>Repeat surveys</td>
<td>WGS/cgMLST / resistome/ virulome</td>
</tr>
<tr>
<td><strong>Human influenza</strong></td>
<td>Continuous, sentinel</td>
<td>Gene sequence/ WGS</td>
</tr>
<tr>
<td><strong>Human Immunodeficiency virus (HIV) infection</strong></td>
<td>Continuous</td>
<td>Gene sequence/ WGS</td>
</tr>
<tr>
<td><strong>Clostridium difficile infection</strong></td>
<td>Continuous, sentinel</td>
<td>PCR-ribotyping</td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td>To be defined</td>
<td>Gene sequence/ WGS</td>
</tr>
<tr>
<td><strong>West Nile virus infection</strong></td>
<td>Seasonal, Sentinel</td>
<td>Gene sequence/ WGS</td>
</tr>
</tbody>
</table>
MSTF ranking of public health value of molecular typing for EU surveillance
Roadmap V2.1 top priorities 2016-18

WGS–based typing for investigation of cross-border foodborne outbreaks (*Listeria*, *Salmonella*, VTEC)

EU wide WGS-based surveillance systems in the near term:

Continuous surveillance:
- *Listeria monocytogenes*
- *Neisseria meningitidis*

Multi-annual pan-EU surveys:
- Carbapenemase-producing *Enterobacteriaceae*
- Antibiotic-resistant *Neisseria gonorrhoeae*
Roadmap V2.1 lower priority pathogens:

WGS-based surveillance deferred until the technical capacity across the EU/EEA is met:

- influenza virus
- *Salmonella enterica*
- Shiga-Toxin producing *E. coli* (STEC) and
- Multidrug-resistant *Mycobacterium tuberculosis*

Explore opportunities and challenges:

- PCR-ribotyping for *Clostridium difficile*
- sequence-based monitoring of anti-viral resistance in human immunodeficiency virus (HIV) and Hepatitis C virus (HCV)
Integration of epidemiological and microbiological data for surveillance and risk assessment

The European Surveillance System

Molecular typing

Structured data:
- Isolates
- Cases

Event Discussion/assessment:
- Microbiological clusters
- Outbreaks

28 EU
2 EEA
Australia
Canada
Japan
New Zealand
South Africa
Switzerland
Turkey
United States
WGS typing for cross-border foodborne outbreaks investigations supported by ECDC, 2015-16

<table>
<thead>
<tr>
<th>Pathogen type</th>
<th>Signal source</th>
<th>No isolates (No of MS)</th>
<th>WGS Cluster size (No of MS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. Oranienburg</em></td>
<td>UI</td>
<td>237 (11)</td>
<td>46 (5)</td>
</tr>
<tr>
<td><em>S. Typhimurium 3-17-10-NA-211</em></td>
<td>MTCI</td>
<td>41 (8)</td>
<td>14 (6)</td>
</tr>
<tr>
<td><em>S. Enteritidis 2-9-7-3-2</em></td>
<td>UI</td>
<td>116 (5*)</td>
<td>88 (3)</td>
</tr>
<tr>
<td><em>S. Braenderup (on-going)</em></td>
<td>UI</td>
<td>34 (4*)</td>
<td>?</td>
</tr>
</tbody>
</table>

* Some MS use a combination the SBS contract and own WGS
European Listeria Typing Exercise (ELiTE) WGS Study objectives

1. To gain a detailed understanding of the genomic epidemiology of listeriosis in EU/EEA analysis of isolates from the period 2010-14.

2. To provide all EU/EEA countries with an opportunity to work with WGS at national level and with other countries.

3. To develop technical options and practical requirements for EU/EEA level surveillance based on WGS.

Current status

- 1254 genomes from 26 EU/EEA countries - DNA samples or sequences.

Source: Ivo Van Walle, Johanna Takkinen, ECDC
Acknowledgements

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