ECDC strategy on using WGS for AMR surveillance

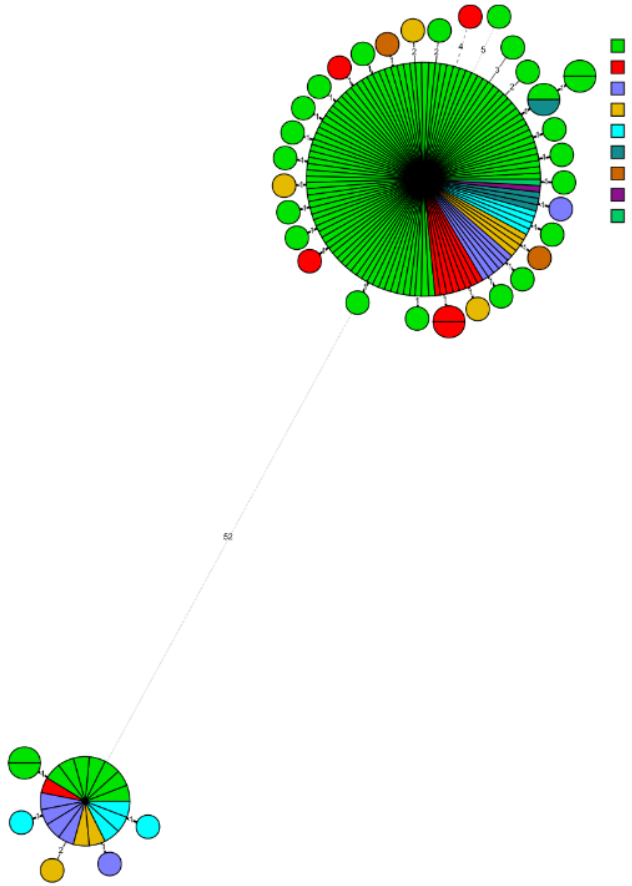
FWD AMR – RefLabCap Network meeting

26-27 April 2023, Cecilia Jernberg and Therese Westrell

WGS – one stop shop for characterisation, typing, cluster analysis of different pathogens under surveillance.

Increased interest and use of sequencing data also for identifying resistance markers for different purposes

blaTEM-1,
strAstrB,
aac(6')-Iaa,
aac(3)-IId,
aph(6)-Id,
aadA-2,
aadA-8b,
aadA-12,
aadA-15
aadA-17,
cmlA1,
floR,
sul2 (+sul3),
dfrA12
tetB
tetM



JOINT ECDC-EFSA RAPID OUTBREAK ASSESSMENT

Multi-country outbreak of monophasic *Salmonella* Typhimurium sequence type 34 linked to chocolate products – first update

18 May 2022

Abstract

On 17 February 2022, the United Kingdom (UK) reported a cluster of cases with monophasic *Salmonella* Typhimurium sequence type 34 infection. As of 18 May 2022, 324 cases had been reported in 12 EU/EEA countries and the UK, including two distinct strains. Most cases are below ten years of age and 41% of all cases have been hospitalised. The two strains are multidrug-resistant and some tested isolates also carry resistance to disinfectants that are based on quaternary ammonium compounds and hydrogen peroxide, but remain susceptible to azithromycin, ciprofloxacin, meropenem, and third generation cephalosporins. Epidemiological investigations suggested specific chocolate products of Brand A, produced by Company A in Processing Plant B in Belgium, as likely vehicles of infection.

Two strains of monophasic *Salmonella* Typhimurium matching the outbreak strains were identified in the buttermilk line at Plant B between December 2021 and January 2022. The buttermilk was provided by an Italian supplier where *Salmonella* was not detected. The Italian supplier delivered the buttermilk to other plants of Company A where, based on the available evidence, *Salmonella* was not detected.

On 8 April 2022, based on official controls, the food safety authority in Belgium decided to withdraw the authorisation for production of the Plant B due to lack of transparency and insufficient guarantees for safe production. Company A globally recalled all products of Brand A produced at Plant B. Public warnings were issued by the competent national authorities in different countries.

This outbreak has evolved rapidly, with children most at risk for severe infection. The closure of Plant B and the global recall of all their products have reduced the risk of exposure. However, eight cases cannot be explained by consumption of chocolate products such as those manufactured at Plant B, suggesting that there may also be other sources of infection.

Surveillance objectives for EU-level monitoring of AMR in *Salmonella* and *Campylobacter* from humans

1. To monitor, in human clinical isolate trends in the occurrence of resistance to antimicrobial agents relevant for treatment of human *Salmonella* and *Campylobacter* infections, including comparison with food/animal isolates
2. To monitor, in human clinical isolates, trends in the occurrence of resistance to other antimicrobial agents of public and animal health importance, including comparison with food/animal isolates
3. To monitor, in human clinical isolates, the prevalence of ESBL, plasmid-encoded Ambler class C β-lactamases (pAmpC) and carbapenemase phenotypes and genotypes
4. To use antimicrobial resistance patterns to characterise human clinical isolates, i.e. as an epidemiological marker, to support identification of outbreaks and related cases
5. To identify and monitor, in human clinical isolates, genetic determinants of resistance that are important for public health e.g. to aid recognition of epidemic cross-border spread of multi-drug resistant *Salmonella* strains
6. To monitor, in human clinical isolates, trends in the occurrence of resistance to antimicrobial agents that may be needed for future therapeutic use

https://www.ecdc.europa.eu/en/publications-data/eu-protocol-harmonised-monitoring-antimicrobial-resistance-human-salmonella-and-0

ECDC strategic framework for the integration of molecular typing into European surveillance and multi-country outbreak investigations – the "roadmap"

- EU-level FWD AMR surveillance objectives integrated in the ECDC molecular surveillance "roadmap"

- WGS data to further support the surveillance objectives for EU-level monitoring of AMR in *Salmonella* from humans

- The same EU surveillance objectives are relevant for *Campylobacter* (except ESBL/AmpC)

Disease programme and pathogen	Objectives for		
	Outbreak investigation	Control-oriented surveillance	Strategy-oriented surveillance
Salmonella enterica	1. Verification of multi-country outbreaks (WGS) 2. Investigation of outbreak sources/vehicles jointly with EFSA (PFGE, MLVA, WGS) 3. Use predicted antimicrobial resistance patterns to characterise human clinical isolates, i.e. as an epidemiological marker, to support identification of outbreaks and related cases	1. Outbreak detection (MLVA, possibly WGS) 2. Identify and monitor, in human clinical isolates, genetic determinants of resistance that are important for public health e.g. to aid recognition of epidemic cross-border spread of multi-drug resistant strains	1. Monitor, in human clinical isolates, trends in the occurrence of predicted resistance to antimicrobial agents relevant for treatment of human Salmonella infections, including comparison with food/animal isolates 2. Monitor, in human clinical isolates, trends in the occurrence of predicted resistance to other antimicrobial agents of public and animal health importance, including comparison with food/animal isolates 3. Monitor, in human clinical isolates, trends in the occurrence of predicted resistance to antimicrobial agents that may be needed for future therapeutic use 4. Monitor, in human clinical isolates, the prevalence of ESBL, plasmid-encoded Ambler class C β-lactamases (pAmpC) and carbapenemase genotypes

https://www.ecdc.europa.eu/sites/default/files/documents/framework-for-genomic-surveillance.pdf

Updated EU regulations, November 2022

Updated ECDC mandate

The Centre should broaden its collection and analysis of data in terms of epidemiological surveillance and related special health issues, progression of epidemic situations, unusual epidemic phenomena or new diseases of unknown origin, including in third countries, **molecular pathogen data** and health systems data.

EUR-Lex - 32022R2370 - EN - EUR-Lex (europa.eu)

Regulation on serious cross-border threats to health

The national competent authorities ….shall communicate the following information…to the participating authorities of the network for epidemiological surveillance:

…molecular pathogen data, if required for detecting or investigating serious cross-border threats to health

Regulation (EU) 2022/2371 on serious cross-border threats to health and repealing Decision No 1082/2013/EU (europa.eu)

EU case definitions (Commission Implementing Decision 2018/945/EU)

In definitions of *Salmonella* and *Campylobacter* enteritidis:

Laboratory Criteria

At least one of the following two:

— Isolation of *Salmonella* (other than *S.* Typhi or *S.* Paratyphi) in a clinical specimen

— Detection of nucleic acid from *Salmonella* (other than *S.* Typhi or *S.* Paratyphi) in a clinical specimen

Note: Antimicrobial susceptibility testing of *Salmonella enterica* should be performed on a representative subset of isolates

Antimicrobial resistance

The results of antimicrobial susceptibility tests must be reported according to the methods and criteria agreed between ECDC and Member States as specified in the EU protocol for harmonised monitoring of antimicrobial resistance in human *Salmonella* and *Campylobacter* isolates ([1]).

- EU case definitions currently under revision but no change proposed for *Salmonella* or *Campylobacter* enteritidis

Phenotypic susceptibility data

- Phenotypic testing gold standard for treatment purposes (choice of method differs)
- Data collected from clinical laboratories normally not covering the full priority panel
- Difficult to motivate testing of antimicrobials with non-clinical relevance – mainly for comparison purposes with animal isolates – One Health. Exception those labs using the vet MIC panels.

Benefits and challenges of WGS for AMR determination

BENEFITS

- The data can be more accurately comparable between countries
- WGS as a method replaces additional typing methods (serotyping, species, sequence type, virulence)
- No need to limit the number of antibiotic resistance markers to report.
- WGS data can also be used for cross border outbreak detection and comparison with food and animal data within the ECDC-EFSA OneHealth system.

CHALLANGES

- Not all countries have financial or staff resources to do it, and FWD might be low priority (?)
- Still a need for phenotypic determination
  - For treatment purposes
  - To detect new genetic variants since only what is known can be detected genotypically
  - Continued phenotypic work needs to be done nationally/regionally

ECDC's vision for EU-level FWD AMR surveillance

- WGS should be the method for EU level *Salmonella* and *Campylobacter* AMR surveillance
- All countries are reporting a representative subset of isolates sequencing data from *Campylobacter* and *Salmonella* for AMR data submission to TESSy

- Transition period, report both phenotypic and genotypic data for the same isolates for validation when possible.

How do we achieve this?

Technical solutions

- Sharing WGS data or predicted resistance is today possible as official annual AMR data submission to ECDC (next presentation)

Sequencing support

- Capacity building by the HERA grants
  - HERA incubator 2021-2022: 61 million EUR
  - Continued support 2023-2024: 39 million EUR
- Capacity building, training, building national networks etc – FWD AMR RefLabCap (HaDEA)
- Training programme in genomic epidemiology and public health bioinformatics - "GenEpi-BioTrain"

How many sequences are needed?

- Minimum number of isolates to sequence (to be discussed):
  - 100 for *Salmonella enterica*, representative serotypes
  - 50 *Campylobacter*, and of these at least 10 *C. coli* in order to estimate % resistance

- How to select a representative subset? Useful guidance in FWD AMR RefLabCap document 'Model protocol for national surveillance of AMR in human *Salmonella* and *Campylobacter* infections'

New: Sequencing support for a subset of Salmonella and Campylobacter isolates

- ECDC is planning to offer sequencing support to countries who have not yet routine WGS typing in place, highest priority to countries with overall limited possibility.
- The sequences will be shared with ECDC as part of countries official AMR reporting
- Provides additional benefit to the ongoing FWD AMR RefLabCap project.

- **In the audience, is there interest in sequencing support within this context?**

Cross-border capacity-building support programme in genomic epidemiology (GenEpi-BioTrain)

Aim:

Increase the capacity for genomic epidemiology

- Value of the contract: ~5.2 Mio EUR for up to 48 months
- The programme started in the beginning of 2023. First training in May (Flu, SARS-CoV-2, AMR).

Consortium "GenEpi-BioTrain":

- Contract project managers are Rene Hendriksen, DTU (main) and Anders Rhod Larsen, SSI (deputy)
- Consortium includes DTU & SSI (DK), Institut Pasteur (FR), Research Center Borstel (DE), THL (FI), Karolinska University Hospital (SE)

Cross-border capacity-building support programme (GenEpi-BioTrain)

Objectives:

- Support countries in building up their capacity in genomic epidemiology and bioinformatics for public health purposes
- Increase the interdisciplinary collaboration between bioinformaticians, epidemiologists and microbiologists within a country
- Facilitate the routine use of genomic information for surveillance, preparedness and outbreak response

Training target groups:

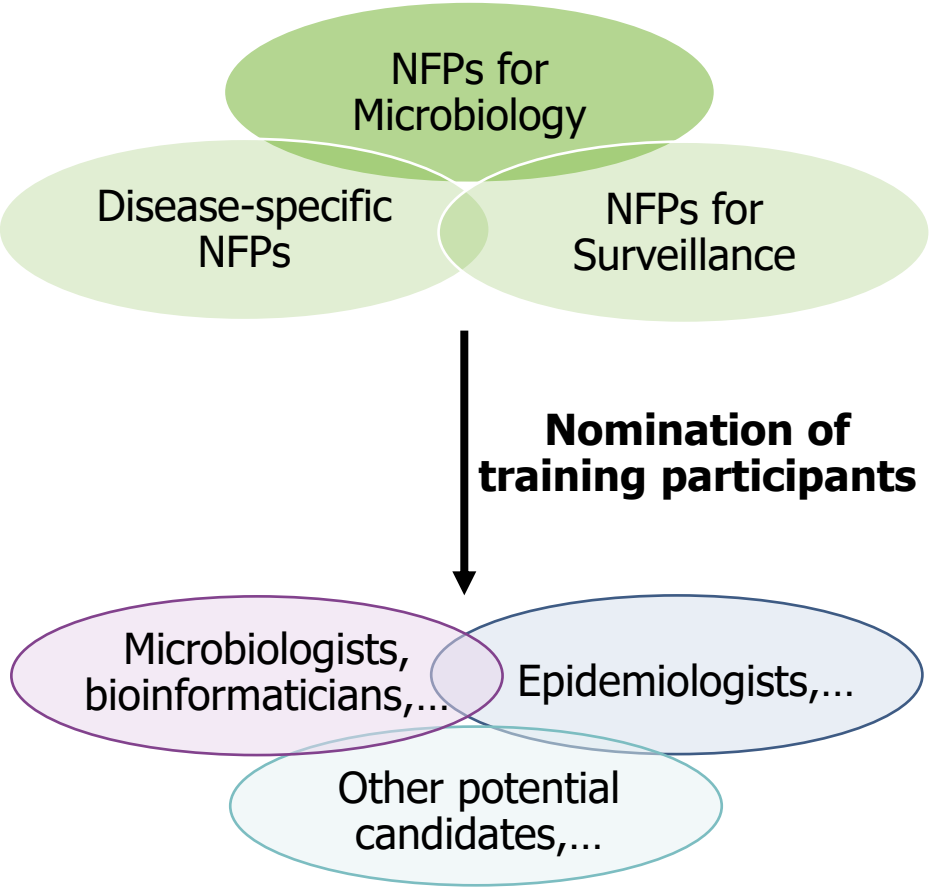
- Professionals working in public health institutions with a background in computational biology/bioinformatics
- Professionals working in public health institutions who **do not** have a specific background in bioinformatics (i.e. microbiologists, epidemiologists, professionals in public health response and surveillance)

Training activities:

- Face-to-face workshops "Bridging the gaps in bioinformatics"
- Face-to-face workshops "Interdisciplinary genomic epidemiology and public health bioinformatics"
- Face-to-face trainings on specific topics in genomic epidemiology and/or public health bioinformatics
- Virtual information and training sessions, exchange visits for bioinformaticians

GenEpi-BioTrain - Nomination of trainees per country

- Training participants should be nominated by the countries
- Coordination of the nomination process amongst the NFPs
- Suggestion: NFPs for Microbiology lead the coordination
- For each country, invitation letters will be sent to the NFPs (with other stakeholders in cc)
- Countries can nominate and rank up to three individuals per training block



PATHOGEN WAVES AND TRAINING SITES

Year			Site
1	Respiratory viruses (SARS-CoV-2, influenza)	AMR (CCRE, MRSA and *C. difficile*)	DK
2	FWD (*Listeria, Salmonella*, STEC, etc)	VPI (*N. meningitidis, B. pertussis*) *(TBC)*	FR
3	Tuberculosis	*TBD*	DE
4	*TBD*	*TBD*	

Thank you for your attention!