TECHNICAL REPORT

ECDC roadmap for integration of molecular and genomic typing into European-level surveillance and epidemic preparedness

Version 2.1, 2016–2019

www.ecdc.europa.eu

ECDC TECHNICAL REPORT

ECDC roadmap for integration of molecular and genomic typing into European-level surveillance and epidemic preparedness – Version 2.1, 2016–19

This report of the European Centre for Disease Prevention and Control (ECDC) was drafted by Barbara Albiger, Katrin Leitmeyer, Joana Revez and Marc Struelens.

The following experts from the ECDC Disease Programmes contributed to the disease specific proposals for integration of molecular typing into EU surveillance and outbreak investigations: Barbara Albiger, Andrew Amato, Eeva Broberg, Erika Duffell, Assimoula Economopoulou, Ole Heuer, Liselotte Diaz Högberg, Pete Kinross, Saara Kotila, Csaba Ködmön, Katrin Leitmeyer, Dominique Monnet, Daniel Palm, Pasi Penttinen, Gianfranco Spiteri, Carl Suetens, Johanna Takkinen, Marieke J. Van der Werf, Ivo Van Walle, Emma Wiltshire and Herve Zeller.

The following ECDC experts contributed to the internal evaluation of the ongoing multistate molecular typing enhanced surveillance 2015: Karin Johansson, Saara Kotila, Csaba Ködmön, Piotr Kramarz, Daniel Palm, Marc Struelens and Ivo Van Walle.

The following ECDC experts provided the preliminary data for the 2014 EULabCap: Csaba Ködmön, Ivo Van Walle and Robert Whittaker.

Acknowledgements
The following ECDC contributors are acknowledged for their contribution in reviewing the draft version of this document: Andrew Amato, Eeva Broberg, Mike Catchpole, Lucia Pastore Celentano, Bruno Ciancio, Denis Coulombier, Karin Johansson, Ole Heuer, Csaba Ködmön, Dominique Monnet, Daniel Palm, Pasi Penttinen, Johanna Takkinen, Marieke van Werf, Ivo Van Walle and Hervé Zeller.

Expert opinion was received during a technical consultation session on ECDC strategy for Whole Genome Sequencing, held in Stockholm on 19 November 2015: Frank Aarestrup, Arta Balode, John Besser, Vitor Borges, Sylvain Brisse, João André Carriço, Hajo Grundmann, Dag Harmsen, Marion Koopmans, Martin Maiden, Eva Moeller Nielsen, Annalisa Pantosti, Maja Rupnik, Leo Schouls, Magnus Unemo and Anne-Mieke Vandamme.

Expert advice was also received during a technical consultation session held in Stockholm on 20 November 2015 from the following members of the Molecular Typing for Surveillance Task Force (MSTF): Joël Mossong, Guido Werner, Franz Allerberger, Steven Van Gucht, Susan Hahné, Dominique Caugant, Pavla Krizova, Rosa Cano Portero, Thea Kølsen Fischer, Hans Blystad and Bruno Coignard.

Expert input was also received from the ECDC Advisory Forum in the form of written consultation (March 2016).

Suggested citation: European Centre for Disease Prevention and Control. ECDC roadmap for integration of molecular and genomic typing into European-level surveillance and epidemic preparedness – Version 2.1, 2016-19. Stockholm: ECDC; 2016.

Stockholm, August 2016

ISBN 978-92-9193-884-1

doi 10.2900/492985

Catalogue number TQ-01-16-574-EN-N

© European Centre for Disease Prevention and Control, 2016

Reproduction is authorised, provided the source is acknowledged

Contents

Figures

Tables

Abbreviations

CCB	Competent Coordinating Body
CDI	*Clostridium difficile* infections
CPE	Carbapenemase-producing *Enterobacteriaceae*
CRE	Carbapenem-resistant *Enterobacteriaceae*
EFSA	European Food Safety Authority
EQA	External Quality Assessment
EEA	European Economic Area
ELiTE project	European *Listeria* Typing Exercise
EU	European Union
EULabCap	EU Laboratory Capability Monitoring System
EuSCAPE	European Survey on Carbapenemase-producing *Enterobacteriaceae*
FWD	Food- and Waterborne Diseases
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
IBD-LabNet	Invasive Bacterial Diseases Laboratory Network
MDR TB	Multidrug-resistant tuberculosis
MIRU-VNTR	Mycobacterial Interspersed Repetitive Units – Variable Number Tandem Repeat
MLST	Multi-Locus Sequence Typing
MLVA	Multiple Loci VNTR Analysis
MRSA	Meticillin-resistant *Staphylococcus aureus*
MSTF	Molecular typing for Surveillance Task Force
NGS	Next Generation Sequencing
NMFP	National Microbiology Focal Point
NSFP	National Surveillance Focal Point
PFGE	Pulsed-Field Gel Electrophoresis
STEC	Shiga toxin-producing *E. coli*
TB	*Mycobacterium tuberculosis*
TESSy	The European Surveillance System
RRA	Rapid Risk Assessment
ROA	Rapid Outbreak Assessment
VNTR	Variable Number Tandem Repeat
WGS	Whole Genome Sequencing
WNV	West Nile Virus

Executive summary

This roadmap Version 2.1, 2016–19 presents the recommended priority list of pathogens/diseases and technical implementation options for the medium-term integration of molecular/genomic typing into EU-level surveillance and epidemic preparedness. It is meant as a strategic framework to guide the consolidation of ECDC activities in relation to molecular typing of human pathogens and to focus the development of genomic-typing-enhanced surveillance over the next four years. It builds upon and synthesises evidence and the opinion of experts in Member States and at ECDC.

The evidence and opinions collated by ECDC demonstrate that this is a fast-moving area, although there are marked variations between pathogens/diseases and countries in the pace of change. In such a complex situation, with the inevitable uncertainties that are associated with the introduction of transformational technology, ECDC proposes to prioritise its implementation plans according to its assessment of the following:

- Public health priority and potential added-value offered by molecular typing data;
- Feasibility of realising the potential added-value (e.g. timely and comprehensive cross-border outbreak detection, more effective outbreak investigation, improved understanding of the determinants of incidence, transmission chain dynamics, or pathogen characteristics);
- Level of resource (at Member State and ECDC level) required to realise the added-value (or to develop future capability) and available (including potential efficiencies to be achieved across systems for different pathogens);
- Potential synergies or duplication in respect of third-party activities.

Information related to these criteria was provided by the relevant disease networks and ECDC disease programmes. As previously endorsed by the Advisory Forum, a Molecular typing for Surveillance Task Force (MSTF) composed of both National Focal Points for Microbiology (NMFPs) and National Focal Points for Surveillance (NSFPs), was asked to provide an independent review of the information collated by the disease networks and ECDC disease programmes by ranking 13 disease-specific proposals for integration of molecular and genomic typing into EU-level surveillance and cross-border outbreak investigation.

The MSTF also advised focusing efforts on diseases with high public health impact at EU/EEA level and net added-value of typing for public health action. It should also be possible to meet the surveillance objectives by typing low-volume samples in accordance with the capacity of the Member State, consistent with the criteria above mentioned.

The MSTF and the second expert consultation on the ECDC strategy to harness whole genome sequencing (WGS) to strengthen EU outbreak investigations and public health surveillance emphasised that ECDC should support Member States during the transition to genome-based typing methods by providing technical guidance, contributing to international surveillance standards and nomenclature and providing multidisciplinary training.

An NMFP survey was performed to map Member States' capability of using WGS for national surveillance.

Based on the above-mentioned criteria and in consideration of the evidence, consultations and recommendations received, in Version 2.1 of the roadmap ECDC proposes categorising pathogens/diseases by time priority:

- **Operationalisation of EU-wide WGS-based surveillance systems in the near term:** start implementation of WGS-based surveillance for *Listeria monocytogenes*, *Neisseria meningitidis*, Carbapenemase-producing *Enterobacteriaceae* and antibiotic-resistant *Neisseria gonorrhoeae*;
- **Operationalisation of WGS-based surveillance systems deferred until the required technical capacity across the EU/EEA is met**: the existing typing methods will need maintenance or improvement for surveillance of human influenza virus, *Salmonella enterica*, Shiga-Toxin producing *E. coli* (STEC) and multidrug-resistant *Mycobacterium tuberculosis* (MDR TB);
- **Further required evidence of the opportunities and challenges**: PCR-ribotyping for *Clostridium difficile* surveillance, and sequence-based surveillance of anti-viral drug resistance in human immunodeficiency virus (HIV) and hepatitis C virus (HCV);
- **Postpone until next roadmap revision in 2018**: West Nile virus (WNV) and meticillin-resistant *Staphylococcus aureus* (MRSA).

In addition, to foster the implementation of its WGS strategy, ECDC will follow the recommendations of the MSTF and expert consultation and also develop, run and evaluate selected pilot implementation studies of WGS-based surveillance. Moreover, it will liaise with other EU and global bodies as appropriate and necessary to ensure coordination and cost efficient delivery of the strategy.

Introduction

The inclusion of molecular typing into EU-level surveillance and epidemic preparedness has been debated with ECDC stakeholders since 2007. Based on these discussions, a concept paper[1] on the integration of molecular typing data into European Union (EU) surveillance was initially developed, followed by the first ECDC strategy and roadmap proposal of a priority list of 12 pathogens/diseases for the gradual integration of molecular typing into EU surveillance and epidemic preparedness[2].

The rapid shift of the 'state of the art' technology and the practice of molecular typing for public health to Next-Generation Sequencing (NGS) and Whole Genome Sequencing (WGS) data analysis for routine surveillance and outbreak studies, and new public health needs for the integration of molecular/genomic data, have underlined the importance of regularly revising the strategy and the roadmap priority list of pathogens/diseases.

The ECDC Microbiology Coordination Section conducted this revision in consultation with a new Task Force – The Molecular typing for Surveillance Task Force (MSTF) recruited on a voluntarily basis from the National Microbiology Focal Points (NMFPs) and National Surveillance Focal Points for Surveillance (NSFPs).

For the revision, ECDC's Microbiology Coordination Section needed input and feedback from the relevant disease networks, ECDC disease programmes and the Molecular Surveillance Operations Group, as well as engaging in strategic discussions on molecular typing with experts, stakeholders, such as the European Food Safety Agency (EFSA) and the European Commission (EC), and competent bodies (e.g. national coordinators, ECDC's Advisory Forum, NMFPs and NSFPs).

The revision involved compiling the updated proposals for 13 priority diseases prepared by the ECDC disease programmes; assessing two internal evaluations of ECDC's ongoing multistate molecular typing enhanced surveillance; conducting a questionnaire among the NMFPs on national plans and capacity for WGS use in outbreak investigation and public health surveillance and drafting the expert opinion on whole genome sequencing for public health surveillance - strategy to harness WGS to strengthen EU outbreak investigations and public health surveillance. The latter document examined the advantages and limitations of WGS-based typing for public health applications and formulated the ECDC vision and strategy on WGS as a generic solution to be taken into consideration in the roadmap. In addition, the revision was supported by inputs from several stakeholder and expert consultations[3]**.**

The present document summarises ECDC's evaluation of ongoing multistate, molecular-typing-enhanced surveillance; Member States' national plans and operational capacity of WGS use for outbreak investigation and public health surveillance across the EU/EEA, and feedback from stakeholders' meetings and expert consultations**.** It proposes a revised list of priority pathogens/diseases with specific surveillance targets and methods, as well as ECDC-generic technical development and guidance actions for implementation into the roadmap Version 2.1, 2016–19. It also takes into consideration the advice received from several stakeholders. This document is a strategic framework to guide work planning for the period 2016–19 within the ECDC disease programmes, Surveillance and Response Unit and EU laboratory networks.

[1] ECDC Surveillance of communicable diseases in Europe – a concept to integrate molecular typing data into EU-level surveillance. Stockholm: ECDC; 2013.
[2] ECDC roadmap for integration of molecular typing into European level surveillance and epidemic preparedness, Version 1.2, 2013. Stockholm: ECDC; 2016.
[3] Expert opinion on whole genome sequencing for public health surveillance – strategy to harness whole genome sequencing to strengthen EU outbreak investigations and public health surveillance. Stockholm: ECDC; 2016

Methodology for the roadmap revision–2015

ECDC's Microbiology Coordination Section undertook the revision of the ECDC strategy and roadmap - Version 1.2, 2013 based on the following inputs:

- ECDC disease-specific proposals for integration of molecular and genomic typing into EU-level surveillance and cross-border outbreak investigation – first revision 2015: based on the new needs for public health and policy requirements and the development of new technologies, ECDC's disease programmes worked with its Surveillance and Response Support Unit, its Microbiology Coordination Section and the respective disease networks to revise the list of priority pathogens for integration of molecular or genomic typing in EU surveillance and outbreak investigations included in the roadmap – Version 1, 2013. They also updated the typing methods and the public health objectives where necessary. Table 1 provides an overview of the proposals in terms of public health objectives and EU-level risk assessment output(s).
- ECDC internal evaluations of the ongoing multistate molecular typing-enhanced surveillance operations for multidrug-resistant tuberculosis (MDR TB) and food- and waterborne diseases (FWD) 2015: in 2014 and 2015, two ECDC teams evaluated the ongoing multistate molecular typing operations for enhanced surveillance in order to verify their fitness for purpose and assess public health outputs since 2013 for MDR TB[4] and for three food- and waterborne diseases (salmonellosis, listeriosis and Shiga toxin-producing *E. coli* (STEC) infection)[5], respectively.
- NMFP questionnaire on the national plans and capacity for WGS use in outbreak investigation and public health surveillance: in the context of rapidly-changing technologies, a survey was compiled in July 2015 to map the current national operational capacity and short-term plans for use of WGS analysis for outbreak investigation and public health surveillance across the EU/EEA countries.
- EU Laboratory Capability Monitoring System (EULabCap): When available, the ECDC Microbiology Coordination Section also cross-checked the number of Member States reporting molecular typing data to ECDC through The European Surveillance system (TESSy) and the EU/EEA typing fraction expressed as notified case coverage, based on the EULabCap indicators (i.e. 2.32, 2.33 and 2.34 for *S. enterica*, MDR TB and *N. meningitidis* typing respectively, see Table 2).
- ECDC's expert opinion on WGS for public health surveillance - strategy to harness WGS to strengthen EU outbreak investigations and public health surveillance: following the advice of the Advisory Forum for ECDC to take a leading role in guiding and facilitating the transition of WGS to a public health application for surveillance and outbreak studies, ECDC's Microbiology Coordination Section and Surveillance and Response Support Unit experts drafted an ECDC vision and strategy document, examining the advantages and limitations of WGS-based typing for public health applications[6].

It also took into account the recommendations from the following stakeholders' meetings and expert consultations:

- **ECDC Second Joint Strategy Meeting:** on 23–24 September 2015, members of the Advisory Forum, NMFPs, NSFPs and national coordinators discussed the molecular typing roadmap's current pace of implementation, ECDC expansion of integrating typing data for new diseases and the transition to WGS.
- **Second expert consultation on ECDC strategy to harness WGS for cross-border outbreak and surveillance:** on 19 November 2015, multidisciplinary experts and the MSTF members' peer-reviewed and provided feedback on the ECDC expert opinion on WGS for public health surveillance, which was further revised[6].
- **First meeting of the MSTF:** on 20 November 2015, the members independently ranked the 13 ECDC pathogen/disease-specific proposals for integration of molecular and genomic typing into EU-level surveillance and cross-border outbreak investigation during a second round of Delphi. The ranking of the specific proposals was performed in two rounds using a modified Delphi consensus technique according to pre-agreed criteria on a Likert scale of 1 to 5. The criteria covered aspects of public health relevance for cross-border transmission, the opportunity for prevention of transmission and available human and technical resources and obstacles at the EU/EEA level for both the surveillance application and outbreak investigations. Each criteria had a pre-agreed weight. As the MSTF expressed concerns regarding two scoring feasibility criteria based on their limited individual awareness and knowledge of the available resources and obstacles at EU-level for both surveillance and outbreak investigations, these were removed from the second round of Delphi ranking. The overall disease typing scores obtained were not significantly different with and without these criteria.

[4] The multidrug-resistant tuberculosis (MDR TB) molecular surveillance status report (December 2014)
[5] ECDC evaluation of the ongoing multistate molecular typing enhanced surveillance 2015, Version 1 (October 2015)
[6] Expert opinion on whole genome sequencing for public health surveillance – strategy to harness whole genome sequencing to strengthen EU outbreak investigations and public health surveillance. Stockholm: ECDC; 2016.

Table 1. Proposed list of priority pathogens, public health objectives and expected EU-level risk assessment output(s) prepared by ECDC disease programmes – September 2015

Pathogen	EU level risk assessment outputs by public health objective		
	Outbreak investigation	Control-oriented surveillance	Strategy-oriented surveillance
S. enterica ***L. monocytogenes*** **Shiga toxin-producing *E. coli* (STEC)**	Rapid risk assessments and joint rapid outbreak assessment with EFSA	1. Outbreak detection 2. Trace back and forward contamination in the food chain and subsequently assess the risk of exposure.	Medium- and longer-term public health risk assessments.
Multidrug-resistant tuberculosis	Not applicable	Identification and investigation of high-risk strains ('super spreaders' and/or MDR/XDR TB).	1. Provision of an overview of MDR TB clusters and strain diversity in the EU/EEA. 2- Identification of high-risk geographical areas and/or population groups.
Antibiotic resistant *Neisseria gonorrhoeae*	Not applicable	1. Detection/delineation of emergence and cross-region/cross-border dissemination of public health relevant strains. 2. Genotypic identification and characterisation of highly virulent, multidrug resistant and/or transmission-successful strains. 3. Understanding the genetic and phenotypic stability of public health relevant strains 4. Identification of high-risk patient population groups associated with the spreading of specific strains.	1. Monitoring trends in the frequency of occurrence of particular genotypes in the population. 2. Understanding the dynamics of antimicrobial resistance in the context of antibiotic stewardship intervention policies.
Carbapenemase-producing *Enterobacteriaceae* **Meticillin-resistant *Staphylococcus aureus***	Not applicable	1. Detection/delineation of cross-region or cross-border dissemination of high-risk clones/plasmids between repeat surveys 2. Identification of high-prevalence geographical areas associated with spreading of specific high-risk clones 3. Detection and genotypic identification of high-risk clones/plasmids	1. Monitoring pluri-annual trends in the frequency of occurrence for particular genotypes in the population and identification of high-prevalence population groups. 2. Impact assessment of prevention and control programmes.
Clostridium difficile	Not applicable	1. Detection of the presence and/or emergence of strains with hypervirulence 2. Detection of the presence and/or emergence of strains with reduced susceptibility to intervention measures	1. Comparative burden of *C. difficile* infections (CDI) in participating countries 2. Trends in endemic CDI transmission
Neisseria meningitidis	RRA of national and international outbreaks	1. Detection, verification and description of national and international outbreaks 2. Identification and prevalence monitoring of vaccine escape variants, based on analysis of outer-membrane protein vaccine targets	1. Detection of emergence and spread of new virulent or epidemiologically successful sequence types. 2. Impact assessment of immunisation programmes.
Human influenza virus	Seasonal and rapid risk assessments. Rapid epidemiological investigation.	1. Detection of potential pandemic influenza strains 2. Detection of genetic change in circulating influenza viruses, vaccine strain selection 3. Early season and season report, weekly surveillance reports (FluNewsEurope)	1. Detection of genetic markers associated with antiviral resistance. 2. Early season and season risk assessment, and vaccine effectiveness analysis.
HIV	Outbreak investigation, cluster analysis and risk assessments	1. Detection of novel, recombinant or emerging HIV strains; overview of HIV clusters and strain diversity in the EU/EEA 2. Identification of at-risk populations and particular areas of high risk.	1. Annual monitoring, risk assessments and RRAs informing Member States of the prevalence and emergence of HIV-resistant strains. 2. Identification of high-risk geographical areas and/or risk groups for HIV transmission. 3. Describing geographical trends of novel, recombinant or emerging virulent HIV strains.
Hepatitis C virus	Not applicable	1. Detection of emerging virulent HCV strains in the EU/EEA 2. Identification of at-risk populations and particular areas of high risk. 3. A report integrating phylogenetic and epidemiological data alongside information on migration to provide an in-depth understanding of transmission dynamics and the impact of migration on the HCV epidemic in EU/EEA.	Annual monitoring, risk assessments and RRAs informing the Member States of the prevalence and emergence of HCV-resistant strains.
West Nile virus	Defining criteria for triggering an alert concerning potential WNV transmission to humans and defining an affected area.	Detection of viral strains and delineation of spread	Impact assessment of prevention and control programmes.

The pathogens/diseases to be included in the roadmap Version 2.1 were categorised by time priority into the following four groups for ECDC action in 2016–19:

- Operationalisation of EU-wide WGS-based surveillance systems in the near term;
- Operationalisation of WGS-based surveillance systems deferred until the required technical capacity across the EU/EEA is met;
- Further assessment of evidence (opportunities and challenges);
- Postponed until next roadmap revision exercise in 2018.

Key findings and integrated analysis of the results

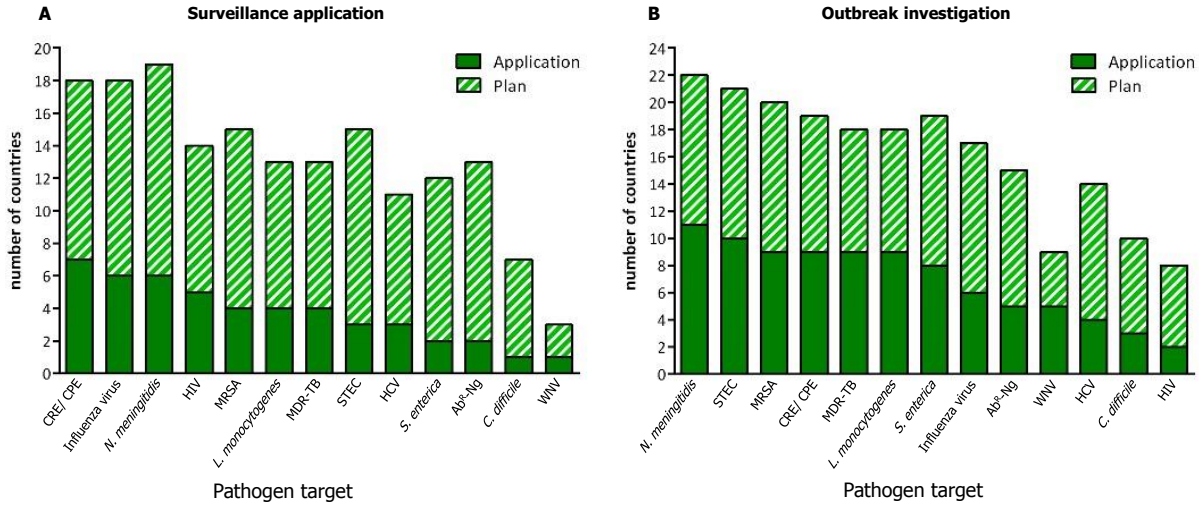
During the second Joint Strategy Meeting, the members of the Advisory Forum, NMFPs and NSFPs and the national coordinators recommended that ECDC should consolidate ongoing molecular typing for surveillance projects and prioritise those pathogens/diseases where it was possible to demonstrate convincing EU public health benefits. Further integration of additional diseases by ECDC must take into consideration that country needs are dependent on the endemic level of the disease and its public health importance within individual countries. In addition, plans should take into account both ECDC resource capacity and the difference in capacities among countries.

The Joint Strategy Meeting advised that use of molecular typing for EU surveillance should not be restricted to the current implementation, but undergo a step-wise transition to NGS/WGS. Support was given for the implementation of WGS-based surveillance of *L. monocytogenes* in the short term. However, ECDC should continue to support traditional typing methods since NGS/WGS methods are not yet standardised. ECDC should ensure that the current techniques are not phased out too early and that more evidence is made available on Member State use and capacity. Standardised methodology, EQA and training, and validation and assessment of NGS/WGS added-value are needed, along with assessment of different technological options. Incentives for sharing molecular typing data, effective integration of molecular typing and epidemiological data, access to user-friendly bioinformatics resources and NGS/WGS standardisation and nomenclature were also outstanding issues to consider. Finally, it was recommended that ECDC should monitor the technological and the scientific knowledge developments and guide Member-States by providing continuous updates on NGS/WGS cost, performance, validation and assessment of public health value while mapping national capacities.

The national capacities for use of WGS in outbreak investigation and public health surveillance in EU/EEA countries were mapped by means of a survey sent to the NMFPs. Twenty-eight NMFPs answered it on behalf of and in collaboration with the national reference laboratories (NRL) for public health in their country. Nineteen Member States reported having access to NGS technology to support outbreak investigations or communicable disease surveillance as of July 2015. Ten countries reported using WGS for communicable disease or antimicrobial resistance surveillance and 17 planned to do so within the next three years. Meanwhile, 18 countries used the technology for outbreak investigations in 2015 and planned to do so over the next three years. Figure 1 presents the number of countries using WGS for surveillance application in 2015, and/or planning to do so within three years, by pathogen/disease.

These results showed that application and use of WGS for surveillance application and outbreak investigations will increase in the EU/EEA in the near future, with around half of the Member States already having access to the technology and applying it to some pathogens.

Figure 1. Number of EU/EEA countries applying (green bar) or planning within three years (hatched green bar) to apply WGS-based typing for (A) surveillance application and (B) outbreak investigations, by pathogen target



CRE/CPE: Carbapenem-resistant Enterobacteriaceae/carbapenemase-producing Enterobacteriaceae; HIV: Human Immunodeficiency virus; MRSA: Meticillin-resistant Staphylococcus aureus; STEC: Shiga toxin-producing E. coli; HCV: Hepatitis C virus; WNV: West Nile virus. (Note: these surveillance systems apply diverse sampling frames that range from survey-based to sentinel and comprehensive longitudinal sampling. These categories are not mutually exclusive, as several Member States have reported both current use and plans for further/expanded use of WGS).

Source: NMFP survey, July 2015 (N=28 respondents).

To facilitate Member States' transition to use of WGS for surveillance application and outbreak investigation, ECDC transcribed its vision into the ECDC expert opinion on WGS for public health surveillance - strategy to harness WGS to strengthen EU outbreak investigations and public health surveillance[7]. This strategy was peer-reviewed by the ECDC Joint Steering Committee for Microbiology and Surveillance, multidisciplinary experts (second expert consultation) and the MSTF.

The key messages from this peer-review were that ECDC should:

- Foster multidisciplinary interpretation of the information arising from the combination of epidemiological data and pathogen sequence characterisation to guide public health action;
- Together with its public health laboratory network partners, EFSA, and research and development projects, define the priorities and identify high-impact diseases or drug resistance issues, for which genome sequence information can make a difference in terms of public health intervention;
- Contribute to a global agreement on WGS analytical approaches, epidemiological interpretation criteria and genomic nomenclature by surveillance objective, while retaining flexibility in order to explore improved methods;
- Help with a multistate evaluation of the public health effectiveness of WGS-based typing by measuring outcomes, in terms of disease prevention or size of outbreaks before and after implementation within a disease surveillance programme;
- Focus training efforts on developing a new, integrative 'genomic epidemiology' discipline, to build a common understanding through continuous professional development.

To support the revision of ECDC roadmap – Version 1.2, 2013, its implementation was reviewed:

- The four multistate, molecular-typing-enhanced surveillance initiatives (MDR TB, *S. enterica*, *L. monocytogenes* and STEC), described in the roadmap – Version 1.2, 2013, were on-going and have been evaluated for their fitness for purpose and public health outputs.
- The Advisory Forum discussed and supported five specific integrated surveillance strategies (human influenza virus, *N. meningitidis*, antibiotic-resistant *N. gonorrhoeae*, CPE, MRSA) that were developed according to the process described in the roadmap – Version 1.2, 2013.

[7] ECDC Expert opinion on whole genome sequencing for public health surveillance – strategy to harness whole genome sequencing to strengthen EU outbreak investigations and public health surveillance. Stockholm: ECDC; 2016.

- Following experts' recommendations, two of the 12 priority pathogens were de-prioritised from the roadmap Version 1 – 2013: *Legionella pneumophila* and *Acinetobacter baumannii* complex. The application of national typing services and support by ELDS-Net were considered sufficient for investigations of *L. pneumophila* outbreaks without the need for further centralisation at the EU/EEA level. Further studies towards understanding the epidemiology of *A. baumannii* complex were deemed fundamental before undertaking molecular-typing-based surveillance activities.
- In December 2015, the Advisory Forum discussed a concept paper on HIV antiretroviral resistance surveillance using molecular methods and advised ECDC to proceed.
- The Advisory Forum also discussed EU level *C. difficile* infection surveillance, for which the molecular typing surveillance module was not included in the roadmap - Version 1.2, 2013. The Advisory Forum was favourable to the initiation of EU-level *C. difficile* infection surveillance, including the option for submission of epidemiologically-linked microbiological data (PCR ribotype and antimicrobial susceptibility), based on the current agreed protocol for European surveillance of *C. difficile* infections[8].

The ECDC disease programmes drafted new pathogen-specific proposals based on the new needs for public health and policy requirements, the development of new technologies and the evaluation of on-going operations. The list of disease priorities for integration of molecular or genomic typing in EU/EEA surveillance and outbreak investigations to be included in the revised roadmap - Version 2.1, 2015 was reviewed. Three new pathogens/diseases were proposed for inclusion in response to new public health needs, as follows: WNV as emerging pathogen in the EU, HCV due to the development of new medical countermeasures and CDI as EU health policy priority for healthcare infection prevention (Table 1). In total, 13 pathogen proposals were submitted to the MSTF for independent appraisal and prioritisation using a modified Delphi consensus technique. The scoring results are shown in Figure 2.

The MSTF commented on the lower number of participants contributing to the second round of priority scoring (n=10) compared to the first one (n=14), the possible limited technical expertise among those members, with only two virologists, four bacteriologists and four epidemiologists, and the wide inter-rate score range, suggesting that the breadth of multidisciplinary expertise elicited and the statistical robustness of consensus scores obtained through this exercise might not have been optimal.

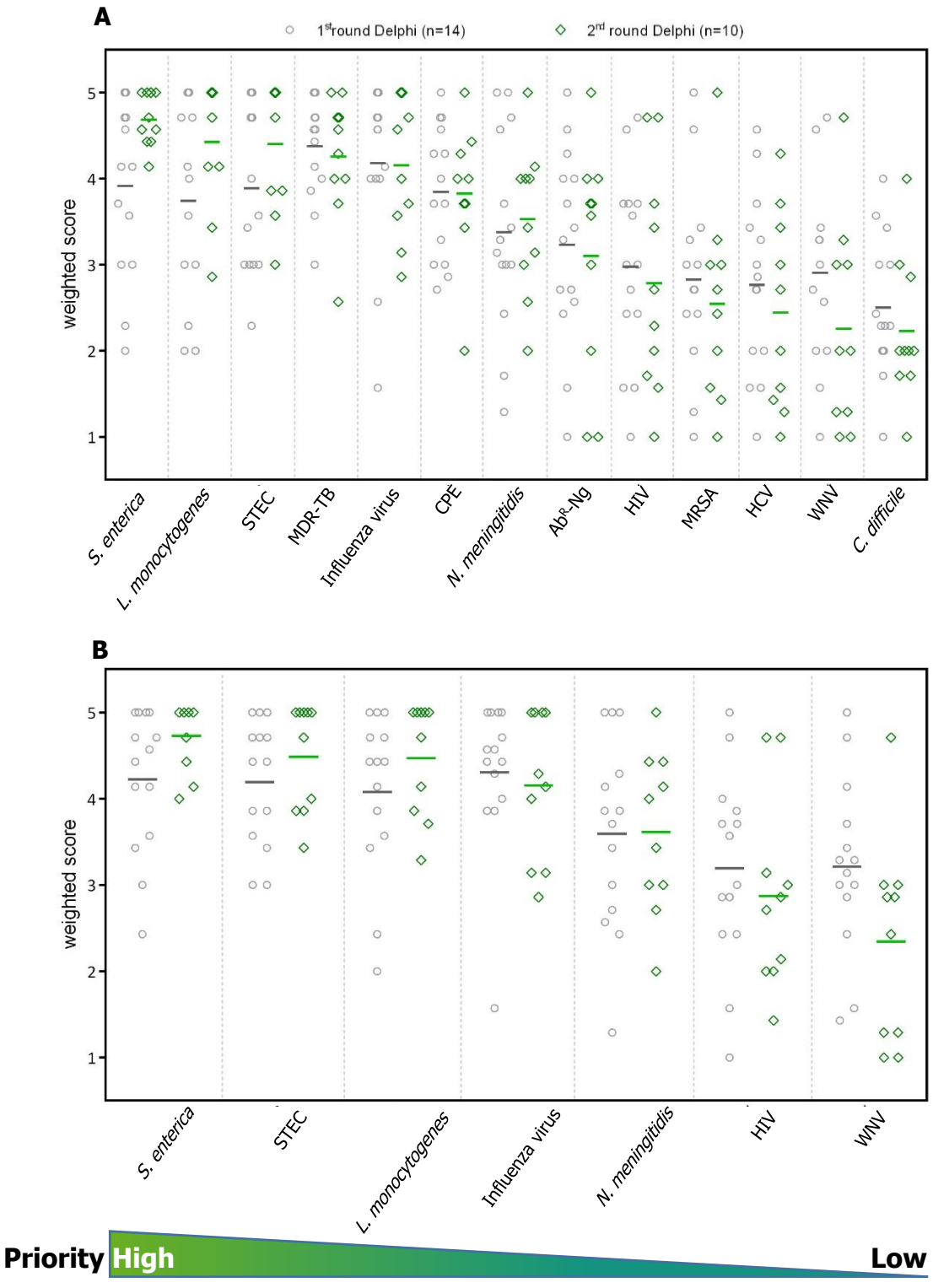
The key messages from the MSTF were to:

- Focus on pathogens/diseases that ranked high in terms of public health impact and relevance of typing AND where the EU surveillance objectives can be met with typing a low sample volume commensurate with Member State capacity;
- Support the Member States and provide technical guidance for the transition to the proposed genomic typing methods. This feedback was in line with the feedback received during the second Joint Strategy Meeting and was included in the ECDC strategy to harness WGS to strengthen EU outbreak investigations and public health surveillance[9].

[8] ECDC, European Surveillance of *Clostridium difficile* infections. Surveillance protocol Version 2.2. Stockholm: ECDC; 2015.

[9] ECDC expert opinion on whole genome sequencing - strategy to harness whole genome sequencing to strengthen EU outbreak investigations and public health surveillance. Stockholm: ECDC; 2016.

Figure 2. Scatter plot of weighted individual (circle/diamond) and mean (horizontal bar) scoring results by Molecular typing for Surveillance Task Force members in decreasing ranking order, for (A) surveillance application (13 pathogens) and (B) outbreak investigation (7 pathogens), presenting the first (○; n=14 participants) and second (◇; n=10 participants) Delphi round results



Roadmap priorities for disease-specific genomic typing development and implementation, 2016–19

Based on all the evidence, consultations and recommendations received, ECDC proposes the following roadmap Version 2.1 priorities for pathogen/disease-specific genomic typing development and implementation, 2016–19. The next revision of the roadmap V2.1 implementation and priorities will take place in 2018.

Diseases proposed for ECDC operationalisation of EU-wide WGS-based surveillance in the short term (2016–19)

It is proposed that ECDC should work with the EU/EEA Member States and EFSA to operationalise EU-wide WGS-based surveillance of the following pathogens in 2016–19:

Listeria monocytogenes

This action is fully in accordance with the high-priority recommendation for WGS-based surveillance of listeriosis made by the Joint Strategy Meeting, MSTF and FWD network members and is aligned with the ECDC 2016 work plan and draft priorities 2017–19. The rationale (Table 3) includes the high health impact and preventable nature of the disease, combined with optimal typing feasibility and cost-efficiency based on a relatively low volume of cases/clinical isolates to type and the public availability of validated WGS-based typing schemes and core genome Multi-Locus Sequence Typing (cgMLST) nomenclature schemes. Member States' capacity within the FWD network is already significant and progressing fast for use of WGS as a complement or replacement technology for PFGE by using their own analytical schemes and databases at national level (Figure 2).

The FWD-NEXT Working Group convened by ECDC has established the requirements for building a consensus methodology for comparable WGS data production, exchange, analysis and EU reporting of *L. monocytogenes.* It will initiate a collaboration with global and EU partners in PulseNet International towards an international WGS-based nomenclature for *L. monocytogenes* and other food-borne bacterial pathogens. The ELiTE II project will be the framework for further development with the FWD network of EU WGS surveillance protocol development, capacity building, technical portability validation trials using various WGS analysis platforms and evaluation of performance and public health outputs. Based on the experience gained in the PFGE pilot project and the ELiTE project, it is anticipated that WGS-based surveillance of listeriosis will be operational with volunteer Member States from 2018 onwards.

The ELiTE II project will be important as a case study for progressing the generic implementation of the ECDC WGS-based surveillance strategy within the FWD programme and beyond in terms of collaboration with public health, food safety and academic partners and internal surveillance system re-engineering and methodological support.

In addition, ECDC will assist Member States by supporting ad-hoc comparative WGS-based typing to aid coordinated investigation and joint assessment with EFSA of multistate listeriosis outbreaks in the EU/EEA.

In parallel, during the 2016–19 transition phase, it will be necessary for ECDC to maintain and improve the completeness, quality and timeliness of data reporting to the PFGE-based EU surveillance system (Table 2), encourage network collaboration, and develop cooperation with EFSA for analysis of the joint molecular typing database. The right balance of ECDC resource allocation between the parallel PFGE-based and WGS-based system operations will require regular adjustment in cooperation with the network participants.

Carbapenemase-producing *Enterobacteriaceae* (CPE)

The EU-wide WGS-based surveillance of carbapenemase-producing *E. coli* and *K. pneumoniae* will be implemented by periodically conducting structured pan-EU hospital surveys following the Advisory Forum-approved molecular surveillance strategy for CPE. This action is fully in accordance with the high-priority recommendation for WGS-based surveillance of CPE made by the MSTF and EuSCAPE project members and is aligned with the ECDC 2016 work plan and draft priorities 2017-19. The rationale (Table 3) includes the high and rapidly increasing health impact of these infections in the EU/EEA and the preventable nature of CPE, combined with optimal typing feasibility based on a relatively low volume of representative survey cases/clinical isolates to type. It is also based on the public availability of validated WGS-based typing schemes and cgMLST nomenclature schemes for *K. pneumoniae* and for the beta-lactamase/resistome profiling. Development of cgMLST nomenclature for *E. coli* typing is in progress. The Member States' capabilities for using WGS to carry out surveillance of CPE and outbreak studies at national level within the EU/EEA network are particularly significant and progressing (Figure 2).

The ECDC business case for the first CPE genomic epidemiology survey and TESSy data integration and reporting will be developed in 2016 in order to establish the consortium to perform the survey from 2017 to 2019 in close collaboration with ECDC and to design and establish interactive analytical processes by interfacing TESSy with WGS repository databases.

The CPE genomic epidemiology survey project will be important as a case study for progressing the generic implementation of the ECDC WGS for surveillance strategy within the ARHAI programme and beyond in terms of collaboration with public health, clinical and academic partners and testing of the re-engineered ECDC surveillance systems and methodological support for TESSy data integration and reporting services.

Invasive *N. meningitidis*

The EU-wide WGS-based surveillance of invasive *N. meningitidis* will follow the Advisory Forum-approved molecular surveillance strategy. It will be based on the business case, translating the conclusions from the pilot EU study of WGS cgMLST vs. gene sequencing as planned in the ECDC 2016 work plan and draft priorities for 2017–19. This action matches the recommendation of medium priority for WGS-based surveillance of *N. meningitidis,* as made by the MSTF, and the expert opinion of the European Meningococcal Society (EMGM) on the cost-efficiency gain of using the WGS technology over Sanger sequence-based meningococcal typing. Indeed, the Member State capabilities for using WGS for surveillance and outbreak studies of *N. meningitidis* at national level are particularly widespread and fast progressing across the EU/EEA (Figure 2). The rationale (Table 3) for action includes the high health impact of these infections in the EU/EEA and the preventable nature of invasive *N. meningitidis* disease combined with optimal typing feasibility based on a relatively low volume of cases/clinical isolates to type per country and the public availability of a validated WGS-based cgMLST typing scheme. In addition, a well-advanced analytical platform is being trialled within the IBD-LabNet by national reference laboratory partners, using the data from the ECDC-supported pan-EU pilot WGS survey on isolates collected in 2011–12.

The ECDC business case for *N. meningitidis* will be developed in 2016 to design linkage of these microbiological data to case data at Member State level and interactive analytical processes interfacing TESSy with EMERT-BIGSdb databases for integrated genomic epidemiological surveillance. It will be then be implemented in close collaboration with the IBD-LabNet consortium.

This genomic epidemiology development project will be important as a case study for progressing the generic implementation of the ECDC WGS for surveillance strategy within the VPD programme and beyond in terms of collaboration with public health, clinical and academic partners and testing the re-engineered ECDC surveillance system and methodological support for TESSy data integration and reporting services.

Antibiotic-resistant *N. gonorrhoeae*

The EU-wide WGS-based surveillance of antibiotic-resistant *N. gonorrhoeae* will be performed by means of repeat structured pan-EU sentinel surveys based on the Euro-GASP surveillance programme methodology. This action is fully in accordance with the medium-priority recommendation made by the MSTF and is aligned with the Advisory Forum-approved molecular surveillance strategy for antibiotic-resistant *N. gonorrhoeae*, the ECDC 2016 work plan and draft priorities for 2017–19. The rationale (Table 3) for prioritisation includes the increasing health impact and preventable nature of antibiotic-resistant *N. gonorrhoeae* infections in the EU/EEA, combined with optimal typing feasibility based on a relatively low volume of representative survey cases/clinical isolates to type, as demonstrated by an experienced surveillance network. Progress is being made to develop a WGS-based typing scheme as part of the first EU-wide *N. gonorrhoeae* WGS data analysis of the Euro-GASP 2014 survey. Member State capabilities for using WGS in surveillance of antibiotic-resistant *N. gonorrhoeae* and outbreak studies at national level is already significant and can easily be supplemented by centralised ECDC-supported testing within the EU/EEA network, if required during initial surveys (Figure 2).

The ECDC business case for the antibiotic-resistant *N. gonorrhoeae* genomic epidemiology survey and TESSy data integration and reporting will be developed in 2016, in order to repeat the 2014 survey during the period 2017–18 in close collaboration with ECDC.

Diseases for which ECDC will defer operationalisation of WGS-based surveillance systems until the required technical capacity across the EU/EEA is met

It is proposed to defer the operationalisation of EU-wide WGS-based surveillance for the following diseases:

Salmonella enterica and Shiga toxin-producing *E. coli* (STEC)

It is proposed to defer the immediate operationalisation of EU-wide WGS-based surveillance for *S. enterica* and STEC until the required technical capacity across the EU/EEA is met and internationally validated WGS-derived nomenclatures and portable protocols are available for genome typing, serotype and drug resistance prediction.

The rationale for deferring the implementation of WGS for surveillance of these food-borne diseases is pragmatic (Table 3). Despite its high potential public health value underscored by the MSTF high priority ratings, high health impact and the preventable nature of salmonellosis and STEC infection in the EU/EEA, it is proposed to focus limited ECDC resources on a technological transition project for listeriosis first and thereafter transfer the know-how to all food-borne pathogens. A major disadvantage for EU-wide WGS-based surveillance of salmonellosis in particular is the high disease incidence and large volume of samples required for typing to be able to fulfil the main surveillance objective of early outbreak detection. While it is clear from the FWD surveillance evaluation report and EU capacity assessment that the disease coverage of 3–5% in terms of current Member State capacity for PFGE/MLVA typing is too limited to achieve this goal (Table 2), it is anticipated that once WGS is well established within the next 5–10 years as the universal front-line pathogen identification and characterisation technology in all Member States, this should allow broad capacity and full disease typing coverage across the EU/EEA for *S. enterica* and STEC.

In the meantime, ECDC will continue to support the surveillance system in place for reporting of PFGE and MLVA type to TESSy. It will also encourage improvement in data quality and timely reporting into the joint molecular typing database, established with EFSA for enhanced EU surveillance of disease trends and lineage frequency, including common genotype cluster detection and investigation over different time spans.

In addition, ECDC will assist Member States by supporting ad hoc comparative WGS-based typing for the coordinated investigation and joint assessment with EFSA of multistate outbreaks of salmonellosis or STEC disease in the EU/EEA. This will be essential for gaining experience and a better understanding of the technical challenges of cross-country WGS data exchange and joint analysis. The work will be done in parallel with the FWD-Next expert group, in collaboration with international partners in PulseNet International and the COMPARE consortium, towards an international WGS-based nomenclature for *L. monocytogenes* and other food-borne bacterial pathogens.

Human influenza virus

It is proposed to defer the immediate operationalisation of EU-wide WGS-based surveillance for human influenza virus until the final technical requirements are met and the collaborative agreement is in place with GISAID for the integration into TESSy of the existing virus sequence data reported to GISAID EpiFlu. This action is fully in accordance with the high-priority recommendation made by the MSTF that human influenza virus should undergo molecular typing for surveillance. It is also appropriate, given the high Member State sequencing capacity (including WGS) (Figure 2) and the strong interest and support from the European influenza surveillance network (EISN). The priority rationale includes the high health impact of disease, pandemic potential and relatively low sentinel sample volume (Table 3).

The strategy and business case toward surveillance harmonisation for emerging pandemic (including zoonotic) influenza strain detection and resistance monitoring has to be refined (2016) and the gene-sequence/WGS-based surveillance implemented (2017) in agreement with WHO (GISAID).

The collaborative agreement with GISAID and the final technical requirements for the existing virus sequence data to be integrated into TESSy are vital to avoid duplication of reporting by Member States.

Multi-drug resistant *Mycobacterium tuberculosis* (MDR TB)

It is proposed to defer the operationalisation of EU-wide WGS-based surveillance for MDR TB until the required technical capacity across the EU/EEA is met and validated nomenclatures and protocols are available for *M. tuberculosis* genome typing and drug resistance prediction. The rationale for deferring the implementation of WGS for surveillance (Table 3) includes the medium health impact of MDR TB across the EU and the difficulties in identifying the place and appropriate role of WGS in resolving TB outbreaks, supporting real-time TB epidemiology and molecular surveillance. This is due to the limited available evidence on national or international surveillance or the cost-effectiveness of WGS in routine settings, as concluded from the ECDC-funded systematic review on the added-value WGS of TB for transmission detection and outbreak tracing. In collaboration with the ERLTB-Net, ECDC will support the development of these technical solutions and the continued assessment of technology to regularly update the EU consensus expert opinion on the public health use of WGS for surveillance of MDR TB and TB.

In the meantime, ECDC will maintain its support to the surveillance system in place for the reporting of MIRU-VNTR type to TESSy, integrating genotypic data into the annual TB case reporting for EU surveillance of disease trends and lineage frequency. The latest data from the 2014 EULabCap survey based on TESSy data showed that the Member State capabilities for reporting MIRU-VNTR typing data are still sub-optimal, with 24% typing coverage of total EU reported cases achieved in 2014 by the 19 participating Member States (Table 2). One of the limitations of the public health usefulness of the current methodology for monitoring cross-border dissemination of MDR TB strains is the limited resolution of MIRU-VNTR for the most prevalent (Beijing) lineage.

These actions are fully in accordance with the high-priority recommendation made by the MSTF in relation to molecular typing for surveillance of MDR TB and take into account the variable volume of isolate samples available for typing based on MDR TB incidence and the insufficient capacity of Member States to meet the agreed typing coverage targets (Table 2).

Member State capabilities for using WGS in MDR TB surveillance and outbreak studies at national level within the EU/EEA network are progressing (Figure 2). ECDC's TB Disease Programme will work with the TB network to monitor progress of international validation of WGS-based identification, drug resistance prediction and typing nomenclature (2016–19). The TB Disease Network Coordination Committee will advise ECDC on activities related to WGS.

Diseases for which ECDC needs to collect further evidence on the opportunities and challenges for implementation of molecular or genomic typing integration for EU-wide surveillance

Human immunodeficiency virus (HIV)

Despite the high health impact and preventable nature of HIV infection, it is proposed to defer HIV WGS-based surveillance design and implementation until the ECDC antiviral resistance surveillance strategy is finalised and the results of Member State technical capacity mapping are available. The rationale includes the technical challenges represented by diverse molecular HIV typing methods used by the Member States and analytical schemes as well as lack of an EU network of public health reference laboratories for HIV (Table 2) and the limited use of WGS for outbreak investigation across the EU/EEA (Figure 2).

ECDC will develop this evidence base as part of its work plan 2016 and draft priorities for 2017–19. In 2015, the Advisory Forum supported the concept of developing a system for EU-wide collection of HIV resistance data from EU/EEA countries that already have such a surveillance system available, to collate and analyse this information and then to report on the overall annual European HIV resistance prevalence in a context of expanding international migration and increased use of antiretroviral drugs for pre-exposure prophylaxis. However, the additional objective of sharing viral sequence information for EU-level analysis of large-scale transmission networks requires further evidence on the opportunities and challenges for implementation and measuring of the public health benefits.

ECDC will now further develop its work with the Member States and scientific partners in obtaining more information on what is available and then proceed to develop options and a surveillance strategy for antiviral resistance of HIV, with a view to feasibility piloting during 2018.

Hepatitis C virus (HCV)

It is proposed to collect further evidence of the opportunities, added value and challenges for the integration of molecular typing into EU surveillance of hepatitis C in order to develop a strategy for surveillance of HCV antiviral resistance. This action is fully in accordance with the low-priority recommendation made by the MSTF in relation to molecular typing for HCV surveillance. Despite the high health impact and now curable, thus preventable nature of hepatitis C, the rationale for lower EU-level implementation priority includes the low Member State capacity (Figure 2), the lack of an established EU/international typing scheme except for major genotype assignation and the need for standardisation of genomic target/analytical protocols internationally.

ECDC will continue to work with Member States and scientific partners to review options for and develop a surveillance strategy for antiviral resistance of HCV as part of its work plan 2016 and draft priorities for 2017–19.

Clostridium difficile

It is proposed to collect further evidence on the feasibility of implementing molecular typing for surveillance of *C. difficile* infections (CDI) based on PCR-ribotyping. This action is fully in accordance with the recommendation of low public health priority given to molecular surveillance by the MSTF, despite the high health impact and preventable nature of these infections in the EU/EEA. The rationale includes the medium-level Member State capacity for PCR-ribotyping (Table 2).

Following a pilot validation study in 2013 (Table 2), in January 2016 ECDC initiated an EU-wide CDI surveillance module based on an agreed protocol supported by the Advisory Forum. The protocol proposes three options - minimal, light surveillance and enhanced surveillance – with only the latter requiring the collection of microbiological data including the PCR-ribotyping and antimicrobial susceptibility testing. This initiative will make it possible during the period 2016–18 to evaluate the Member State capacity for PCR-ribotyping and its routine feasibility and usefulness for EU-wide CDI surveillance.

There is currently no internationally standardised WGS-based typing scheme or WGS type nomenclature available for CDI, even though local and international studies have shown superior resolution of WGS typing over PCR-ribotyping for delineation of transmission networks. The 2015 survey indicates low Member State capacity for WGS

applied to CDI surveillance and outbreak investigations (Figure 2). ECDC will monitor technical development and the progress of international validation for WGS-based typing of CDI.

Diseases to postpone until 2018 for the next revision of the roadmap

Meticillin-resistant *Staphylococcus aureus* (MRSA)

It is proposed to postpone the development of the business case of EU-wide WGS-based surveillance for MRSA and its implementation by periodically conducting structured pan-EU hospital surveys until 2018. This action is fully in accordance with the recommendation of lower public health priority by the MSTF and the decreasing, albeit still high, health impact of MRSA in the EU/EEA. The rationale for postponing the implementation of WGS for MRSA surveillance is pragmatic. Despite the already high Member State capacity for WGS-based surveillance of MRSA and its frequent use for outbreak investigations (Figure 2), it is proposed to initially focus the limited ECDC resources on supporting the more urgent assessment of the pan-drug-resistance associated with the CPE epidemics.

The ECDC business case for the second MRSA genomic epidemiology survey and TESSy data integration and reporting will be developed in 2017–18 in order to establish the consortium able to perform the survey in 2019–20 in close collaboration with ECDC.

West Nile virus (WNV)

It is proposed to postpone the development of the strategy for and operationalisation of EU-wide WGS-based surveillance for West Nile virus (WNV) based on sequence/WGS. This action is fully in accordance with the low public health priority recommendation given by the MSTF. The rationale includes the low health impact and the low incidence in a limited number of EU/EEA countries. There is also limited Member State WGS capacity (Figure 2) and standards for genomic investigation are lacking. More knowledge needs to be obtained to link sequence information to pathogenicity. ECDC will continue to monitor the scientific developments in the field of WNV infections and genomics in collaboration with the EVD network experts.

Table 2. Overview of current status of molecular typing schemes by pathogen, latest reported Member State capacity and EU typing coverage estimates for priority diseases

Pathogen	Status	Typing method(s)	Number of EU/EEA countries reporting typing data to TESSy or EU-wide networks (% of notified case coverage)[1]
S. enterica	In operation	PFGE MLVA	16 (3)*
		WGS use for outbreak studies	
L. monocytogenes	In operation	PFGE	10 (17)**
		WGS-based pilot surveillance	
STEC	In operation	PFGE	8 (5)**
		WGS use for outbreak studies	
MDR TB	In operation	MIRU-VNTR	19 (24)*
N. meningitidis	Business case based on conclusions from the pilot EU survey of WGS cgMLST vs. gene sequencing (IBD-LabNet project)	Serogroup; 10 loci sequence scheme; WGS	28 (88)*
Antibiotic-resistant *N. gonorrhoeae*	Business case based on conclusions from the pilot EU survey of WGS versus gene sequencing (Euro-GASP project)	NG-MAST two loci sequence scheme; WGS	21~ (NA)
CPE	Business case based on the WGS pilot study (EuSCAPE project)	WGS/ resistome/virulome	29 (NA)¥
MRSA	Business case postponed; WGS pilot done (SRL project)	WGS/resistome/virulome	21 (NA)#
C. difficile	Technical feasibility started	PCR-ribotyping	14 (NA)±
Human influenza virus	Pilot surveillance based on antigenic and genetic characterisation	Gene sequence	28§
HIV	Concept paper; Member State capacity analysis paper in preparation; strategy in development	Gene sequence	NA
HCV	Strategy to be developed	Gene sequence	NA
WNV	Strategy to be developed	Gene sequence	NA

[1]Data extracted from TESSy, ECDC networks and stakeholders surveys;
*Data collected by the EULabCap 2014 (unpublished data);
**Data extracted from the TESSy as of 7 December 2015;
~ Data from 2009-2010 collected by the European Gonococcal Antimicrobial Resistance Surveillance Programme (Euro-GASP;
¥ Data from 2013-2014 collected by the European Survey for Carbapenemase-producing *Enterobacteriacae* (EuSCAPE) project;
Data from 2011 collected by the European Staphylococcal Reference Laboratory Working Group (SRL);
± Data *from 2013 pilot test of the European surveillance protocol by ECDC's* European Clostridium difficile Surveillance Network (ECDIS-Net) project.
+ Data collected by the Invasive Bacterial Disease Laboratory Network (IBD-LabNet) 2011-12 WGS survey;
§ Data from 2013 collected by the Global Initiative on Sharing All Influenza Data (GISAID) EpiFluTM sequence database. Percentage of EU/EEA case coverage was calculated as number of isolates genotyped and reported to TESSy/number of total isolates/cases notified to TESSy *100;
NA: not available or not applicable

Table 3. Summary of rationale for and ECDC technical actions proposed during the period 2016-19 for pathogen-specific genomic typing integration into EU surveillance and epidemic investigations

Near term operationalisation of EU-wide WGS-based surveillance systems							
Pathogen	Rationale						Proposed actions 2016-19
	MSTF priority	Health impact	Volume	Member State capacity	EU network/ consortium	International WGS typing scheme	
L. monocytogenes	High	High	Low	Medium	Active	WGS typing schemes in advanced stage for EU trial testing	- Development and trial testing of WGS-based surveillance, including international nomenclature and epidemiological validation (ELiTE II study) (2016-17) - Maintenance of PFGE EU data collection, quality assurance and analysis system extended to EFSA collaboration (2016-18) - Implementation of WGS based surveillance (2018-19)
CPE	High	Increasing	Low	High	Active	WGS schemes available for *K. pneumoniae* cgMLST typing and for carbapenemase identification	- Business case based on the EuSCAPE 2014 survey (2016) - First WGS-based EU survey (2017-18)
Neisseria meningitidis	Medium	High	Low	High	Active	Mature cgMLST WGS typing scheme under EU trial testing	- Business case based on strategy for TESSy-EMERT integrated analysis and pilot survey (2016) - Implementation of case based- WGS data linkage (2017-18) - Implementation of WGS based surveillance (2018-19)
Antibiotic-resistant *Neisseria gonorrhoeae*	Medium	Medium	Low	Medium	Active	No agreed WGS typing scheme but alternative analytical approaches being studied.	- Business case based on pilot Euro-GASP WGS survey 2014 (2016) - WGS-based EU survey (2017-18)
Operationalisation of WGS-based surveillance systems deferred							
Pathogen	Rationale						Proposed actions 2016-19
	MSTF priority	Health impact	Volume	Member State capacity	EU network/ consortium	International WGS typing scheme	
Salmonella enterica	High	High	High	Low	Active	In development	- Maintenance of PFGE/MLVA quality assurance and EU data collection and analysis system extended to EFSA collaboration (2016-18) - WGS: focus on data sharing and analysis for outbreak investigation including testing of open access analysis platforms (2016-19) - No transition to WGS-based surveillance until Member State capacity increases; contribute to design of international WGS nomenclature
STEC	High	Medium	Low	Low	Active	In development	
MDR TB	High	Medium	Medium	Low	Active	In development	- Maintenance of MIRU-VNTR quality assurance and EU data collection and analysis (2016-18) - WGS: monitor progress on international validation of WGS-based identification, drug resistance prediction and typing nomenclature (2016-19) - No transition to WGS-based surveillance until Member State capacity increases
Human influenza virus	High	High	Low	High	Active	Diverse typing schemes used and in development	- Implement business case in relation to surveillance for emerging pandemic (including zoonotic) strain detection and drug resistance monitoring (2016) - Implementation of sequence-based surveillance in agreement with GISAID (2016) - No transition to WGS-based surveillance until Member State capacity increases.

Further collection of evidence on the surveillance opportunities and challenges							
Pathogen	**Rationale**						**Proposed actions 2016-19**
	MSTF priority	**Health impact**	**Volume**	**Member State capacity**	**EU network/ consortium**	**International WGS typing scheme**	
HIV	Medium	High	Medium	Medium	No	In development	Develop antiviral resistance surveillance strategy Map capacity
HCV	Low	High	Medium	Low	No	Not available	Develop antiviral resistance surveillance strategy Map capacity
Clostridium difficile	Low	High	Medium	Medium	Active	In development	Evaluation of EU surveillance feasibility and utility with PCR-ribotyping (2016-18) WGS: monitor progress on international validation of WGS-based typing
Postpone until 2018 for next revision of the roadmap							
Pathogen	**Rationale**						**Proposed actions 2016-19**
	MSTF priority	**Health impact**	**Volume**	**Member State capacity**	**EU network/ consortium**	**International WGS typing scheme**	
MRSA	Low	Decreasing	Low	High	Active	Diverse typing schemes	Postpone business case to 2018
WNV	Low	Low	Low	Low	No	Not available	Postpone strategy to 2018

ECDC generic support actions to implement the WGS strategy

In addition to the development and implementation of the disease-specific genomic-based surveillance strategies above, ECDC's Microbiology Coordination Section together with the Epidemiological Methods Section, Country Preparedness Support and Training Sections will contribute the following cross-disease support actions together with the relevant disease programmes in 2016-19:

- Map the WGS-based public health initiatives and engage partnerships. This includes advising on the objectives and design of EU-funded research projects and working with EFSA on joint nomenclature, databases and surveillance systems in a 'one-health' approach to food-borne pathogens.
- Lead on the integrated analysis of epidemiological and WGS data. This includes working with the Member States to formulate the needs for data and analyses that will meet surveillance objectives and ensuring that case-based linkage of the epidemiological and microbial information is established at national reporting level. ECDC will support the testing of WGS analytical platform options to share sequence information and related epidemiological data.
- Provide guidance on appropriate use and validation of WGS-based bio-informatics methods for surveillance. ECDC will contribute to the development of international and cross-sector agreements on WGS quality standards, analytical schemes and genomic type nomenclature for the disease agent/resistance determinants under monitoring, in collaboration with the scientific community, EU and international health agencies and national reference laboratories.
- Support the Member State and ECDC staff professional development in applied bioinformatics and genomic epidemiology by organising multidisciplinary training workshops for public health microbiologists, epidemiologists and risk managers about analysis, reporting, interpretation and use of integrated genomic epidemiology data.
- Develop, run and evaluate selected pilot implementation studies. ECDC will contribute to the evaluation of operational performance, epidemiological validity and effectiveness of the disease-specific WGS-based surveillance selected in the updated roadmap. This includes the design and monitoring of surveillance system performance indicators and disease prevention metrics for the evaluation of public health benefits of system implementation using longitudinal time series analysis.

Furthermore, to ensure a coordinated, harmonious and timely development of surveillance methods and tools and to keep up with the WGS developments, ECDC will:

- Starting from 2016, organise joint annual meetings between NFPs for Surveillance and NMFPs where key WGS developments and their impact will be appraised and decisions taken on how the EU surveillance system should be adapted. Ensure regular reviews of progress with the WGS strategy implementation in the disease networks during annual meetings and ad hoc workshops.
- Develop and pilot test surveillance process and tool functionalities based on a range of assumptions concerning type of data sources, envisaged data flows, ECDC proposed strategies and surveillance objectives. This will be done within the framework of the Surveillance Systems Re-engineering project.
- Liaise with the European Commission Directorate General for Health and Food Safety (DG SANTE) to ensure prioritisation of notifiable diseases and timely integration of new surveillance case definitions in the legal text.
- Liaise with other EU and global initiatives as appropriate to ensure coordination and cost-efficient delivery of the strategy.

Follow-up and next revision of the ECDC roadmap for integration of molecular and genomic typing into European level surveillance and epidemic preparedness

It is proposed that ECDC should continuously monitor the performance of the molecular typing or WGS-typing enhanced surveillance operations using the agreed performance indicators at the operational level. It should offer regular feed-back to surveillance network participants and provide annual summaries for the competent body progress reports.

An annual review and evaluation by ECDC of the Roadmap Version 2.1 actions included in ECDC annual work plans, key milestones achieved and a summary of operation performance indicators will be carried out in 2016 and 2017 in consultation with the MSTF, Advisory Forum and competent bodies. Data on the pre-defined public health outcome indicators will be collated and analysed for each disease-specific surveillance system.

It is proposed that the next round of revision and prioritisation of disease-specific proposals for WGS-based surveillance (Roadmap Version 3) be undertaken in 2018 based on the above internal evaluations, identification of new opportunities and changing public health needs and in the light of any relevant results from the evaluation of EU/EEA surveillance systems.

European Centre for Disease Prevention and Control (ECDC)

Postal address:
Granits väg 8, SE-171 65 Solna, Sweden

Visiting address:
Tomtebodavägen 11A, SE-171 65 Solna, Sweden

Tel. +46 858601000
Fax +46 858601001
www.ecdc.europa.eu

An agency of the European Union
www.europa.eu

Subscribe to our publications
www.ecdc.europa.eu/en/publications

Contact us
publications@ecdc.europa.eu

Follow us on Twitter
@ECDC_EU

Like our Facebook page
www.facebook.com/ECDC.EU

ECDC is committed to ensuring the transparency and independence of its work

In accordance with the Staff Regulations for Officials and Conditions of Employment of Other Servants of the European Union and the ECDC Independence Policy, ECDC staff members shall not, in the performance of their duties, deal with a matter in which, directly or indirectly, they have any personal interest such as to impair their independence. Declarations of interest must be received from any prospective contractor(s) before any contract can be awarded.
www.ecdc.europa.eu/en/aboutus/transparency

HOW TO OBTAIN EU PUBLICATIONS

Free publications:

- one copy:
  via EU Bookshop (http://bookshop.europa.eu);
- more than one copy or posters/maps:
  from the European Union's representations (http://ec.europa.eu/represent_en.htm);
  from the delegations in non-EU countries (http://eeas.europa.eu/delegations/index_en.htm);
  by contacting the Europe Direct service (http://europa.eu/europedirect/index_en.htm) or
  calling 00 800 6 7 8 9 10 11 (freephone number from anywhere in the EU) (*).

  (*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Priced publications:

- via EU Bookshop (http://bookshop.europa.eu).

Publications Office