MEETING REPORT

ECDC technical consultation on harnessing genomics for epidemiological surveillance

Paris, 1–2 October 2013

Executive summary

The aim of the technical consultation was to review ECDC's molecular surveillance strategy and roadmap with leading scientists in molecular epidemiology and public health microbiology. The consultation also evaluated opportunities for the application of novel surveillance study designs and methodologies, the sustainability of current typing methods, and the transition to genome-wide analysis based on next-generation sequencing (NGS).

The meeting brought together 30 experts who confirmed that NGS-based methods are in the process of significantly changing public health microbiology. While some of these methods have already been introduced to public health laboratories, challenges remain in terms of access to the technology, data analysis and storage, and translating the data into information for public health use at the European level.

The experts made a number of recommendations in areas where ECDC should support Member States and their laboratories, which were then presented to the ECDC National Microbiology Focal Points and National Surveillance Focal Points for further discussion.

1 Background

ECDC supports EU Member States and the European Commission through integrated epidemiological and laboratory surveillance of communicable diseases and technical assistance in outbreak investigation, which includes collaboration with networks of experts and reference laboratories. As part of its *Public health microbiology strategy 2012–2016*, ECDC has produced, together with the Member States, a *Strategy and roadmap for integration of molecular typing into European surveillance and epidemic preparedness*, which outlines objectives, enabling steps and disease priorities over the next five years.

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Stockholm, January 2014

The aim of the technical consultation in October 2013 was to review the ECDC molecular surveillance strategy and roadmap with leading scientists in molecular epidemiology and public health microbiology and assess opportunities for the application of emerging surveillance study designs and methodologies, sustainability of current typing methods, and possibilities for rapid transition to genome-wide analysis based on next-generation sequencing (NGS) and the latest bioinformatics applications.

The meeting brought together 30 leading experts on genomic epidemiology and population biology of viral and bacterial pathogens[1], as well as public health microbiologists and bioinformaticians in charge of molecular surveillance programmes. Participants included experts from public health institutes, reference laboratories, research institutes, and academic centres in the United States and the European Union, all specialising in different areas and with diverse technical capabilities (see Annexes 1 and 2: list of participants and meeting programme).

There are two concepts in this field that are sometimes referred to interchangeably but actually have different meanings:

- Next-generation sequencing (NGS; also known as high-throughput sequencing) covers a range of technologies that parallelise the sequencing process of nucleic acids, producing thousands or millions of sequences concurrently at much lower cost than standard Sanger dye-terminator sequencing.
- Whole-genome sequencing (WGS) is a laboratory process that determines the complete DNA or RNA sequence of an organism's genome in a single, integrated process.

2 Meeting presentations

Marc Struelens opened the meeting by presenting the rationale, objectives and expected outputs of the consultation.

Karin Johansson (ECDC) started the meeting with a talk on ECDC's current strategy and activities in the field of molecular typing for public health. She presented the priorities of ECDC's *Roadmap for integration of molecular typing into European surveillance and epidemic preparedness* and explained the ongoing activities of the ECDC molecular typing pilot project. The presentation gave the participants a common understanding of the ECDC position in the field and clarified the plans and decision-making processes which are supposed to govern EU-wide molecular surveillance in the future. She also emphasised ECDC's commitment to facilitate access to whole-genome sequence-based datasets for the European public health microbiology community, and support the appropriate use of these data.

Martin Maiden (University of Oxford) gave a presentation on 'Genomic epidemiology of invasive meningococcal disease', in which he described approaches to whole-genome sequence (WGS) analysis, using *Neisseria meningitidis* as an exemplar. The talk included practical web-based methods for whole-genome sequence analysis and the Oxford-developed gene-by-gene WGS pipeline: sample preparation, multiplex sequencing, automated data assembly, annotation, and analysis. He showed how WGS data can be compared hierarchically with variable numbers of loci (7 to 2000) in the bacterial genome, including core and accessory loci, in order to rapidly and accurately identify and illustrate genetic relationships among isolates. The running costs of WGS in this setup are less than £60/strain, which is comparable to seven-locus MLST (multilocus sequence typing) using conventional techniques.

The added value of WGS analysis was demonstrated for outbreak investigations that used subsets of genes such as ribosomal MLST (rMLST) ad whole-genome MLST (wgMLST), compared to the current EU-standard 10-loci sequence-based 'fine typing scheme'. In a case study of a university outbreak caused by *N. meningitidis* serogroup C ST 11 ET15 epidemiologically unrelated isolates from epidemic strains were excluded. The establishment of a baseline dataset for *N. meningitidis* which includes all invasive disease isolates from England from the past three years has made it possible to establish the population structure of *N. meningitidis* and examine the determinants of its genomic diversity (Meningitis Research Foundation Meningococcus Genome Library). Although the data on distribution of antigenetic determinants made it possible to produce a minimum estimate of the preventable fraction of invasive meningococcal disease in England through immunisation with a novel meningococcal serogroup B vaccine (29% of isolates were harbouring one or more vaccine-targeted antigens), it was recognised that such sequence-based estimates do not predict cross-reactivity among related but distinct antigens.

Stefan Niemann (Forschungszentrum Borstel) gave a presentation explaining the development and validation of bioinformatic tools for WGS data analysis and their application to outbreak detection and epidemiological

[1] In this context, ECDC-monitored pathogens (described as 'priority pathogens' in the roadmap document) which cause communicable diseases and transmissible drug resistance were of particular interest.

investigations. The WGS pipeline used takes approximately 72 h to produce data for analysis. Mr Niemann also presented examples of MDR-TB2 investigations where NGS data improved the genetic resolution, as compared to traditional methods, and helped resolve close clusters within local and regional outbreaks. In a detailed investigation of TB transmission in families and close contacts, the WG molecular clock was estimated as less than three SNPs[3] in a single human-to-human transmission event and less than 10 SNP in a short-term transmission cluster. These observations are important when screening for clusters which require contact tracing because this would avoid the investigation of 'false clusters'. Typically, 'false clusters' are predicted to occur in 60% of all instances where lower-resolution typing methods (e.g. MIRU-VNTR) are used. Mr Niemann, in comparing current advantages and limitations of WGS to classic genotyping for TB, pointed out that while WGS adds critical resolution and can accurately predict phenotype, there were still unresolved issues, for example the detection bias in minor subpopulation analysis to predict the drug resistance status for diagnostic purposes, the lack of standardised formats for analysis and data exchange, and the lack of an online database with structured genomic *Mycobacterium tuberculosis* sequences.

These two presentations on practical typing applications of NGS methodologies were followed by a discussion on a number of related topics.

Backwards compatibility and comparability was discussed, weighing the advantages of NGS-based methods against the disadvantage of losing part of the historical dataset for analysis. It was stated that there is a need to first agree on analytical methods and produce a dictionary of sequence types at the international level. However, the need for historical comparability is not a valid reason for delaying the development of NGS-based typing methods. Historical comparability was considered a transient problem that can be alleviated by NGS analysis of strategically selected historical datasets. For sequence-based (such as bacterial MLST or viral resistance genotype) or sequence-predicted markers (such as antibiotype and serotype), WGS still provides 'classic' nomenclature type labels from sequenced isolates.

The meeting participants unanimously agreed that – provided that NGS-based typing methods evolve to meet all technical requirements (sequencing, software, IT-infrastructure) – NGS will replace current typing techniques for surveillance and outbreak investigation. There is some debate about how to apply NGS for routine surveillance and rapid outbreak detection. Different strategies for WGS data analysis exist (e.g. SNP-based, gene-by-gene-based and K-mer-based). These approaches differ in their computing time, initial requirements and type of information they provide. Therefore, the respective benefits of the different approaches would need to be evaluated.

It was concluded that more systematic comparative studies between NGS-based and traditional typing methods are key to demonstrating the specific advantages of NGS-based methods to the public health community and that such studies could improve the acceptance of NGS-based methods. The fact that some laboratories in the Member States do not have access to the technology is due to a lack of funds and/or political will.

One point of discussion concerned the number of investigated pathogens and the volume of typed isolates per reference laboratory: at which volume would the investment in an NGS-based platform and analytical pipeline be justified? This is particularly relevant for some laboratories in smaller countries which already face shortages in financial support for equipment and running costs.

The participants stressed that there was a need for evidence-based studies demonstrating the economic efficiency and financial advantages of using NGS/WGS for public health as opposed to traditional typing methods.

Jonathan Green (Public Health England, PHE) presented the NGS core sequencing facility currently being developed at PHE, comprising four NGS instruments (two Illumina HiSeq 2500, two Illumina MiSeq) and a bioinformatic service, set up to support translational research and development. Mr Green also described the current projects which evaluate the potential routine use of NGS to replace certain geno- and phenotyping activities performed on a set of priority pathogens/situations. These include:

- Emergency response to emerging pathogens, such as MERS-CoV
- *Salmonella* spp.
- *S. aureus*
- *S. pneumoniae*
- Influenza virus
- Blood-borne viruses and bacteria and drug resistance determination

Whether NGS applications can replace traditional typing is evaluated in a first project which compares cost-effectiveness of NGS and traditional methods, for example the cost of a whole-genome sequence compared to serotyping, PFGE, and antimicrobial resistance testing of a *Salmonella* strain. Sequence data generated in this

[2] MDR-TB: Multidrug-resistant tuberculosis

[3] SNP: Single nucleotide polymorphism

project are currently stored locally but will later be routinely released to the NCBI Short Read Archive. PHE await possible solutions from the Global Microbial Identifier[4] initiative for future dedicated storage and global sharing of microbial NGS data.

Regarding *Salmonella*, it is anticipated that approximately 10 000 isolates per year will be received at the PHE reference laboratory. After an initial trial phase during which serotyping, antibiogram and PFGE/phage-typing with WGS analysis will be run in parallel in order to compare costs and time, all isolates will be whole-genome-sequenced. With over 1 000 isolates tested so far, the PHE reference laboratory accurately predicted the serovars in approximately 97% of all cases through inference from MLST, based on the association of serovar with allelic types from seven housekeeping genes; the majority of problems occurred with rarer serotypes. For pneumococci, WGS-based inference of capsular serogroups and types looks promising but is still limited by a lack of sequence data for some rare serotypes.

Real-time WGS has been deployed at PHE for surveillance and investigating outbreaks caused by *Shigella flexneri*, *M. tuberculosis*, verocytotoxin-producing *E. coli*, *Listeria monocytogenes* and Group A beta-haemolytic streptococci. This has given additional insight into outbreaks; however, caution in interpretation is needed due to the lack of complete reference genome datasets. There is also a need for calibration of SNP drift during short-term transmission.

The next steps include assay validation for accreditation, clinical and public health validation of WGS interpretation criteria, use of NGS in legal forensic investigations, and the equipment of reference laboratories with additional decentralised bench-top NGS instruments. PHE is developing a genomics strategy that will include priorities for local and national public health surveillance and outbreak investigations.

In the subsequent discussion some meeting participants suggested that it was preferable to define finer genomic typing units/nomenclature rather than reproducing old classifications such as serotype with WGS. Others raised concerns about retraining laboratory staff because of the shift from wet lab technology to new types of expertise, e.g. population biology of specific microorganisms in relation to human diseases. Furthermore, participants supported the need for (international) multi-centre studies to further evaluate data comparability when applying NGS to public health typing purposes.

[4] GMI: Global Microbial Identifier (http://www.globalmicrobialidentifier.org); the project was represented by Rene Henriksen

3 Working groups

3.1 The roadmap for EU disease surveillance: objectives and typing methods

Working group 1 was moderated by Tim Harrison (Public Health England); topics included the objectives for EU-wide surveillance of the priority pathogens included in the roadmap and whether the proposed typing methods can meet the objectives or if there are methodologies which are better suited. For most pathogens, the objectives and methods contained in the roadmap were confirmed as valid and still relevant (with some adjustments suggested for HIV), but the cross-pathogen approach for the typing of AMR (antimicrobial resistance) markers needs to be better defined with respect to included pathogens, markers, sequencing targets, etc. ECDC will be organising an expert meeting on these issues in 2014.

A number of general points were discussed:

- The working group agreed that ECDC/TESSy should not host NGS/WGS sequence data, unless absolutely necessary. TESSy should be linked to, and make use of, external public sequence databases and analytical tools so that sequences can be shared while access to potentially sensitive metadata could be restricted. In some instances the entire sequence could be considered sensitive; HIV sequence data, for example, may not be suitable for systematic public database submission. Further discussions are needed to decide whether sensitive sequences should be submitted directly to ECDC as the data host.
- Sequence-based methods need systematic quality control. Sequence database curation, external quality assessment (EQA) and quality assurance management are also essential for NGS-based methods.
- Linking epidemiological and laboratory data is generally a big problem. The situation in the EU is very heterogeneous as the Member States have different systems and often apply different rules at the various administrative levels.

3.2 Study design for EU level molecular surveillance initiatives

Working group 2 was moderated by Marc Struelens (ECDC). The group discussed various aspects of study design related to initiatives on molecular surveillance at the EU level, including the question whether repeated structured surveys could be an alternative approach when introducing molecular typing at the EU level, and if so, how this would influence data quality/comparability and promote the combination of laboratory and epidemiological data.

The group identified significant advantages in applying the structured survey approach for EU-level surveillance. There have been several practical examples where this has proven to be successful (gonorrhoea, MRSA, etc.). Structured surveys allow for a more controlled data collection compared to routine comprehensive surveillance. They improve data representativeness and comparability, and should be seen as a necessary complement to routine surveillance. Structured surveys also allow for the planning of a defined sample size, a contained budget and a controlled workload. For this approach to be effective, the surveys must include capacity-building components through ad hoc technical training within the networks, resulting in decentralised typing at the national level and improved public health microbiology capability across the entire EU. Another important prerequisite for success is to develop and sustain a team spirit through shared ownership of the outputs and recognition of the contribution of all partners.

Intrinsic limitations of the structured survey approach include that outbreaks are not likely to be picked up, and the danger of inferring a representative population reference point from a snap-shot view generated in one survey. In addition, results from the structured survey approach are likely to differ from those captured in routine surveillance.

The structured survey approach should be considered if there is a defined public health value, if there are resources to conduct regular surveys, if data and analysis can be easily fed back to the data providers, and if a typing methodology can be established at the national level. Shared bioinformatics platforms and agreed nomenclature are needed to maintain consistency and comparability of data generated by different network members.

It should be noted that a structured survey approach is not needed where extensive typing is already being performed as part of routine healthcare practice (for example: HIV). Analysing results from the full surveillance system, including point prevalence studies, and introducing new sample frames in surveillance, increases complexity but also the understanding of the epidemiological picture of the disease.

An alternate approach to the point prevalence survey is the structured laboratory-based sentinel survey programme, as practiced by public health laboratory networks in the USA and Canada, where a defined sample size of isolates

are further referred for typing and characterisation to answer specific surveillance questions. Bilateral communication and feedback to participants, as well as shared scientific publications, are key to sustaining network participation.

Another question discussed by working group 2 was whether surveillance of transmissible clones and mobile genetic determinants of antimicrobial resistance was applicable at the EU level, and how such an initiative might influence the quality of scientific output and lead to increased complexity in retrieving comparable data.

The working group concluded that monitoring of mobile genes/genetic vectors of acquired resistance is still more applicable to research than to real-time surveillance. Participants discussed obstacles to such an approach, including the current difficulty to draw public health-relevant conclusions and engage in appropriate actions based on such data. Participants agreed that there was a need to learn from ongoing initiatives before introducing measures on a routine basis at the EU level.

3.3 Prerequisites for NGS data standardisation and interpretation

Working group 3 was moderated by Flemming Scheutz (Statens Serum Institute) and discussed prerequisites for NGS data standardisation and interpretation, starting from a list of potential issues related to instrument and sample preparation, standards and data comparability, analysis, interpretation, and demonstration of practical value. The discussion covered all above topics, some in more detail than others. It should also be noted that the recent GMI global survey of NGS capacity and use among GMI participants covers many of the issues discussed in the working group.

Participants agreed that there is a need to objectively review, compare and assess genome-based analysis pipelines. It is not quite clear yet whether the community will converge towards a few 'validated' pipelines, or if it will be sufficient to compare data from pipelines that have passed certain performance criteria. It may also be necessary to use multiple analysis pipelines, as for HIV. Assessing the individual analytical performance of laboratories will also be a crucial part of a functioning NGS analysis system, and NGS performance should be included in future EQAs.

Nomenclature in the NGS era was described by the group as a very important and generally underdeveloped topic. Current nomenclature is generally not adapted to NGS, leading sometimes to squeezing NGS data into old nomenclature 'boxes'. The group recommended that existing nomenclature should be kept if consistent with NGS technology (for example *Salmonella* serotyping) and redefined in the NGS context; where gaps are identified, a new NGS-based nomenclature needs to be developed.

Perhaps the most crucial part of the discussion focused on the demonstration of the practical value of NGS-based methods for public health. As more scientific evidence is accumulated, demonstrating the advantages of NGS-based methods over traditional methods for public health application, different target audiences need to be addressed:

- In the public health sector, the network approach will be very important for organism-specific solutions; there is also a need for a forum where Member States and laboratories exchange experiences and best practices.
- Policy makers need invest in NGS on a larger scale. Here, cost-benefit studies will be instrumental, and synergies, in particular with a future EU public health reference laboratory system, should be reviewed.

3.4 Need for guidance on epidemiological validation studies for NGS applications

Working group 4, moderated by Alex Friedrich (University Medical Center Groningen), addressed the need for guidance on epidemiological validation studies for NGS applications. Two phases of NGS introduction into public health laboratories were foreseen. In phase 1, methodologies will be tested as new equipment and techniques become available. Interpretation issues, lack of standardisation and data comparability, and interpretation questions dominate the picture. In phase 2, the NGS methodologies are taken on board and integrated into laboratory practice. This will lead to a radical change in laboratory work and will require new competences and equipment compared to the traditional laboratory. Public health authorities and laboratories will need to actively initiate standardisation to improve data comparability, improve quality and backward compatibility, and produce reference data sets and ring trials. Working group 4 identified the current state as a transit phase between phases 1 and 2, indicating that there is a need to address all data quality, interpretation and comparability issues.

The group concluded that ECDC's role would be to start a consortium to develop guidance for the validation of NGS for public health purposes. This consortium should have representatives from centres involved in the early testing

of NGS methodologies and should identify all questions relevant for methodology validation. This includes technical, biological and epidemiological aspects of data generation and interpretation. Results from this work should be published to support implementation and give guidance to Member States that have not yet started to implement NGS applications in their public health or clinical laboratories.

As a second step, the group suggested that ECDC should consider launching calls for tender for technical work in connection with this guidance, e.g. for specific pathogens. It should include pilot validation of NGS-based typing and be executed in collaboration with other international initiatives in this field. The practical validation should include multi-centre comparison of data, comparison between traditional and NGS-based methodologies, quality assessment/standardisation and nomenclature, as well as capacity building components and access to bioinformatic solutions.

4 Conclusions from the expert consultation and recommendations for ECDC action

- ECDC should explore how to refine objectives and support the implementation of sequence-based typing methods for the priority pathogens listed in the molecular surveillance roadmap; pathogens currently covered by the pilot project should be included.
- ECDC should promote the transition to NGS-based technologies. This could be achieved through several measures:
  - Guidance on the validation of public health applications of WGS-based methods: ECDC should help in the development of such guidance, in collaboration with its international partners.
  - Surveying the current access to, and use of, WGS-based methods for surveillance and outbreak investigation by public health laboratories in the Member States.
  - Supporting comparative studies (WGS-based methods compared to conventional typing methods) for selected priority pathogens as defined in the roadmap document; studies should also cover the financial aspects and provide an economic justification.
  - Facilitating network agreements on the use of common analytical pipelines for WGS data and genomic type nomenclature, in collaboration with international initiatives.
  - Organising access to WGS technology software by providing access to existing bioinformatics solutions and by conducting training workshops on WGS data analysis and use.
  - Organising, within the laboratory networks, ring trials to test real-life proficiency with WGS data production, analysis and comparability, and subsequently support EQAs for public health application of WGS-based methods and analytical pipelines.
  - Exploring options for efficient and timely sharing of sequence information and related epidemiological surveillance data through the use of general open access databases vs. public health systems with more restricted access.

Annex 1. List of participants

IMMEM satellite technical consultation: participants

1–2 October 2013, Paris, France

#	Country	Name	Affiliation
1.	Belgium	Anne-Mieke Vandamme	University of Leuven
2.	Croatia	Vera Katalinic-jankovic	National Institute of Public Health
3.	Denmark	Rene Hendriksen	Technical University of Denmark
4.	Denmark	Robert Skov	Statens Serum Institute
5.	Denmark	Flemming Scheutz	Statens Serum Institute
6.	Estonia	Kardi Toit	Tartu University Hospital
7.	France	Philippe Glaser	Pasteur Institute, France
8.	France	Sylvain Brisse	Pasteur Institute, France
9.	France	Carmen Buchrieser	Pasteur Institute, France
10.	Germany	Dag Harmsen	Universitätsklinikum Münster
11.	Germany	Stefan Niemann	Molecular Mycobacteriology, Research Center Borstel
12.	Greece	Dimitrios Paraskevis	National and Kapodistrian University of Athens
13.	Greece	Panayotis T. Tassios	National and Kapodistrian University of Athens
14.	Italy	Alessandra Carattoli	Istituto Superiore di Sanità
15.	Netherlands	Alex Friedrich	University Medical Center Groningen
16.	Netherlands	Hajo Grundmann	University Medical Center Groningen
17.	Netherlands	Ellen Stobberingh	National Institute for Public Health and the Environment (RIVM)
18.	Norway	Olav Hungnes	The Norwegian Institute of Public Health
19.	Poland	Grzegorz Madajczak	National Institute of Public Health
20.	Poland	Radoslav Izdebski	National Medicines Institute
21.	Sweden	Magnus Unemo	Örebro University Hospital
22.	Slovenia	Maja Rupnik	Institute of Public Health Maribor
23.	United Kingdom	Keith Jolley	University of Oxford
24.	United Kingdom	Martin Maiden	University of Oxford
25.	United Kingdom	Tim Harrison	Public Health England
26.	United Kingdom	Jonathan Green	Public Health England
27.	USA	Peter Gerner-Smidt	Centers for Disease Control and Prevention (CDC)
28.	Canada	Mathew Gilmour	University of Manitoba
29.	EU/EEA	Marc Struelens	ECDC
30.	EU/EEA	Daniel Palm	ECDC
31.	EU/EEA	Karin Johansson	ECDC
32.	EU/EEA	Milka Docheva	ECDC

Annex 2. Meeting programme

ECDC technical consultation on harnessing genomics for epidemiological surveillance

1–2 October 2013

Institut Pasteur, Paris, France

Tuesday, 1 October 2013 **Room: Dedonder, Pasteur Institute**	
12:00–12:30	**Registration and sandwich lunch**
12:30–12:40	**Welcome and introduction** Marc Struelens, ECDC
12:40–14:30	**Session 1: Molecular versus genomic typing for public health surveillance** Chair: Daniel Palm, ECDC
12:40–12:55	**ECDC strategy and roadmap for integration of molecular typing into European surveillance and epidemic preparedness** Karin Johansson, ECDC
12:55–13:15	**Genomic epidemiology of invasive meningococcal disease** Martin Maiden, University of Oxford
13:15–13:35	**Applying genome based tools to understanding pathogen transmission – Lessons from *Mycobacterium tuberculosis*** Stefan Niemann, Research Center Borstel
13:35–14:20	**Discussion**
14:20–14:30	**Introduction to working group session** Daniel Palm, ECDC
14:30–15:00	**Coffee break**
15:00–17:30	**Session 2: Guidance for EU-level molecular surveillance** **Break-out working groups** (WG) • **WG1: Typing methods for EU-wide surveillance of priority pathogens: ECDC proposed versus emerging methods** Moderator: Tim Harrison, PHE; rapporteur: Karin Johansson, ECDC • **WG2: Study design for EU level molecular surveillance (sampling strategies, centralised vs. distributed typing, data management and analysis)** Moderator: Marc Struelens, ECDC; rapporteur: Daniel Palm, ECDC
17:30	**End Day 1**
Wednesday, 2 October 2013	
8:30–9:00	**Session 3: Public health microbiology in the genomic era** Chair: Peter Gerner-Smidt, CDC **NGS as universal microbial typing platform: A national public health study** Jonathan Green, PHE
9:00–10:30	**Session 4: Implementation of EU-level molecular surveillance during a technology shift** **Break-out working groups** • **WG3: What are the prerequisites for NGS data standardisation and interpretation?** Moderator: Flemming Scheutz, SSI; rapporteur: Karin Johansson, ECDC • **WG4: What is the need for guidance on epidemiological validation studies for NGS applications?** Moderator: Alex Friedrich, University Medical Center Groningen; rapporteur: Daniel Palm, ECDC
10:30–11:00	**Coffee**
11:00–12:15	**Session 5: Report from break-out groups and plenary discussion** Chair: Alex Friedrich, University Medical Center Groningen
12:15–12:30	**Summary and conclusions** Marc Struelens, ECDC
12:30	**End of consultation meeting** Participants to IMMEM-10 conference can register at conference welcome desk.

Breakout group 1	Breakout group 2
Alessandra Carattoli, Istituto Superiore di Sanità, Italy	**Alex Friedrich**, University Medical Center Groningen, The Netherlands
Anne-Mieke Vandamme, University of Leuven, Belgium	**Dag Harmsen**, Universitätsklinikum Münster, Germany
Radoslav Izdebski, National Medicines Institute, Poland	**Hajo Grundmann**, University Medical Center Groningen, The Netherlands
Jonathan Green, Public Health England, UK	**Matthew Gilmour**, University of Manitoba, Canada
Olav Hungnes, Norwegian Institute of Public Health, Norway	**Keith Jolley**, University of Oxford, UK
Martin Maiden, University of Oxford, UK	**Marion Koopmans**, RIVM, The Netherlands
Sylvain Brisse, Pasteur Institute, France	**Peter Gerner-Smidt**, Centers for disease control and prevention, US
Tim Harrison, Public Health England, UK	**Stefan Niemann**, Research Center Borstel, Germany
Flemming Scheutz, Statens Serum Institute, Denmark	**Robert Skov**, Statens Serum Institute, Denmark
Grzegorz Madacjzak, National Institute of Public Health, Poland	**Vera Katalinic-Jankovic**, National Institute of Public Health, Croatia
Panayotis T. Tassios, National and Kapodistrian University of Athens, Greece	**Carmen Buchrieser**, Pasteur Institute, France
Rene Hendriksen, Technical University of Denmark, Denmark	**Kadri Toit**, Tartu University Hospital, Estonia
Magnus Unemo, Örebro University hospital, Sweden	**Dimitrios Paraskevis**, National and Kapodistrian University of Athens, Greece
Karin Johansson, ECDC	**Maja Rupnik**, Institute of Public Health Maribor, Slovenia
	Philippe Glaser, Pasteur Institute, France
	Daniel Palm, ECDC
	Marc Struelens, ECDC