

## FINAL REPORT

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## Background

The ECDC Fellowship Programme is a two-year competency-based training with two paths: the field epidemiology path (EPIET) and the public health microbiology path (EUPHEM). After the two-year training, EPIET and EUPHEM graduates are considered experts in applying epidemiological or microbiological methods to provide evidence to guide public health interventions for communicable disease prevention and control.

Both curriculum paths provide training and practical experience using the 'learning by doing' approach at acknowledged training sites across European Union (EU) and European Economic Area (EEA) Member States.

According to Article 9 (6), Article 5 (8) and Article 11a (1) of Regulation (EU) 2022/2370 of the European Parliament and of the Council of 23 November 2022 amending Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (the ECDC Founding Regulation):

Article 9 (6) 'The Centre shall, as appropriate, support and coordinate training programmes, in particular in relation to epidemiological surveillance, field investigations, preparedness and prevention, response to public health emergencies, public health research and risk communication. Those programmes shall take into consideration the need for training to be kept up-to-date, take into account the training needs of Member States and shall respect the principle of proportionality.'

Article 5 (8) 'By encouraging cooperation between experts and reference laboratories, the Centre shall foster the development of sufficient capacity within the Union for the diagnosis, detection, identification and characterisation of infectious agents that have the potential to pose a threat to public health. The Centre shall maintain and extend such cooperation and support the implementation of quality assurance schemes'.

Article 11a (1) 'The Centre shall establish a EU Health Task Force and ensure that there is a permanent capacity and an enhanced emergency capacity to mobilise and use it. The EU Health Task Force shall provide assistance with regard to requests for prevention, preparedness and response planning, local responses to outbreaks of communicable diseases and after-action reviews in Member States and in third countries, in cooperation with the WHO. The EU Health Task Force shall include the Centre's staff and experts from Member States, fellowship programmes and international and non-profit organisations'.

Moreover, Article 47 of the Lisbon Treaty states that 'Member States shall, within the framework of a joint programme, encourage the exchange of young workers.' Therefore, ECDC initiated the two-year EUPHEM training programme in 2008. EUPHEM is closely linked to the European Programme for Intervention Epidemiology Training (EPIET). Both EUPHEM and EPIET are considered 'specialist pathways' of the two-year ECDC fellowship programme for applied disease prevention and control.

This final report describes the output of the fellow and the competencies they acquired by working on various projects, activities, theoretical fellowship training modules, other modules or trainings and international assignments or exchanges during the fellowship.

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# Pre-fellowship short biography

Adrienn Hanczvikkel had two carrier paths before the EUPHEM fellowship. She graduated as a biology and ecology teacher and taught for five years in a secondary school and for eighteen months at a university. Teaching has contributed to Adrienn's commitment to lifelong learning and her dedication to sharing knowledge. Her enthusiasm for microbiology began during her MSc studies, when she investigated *Streptococcus pneumoniae*. Her commitment was further strengthened during her doctoral study, when she examined the effectiveness of antibacterial agents against nosocomial pathogens. After obtaining her PhD, she started to work in the Hungarian National Center for Public Health and Pharmacy with healthcare-associated, multidrug-resistant Gram-negative bacteria. During the pandemic she was also involved in COVID-19 molecular diagnostics. This difficult period made Adrienn aware of the importance of interdisciplinary knowledge and the need for collaboration among healthcare professionals. Adrienn's interest in public health, combined with her desire for self-improvement, led her to apply for the EUPHEM training.

## Results

The objectives of these core competency domains were achieved partly through project and activity work and partly by participating in the training modules. Results are presented in accordance with the EPIET core competencies, as set out in the ECDC Fellowship Manual<sup>1</sup>.

### 1. Epidemiological investigations

#### 1.1. Outbreak investigations

##### *Multidisciplinary investigation of a nosocomial outbreak caused by disinfectant-resistant *Serratia marcescens* in an adult intensive care unit, Hungary, February–March 2022*

**Supervisors:** Ágnes Hajdu, Ákos Tóth

**Category:** Healthcare-associated infections and antibiotic resistance

Eight cases of bloodstream infection (five fatal) caused by non-multidrug-resistant *Serratia marcescens* were identified in an adult intensive care unit (ICU-1). The outbreak investigation team (OIT), which comprised a public health physician, two microbiologists, the infection control doctor, infection control nurse and two intensive care physicians aimed to identify the reservoir and mode of transmission. A matched case-control study was conducted: a confirmed case was a patient with a *S. marcescens* positive haemoculture, treated in ICU-1 between 9 February 2022 and 21 March 2022; controls had no *Serratia*-positive samples and were matched to cases by stay in ICU-1 ( $\geq 24$ hrs before haemoculture sampling of a case). Matched odds ratios (mOR) were calculated for procedures, medications and bed location using conditional logistic regression. The OIT conducted cgMLST cluster analysis of 14 *S. marcescens* from eight cases, two non-cases and four environmental samples (Ridom SeqSphere+). Minimum inhibitory concentrations of the quaternary-ammonium containing surface disinfectant used in ICU-1 were measured and compared to the manufacturer's recommendation (QAC-SfD MIC%). The OIT found that cases were more likely to be located around 'Sink-2' (mOR=25; 95% CI: 1.5-420) and had significantly ( $p < 0.01$ ) more procedures/medications (mean $\pm$ SD: 37 $\pm$ 6) than controls (mean $\pm$ SD: 25 $\pm$ 7). Case isolates clustered together (0-1 allele-difference, complex type (CT) 809), two environmental isolates (cleaning cloth, cleaning bucket) were closely related to them (17-19 allele-difference, CT810). All other isolates were distinct ( $\geq 1956$  allele-difference). The QAC-SfD MIC% values of case and environmental isolates were close to or above (78–312%) the recommended concentration. The OIT concluded that the reservoir of the outbreak strain was most probably around 'Sink-2', and the outbreak strain was able to survive there, despite regular cleaning/disinfection. More frequent manipulation, combined with hand hygiene breaches presumably increased the exposure of cases and the likelihood of bloodstream infection. The OIT recommended replacing the QAC-SfD, discarding the cleaning equipment and improving hand hygiene compliance.

Role: co-investigator

With regular consultation and under the guidance of the supervisors, the fellow was involved in every step of the outbreak investigation. Adrienn created the data collection sheets, visited the ICU-1 site to draw its floorplan and collect data, did the statistical calculations, measured the sensitivity of the *S. marcescens* isolates against the disinfectant used, summarised the antibiotic sensitivity results, assisted in whole genome sequencing and analysed the results using bioinformatics tools. The fellow was responsible for liaising with the other members of the OIT team and communicating the results to the OIT and ECDC advisors [4]. Adrienn wrote an abstract for the 33<sup>rd</sup> ECCMID 2023 (accepted as poster presentation, [16]) and for the 20<sup>th</sup> Congress of the Hungarian Society for Infection Control Hungarian conference (accepted as an oral presentation [15]) about the project. The fellow prepared and presented the ECCMID poster [16] and the oral presentation [15] for the Hungarian conference. The final output of the project was a manuscript submitted to Eurosurveillance [1].

<sup>1</sup> European Centre for Disease Prevention and Control. European public health training programme. Stockholm: ECDC; 2020. Available from: <https://www.ecdc.europa.eu/en/publications-data/ecdc-fellowship-programme-manual-cohort-2021>

## **Educational outcome**

Prior to the EUPHEM program, the fellow was only indirectly involved in outbreak investigations by conducting antibiotic susceptibility tests and investigating the antibiotic resistance mechanisms of outbreak strains. During this project, the fellow had the opportunity to be involved in every step of a healthcare-associated outbreak investigation. She developed her competence in public health management and communication (such as organising workflows and communicating results), in applied microbiology and laboratory investigations (especially in whole genome sequencing) and in basic epidemiological tasks (such as data collection and data analysis with basic statistical methods).

### **1.2. Surveillance**

#### **1.2.1 Evaluation of the Hungarian invasive meningococcal disease surveillance system due to a dramatic drop in the notification rate of IMD during epidemiological season 2020/2021. A real decrease?**

Supervisors: Ákos Tóth, Tímea Erdósi, Zsófia Bognár

The notification rate of invasive meningococcal disease (IMD) halved in Hungary during epidemiological season 2020/2021 (0.23/100 000 population) compared to the previous nine seasons (mean±SD 0.44±0.06/100 000). This project investigated whether the epidemiology of IMD had actually changed or whether the COVID-19 pandemic affected the functioning of the Hungarian IMD Surveillance System (IMD-SS), causing a pseudo-decrease in the notification rate. The objectives were to describe the epidemiology of IMD, evaluate the IMD-SS and to make recommendations for its further improvement. Incidence, seasonality, case-fatality and age-distribution of cases were estimated in all seasons from 2011/2012 to 2020/2021. The operation of IMD-SS was evaluated and compared in seasons 2018/2019 (pre-COVID-19) and 2020/2021 (during-COVID-19) using ECDC-defined surveillance attributes: external/internal completeness, usefulness, positive predictive value, timeliness, simplicity and flexibility. The results showed that in 2020/2021 the IMD incidence decreased by -3.5 standard deviation (SD), the rate of <1-year old cases increased by 3.3 SD, and the usual seasonality of IMD was not observed compared to previous seasons. The case fatality did not change, but it was higher (16±3.6%) than the EU/EAA average (10%) in all seasons. The surveillance attributes showed no significant differences before and during the COVID-19 pandemic; the IMD-SS found all cases, prevented further ones and the internal completeness, positive predictive value and timeliness variables fitted for purpose. It was determined that the IMD-SS could be simplified (paper-based notification form), that there were missing/incomplete metadata sets and that parts of the epidemiological and microbiological information systems were incompatible. The conclusion was that the IMD-SS met its objectives before and also during the COVID-19 pandemic, the changes in IMD epidemiology in 2020/2021 were real and could possibly be explained by COVID-19 control measures since *Neisseria meningitidis* spreads from person to person. Elimination of paper-based reporting, improvement of metadata sets/IT systems, and further investigation into the reasons for the high case fatality were recommended.

Role: Adrienn conducted the whole surveillance evaluation, with the regular consultation and guidance of the supervisors. The fellow assisted in defining the specific objectives of the evaluation, described the surveillance system, calculated and compared the epidemiological attributes and indicators, evaluated the clinical, epidemiological and microbiological subparts of the surveillance system, summarised the findings, drew conclusions and made recommendations for the further improvement of the system. She wrote a surveillance report [3] and also an abstract for ESCAIDE 2023 (not accepted) [18].

#### **1.2.2 Summary and analysis of epidemiological data and microbiological results for confirmed and suspected mpox patients in Hungary during the 2022/2023 international mpox outbreak**

Supervisors: Bernadett Pályi, Zoltán Kis, Dániel Déri

Although mpox (formerly monkeypox) is originally a zoonotic disease, the international mpox outbreak 2022/2023 primarily affected men who have sex with men (MSM), with no evidence of sustained transmission outside of these networks. From 1 January 2022 to 5 June 2023, a total of 87 929 laboratory confirmed cases and 1 095 probable cases, including 146 deaths, were reported to WHO from 111 Member States across all six WHO Regions. In Hungary, 80 cases were confirmed during this time period. Patient samples were sent to the National Center for Public Health and Pharmacy (NCPHP) for differential diagnosis (i.e. in addition to confirmatory testing for mpox, samples were also tested for other rash-causing and/or sexually transmitted diseases due to the similarity of symptoms, uncertainty of clinical diagnosis and for surveillance purposes). After the active phase of the outbreak in Hungary, it was important to collect, tabulate, summarise and analyse the results of epidemiological questionnaires and differential microbiological diagnoses in order to draw conclusions and if necessary, to determine further public health measures. This activity was a small but important step towards achieving these goals.

Role: the fellow organised, analysed and summarised the data from the patient samples with suspected mpox infection, sent to the NCPHP between 1 March 2022 and 1 June 2023. She processed the epidemiological questionnaires and tabulated the results for further analysis (e.g. basic demographic data, sexual orientation,

possible exposures, onset of symptoms, symptoms, etc.). Adrienn combined the epidemiological data with the results of differential microbiological diagnosis (human immunodeficiency virus (HIV), herpes simplex virus (HSV), varicella zoster virus (*Varicellovirus humanalpha3*), hepatitis A virus (HAV), *Treponema pallidum* subspecies *pallidum*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*). She described and analysed the data with basic descriptive epidemiological and statistical methods. The fellow wrote a short report [10] on the results for the research team at the NCPHP as a basis for further, in-depth investigation.

### **Educational outcome**

During the fellowship Adrienn learned a lot about the role, objectives, types and operation of surveillance systems, the importance of cooperation among clinicians, epidemiologists and microbiologists, the methods of national and European level data collection, analysis and report, etc. She developed her competencies in description of surveillance systems, drawing flow charts for their structure/operation, defining, calculating and evaluating epidemiological indicators and surveillance attributes, and writing output documents, such as reports and scientific abstracts.

## **2. Applied public health microbiology and laboratory investigations**

### **2.1 Carbapenem-resistant *Acinetobacter baumannii* causing healthcare-associated bloodstream infections in Hungary: a surge in incidence-density during the pandemic without changes in pathogen population**

Supervisors: Ágnes Hajdu, Ákos Tóth

From 2018–2019 to 2020–2021, the number of haemocultures positive for carbapenem-resistant *Acinetobacter baumannii* (CRAB) increased by 287% in Hungary (EARS-Net database). This project aimed to investigate whether the incidence-density of healthcare-associated bloodstream-infections caused by CRABs (CRAB-HA-BSI) increased concomitantly during the COVID-19 pandemic and whether this could have been caused by changes in the population structure of the pathogen (e.g. due to new sequence type (ST), resistance mechanisms, etc.). National and hospital CRAB-HA-BSI incidence-densities were calculated using infection and patient-day data from national surveillance and healthcare administration datasets. Using a purposive sample of hospitals considering incidence-density and geographical location, the research team conveniently selected CRABs isolated from haemocultures sent to the national biobank before and during the pandemic. The resistome and virulome of CRABs were compared and their clonal relatedness (cgMLST) was analysed using Ridom-SeqSphere+. The results showed that the CRAB-HA-BSI incidence-density increased from 1.8 to 7.8 infections/100 000 patient-days nationally from 2018–2019 to 2020–2021. The genomic analysis involved 25 (2018–2019) and 107 (2020–2021) CRABs from 12 hospitals with increases in incidence-density ranging from 3% to 721%. The resistome and virulome of CRABs did not change during the pandemic. In both periods, ST2 clone carrying *bla*<sub>OXA-23</sub>+*bla*<sub>OXA-58</sub> and ST636 clone carrying *bla*<sub>OXA-72</sub> caused BSIs. Clusters were identified in both clones that persisted for all four years and/or spread in ≥2 hospitals. The incidence-density of CRAB-HA-BSI increased dramatically in Hungary during the COVID-19 pandemic. However, the population structure of CRABs did not change; the same clones with unvaried resistome and virulome caused BSIs in both investigated periods. The scale of incidence-density changes, long-persisting clusters and inter-hospital spread suggested poor compliance with infection control measures, probably aggravated by the burden on the healthcare system during the pandemic. A post-pandemic review of lessons learned and reinforcement of comprehensive patient safety measures in hospitals were recommended.

Role: Adrienn was involved in the routine testing of the *A. baumannii* strains, performing antimicrobial susceptibility tests and investigated the isolates' resistance mechanisms using conventional multiplex PCR. She learnt and applied the methods of DNA isolation, library preparation, short-read sequencing and data analysis with bioinformatics tools. Adrienn was also responsible for calculating national, county and hospital incidence-density values using infection and patient-day data collected by the epidemiologists in the Department of Communicable Disease Epidemiology and Infection Control. The fellow summarised the results and wrote an abstract for ESCAIDE 2023 (not accepted) [19]. She gave an oral presentation in Hungarian at the 50<sup>th</sup> Congress of the Hungarian Infectology and Clinical Society of Microbiology on 30 September 2023 [17]. The main output of the project was an oral presentation for the Project Review Module [16]. The manuscript on this topic is currently being prepared [2].

## 2.2 Serological diagnosis of human West Nile virus infections

Supervisors: Anna Nagy, Orsolya Nagy

West Nile virus (WNV) is one of the major public health threats in the tropical and subtropical regions, but due to climate change it has recently become a medical concern even in temperate zones such as Hungary. Between 2008 and 2021 the mean notification rate was  $0.35 \pm 0.59/100\ 000$  people in Hungary, showing an increasing trend ( $y=0.036x+0.075$ ). The upward trend is in line with the predictions that the recent changes in climatic conditions, particularly the increased ambient temperature and the fluctuations in rainfall amounts, are favourable for vector competence (the ability of *Culex sp.* to acquire, maintain and transmit the virus), the vector population dynamic and the virus replication rate within the mosquito. As no specific prophylaxis or treatment exists against serious WNV infections (West Nile Neuroinvasive Disease), prevention of the population at risk is even more important. Real-time surveillance of WNV infections, collecting reliable and accurate data on cases and high-risk areas and early warning of clinicians and public health authorities are essential for effective and targeted prevention measures. In Hungary, the National Reference Laboratory for Viral Zoonoses is exclusively responsible for the microbiological diagnosis of human WNV infections across the entire country. In the reference laboratory cost-effective, in-house Indirect Immunofluorescence Antibody Assay (IIFA) test slides are produced for surveillance and research purposes before every season. During this activity ~120 in-house WNV IIFA test slides were produced as part of the preparation for the 2023 WNV season. All work was carried out according to the Standard Operating Protocols (SOP) of the National Reference Laboratory for Viral Zoonoses. For the production of IIFA test slides, WNV lineage 2 578/10 strain (GenBank accession number: KC496015.1) and VERO E6 cell line (CRL-1586™) were used. The functionality of the slides was confirmed by testing with positive and negative controls. We confirmed that the slides worked properly and that they were suitable for WNV screening and WNV antibody titration of patient samples.

Role: as the fellow had no previous experience not only with flaviviruses, but also with viruses in general, she was only an intern for this activity. Adrienn acquired knowledge of flaviviruses and improved her understanding of the principles, techniques and challenges of their microbiological diagnosis. During the practical part of the activity she observed and applied some of the techniques used at the National Reference Laboratory for Viral Zoonoses. She participated in the maintaining and passaging of cell cultures, checked the titer of the newly produced virus stock solution, produced 120 pcs in-house IIFA slides, and verified the operability of the in-house IIFA slides with positive and negative controls. During routine diagnostic work, she observed and tried the reading and interpretation of the in-house and commercially available IIFA test (Flavivirus Mosaic 1 IIFT – EUROIMMUN Medizinische Labordiagnostika AG). The fellow wrote a reflective note on this activity [5].

## 2.3 HERA2 Microbial genomics workshop, bacterial typing and antimicrobial resistance

Supervisors: Ákos Tóth

The HERA2 Microbial genomics workshop was set up by the HERA2 project and was led and coordinated by the Austrian Agency for Health and Food Safety (AGES), with equal contributions from the competent public health authorities of Croatia (CIPH), Greece (EODY) and Hungary (NNGYK). HERA2 is funded by the European Health and Digital Executive Agency (HaDEA) under the framework of the EU4Health programme, HERA2 - Consolidation of WGS/RT-PCR and infrastructure processes in outbreak surveillance and investigation. The training was hosted by the School of Medicine at the University of Crete, Heraklion, Greece on 2–3 May 2023. The scientific programme for the workshop combined seminars on highly relevant public health topics, such as antimicrobial resistance, with live demonstrations of genomic/bioinformatics data analysis tools for outbreak scenarios.

Role: Adrienn was one of the Hungarian participants at this workshop. The workshop was a great opportunity for the fellow to learn more about her future tasks. She obtained a certificate and wrote a reflective note on the activity [13].

### **Educational outcome**

During the CRAB project, the fellow developed her competencies in conducting all stages of a PHM research project, from planning to the communication of results, but especially in WGS and bioinformatics analysis of sequencing data, the use and calculation of basic descriptive epidemiological indicators, data analysis, abstract and manuscript writing. During the activities, Adrienn gained useful new knowledge of human pathogens, and learned new techniques and microbiological testing methods.

## 3. Biorisk management

### 3.1 BLS-3 training

Supervisors: Bernadett Pályi, Zoltán Kis, Dániel Déri

One of the minimum requirements of the EUPHEM training programme is a BSL-3 level laboratory training. Adrienn developed her theoretical knowledge to understand the basic skills and competences needed to work with pathogens posing a high risk to personnel, the community and/or the environment, with a special focus on the SARS-CoV-2 virus as a result of her related respiratory disease/SARS-CoV-2 activity. The theoretical part of the fellow's training programme took the form of discussions, explanations and readings, moving from general concepts to laboratory-specific knowledge. Some of the topics included international and national legislation on biosafety and biosecurity; basic definitions (hazard, threat, likelihood, risk, etc.), and the classification of microbes in risk groups and laboratories in BSL-levels in view of recent WHO recommendations to adopt a risk and evidence-based approach to biosafety rather than a prescriptive approach. She also learned about the equipment and procedures; biorisk assessment tools; biorisk mitigation; biorisk performance; laboratory and pathogen (SARS-CoV-2) specific biosafety regulations and strategies. The practical training started with the demonstration of the procedures/techniques (use of PPE, protocols for entry and exit, documentation, the facility's maintenance routine, biosafety cabinet procedures, etc.) by the supervisors. This was followed by practical work, applying the procedures/techniques in a BSL-2 environment. The practical training was completed by practising the procedures/techniques in a BSL-3 environment.

Role: During this activity the fellow was a trainee.

#### *Educational outcome*

As Adrienn had never worked in a BSL-3 environment before, this activity was a great opportunity to gain experience working with high-risk pathogens. She also gained a broad theoretical knowledge of the role, purpose and operation of a BSL-3 laboratory. The fellow had the opportunity to practise many of the basic BSL-3 procedures, and also some basic virology techniques (such as passaging cell cultures or virus neutralisation) in a BSL-2 environment.

### 3.2 Observing/assisting with SARS-CoV-2 routine work in a BSL-2 and BSL-3 laboratory

Supervisors: Bernadett Pályi, Zoltán Kis, Dániel Déri

UP to 16 April 2023, over 763 million confirmed COVID-19 cases and over 6.9 million deaths had been reported globally. The COVID-19 pandemic shook the foundations of the world's economic, social and health systems and exposed a serious lack of preparedness. Although the COVID-19 pandemic has declined, the SARS-CoV-2 virus has not disappeared and as it continues to circulate, it is evolving and adapting itself through mutations. While most emerging mutations have no significant impact on the spread of the virus, some mutations, or combinations of mutations provide the virus with a selective advantage (e.g. increased transmissibility or the ability to evade the host immune response) Depending on these mutations, several future scenarios are possible. In order to ensure preparedness for a possible new pandemic, it is essential to further investigate, identify and report the distribution of different variants of the virus, to place clinical samples and virus isolates in a biobank, to set up serological assays for research and vaccinology studies and to train microbiologists for the laboratory work with SARS-CoV-2 in a BSL-3 environment. This is extremely important as the lack of qualified staff has been a critical bottleneck to conducting fundamental research on SARS-CoV-2 in many countries. In line with these objectives, Adrienn observed and assisted the routine work with SARS-CoV-2 under BSL-2 and BSL-3 conditions.

Role: Adrienn's role was to observe and assist with the daily work of the SARS-CoV-2 working group in a BSL-2 and BSL-3 environment. She worked on the passaging of cell cultures and SARS-CoV-2 virus neutralisation. She wrote a reflective note on her activities [12].

#### *Educational outcome*

This activity was directly based on Adrienn's BSL-3 training, so she was able to use the principles and techniques she had learned there, complemented by agent-specific knowledge (e.g. SARS-CoV-2, handling infectious virological clinical samples, virus strains and cell cultures, isolating SARS-CoV-2, performing virus neutralisation tests and doing basic biobanking). The fellow joined the SARS-CoV-2 working group and assisted in its daily work. Adrienn wrote a reflective note on the methods learned and used, the experiences gained and the skills acquired.

## 4. Quality management

### 4.1 INSTAND External Quality Assessment Bacterial Genome Detection: Carbapenemase-Genes

Supervisors: Ákos Tóth

Investigation of the mechanisms underlying antibiotic resistance is a high priority task for the HAI and AMR National Reference Laboratory (NRL-AMR). Acquired carbapenemase-encoding antibiotic resistance genes pose a serious, ongoing public-health problem and their spread can lead to serious bacterial infections, or even outbreaks with limited treatment options and increased mortality. The 'gold standard' detection method for the identification of carbapenemase encoding genes is the polymerase chain reaction (PCR)-based assay. Participation in and successful completion of the 'INSTAND EQA - Bacterial Genome Detection, Carbapenemase-Genes' not only ensured the consistent, high-quality work of the NRL-AMR, but was mandatory for the renewal of accredited status for procedures. In 2021 eighty-eight laboratories participated in the INSTAND EQA, and 96.6% (85/88) completed the process successfully. The NRL-AMR was one of the laboratories that fulfilled the requirements for INSTAND EQA and obtained a certificate on 9 December 2021.

Role: As Adrienn already had experience in identifying carbapenemase genes using conventional PCR-based assays, she was tasked with leading and documenting the examinations during the 'External Quality Assessment (EQA) of INSTAND e.V - Bacterial Genome Detection, Carbapenemase-Genes' and reporting the results via the online interface. The fellow wrote two reflective notes on the project [8].

### 4.2 Accreditation procedure at the Department of Bacteriology, Mycology and Parasitology

Supervisors: Ákos Tóth, Brigitta Berta

Accreditation of clinical and public health laboratories is the process by which an independent and authorised agency evaluates their quality system and competence, on the basis of certain pre-defined standards. In Hungary, the National Accreditation Authority (NAA) issues an accreditation certificate, the accredited status is valid for five years on condition that the 'Client' meets the requirements for interim inspections (at least three times with no more than two years between on-site visits). The National Center for Public Health and Pharmacy (NCPHP) in Hungary had eighteen areas accredited under MSZ EN ISO 15189:2013 'Medical laboratories, requirements for quality and competence' and another three areas accredited under MSZ EN ISO/IEC 17025:2018 'General requirements for the competence of testing and calibration laboratories'. In 2021, the NCPHP applied for the renewal of the status of already accredited areas and the accreditation of several new areas. The accreditation procedure consisted of a multi-stage assessment (evaluation of documentation, on-site visit) and decision-making phase. On 10 March 2022, the NAA issued the accreditation certificate for the Bacteriology, Mycology and Parasitology department where the fellow was working. The department complied with the criteria for the MSZ EN ISO 15189:2013 and MSZ EN ISO/IEC 17025:2018 standards, and was assigned the status of a 'Medical Testing Laboratory' (registration number NAH-9-001/2022). The start date for the accredited status was 10 March 2022 and the expiry date is 10 March 2027.

Role: Adrienn's responsibilities were to overview and improve the SOP for conventional PCR methods detecting Extended Spectrum  $\beta$ -Lactamases in *Enterobacteriaceae* isolates and the SOP for conventional PCR methods for detecting carbapenemase genes in *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates. She was also tasked with drafting a new SOP for conventional PCR method detecting the carbapenem-hydrolyzing class D  $\beta$ -lactamases in *Acinetobacter baumannii* isolates; and reviewing and improving the annexes of the SOP 'MUTb1-04-04: Evaluation of antibiotic susceptibility of bacteria using phenotypic methods'. The fellow collected and checked all the documentation required for the on-site-visit, and demonstrated the testing method for 'Phenotypic testing of bacterial susceptibility to antibiotics by disc diffusion' during the visit. The fellow wrote two reflective notes on the project [6,7].

### 4.3 Campylobacter-Salmonella antimicrobial susceptibility and whole genome sequencing EQAs

Supervisors: Tünde Mag, Andrea Balázs Sigmond, Szilárd Tóth, Jozefina Raibli, Erika Ungvári, Ákos Tóth

Campylobacteriosis and salmonellosis are the most commonly reported foodborne zoonotic diseases in the EU/EEA countries. *Campylobacter sp.* and *Salmonella sp.* are commonly found in the intestines of healthy, food-producing animals and can enter the human body via the consumption of contaminated food or drinking water. Due to the close integration of the livestock, food producing and human health sectors, a 'One-Health' approach is essential to reduce the burden of these diseases. For a 'One-Health' approach, the surveillance systems, testing methods and interpretation protocols need to be harmonised across all the different sectors in every EU/EEA country. Every year, the Food- and Waterborne Diseases and Zoonosis Network (FWD-Net) and the Food- and Waterborne Diseases Antimicrobial Resistance - Reference Laboratory Capacity Project (FWD AMR-RefLabCap) organise several external quality assessments (EQA) to ensure the reliability of the results from the European FWD Reference Laboratories, and to support capacity building in the EU/EEA countries. These EQAs represent the first,

indispensable steps towards harmonisation. The Hungarian FWD National Reference Laboratory (FWD-NRL) participates in these EQAs every year. In 2022, the FWD-NRL applied for the eighth EQA of antimicrobial susceptibility test for *Campylobacter sp.* and *Salmonella sp.* (EQA8-AST) and for the first supplementary EQA exercise for WGS-based characterisation of *Salmonella sp.* and *Campylobacter sp.* (EQA1-WGS-AMR). The aim of the FWD-NRL was to successfully complete these EQAs. The fellow's aim was to provide professional help in areas she was already familiar with (antimicrobial susceptibility testing) and to gain basic knowledge in new areas. The FWD-NRL fulfilled the requirements of the EQAs with only some minor deviations and slight inaccuracies.

Role: Adrienn provided professional support and quality control during the antibiotic-susceptibility tests. She helped suggest the appropriate methodology according to EUCAST protocols, performed quality control and managed the equipment used for antibiotic susceptibility testing. She provided control strains and specific antibiotics, assisted with the correct application of the tests, learned and assisted with the Whole Genome Sequencing process. Adrienn's other main responsibility was to identify the resistance mechanisms of *Salmonella sp.* test strains using pheno- and conventional genotypic (PCR) methods. She also contributed to the reporting of the results of EQA8-AMS and EQA1-WGS-AMR. As a trainee, she learned new techniques, such as culturing, identification, pheno- and genotypic investigation and serotyping of *Salmonella sp.* and *Campylobacter sp.* isolates, WGS and WGS data analysis. She wrote a reflective note on her activities [9].

### **Educational outcome**

During the accreditation project, Adrienn learned more about the role and the process of accreditation. She was involved in every step of an accreditation audit. During the EQA activities she developed her competencies in performing and reporting EQAs, mainly in the area of antimicrobial susceptibility testing, identification of resistance genes using conventional PCR-based assays and whole genome sequencing. She also learned about other laboratory methods which were totally new for her, such as *Salmonella* serotyping (non-sequencing typing methodology), the challenges involved in selective culturing techniques for stool samples and the special incubating conditions for *Campylobacter* spp. isolates.

## **5. Public health microbiology management**

### **5.1 Multidisciplinary investigation of a nosocomial outbreak, caused by disinfectant-resistant *Serratia marcescens* in an adult intensive care unit, Hungary, February–March 2022**

Supervisors: Ágnes Hajdu, Ákos Tóth

This project involved a healthcare-associated bloodstream infection outbreak, requiring multidisciplinary approach. The details are set out in the section on outbreak investigation. The fellow was involved in every step of the outbreak investigation and learned a great deal about public health management and communication. The fellow was responsible for liaising with the other members of the Outbreak Investigation Team (OIT), organising and carrying out data collection in the hospital's intensive care unit and hygiene department, organising meetings and communicating the results to the OIT and ECDC advisors via a report and an online meeting. While writing the abstract/manuscript, she consulted with the other co-authors.

### **5.2 National point-prevalence survey of healthcare-associated infections and antimicrobial use in hospitals in 2022**

Supervisors: Ágnes Hajdu

The aim of this project was to train infection prevention and control (IPC) professionals, public health doctors and public health officers in the methodology of the national point-prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals (PPS). This project was primarily a teaching opportunity for Adrienn (see the details in the Teaching and Pedagogy section), but it was also a great opportunity to observe and participate in the organisation of a national survey, which only takes place every five years. Adrienn was an intern in the national coordination team for the 2022 PPS. She participated in the meetings, assisted in planning, discussing and dividing the tasks and compiling the schedule, found solutions for emerging problems and took notes on questions and comments during the training events.

### **5.3 WHO Public Health Laboratories: Laboratory Leadership Webinar Series**

Supervisors: Ákos Tóth

The fellow participated in an online webinar organised by the WHO Public Health Laboratories: Laboratory Leadership Webinar Series. This course proved to be a great introduction to the subsequent module 'Management, Leadership and Communication in Public Health'. She learned about the theory of general management, roles and styles, the optimisation of laboratory workflow, different personality traits, motivation types, and effective cooperation in teams. She acquired some useful techniques and tools and, following a successful outcome in the final exam, she obtained a certificate.



## 5.4 Inventory and education manager tasks

At the National Center for Public Health and Pharmacy, each working group needs to have an inventory manager and an education manager who know the local conditions (e.g. colleagues, rooms, laboratories and equipment belonging to the working group), can manage the tasks on the spot and pass on all necessary information to the central inventory department and the central accreditation working group. Adrienn has been responsible for these two tasks in the Bacteriology I. working group. These tasks, mainly involving administration and communication, were useful for developing competencies in institutional public health management. The fellow wrote a reflective note summarising these tasks [14].

### *Educational outcome*

All projects and activities provided opportunities for Adrienn to develop her competencies in public health management, especially within the public health institution and with colleagues (e.g. via meetings, joint planning of projects, organisation of workflows, reconciling different interests, solving problems, discussing and communicating results.) Several of the projects/activities also provided opportunities to practice interdisciplinary communication with doctors, hospital hygiene professionals, nurses, epidemiologists and public health officers.

## 6. Teaching and pedagogy

### *6.1 National point prevalence survey of healthcare-associated infections and antimicrobial use in hospitals in 2022*

Supervisors: Ágnes Hajdu

The aim of this project was to train infection prevention and control (IPC) professionals, public health doctors and public health officers in the methodology of the national point-prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals' (PPS). This activity was mainly a teaching opportunity for Adrienn, but she also gained a great deal of knowledge and skills in public health management (see details in the section 'Public Health Microbiology Management'). In 2022, four training courses were organised for healthcare professionals on the data collection and reporting process during the Hungarian PPS. The training courses were held online due to the COVID-19 pandemic. Adrienn participated in the planning, discussions, updates and presentation of educational materials. She updated the online presentation 'Timetable and institutional organisation of the PPS - Sharing tips and good practices' [21] and also created a 30-minute, anonymous real-time, interactive quiz, as a summary of the educational material for the final session [22]. She also participated in the preparation of online, self-paced, practice PPS quizzes for the participants, as exercises that could be used independently during preparation for the survey. Each training event was attended by 80–150 participants and according to their feedback, they found the activities and materials very useful in preparing for the PPS.

### *6.2 Béla Lányi Science Day*

Supervisors: Ákos Tóth

The 'Béla Lányi Science Day' is an annual, accredited training event, organised jointly by the National Center for Public Health and Pharmacy, the Semmelweis University, the Hungarian Academy of Sciences and the Hungarian Society of Microbiology. The Béla Lányi Science Day is designed for microbiologists, clinicians, infectologists, epidemiologists, public health specialists and healthcare professionals. The fellow gave a 35-minute oral presentation, including 10 minutes discussion time, in Hungarian on *Acinetobacter baumannii* [20], and made three test questions for the end-of-course exam on her topic. The objectives of her presentation were to draw attention to the increasing public health threat of the multidrug-resistant *A. baumannii*, and to provide an insight into its origins, spread, resistance patterns and treatment options. There were 203 participants at the Science Day. Based on the feedback obtained, the audience found the lectures very useful and interesting.

### *Educational outcome*

Teaching and pedagogy played a less prominent role in Adrienn Hanczvikkel's EUPHEM training, due to her specific background in teaching. Despite her previous experience, the educational project and activity provided useful experience, especially as teaching features prominently in her future plans. The 'state-of-the-art', 'learning-by-doing' methodology used in the EUPHEM/EPIET training, the interactive case studies, role plays, working and brainstorming in small groups was very inspiring. During the fellowship, Adrienn developed her skills and competencies in many areas of pedagogy, including identifying training needs, planning and organising courses, understanding the adult learning process and the role of interpersonal skills. She expanded her repertoire of teaching strategies, e.g. by using visual aids, incorporating real-life examples and using interactive activities. She hopes that what she has learned during the fellowship will help to refine her teaching style and adapt her methods to the different learning preferences and needs of future audiences. The fellow wrote a reflective note to summarise her experiences [11].

## 7. Communication

### 8.1 Publications related to the EPIET fellowship

#### 8.1.1 Manuscripts published in peer-reviewed journals

1. Submitted manuscript to Eurosurveillance:  
Hanczvikkal A, Tóth Á, Kopcsóné Németh IA, Bazsó O, Závorszky L, Buzgó L, Lesinszki V, Göbhardt D, Ungvári E, Damjanova I, Erőss A, Hajdu Á. Nosocomial outbreak caused by disinfectant-resistant *Serratia marcescens* in an adult intensive care unit, Hungary, February-March 2022
2. Manuscript on the CRAB research project is in preparation.

#### 8.1.2 Other reports

3. Hanczvikkal A, Tóth Á, Erdősi T, Bognár Zs. Description and evaluation of the Invasive Meningococcal Disease Surveillance System of Hungary (IMD-SS). Institutional surveillance report (in English); 2023. pp 1-50.
4. Project report: Interim summary of the *Serratia marcescens* outbreak investigation.
5. Activity report: Serological diagnosis of human West Nile virus infections.
6. Project report: Reflective note on SOP development during the accreditation process.
7. Project report: Reflective note on the on-site visit during the accreditation process.
8. Project report: Reflective note on the INSTAND EQA.
9. Activity report: Reflective note on the *Campylobacter-Salmonella* EQA.
10. Activity report: Summary and analysis of epidemiological data and microbiological results of confirmed and suspected mpox patients in Hungary during the 2022/2023 international mpox outbreak.
11. Activity report: Summary of experience, usefulness and self-improvement through the teaching exercises.
12. Activity report: Observing/assisting SARS-CoV-2 routine work in BSL-3 laboratory.
13. Activity report: HERA2 Microbial genomics workshop, bacterial typing and antimicrobial resistance.
14. Reflective note on my tasks as inventory manager and education manager.

### 8.2 Conference presentations

15. Hanczvikkal A, Tóth Á, Kopcsóné Németh IA, Bazsó O, Závorszky L, Buzgó L, Lesinszki V, Göbhardt D, Kiss Zs, Ungvári E, Damjanova I, Erőss A, Hajdu Á. Felületfertőtlenítőszer-rezisztens *Serratia marcescens* által okozott véráramfertőzés járvány multidiszciplináris kivizsgálása és tanulságai Magyarországon. 20th Congress of the Hungarian Society for Infection Control, 20-21/10/2022, Gyula, Hungary, Oral presentation in Hungarian about the *Serratia* outbreak investigation for infection control experts.
16. Hanczvikkal A, Tóth Á, Kopcsóné Németh IA, Bazsó O, Závorszky L, Buzgó L, Lesinszki V, Göbhardt D, Kiss Zs, Ungvári E, Damjanova I, Erőss A, Hajdu Á. Multidisciplinary investigation of a nosocomial outbreak caused by disinfectant-resistant *Serratia marcescens* in an adult intensive care unit. 33rd ECCMID Conference, 14-19/04/2023, Copenhagen, Denmark, Onsite poster presentation with a 2-hour poster presentation session (in English).
17. Hanczvikkal A, Hajdu Á, Buzgó L, Ungvári E, Tóth Á. Nozokomiális véráramfertőzéseket okozó multirezisztens *Acinetobacter baumannii* epidemiológiája és populációstruktúrája a COVID-19 pandémia előtt és alatt. 50th congress of the Hungarian Society of Infectology and Clinical Microbiology, 28-30/09/2023, Bük, Hungary (oral presentation).
18. Hanczvikkal A, Tóth Á, Erdősi T, Bognár Zs. Dramatic drop in the notification rate of invasive meningococcal disease in Hungary, in epidemiological season 2020/2021. A real decrease? ESCAIDE 2023, 22-24/11/2023, Barcelona, Spain (abstract not accepted).
19. Hanczvikkal A, Hajdu Á, Buzgó L, Ungvári E, Tóth Á. Carbapenem-resistant *Acinetobacter baumannii* causing healthcare-associated bloodstream infections in Hungary: a surge in incidence-density during the pandemic without changes in pathogen population. ESCAIDE 2023, 22-24/11/2023, Barcelona, Spain (abstract not accepted).

### 8.3 Other presentations

20. Hanczvikkel A, Tóth Á. A MACI, a PACI és a Trójai Faló, avagy a multirezisztens *Acinetobacter baumannii* története. Béla Lányi Science Day, 23/02/2022, online, 35-minutes oral presentation with 10-minutes discussion about the origin and the characteristics of the multidrug-resistant and the pan-resistant *Acinetobacter baumannii* in Hungary.
21. Hanczvikkel A, Veress I, Szeberényi K, Székely-Szabó E, Hajdu Á. A PPV megszervezése az intézményben. Training events of the 'National Point Prevalence Survey of Healthcare-Associated Infections and Antimicrobial Use in Hospitals in 2022', 02/03/2022; 08/03/2022; 10/03/2022 (online, oral presentation).
22. Hanczvikkel A, Veress I, Szeberényi K, Székely-Szabó E, Hajdu Á. 30-minutes anonym, real-time, interactive, playful quiz. Training event of the 'National Point Prevalence Survey of Healthcare-Associated Infections and Antimicrobial Use in Hospitals in 2022', 22/03/2022 (oral presentation).
23. The molecular epidemiology of multidrug-resistant *Acinetobacter baumannii*: characterization and comparison of two clones dominant during the COVID-19 pandemic, 22/04/2022, Project review module, Spetses, Greece, (oral presentation).
24. The molecular epidemiology of multidrug-resistant *Acinetobacter baumannii*: characterization and comparison of two clones dominant during the COVID-19 pandemic, 28/08/2023, Project review module, Lisbon, Portugal, (oral presentation).
25. Buzgó L, Hanczvikkel A, Both A, Ungvári E, Tóth Á. Cefiderocol susceptibility testing against carbapenem and colistin resistant *Acinetobacter baumannii* isolates. ECCMID 2022, 23-26/04/2022, Lisbon, Portugal (poster presentation) co-author.

### 9. EPIET/EUPHEM modules attended

1. Introductory course, 20/09/2021 – 8 October 2021, online.
2. Inject Days part 1: Phylogeny and WGS course, 20 October 2021, online.
3. Inject Days part 2: Operational Research course, 27-28 October 2021, online.
4. Inject Days part 3: Data Collection and Management, 10-11 November 2021, online.
5. ESCAIDE Conference 2021, 16-19 November 2021, online.
6. Outbreak Investigation Module, 06-10 December 2021, online.
7. Outbreak Investigation Module – Discussion of the homework, 13 January 2022, online.
8. Biorisk and Quality Management module, 17-18 January 2022, online.
9. Multivariable Analysis Module, 14-18 March 2022, online.
10. Multivariable Analysis Module – Inject Day, 30 March 2022, online.
11. Introductory Course 2021 part 2 + Project Review module, 20-29 April 2022, Spetses, Greece.
12. Rapid Assessment and Survey Method module, 06-10 June 2022, Stockholm, Sweden.
13. Project Review Module, 29/08/2022 – 02 September 2022, Lisbon, Portugal.
14. Time Series Analysis Module, 07-11 November 2022, Bilthoven, Netherlands.
15. ESCAIDE Conference 2022, 23-26 November 2022, Stockholm, Sweden.
16. Vaccinology module, 13-17 February 2023, online.
17. Management, Leadership and Communication in Public Health module, 08-12 May 2023, Stockholm, Sweden.
18. Project Review Module, 28 August 2023 – 1 September 2023, Lisbon, Portugal.
19. ESCAIDE Conference 2023, 22-24 November 2023, Barcelona, Spain.

## 10. Other training

1. ECDC course - Understanding Vaccine Acceptance & Strategies to Increase Vaccine Uptake, 17 December 2021, online.
2. WHO course - Public Health Preparedness for Mass Gathering Events, 21 May 2022, online.
3. UNDSS course – Bsafe, security awareness training, 27 May 2022, online.
4. ECDC course - Epidemic Intelligence, 31 May 2022, online.
5. WHO Public Health Laboratories Knowledge Sharing Webinar – Monkeypox virus, 1 June 2022, online.
6. ECDC course – Rapid Risk Assessment, 2 June 2022, online.
7. WHO Public Health Laboratories Knowledge Sharing Webinar - Scientific Writing, 29 June 2022, online.
8. PHM lecture series of EUPHEM C2020, 1 July 2022, online.
9. EURGen-RefLabCap webinar series – Simulation exercise about WGS based outbreak investigation, 26 September 2022, 10 October 2022, online.
10. WHO webinar - Comparison of new diagnostic techniques multiplex PCR and WGS enteric infection surveillance with conventional diagnostic procedures, 4 October 2022, online.
11. ESCAIDE webinar – Using genomics for antimicrobial resistance at the public health and clinical interface, 11 October 2022, online.
12. Scientific meetings at the training site – Department’s demonstration of their scientific work, 17 January 2023, 7 February 2023, 28 February 2023, Budapest, Hungary.
13. WHO Public Health Laboratories Knowledge Sharing Webinar - Biobanking, 8 February 2023, online.
14. 33rd ECCMID Conference, 14-19 April 2023, Copenhagen, Denmark.
15. HERA2 The Next Generation Sequencing Workshop, 02-03 May 2023, Heraklion, Greece.

## 11. Missions

The fellow did not participate any missions.

## 12. Other activities

1. EURGen-RefLabCap AMR meeting, 20-21 June 2023, Copenhagen, Denmark.

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I would also like to extend my gratitude to my training site, the National Centre for Public Health and Pharmacy in Hungary, for the opportunity to carry out my projects and activities there. Although I was already working at this institute before the fellowship, I met many new and excellent colleagues during my EUPHEM projects and activities. I am truly grateful to my supervisors and all the other colleagues for giving me a glimpse into their work and for introducing me to wonderful new areas of microbiology. I look forward to working with them on many great projects in the future.

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