

The main title "Summary of work activities" in a bold, white, sans-serif font, set against a blue background.The author's name "Francesca Latronico" in a white, sans-serif font, positioned below the main title.The subtitle "European Public Health Microbiology Training Programme (EUPHEM), 2014 cohort" in a white, sans-serif font, positioned below the author's name.The section header "Background" in a bold, blue, sans-serif font.

According to Articles 5 and 9 of ECDC's founding regulation (EC No 851/2004) 'the Centre shall, encourage cooperation between expert and reference laboratories, foster the development of sufficient capacity within the community for the diagnosis, detection, identification and characterisation of infectious agents which may threaten public health' and 'as appropriate, support and coordinate training programmes in order to assist Member States and the Commission to have sufficient numbers of trained specialists, in particular in epidemiological surveillance and field investigations, and to have a capability to define health measures to control disease outbreaks'.

The ECDC Fellowship Training Programme therefore includes two distinct curricular pathways: Intervention Epidemiology Training (EPIET) and Public Health Microbiology Training (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 paths that provide competency based training and practical experience using the 'learning by doing' approach in acknowledged training sites across European Union (EU) and European Economic Area (EEA) Member States.

European preparedness for responding to new infectious disease threats requires a sustainable infrastructure capable of detecting, diagnosing, and controlling infectious disease problems, including the design of control strategies for the prevention and treatment of infections. A broad range of expertise, particularly in the fields of epidemiology and public health microbiology, is necessary to fulfil these requirements. Public health microbiology is required to provide access to experts in all relevant communicable diseases at the regional, national and international level in order to mount rapid responses to emerging health threats, plan appropriate prevention strategies, assess existing prevention disciplines, develop microbiological guidelines, evaluate/produce new diagnostic tools, arbitrate on risks from microbes or their products and provide pertinent information to policy makers from a microbiological perspective.

According to the European Centre for Disease Prevention and Control (ECDC) Advisory Group on Public Health Microbiology ('national microbiology focal points'), public health microbiology is a cross-cutting area that spans the fields of human, animal, food, water, and environmental microbiology, with a focus on human population health and disease. Its primary function is to improve health in collaboration with other public health disciplines, in particular epidemiology. Public health microbiology laboratories play a central role in detection, monitoring, outbreak response and the provision of scientific evidence to prevent and control infectious diseases.

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Stockholm, Month YEAR

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This report summarises the work activities undertaken by Francesca Latronico, cohort 2014 of the European Public Health Microbiology Training Programme (EUPHEM) at the National Institute for Health and Welfare (THL), Helsinki, Finland.

All EUPHEM activities aim to address different aspects of public health microbiology and underline the various roles of public health laboratory scientists within public health systems.

Pre-fellowship short biography

Francesca is an Italian veterinary microbiologist with interest in zoonotic diseases and a strong supporter of the One Health approach. After graduating in Veterinary Medicine she worked at the veterinary diagnostic laboratories at the University in Bari where she also did her Doctorate fellowship in "Animal Pathology and Health". Before joining EUPHEM she has been involved in different projects on antimicrobial resistance and host-pathogen interactions in Italy, Denmark and USA. Francesca joined the EPIET/EUPHEM programme to broaden her knowledge on public health microbiology and intervention epidemiology, to gain an inside experience on outbreak investigation and surveillance activities within public health institutions, and to actively engage in order to strengthen the ties between human and animal health at the European level.

Fellowship assignment: Public Health Microbiology (EUPHEM) path

Methods

This report accompanies a portfolio that demonstrates the competencies acquired during the EUPHEM fellowship by working on various projects, activities and theoretical training modules.

Projects included epidemiological investigations (outbreaks and surveillance); applied public health research; applied public health microbiology and laboratory investigation; biorisk management; quality management; teaching and public health microbiology management; summarising and communicating scientific evidence and activities with a specific microbiological focus.

The outcomes include publications, presentations, posters, reports and teaching materials prepared by the fellow. The portfolio presents a summary of all work activities conducted by the fellow, unless prohibited due to confidentiality regulations.

Results

The objectives of these core competency domains were achieved partly through project or activity work and partly through participation in the training modules. Results are presented in accordance with the EUPHEM core competencies, as set out in the EUPHEM scientific guide¹.

1. Epidemiological investigations

1.1. Outbreak investigations

A. Norovirus outbreak in a sport training facility, Finland, January 2016

Supervisor: Ruska Rimhanen-Finne

A cluster of gastrointestinal disease among 30 participants attending a training camp in a sport facility in western Finland was notified from the local outbreak investigation team to THL through the National Registry for Food and Waterborne Disease (RYMY) in January 2016. Both EPIET and EUPHEM fellows joined the THL outbreak investigation team and participated in all stages of the outbreak investigation in order to identify the source and the aetiology of the infections, the mode of transmission, undertake control measures and prevent similar outbreaks in the future. Questionnaires in Finnish and Swedish were sent by email to participants of the training camps and to staff members of the sport facility, environmental and laboratory investigations were conducted. A case was defined as a person who attended a training camp during 2-10 January 2016 or was a staff member at the sport facility and developed symptoms of diarrhoea or vomiting or abdominal pain between 5-13 January 2016. A total of 148 (45%) of 331 persons interviewed answered the questionnaires and 28 (19%) of the responders met the case definition. Nine food items served during the camp were significantly associated with the illness. Norovirus (NoV) GI was detected in a stool specimen provided by a kitchen staff member. Unfortunately no other timely collected stool specimen was available for NoV testing as stool specimens are not routinely collected in case of gastrointestinal illness, and when collected they are usually tested for bacterial pathogens and rarely for NoV and other viruses. The outbreak was effectively controlled due to the implementation of THL guidelines for cleaning

¹ European Centre for Disease Prevention and Control. European public health training programme. Stockholm: ECDC; 2013. Available from: <http://ecdc.europa.eu/en/publications/Publications/microbiology-public-health-training-programme.pdf>

and disinfection, and no further cases were reported to the sport facility and to local outbreak investigation team during January-February. By participating within all steps of the outbreak investigation, including development of questionnaires, data cleaning and analysis, virus characterisation and communication of the findings by a report the fellow was able to obtain insights into epidemiologist and microbiologist's activities and challenges regarding a foodborne disease outbreak investigation and worked closely with the EPIET fellow in a multidisciplinary team.

B. Influenza A outbreak in a nursing home, Eastern Finland, 2014-2015

Supervisors: Outi Lytikäinen, Niina Ikonen

During autumn 2014, the infectious diseases specialist at the Infectious Diseases Control Unit (INTA), THL received a phone call from a nurse to report an ongoing influenza A outbreak in an elderly nursing home in Eastern Finland. Twelve patients and an undefined number of healthcare workers were reported to have influenza-like illness (ILI) symptoms. All 12 patients were Influenza A positive by polymerase chain reaction (PCR) assay. THL investigated this influenza outbreak further because of its unusual time of occurrence as influenza peak activity is usually during middle winter-early spring and its unusual high morbidity among healthcare workers. Demographic data were collected from the patients together with information regarding ward of nursing home stay, symptoms, and vaccination status. In total, 21 patients and eight healthcare workers were reported to be positive for influenza by PCR or serology. Ten respiratory specimens were sent to the National Influenza Centre (NIC) at THL for confirmation and typing and they were characterised as influenza A H3 by multiplex real-time reverse transcriptase PCR (RT-qPCR). In addition two respiratory specimens were further characterized as Influenza A H3N2 3c.2a by sequencing, and their hemagglutinin (HA) and neuraminidase (NA) sequences were submitted to Global Influenza Sharing All Influenza Data (GISAID), a publicly international platform for sharing data of influenza. This influenza virus was antigenically different from the virus component of the 2014-2015 Northern Hemisphere influenza vaccines. The fellow participated in data collection and data analysis together with a virologist at NIC and an epidemiologist at INTA. Following the analysis and discussion of laboratory results, recommendations on the use of antivirals for prophylaxis and for infection treatments were given. In addition the data contributed towards the global database for influenza data.

C. Salmonella infections among international ice-hockey tournaments participants in Riga Cup 2015

Supervisor: Saara Salmenlinna

A multinational outbreak of *Salmonella enterica* serovars Enteritidis affecting participants of the ice hockey Riga Cup 2015 was detected by the Finnish health authorities in the middle of April 2015. Following the inquiry through the Epidemic Intelligence Information System for Food and Waterborne Diseases (EPIS-FWD), cases from five other different countries (Sweden, Norway, the UK, Lithuania and Estonia) were identified. Fourteen human faecal *Salmonella* isolates from cases were typed by serotyping, phage typing, multilocus variable-number tandem repeat analysis (MLVA), and five also by whole genome sequencing (WGS) at the Reference Laboratory at THL. All were PT1 with MLVA profile 3-10-6-4-1. WGS data were *de novo* assembled using SPAdes genome assembler and compared to outbreak and non-outbreak related *S. Enteritidis* isolates by gene-by-gene protocols developed at THL. The fellow was involved in the laboratory part at THL and became acquainted with the different methods used to type *Salmonella* isolates for outbreak investigations understanding also the importance of standardized typing methods in the settings of multinational outbreak investigation.

Training modules

The EPIET/EUPHEM introductory course familiarised participants with the methods and logistical aspects of outbreak investigations. The module 'Computer tools in outbreak investigations' taught essential data management skills (entering, validating and cleaning data), dataset management and how to perform case-control studies, descriptive and cohort studies, including stratified analyses. Building on these courses, the module on 'multivariable analysis' demonstrated the principles, application and interpretation of multivariable analysis and its role in field epidemiology.

Educational outcome: Understanding the need for a cooperative teamwork among laboratories, local and central authorities, including international collaboration; involvement in the outbreak investigations (case definitions, active case-finding, data collection, data analysis); integration of microbiological and epidemiological knowledge to investigate outbreaks.

1.2. Surveillance

A. Surveillance of respiratory viruses in Finland. Analysis of the data from the last three influenza seasons (2013-2014, 2014-2015, and 2015-2016)

Supervisors: Carita Savolainen-Kopra, Soile Blomqvist, Niina Ikonen, Outi Lyytikäinen

The influenza surveillance system in Finland includes the national laboratory-based surveillance, clinical and virological surveillance, coordinated by the National Institute for Health and Welfare. Specifically the virological surveillance consists of a sentinel surveillance network that includes healthcare centres, healthcare centres of garrisons, pediatric clinics and intensive care units distributed all over the country. During the influenza season (week 20-40) each sentinel collaborative centre is invited to send 3-5 respiratory specimens per week except intensive care units that are requested to send 5-10 respiratory specimens. In addition to the detection and characterization of influenza viruses among the respiratory specimens other viral respiratory pathogens such as respiratory syncytial virus (RSV), adenovirus (AdV), rhinovirus (HRV) and human coronavirus (HCoV) are included in the laboratory panel. Every year the collected data are reported nationally and internationally to ECDC and WHO but so far in Finland no study has been conducted to analyse and to compare the data of different viral respiratory pathogens from different influenza seasons characterized by different influenza virus activity and influenza vaccine effectiveness. The project's objectives were to analyse influenza surveillance data obtained among Finnish population during the influenza seasons over the last three years (2013-2014, 2014-2015 and 2015-2016) together with other viral respiratory pathogens (respiratory syncytial virus, adenovirus, rhinovirus and human coronavirus), and to estimate how they varied. At the National Influenza Centre, the fellow performed the RT-qPCR on a subset of respiratory specimens to detect and characterise the different respiratory viruses, the descriptive analysis of laboratory results, and drafted the scientific manuscript. Sixty-seven percent (1,027/1,542) respiratory specimens were positive at least to one viral respiratory pathogen included in the laboratory panel, and 12% were positive to more than one with coinfection of AdV and HRV being the more common combination. Virus activity was different among years, and within the same year considering the influenza season period vs period between seasons (inter-season, week 21-39). All viral respiratory pathogens under surveillance were detected during the three influenza seasons included in the study but there was variation regarding virus intensity of virus activity, time of peak intensity and trend level. During the three inter-seasons only AdV, HRV, and to less extend HCoV were detected. Influenza A and AdV were the most detected viruses among females (41%; median age, 37 yrs; range, 0-87), and among males (31%; median age, 19 yrs; range, 0-90) respectively. . Data obtained from this study will be used to preliminarily evaluate the current influenza sentinel surveillance system, potentially to update national laboratory guidelines. The study also contributed towards data on viral respiratory pathogens at national, European and international level.

B. Domestically acquired salmonellosis in Finland, 2011-2015: One Health approach

Supervisors: Saara Salmenlinna, Taru Lienemann, Sinikka Pelkonen

Salmonella enterica serovars Typhimurium and Enteritidis are world-wide important zoonotic pathogens that can cause salmonellosis with different ranges of severity, from self-limiting gastrointestinal infections to deadly systemic infections. The last EFSA-ECDC summary report on trends and sources of zoonosis, zoonotic agents and foodborne outbreaks describes an overall declining trend of salmonellosis during 2009-2013. In Finland despite a decrease among imported salmonellosis the rate of domestically acquired salmonellosis has remained stable between 15-20% during the last years. More specifically during 2011-2015, 1,621 human domestically acquired *Salmonella* isolates were typed at THL, and nearly half of them were identified as *S. Typhimurium* (457/1621, 29%) and *S. Enteritidis* (284/1621, 18%). For most of them, the source of infection remained unknown, thus the need to compare Finnish *S. Typhimurium* and *S. Enteritidis* isolates of different origin both human and non-human (wildlife and pets, foodstuff, food-producing animals and feed/farm-environment). A total of 680 *S. Typhimurium* (428 human clinical isolates, 252 non-human isolates) and 389 *S. Enteritidis* (286 human clinical isolates, 103 non-human isolates) were characterized by multiple-locus variable number tandem repeat analysis (MLVA) using recently implemented ECDC protocols. Human isolates were obtained through surveillance of gastroenteritis from clinical microbiological laboratories, while non-human isolates were selected from veterinary strain collection of surveillance programmes and diagnostic activities at the Finnish Safety Authority (Evira). Among *S. Typhimurium* isolates, 233 MLVA profiles were detected, 126 among human and 133 among non-human isolates. Among *S. Enteritidis* isolates, 94 MLVA profiles were detected, 83 among human and 33 among non-human isolates. Fifty-seven percent *S. Typhimurium* isolates and 43% *S. Enteritidis* isolates were shared among human and non-human isolates. The fellow performed MLVA including DNA fragment analysis by Peak Scanner software on a subset of isolates mainly of non-human origin, data analysis and drafted the scientific manuscript. This study has made available harmonized molecular typing data for *Salmonella* isolates of different origins and represents the background material for the development of source attribution models to be developed in the future. The comparison of *Salmonella* MLVA profiles of human and non-human origin enabled the identification of potential sources and may potentially lead to targeted interventions to improve control strategies not only at national but potentially also at European level.

C. Food- and waterborne parasites and parasitoses in Finland

Supervisor: Ruska Rimhanen-Finne

Food- and waterborne parasitoses (FWP) surveillance at EU level is particularly variable, subject to both gross under-ascertainment and under-reporting in comparison with surveillance of other food- and waterborne diseases. In addition, data on FWP collected through the surveillance system are often not regularly analysed, resulting in delays in public health intervention. The aim of this study was to describe the FWP surveillance system and demographic determinants of FWP cases notified to the National Infectious Disease Register (NIDR) in Finland during 1995-2015 due to the most important food- and waterborne parasites (*Cryptosporidium* spp., *Echinococcus granulosus*, *Echinococcus multilocularis*, *Giardia lamblia*, *Toxoplasma gondii*, and *Trichinella spiralis*) as recently ranked by WHO/FAO and further highlighted by the ECDC project on inventory of national surveillance system for food- and waterborne parasitic diseases in the EU. The fellow contributed to data cleaning, data analysis and communication of the results. The results of this study indicated that in general the level of parasite exposure remained low and the numbers of parasitoses cases remained stable in Finland, although an increased number of cryptosporidiosis cases was observed from 2009 and beyond following two salad-borne *Cryptosporidium* outbreaks and possible increased awareness among medical doctors and the population. Data from this study will be used to evaluate the state of diagnostics and surveillance for FWP in humans and in infectious sources, and possible needs to develop diagnostics to potentially contribute towards more accurate FWP surveillance.

Training modules

The EPIET/EUPHEM introductory course familiarised participants with the development, evaluation and analysis of surveillance systems.

Educational outcome: Becoming acquainted with different surveillance systems (influenza, salmonellosis) at national and international levels (NIC, TESSy, WHO); analysis and evaluation of sentinel surveillance system data; integrate data from different surveillance (human and non-human) programmes in order to identify potential source of infections to be used in the future for source attribution models; data use to inform intervention and surveillance strategies.

2. Applied public health microbiology research

A. Epidemiological and molecular aspects of bacteremic Group A *Streptococcus* type *emm89* in Finland, 2004-2014

Supervisors: Jaana Vuopio, Outi Lyytikäinen, Jari Jalava

Group A *Streptococcus* (GAS) is a gram-positive human-adapted pathogen with ability to cause diseases with a wide clinical range from mild infections such as pharyngitis to severe infections such as bacteraemia and necrotising fasciitis, known as invasive group A *Streptococcus* (iGAS) infections. The *emm* gene encodes M protein, the most important GAS virulence factor, and is also used for typing purposes. The distribution of *emm* types differs among countries worldwide. Some *emm* types, as *emm1*, have been found to be more virulent and more frequently associated with high case fatality (CF) over time. A study conducted by the previous EUPHEM fellow Pieter Smit hosted at THL described the epidemiology and *emm* types of iGAS infections in Finland and showed that although the overall incidence of iGAS infections remained relatively stable during the last few years, cases caused by *emm89* strains increased. In this study, the aim was to describe the emergence and the spread of *emm89* bacteremic GAS infections, and to analyse in detail temporal, spatial, genomic, and clinical aspects of *emm89* bacteremic GAS infections in Finland occurring during 2004-2014. Demographic data of notified bacteremic GAS cases were collected from the National Infectious Disease Register (NIDR), linked by the personal identity code to the National Population Register (NPR) to obtain place of residence and date of death to assess 7-day and 30-day CF, and to *emm* typing and whole genome sequencing (WGS) data of the corresponding isolates in order to determine pathogenic genetic factors related to the increase of *emm89* bacteremic GAS. The fellow performed descriptive and statistical analysis on the demographic data of notified bacteremic GAS and *emm89* bacteremic GAS cases retrieved from NIDR and NPR, laboratory reporting system at the National Reference Laboratory, linked them to the results obtained by WGS, analysed the data and subsequently, presented the preliminary research findings at international conference, and produced the manuscript. Clades and subclades within *emm89* were defined based on mean genetic distance measured as differences in the core chromosomal single nucleotide polymorphisms. The results showed that a new *emm89* clone, clade 3, emerged in 2009 and spread rapidly in Finland and patients infected with certain subclades of clade 3 were significantly more likely to die. A specific PCR assay was developed to rapidly detect a specific subclade during 2015 and onwards. This project showcased the importance of combining comprehensive, population-based surveillance data and full genome analyses to better understand evolution and spread of pathogens, and potentially could contribute to development of targeted vaccines.

B. Assessing seroprevalence of Puumala hantavirus and associated risk factors in Finland using population-based serum bank material and registry linkage

Supervisors: Jussi Sane, Outi Lyytikäinen, Olli Vapalahti

Puumala virus (PUUV) is a Hantavirus responsible for a zoonotic disease known as hemorrhagic fever with renal syndrome (HFRS) or nephropatia epidemica (NE) transmitted through aerosolised rodent host excreta. PUUV

infection can be asymptomatic or if symptomatic can vary from mild to severe disease with ~52% of cases being hospitalised for at least seven days and ~5% requiring dialysis treatment or prolonged intensive-care. In Finland and Sweden, PUUV is considered to be endemic and PUUV infections are a major public health problem. Previous studies to estimate the disease burden of PUUV infections and to evaluate the increased risk of acute myocardial infarction and stroke following HFRS have been based only on cases reported to national patient registers. This study aimed to perform a population-based seroprevalence study using a cross-sectional serosurvey, and after linkage to national registers (hospital discharge register, primary healthcare visit register) to explore the risk factors linked to PUUV seroconversion in the Finnish population. A total of 2,000 serum specimens randomly selected from THL Biobank Health Examination 2011 Survey (Health 2011) were tested for PUUV-specific IgG using an in-house developed indirect Immunofluorescence Assay (IFA) at the Haartman Institute in Helsinki, and in case of unclear result, the serum was also tested with an enzyme-linked immunosorbent assay (ELISA) and immunoblotting. Following the laboratory analysis of the sera, population seroprevalence were estimated using complex survey methodology to address stratification and clustering. Sampling weights were used to correct the distributions in the data to match up those in the population, and to explore risk factors associated with PUUV-specific IgG seropositivity laboratory results were linked to the questionnaire annexed to Health 2011 survey and to the Finnish national hospital discharge register data. The fellow performed IFA on a subset of sera, and statistical analysis. The overall estimated PUUV seroprevalence in the Finnish population was 12.5% with variation respect to region, sex and age, while at this stage the study of risk factors associated with PUUV-seropositivity is still under investigation. This study highlighted the importance of the use of an unbiased sample population to assess the burden of disease, in order to inform public health authorities and to prioritise targeted interventions at national and international level in transboundary areas where PUUV infections occur.

Training modules

While the EPIET/EUPHEM introductory course focused on the development and presentation of study protocols, the module 'Initial management in public health microbiology' focused on laboratory aspects, time management and collaboration as a team. In addition 'Rapid risk assessment and mass gathering' concentrated on data analysis of complex surveys addressing stratification and clustering.

Educational outcome: Conduct all stages of a PHM research project, from planning to writing a scientific paper, including reviewing of the literature, designing study protocols, conducting meetings with collaborators from academia to focus on strategic research, registry linkage, analysis of data from complex surveys, scientific presentation to a conference, and publication process.

3. Applied public health microbiology and laboratory investigations

A. Detection and characterization of human enterovirus D68 isolates in Finland, 2014

Supervisors: Carita Savolainen-Kopra, Soile Blomqvist, Niina Ikonen

EV-D68 was first isolated and described amongst children in California in 1962. Since then only few cases were reported worldwide until the mid-August 2014 when an unusually high number of children with severe respiratory disease was observed in North America and cases of respiratory illness followed by neurological symptoms were reported to CDC. Non-polio enterovirus surveillance systems are in place only in a few European countries and the absence of baseline data on the circulation of EV-D68 among the Member States represents a limitation to detect unusual increased trends and outbreaks. Following an initiative of the European Society for Clinical Virology (ESCV) in collaboration with ECDC, the aim of this study was to provide baseline data on the circulation of human EV-D68 in Finland that together with data collected by other European countries could enable the detection of unusual changes of trends in non-polio enterovirus infections and to assess the risk of EU citizen to the exposure of EV-D68. All 91 combined nasal and throat swabs (range by age, 18-79 years) collected for the national influenza surveillance system between August-November 2014 were tested using specific EV-D68 real-time PCR provided by ESCV-ECDC. EV-D68 was identified in three (3.3%) of 91 tested specimens. Of the three patients (range by age, 18-21 years; 100% male) tested positive for EV-D68, one was co-infected with Rhinovirus, and one was co-infected with Adenovirus. Sequencing of the partial VP1 region for phylogenetic analysis and virus isolation in Vero and RD cell cultures were attempted for all the positive specimens but successful only in one. The collection of data from the 19 EU/EEA Member States participating in the survey contributed towards establishing a baseline of EV-D68 strains circulating in Europe that enables the detection of unusual changes of trends that may occur in the future. The genotypic characterization of the detected strains provided information on diversity among different EV-D68 circulating in Europe and on similarity with EV-D68 responsible of outbreaks that occurred in North America during 2014.

B. Detection of Human Coronaviruses using multiplex real-time reverse-

transcription polymerase chain reaction during virological surveillance of influenza, Finland October 2013-September 2014

Supervisors: Carita Savolainen-Kopra, Niina Ikonen, Soile Blomqvist, Outi Lyytikäinen

Human Coronaviruses (HCoVs) are among several groups of viruses responsible for respiratory infections. To date six species of HCoVs have been discovered: 229E, HKU1, NL63, OC43 that usually cause mild upper respiratory infections, in addition to the highly pathogenic severe acute respiratory syndrome-CoV (SARS-CoV) and the newly discovered Middle-East respiratory syndrome-CoV (MERS-CoV) that cause severe and potentially lethal disease. While cases of illness due to SARS-CoV and MERS-CoV infections are detected because of their severe symptoms, the infections caused by 229E, HKU1, NL63, OC43 remain undetected although they can sometimes lead to severe illness in children, adults with underlying disease, and the elderly. More than one third of respiratory specimens collected under the Finnish influenza surveillance during October 2013-September 2014 were negative for all tested viral pathogens (influenza A, influenza B, respiratory syncytial virus, adenovirus, rhinovirus) included in the diagnostic panel used at the National Influenza Centre laboratory (NIC). The main aim of this project was to enhance laboratory diagnosis and identification of uncharacterized cases of respiratory illness under surveillance and to estimate the occurrence of HCoVs in respiratory infections in Finland in order to close the diagnostic gap among influenza-like illness (ILI), acute respiratory infection (ARI) and severe acute respiratory infection (SARI) cases included in the national influenza surveillance system. The fellow tested 581 respiratory specimens collected in garrisons, healthcare centres (HCC) and intensive care units (ICU) for the laboratory-based influenza surveillance during 30.9.2013 - 28.9.2014 to detect HKU1, 229E, NL63, and OC43 using a multiplex real-time reverse-transcription polymerase chain reaction (RT-qPCR), and analysed epidemiological distribution across seasons, place of origin, and age groups. HCoVs were detected in 41 (7.1%; median age: 19 years, range: 16-74; 88% male) of 581 specimens. Six persons were co-infected with two HCoVs and 22 with at least one other respiratory virus included in the diagnostic panel. HKU1 was most frequently detected (26/41), followed by 229E (13/41), NL63 (5/41), and OC43 (3/41). HCoVs were detected during January-April and peaked in February (25/41) simultaneously with high influenza activity. Among persons with HCoV positive finding, 31 were from garrisons, six from HCC and four were from ICU. No other respiratory virus was detected in the four specimens from ICU. This was the first study undertaken to set a baseline of HCoVs circulating in the community, including information on seasonal variations in Finland, and created awareness on HCoV as cause of respiratory infections at national and international level. At the moment HCoV are not routinely included in the panel for respiratory specimen testing in many countries in EU and worldwide. The results guided the decision to include HCoVs RT-qPCR in the diagnostic panel at NIC to close the diagnostic gap of respiratory viral infections under surveillance.

C. Validation of whole genome sequencing for surveillance and outbreak investigations of invasive *Neisseria meningitidis* diseases at Bacterial Infections Unit (INBA) in THL, Helsinki

Supervisors: Maija Toropainen, Anni Vainio

Neisseria meningitidis (meningococcus) is a gram-negative bacterium of a global importance that can either infect humans without causing any symptoms or be responsible of severe diseases as meningitis and septicemia, also known as invasive meningococcal disease (IMD). An increasing number of studies have been and are performed worldwide to demonstrate importance, feasibility, and need of whole genome sequencing (WGS)-based methods in the public health sector. THL has also recognized a need to renew its strategy on microbiological reference laboratory methodologies for the transition from conventional typing to next-generation sequencing (NGS)-based methods for public health microbiology purpose. Thus protocols to effectively implement NGS-based methods for surveillance and outbreak investigation of IMD are needed within the Bacteriological Infections Unit (INBA). The aim of this project was to validate the recently developed NGS protocols at THL to be implemented for IMD surveillance and outbreak investigation in Finland, and to acquire knowledge on available genome based typing schemes and their suitability for disease surveillance. The method under validation was WGS pipeline that included DNA extraction using Qiagen MagAttractHMW DNA Kit, library preparation using Illumina Nextera XT DNA library kit, use of MiSeq Sequencer to run DNA libraries, and *de novo* assembly of sequences using Velvet integrated in RIDOM SeqSphere software. The protocol was validated by testing in duplicates 32 *N. meningitidis* strains belonging to a global meningococcal MLST reference strain collection that had been previously analysed by WGS at the University of Oxford during validation of their WGS protocol with respect to Sanger sequencing. The validation included the assessment of sensitivity, specificity, and repeatability for sequence data of 16 pre-selected loci relevant for national surveillance (MLST, finotyping, and serogroup B vaccine antigen loci), and serogroup specific loci responsible for the synthesis of meningococcal capsular polysaccharide. The validated WGS-based pipeline gave reliable and reproducible results and thus proved suitable for national surveillance and outbreak investigation of IMD it has been implemented at THL, although due to inadequate sensitivity, the current pipeline is however not suitable for the prediction of capsular serogroup; this still requires conventional phenotypic methods. The development of this pipeline could contribute towards the ECDC strategy to standardise the use of WGS-based data for public health purposes at the European level.

Training modules

Phylogeny and Bioinformatics´ module provided fellows the basic tools for bioinformatics and phylogenetics to allow the fellow to use them and further deep their knowledge during the fellowship.

Educational outcome: Apply concepts of virology, bacteriology and immunology to the public health disciplines; understanding the use and limitation of diagnostic and typing methods and their interpretation; analysing WGS data and interpret them; understanding attributes of laboratory method validation.

4. Biorisk management

A. Theoretical and practical biosafety level 3 (BSL-3) training, THL, Finland

The training consisted of a two-day theoretical part which includes biosafety/biosecurity practice and legislation in Finland and one-week practical training in the BSL-3 laboratory at THL.

Training modules

A. Biorisk and quality management module, ECDC, Sweden

This five-day module provided techniques for biorisk/biosafety assessment and mitigation, including WHO recommendations on biosafety management in laboratories. One day focused on training of international shipping and international regulations for the transportation of infectious substances and dangerous goods, as determined by International Civil Aviation Organization (ICAO) and WHO. This module included also a visit to the BSL-4 facility at the Public Health Agency of Sweden, Stockholm.

Educational outcome: Understanding processes associated with BSL3/BSL4 laboratories, experience different personal protective equipment; understanding the principles and practices of biorisk management, biorisk assessment and biorisk mitigation, shipment procedures for dangerous goods.

5. Quality management

A. External Quality Assessment (EQA) for Influenza

Supervisor: Niina Ikonen

The Finnish National Influenza Centre is part of the European Influenza Surveillance Network (EISN), a network coordinated by ECDC that combines epidemiological and virological surveillance of influenza. Each laboratory of the network is also part of the European Reference Laboratory Network for Human Influenza (ERLI-Net), a sub-network within EISN that coordinates virological surveillance activities. The data produced for the virological surveillance activities are reported during each influenza season to The European Surveillance System (TESSy) providing information useful to take timely appropriate actions at the European level. As part of ERLI-Net the Finnish National Influenza Centre was invited to participate to the external quality assessment (EQA) which takes place every two years in order to assess the reliability and robustness of technologies for influenza detection and typing used in its laboratories, and to assure quality of the data submitted to TESSy. The samples of EQA influenza panel were tested for rapid detection of influenza virus (reverse-transcriptase real-time PCR), virus isolation on cell lines MDCK and/or MDCK-SIAT, antigenic characterization (haemagglutination inhibition assay, HI), genetic characterization (sequencing of HA gene), and genetic antiviral susceptibility testing (sequencing of NA gene). The analysis and interpretation of the results reported to Quality Control for Molecular Diagnostics (QCMD) was performed using MEGA5 software to analyse the sequences, create phylogenetic trees, and check for genetic antiviral susceptibility. The laboratory performed well in the EQA and was correct in the typing of all strains in the recent distribution from QCMD. The fellow participated in all steps of the EQA from assisting the laboratory technicians to test the samples by different methods, analysing and reporting the results, and discussing the quality performance of the laboratory.

B. WHO Accreditation visit for the polio laboratory at THL

Supervisors: Carita Savolainen-Kopra, Soile Blomqvist

The fellow assisted as auditor to WHO accreditation visit that was performed to evaluate the polio laboratory at THL by Dr Ousmane Diop (WHO, HQ, Geneva) and Dr Eugene Gavrilin (WHO EURO) during April 2015. Following the different steps of the WHO accreditation visit at the polio laboratory at THL the fellow became acquainted with WHO accreditation system, the polio environmental surveillance system at national and international levels, and the global polio eradication initiative.

C. Internal Quality Audit at Viral Infections Unit, THL

Supervisors: Tarja Sarjakoski, Soile Blomqvist

Periodically every accredited laboratory at THL conducts internal audits of activities to verify that operations continue to comply with the requirements of the management system and standard. Laboratory quality manual is common to all laboratories in THL and conforms to the international standard SFS-EN ISO/IEC 17015:2005. The laboratory management system policy related to quality is defined in this manual while every accredited laboratory at THL has also its own additional laboratory quality manual, where laboratories describe among other things their special characteristic functions, special legislation and persons in charge. The fellow discussed the pre-audit checklist and the audit findings of the internal audit of operation systems at Viral Infections unit (INVI) with the auditor and the laboratory manager. This activity highlighted challenges and importance of quality management in laboratories in order to assure good laboratory practices and to detect targets for development.

Training modules

Biorisk and quality management' module provided training for quality management in biomedical laboratories, mainly according to ISO 15189. In addition laboratory quality system training was organized for the fellow to get acquainted of quality system at THL.

Educational outcome: Understanding and applying the concept of EQA, describing the quality assurance, analysing, reporting and evaluating the results of EQA regarding specific methodologies for influenza virus according to international and EU directives. Understanding principles and requirements of different European accreditation systems.

6. Teaching and pedagogy

A. Infectious Disease Epidemiology course at the University of Tampere

The fellow participated in the planning and preparation of teaching materials for a one-week course on infectious disease epidemiology to postgraduate and master students at University of Tampere, Tampere, Finland. Lectures to provide theoretical background on epidemiology and on microbiological aspects including diagnostics for specific infectious diseases (influenza, measles, Ebola virus disease, salmonellosis, and coronavirus infections) were given. The fellow also moderated three sessions using case-studies on Salmonella outbreak and surveillance in the Caribbean, trichinellosis outbreak in Paris, and respiratory illness in a rural area in the Netherlands. The presentation of microbiological aspects including diagnostics for infectious diseases was introduced this year for the first time and it was highly appreciated from course participants.

B. Outbreak investigation and healthcare settings module at the University of Applied Sciences in Vantaa

The fellow prepared and gave a lecture on outbreak investigation and more specifically on outbreak investigation in healthcare settings to master students attending the Epidemiology, Biostatistics and Intervention research course, Master in Global Development and Management of Health Care, LAUREA University of Applied Sciences, Vantaa, Finland. In addition the fellow together with EPIET fellow moderated the case study on "Gastroenteritis outbreak in Sweden". The feedback from the students and the inviting course organizer was positive suggesting to further develop this subject and especially to further implement the use of case studies in the course.

C. Nordic Society of Veterinary Epidemiology course, Turku

The fellow participated in the planning and preparation of teaching materials for the annual course of the Nordic Society of Veterinary Epidemiology (NOSOVE). This course is an international course that targets a broad range of participants from veterinarians, epidemiologists, medical doctors, biologists, media representatives, to all others interested in the topics. More specifically the fellow gave a lecture on surveillance of parasitic infections in Finland and moderated the case study on trichinellosis outbreak in France, which material was adapted from the EPIET/EUPHEM introductory course to give course participants a better understanding of public health microbiology on human parasitic infections in practice. The participants of the course gave a very enthusiastic feedback of the course activities.

Educational outcome: Identifying training/educational needs, planning and organising courses, preparation of teaching materials, moderating case studies, giving lectures and performing pedagogical teaching to persons from diverse backgrounds, course/lecture evaluation.

7. Public health microbiology management

A. Public health microbiology management components as part of regular projects

Public health microbiology was an integral component of all projects and activities during the fellowship. This included laboratory management, ethical and integrity considerations, team building and coordination, research

collaboration, time management, management of cultural differences in international contexts and working in a multidisciplinary team with microbiologists, physicians, laboratory technicians, epidemiologists, statisticians, government officials, public health officers and logisticians.

Training modules

A. Initial management in public health microbiology, ECDC, Stockholm, Sweden

This one week module focused on understanding roles and responsibilities in public health management. Topic included the identification of different management styles, team roles and team evolution, the delegation of tasks and the provision of structured feedback. In addition communication exercises to different kind of audience and for different purposes were conducted.

Educational outcome: Working in a multidisciplinary public health team; understanding team management; planning, scheduling and organizing research projects; understanding the role and responsibilities to be an inspiring leader and an effective manager within public health environment; understanding different management styles; understanding team roles and team evolution to ensure the best possible results; motivation of team; conflict management, structured feedback to improve performance and minimize disruption in a conflict; communication with authorities, the public, and the media.

8. Communication

A. Publications

1. Latronico F, Nasser W, Puhakainen K, Ollgren J, Hyyryläinen H, Beres SB, Lyytikäinen O, Jalava J, Musser JM, Vuopio J. Genomic tracks behind spread of bacteremic Group A *Streptococcus* type *emm89* in Finland, 2004-2014. *J Infect Dis* 2016 doi: 10.1093/infdis/jiw468
2. Poelman R, Schuffenecker I, Van Leer-Buter C, Josset L, Niesters HGM, Lina B, on behalf of the ESCV-ECDC EV-D68 study group. European surveillance for enterovirus D68 during the emerging North-American outbreak in 2014. *J Clin Virol* 2015 71:1-9 doi:10.1016/j.jcv.2015.07.296
3. Latronico F, Mäki S, Ollgren J, Lyytikäinen O, Vapalahti O, Sane J. Population-based seroprevalence of Puumala hantavirus in Finland: smoking as a risk factor. (in preparation)
4. Latronico F, Ikonen N, Blomqvist S, Lyytikäinen O, Savolainen-Kopra C. Surveillance of respiratory viruses in Finland, 2013-2016. (in preparation)
5. Latronico F, Skufca J, Huusko S, Ollgren J, Rimhanen-Finne R. Norovirus outbreak in a sport facility, Finland, 2016. (in preparation)
6. Latronico F, Lienemann T, Kuronen H, Pelkonen S, Rimhanen-Finne R, Salmenlinna S. Domestically acquired salmonellosis in Finland, 2011-2015: One Health approach. (in preparation)

B. Reports

1. Validation report on whole genome sequence pipeline for surveillance and outbreak investigation of invasive *Neisseria meningitidis* diseases at Bacterial Infections unit at THL
2. Norovirus outbreak in a sport facility, Finland, 2016
3. WHO-exposé visit, Geneva, Switzerland, 2016
4. Influenza A outbreak in a nursing home, Eastern Finland, 2014

C. Teaching materials

Revision of case study on "an outbreak of trichinellosis in Paris" for the NOSOVE course.

D. Conference presentations

1. Latronico F, Lienemann T, Kuronen H, Pelkonen S, Rimhanen-Finne R, Salmenlinna S. Domestically acquired salmonellosis in Finland, 2011-2015: One Health approach. European Scientific Conference on Applied Infectious Disease (ESCAIDE), Stockholm, Sweden, 28-30 November 2016 (Accepted for poster presentation)
2. Vainio A, Latronico F, Halkilahti J, Toropainen M. Validation of whole genome sequencing for surveillance of invasive meningococcal disease at the national reference laboratory in Finland. International Pathogenic Neisseria Conference (IPNC), Manchester, United Kingdom, 4-9 September 2016 (poster)
3. Zoldi V, Latronico F, Rimhanen-Finne R. Surveillance of Cryptosporidium and Giardia infection in Finland, 2006-2015. 12th European Multicollquium of Parasitology (EMOP), Turku, Finland, 20-24 July 2016 (poster)

4. Latronico F, Nasser W, Puhakainen K, Ollgren J, Hyyryläinen H, Beres SB, Lyytikäinen O, Jalava J, Musser JM, Vuopio J. Genomic tracks behind spread of bacteremic Group A *Streptococcus* type *emm89* in Finland, 2004-2014. European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Amsterdam, Netherlands, 9-12 April 2016 (oral presentation)
5. Latronico F, Ikonen N, Blomqvist S, Lyytikäinen O, Savolainen-Kopra C. Detection of human coronaviruses using multiplex real-time reverse-transcription polymerase chain reaction during virological surveillance of influenza, Finland October 2013-September 2014. European Scientific Conference on Applied Infectious Disease (ESCAIDE), Stockholm, Sweden, 11-13 November 2015 (poster)

E. Other presentations

1. Latronico F. Surveillance of human parasitic infections in Finland. NOSOVE course, Turku, Finland, July 2016
2. Latronico F, Skufca J. EPIET/EUPHEM experiences as EU track fellows in Finland. Epidemiology of food hygiene course, Doctoral Program in Food Chain and Health, Department of Food Hygiene and Environmental Health, Faculty of Veterinary Medicine, University of Helsinki, May 2016
3. Latronico F. Baseline study of domestically acquired *Salmonella enterica* serovars Typhimurium and Enteritidis. Mini Nordic project review 2016, Stockholm, Sweden,
4. Latronico F. Outbreak investigations in healthcare settings. Epidemiology, Biostatistics and Intervention research course, Master in Global Development and Management of Health Care, LAUREA University of Applied Sciences, Vantaa, Finland, March 2016
5. Latronico F. Microbiological aspects and diagnostic tests for infectious diseases. Essential of Infectious Disease Epidemiology Course, University of Tampere, Finland, December 2015
6. Latronico F. Validation of whole genome sequencing for surveillance and outbreak investigation of invasive *Neisseria meningitidis* diseases at THL. INFO-TUSO joint-research seminar, THL, Helsinki, Finland, 10 February 2016
7. Latronico F, Milhano N. Vaccine development against Group A *Streptococcus* infections. Vaccinology Module, Krakow, Poland, April 2015
8. Latronico F. Surveillance of respiratory viruses in Finland, 2013-2016. Mini Nordic project review 2015, Copenhagen, Denmark
9. Latronico F. Ebola Preparedness and Response plan in Finland, IMPHM Module, Stockholm, Sweden, 13 February 2015
10. Harvala-Simmonds H, Latronico F. Carbapenem-resistant *Enterobacteriaceae* - epidemiology and role of travel. EPIET/EUPHEM Introductory course, Spetses, Greece, October 2014

9. EPIET/EUPHEM modules attended

1. EPIET/EUPHEM introductory course, Spetses, Greece (three weeks)
2. Computer tools in outbreak investigations, Robert Koch Institute, Berlin, Germany (one week)
3. Initial management in public health microbiology module, ECDC, Stockholm, Sweden (one week)
4. Biorisk and quality management module, ECDC, Stockholm, Sweden (one week)
5. Multivariate analysis module, Vienna, Austria (one week)
6. Vaccinology module, Krakow, Poland (one week)
7. Rapid risk assessment and mass gathering, Athens, Greece (one week)
8. Project review 2015 module, Lisbon, Portugal (one week)
9. Phylogeny and Bioinformatics module, Stockholm, Sweden (three days)
10. Project review 2016 module, Lisbon, Portugal (one week)

10. Other training/courses

1. WHO-exposé visit, Geneva, Switzerland (one week)
2. Ebola in the context: understanding transmission, response and control, (four weeks) free online course, London School of Hygiene & Tropical Medicine, UK
3. Preventing the Zika Virus: Understanding and Controlling the Aedes Mosquito, (three weeks) free online course, London School of Hygiene & Tropical Medicine, UK
4. NOSOVE course, Turku (three days)
5. Zika seminar, Biomedicum Campus, Helsinki, Finland (one day)
6. Annual meeting of the Finnish Study Group for Antimicrobial Resistance (FiRe), THL, Helsinki, Finland (one day)
7. S. Juselius Symposium series 2015 on Emerging Infections, Hanasaari, Espoo, Finland (four days)

Discussion

Coordinator's conclusions

One of the main goals of the EUPHEM programme is to expose fellows to diverse and multidisciplinary public health experiences and activities, thus enabling them to work across different disciplines. This report summarises all activities and projects conducted by Francesca Latronico during her two-year EUPHEM fellowship (cohort 2014) as an EU track fellow at the National Institute for Health and Welfare (THL), Helsinki, Finland. The projects described in this portfolio demonstrate the breadth of public health microbiology. Outbreak investigation activities extended from regional, national and to potential international outbreaks with excellent public health outputs, analysis of national databases and contribution towards disease specific networks at the national and European level. The surveillance core competency was fulfilled through national and internationally linked surveillance in the field of food and waterborne diseases from influenza surveillance in Finland to a 'one health approach' on domestically acquired salmonellosis in Finland which could impact upon targeted interventions and improvements in control strategies. The laboratory and epidemiologically based projects covered a diverse range of disease programmes involving multidisciplinary working and teamwork on all levels such as physicians, laboratory technicians, epidemiologists, statisticians, government officials and public health officers, strengthening the fellow's ability to work within such an environment(s). Activities were in line with the 'learning by doing' and 'on the job training' ethos of the EUPHEM programme and fulfilled the core competency domains described for professionals in their mid-career and beyond. Activities were complimented by nine training modules providing theoretical knowledge. Projects had a clear outcome, with results communicated in scientific journals and at conferences. The EUPHEM Coordinator Team concludes that the fellow has succeeded in performing all her tasks and has fulfilled the core competencies of the EUPHEM programme to a high standard and with a professional attitude. We wish the fellow every success in her future career as a public health microbiologist.

Supervisor's conclusions

DVM Francesca Latronico was the second EU track EUPHEM fellow based at the National Institute for Health and Welfare (THL). Her fellowship was also the first for me as the main supervisor for EUPHEM. During the entire two-year-period, Francesca's presence has been a joy for the whole team. Projects performed have turned out to be successful and beneficial for both the fellow and the host institute. One of the key goals achieved has been the strengthened collaboration between microbiological laboratories and epidemiological unit. Together with Francesca, we all have learned a lot.

During the fellowship I have seen Francesca to grow to a mature microbiologist with new professional skills. Especially she has become confident in bridging between public health microbiology and epidemiology within the Department of Infectious Diseases. Francesca is an excellent team player taking into account various views and sometimes conflicting interests. She has accomplished her tasks with flying colours without lowering her own high standards. When finishing her projects, she said to me: "I think I've changed! I've changed from a microbiologist to a person with a broader view on public health". This, to me, is a sign of a mission accomplished. I am fully confident that Francesca's path in public health microbiology will continue successfully.

Personal conclusions of fellow

Two-year EUPHEM fellowship is very intense public health training and passes by very fast. The success of every single fellow is the result of team work from the main and project supervisors and administrative staff at the host site, ECDC coordinators and fellowship programme office, and all the other EPIET/EUPHEM fellows around Europe that create a knowledgeable network for rapid data-sharing and support. The EUPHEM fellowship has been a great and unique opportunity to be trained in the fields of public health microbiology and epidemiology developing a broad range of competencies and skills by 'learning-by-doing' method. A key objective of the EPIET family programmes is to improve working relationships between disciplines, especially public health microbiology and epidemiology. Throughout the fellowship, my projects and activities have incorporated both these elements and they have also served to strength the ties between public health microbiologists and epidemiologists at the National Institute for Health and Welfare. Finally the EUPHEM fellowship structure enables and encourages a network of European public health laboratories contributing to the growing field of public health microbiology, and together with the EPIET fellowship between microbiologists and epidemiologists around Europe, emphasising the need for close collaboration in order to benefit public health.

Acknowledgements of The fellow

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Last but not least I would like to thank all my EPIET/EUPHEM co-fellows for friendship, support through the challenges, team-spirit and amazing company. This two-year fellowship has been a wonderful journey and I am looking forward to the next step confident that at any time, everywhere I may count on you.