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Natacha A.K.F. Milhano

European Public Health Microbiology Training Programme (EUPHEM), 2014 cohort

Background

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.

This report summarises the work activities undertaken by Natacha Alexandra Korn da Fonseca Milhano, cohort 2014 of the European Public Health Microbiology Training Programme (EUPHEM) at the Norwegian Institute of Public Health (NIPH), Oslo, Norway.

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

Prior to her EUPHEM fellowship, Natacha Milhano had been working on tickborne diseases for eight years, and was completing her PhD in Veterinary Sciences, which focused specifically upon the vector-host-pathogen interface in rickettsial diseases, particularly Mediterranean spotted fever. Her Bachelor degree is in Biochemistry, and later she pursued a Master degree in Forensic Sciences. Natacha embarked on the EUPHEM program as a means to gain a broader interconnecting knowledge between Public Health microbiology and epidemiology, to obtain hands-on experience in outbreak investigations, and to broaden and deepen her knowledge on infectious diseases in line with the One Health approach.

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 specific 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

Supervisors: Katrine Borg, Line Vold

A.A gastrointestinal outbreak among high school pupils on a school trip to Frøya, Sør-Trøndelag, May 2015

An outbreak of gastrointestinal illness among 15 pupils from Trondheim, Sør Trøndelag, attending a school trip to Frøya, Sør-Trøndelag, on the weekend of 29-31 May was reported to the Municipal Health Office in Trondheim, who subsequently informed the Norwegian Food Safety Authority (NFSA) Central Region. All pupils became ill with symptoms that included nausea, vomiting, abdominal pain, fever and diarrhoea. An outbreak investigation involving the NFSA, Municipal Health Authorities and the Norwegian Institute of Public Health (NIPH) was initiated on June 1. A questionnaire was developed and distributed among the pupils to ascertain source of infection and mode of transmission. Epidemiological analysis suggested the water from the stream as the source of infection, as all the ill students had consumed this water, except the teacher, who did not become ill. The microbiological analysis performed on stool samples recovered from three pupils showed that all were positive for Norovirus genogroup II and intestinal *E. coli*, and one sample was also positive for *Clostridium perfringens*. Further microbiological analysis was performed on water samples taken from the lake and stream, and showed higher than the defined threshold levels for *Clostridium perfringens*, intestinal enterococci and *E. coli* in drinking water. The combination of epidemiological and microbiological results strongly suggests consumption of contaminated surface water as the potential source of infection in this outbreak. A final outbreak report was prepared and sent to the NFSA, who then addressed it with the Municipal Health Office in Trondheim and the high school. The outbreak was

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>

published online on the local news website, highlighting advisory safe water consumption procedures such as drinking only bottled water and not from the lake or surrounding streams.

Natacha Milhano participated in all stages of the outbreak investigation, from devising questionnaires, receiving and analysing the data to writing the final outbreak report.

B. A foodborne outbreak after a wedding party in Stavern, Norway, June 2015

On Tuesday 9 June 2015, the Vestfold office of the Norwegian Food Safety Authorities (NFSA) reported 21 cases of gastroenteritis to the Norwegian Institute of Public Health (NIPH), among 27 guests attending a wedding party on Saturday 6 June. The guests attended a wedding dinner in hotel X and were served a set three-course menu. In addition, the wedding guests brought homemade and purchased cakes. In addition to the wedding party, the hotel hosted two other large parties on the same day, and their restaurant was open to other guests. To assess the association between food exposure and illness, we developed a short self-administered online questionnaire, including all food items served during the dinner on 6 June 2015. This questionnaire was sent to all the wedding guests. In total, 23 individuals (85%) completed the questionnaire and 17 (73%) reported being ill, with symptoms including nausea (100%), stomach pain (88%), diarrhoea (77%), vomiting (77%), fever (71%) and joint pain (65%). Onset of symptoms was reported from 12pm on Sunday 7 June to 11am on Monday 8 June, and the median duration of illness was two days. Due to high attack rates and high exposure, statistical analyses could not identify any one specific food item associated with illness. One patient stool sample tested negative for *Salmonella*, *Yersinia*, *Shigella* and *Campylobacter*, and seven food samples were taken and all tested negative for *E.coli*, *Enterococcus*, *Enterobacteriaceae*, *Clostridium perfringens*, *Bacillus cereus*, *Staphylococcus* and *Salmonella*. Environmental investigations identified minor problems with kitchen hygiene, which could not be related to the outbreak. None of the other guests dining at the same hotel on 6 June reported gastrointestinal illness. In conclusion, this was a point source outbreak; however the most likely point source could not be determined from our investigations.

Natacha Milhano contributed towards the design of the online questionnaire and writing the final report with EPIET fellow from cohort 2014 Hinta Meijerink, who was the main investigator of the outbreak. Advised on microbiological findings and the significance of the findings in this outbreak investigation.

Training modules

The EPIET/EUPHEM introductory course familiarised fellows with the methodology and logistical part of outbreak investigations. The module, 'Outbreak investigation: From data analysis to communication of findings' allowed fellows to acquire skills and competencies in all practical aspects of both data management and analysis during outbreak investigations, and also interpreting and communicating findings. In addition, the multivariable analysis module was fundamental as a follow-up to outbreak module, as it allowed fellows to learn about and perform and interpret multivariable analysis in an outbreak situation (as well as others where further analytical interpretation may be needed) as well as how to best communicate the results.

Educational outcome: The fellow had hands-on experience in outbreak investigations, from case definitions, active case-finding, questionnaire development, data collection, data analysis, communicating results in a clear and efficient manner to a multidisciplinary team, and writing outbreak reports. Natacha also perceived the important role of a EUPHEM fellow acting as a link between the laboratory and epidemiologist in an outbreak setting, both through hands-on experience through working on national outbreaks as well as in an international context.

1.2. Surveillance

Supervisors: Susanne Dudman, Katrine Borgen

A. Evaluation of the acute flaccid paralysis (AFP) surveillance system in Norway

Poliomyelitis is a notifiable disease in Norway, and in accordance with the Global Polio Eradication Initiative (GPEI), launched by WHO, Norway implemented a national plan of action to sustain the poliomyelitis-free status, based on several measures. These included high routine vaccination coverage, high quality monitoring, which in Norway is based on an AFP surveillance system, and containment of wild polioviruses in WHO-certified laboratories. The aim of this project was to determine whether the AFP surveillance system met its ultimate surveillance purpose, i.e., to sustain the polio free status of Norway, along with other measures in the Norwegian plan of action. This was performed through a descriptive study of the system and analysing attributes in order to identify both strengths/weaknesses and/or potential gaps that may need to be addressed, and should this be the case, to recommend remedial strengthening measures to be implemented in the Norwegian action plan. The system was found to be sensitive and flexible, however improvements needed to be made in terms of timeliness of case investigation and follow-up of cases. As a result of this study, changes to the current AFP surveillance system in Norway will be implemented in order to conform with WHO guidelines.

The fellow was the main investigator of this project, participating in all stages, namely working closely with stakeholders devising and sending out questionnaires for attribute assessment, performing data analysis and writing a final report, which was distributed to the key stakeholders of the surveillance system. The results of this evaluation were presented at the National Certification Committee meeting held at NIPH, and presented at the 18th Annual Meeting of the European Society for Clinical Virology meeting in September 2015.

B. Establishment of a laboratory-based surveillance of enterovirus-D68 for the season of 2015

Enterovirus-D68 (EV-D68), a member of the enterovirus genus also including rhinoviruses, coxsakiviruses and poliovirus, was first reported in 1967, following its isolation from children that presented with bronchiolitis and pneumonia in California in 1962. From August 2014 onwards, an alarming increase in the number of cases of EV-D68 was reported in the US and Canada, many of them associated with AFP, and many cases were also detected in Europe, including Norway. In light of these detections, risk assessments were performed and strengthening of EV surveillance was recommended to all countries in the EU/EEA. The goal of this project was to establish a laboratory-based surveillance system in Norway in order to assess the circulation of EV and of EV-D68 specifically, from July to December 2015. Only three cases of EV-D68 were detected during that period, whereby the project was expanded to include other enteroviruses, and perform a descriptive genotypic analysis of samples received at NIPH and St. Olav's hospital in 2014 and 2015. The overall typing analysis for both years for NIPH showed a predominance of echo 18 and echo 30, with a threefold increase of Coxsackie B5 from 2014 to 2015. For the St. Olav's 2015 data, Coxsackie A6 (20%), EV71 (4.8%) and echo 3 (3.4%) were the most commonly detected types. This study showed the seasonal fluctuation in circulating EV genotypes from one year to the next, and highlighted the importance of continued EV surveillance in Norway, in order to ascertain the virulence of circulating and upcoming EV genotypes, and appropriately guide specific Public Health recommendations at a national level. During 2016, as a result of the continued surveillance at the major laboratories in Norway, an increase in EV-D68 cases has been detected, thus the surveillance established by this project will continue at a national level. The fellow was the main investigator and participated in all stages of this project, from outline of initial protocol, sending out the proposal for participation in the surveillance, data collection and analysis of results, to writing a final manuscript as first author.

The results of this project will be presented at the 19th Annual Meeting of the European Society for Clinical Virology meeting in September 2016.

C. Establishment of a syndromic surveillance system for the asylum seeker camp in Råde, Norway

A reception centre for asylum seekers opened in Råde, Norway, in the context of the refugee crisis in Europe, for which assistance from NIPH was requested in order to establish a surveillance system. After regular visits and meetings with the community doctor responsible for the centre, it was decided to set up a syndromic surveillance system, which, once put in place, will enable monitoring of syndromes that could lead to/or be indicative of specific diseases such as scabies, influenza, and other diseases more likely to occur in such settings, and trigger immediate appropriate infection control measures. This surveillance system was established to complement the Norwegian notification based surveillance system (MSIS). A protocol was developed for this purpose to monitor health trends, and also to detect and assist in potential outbreak investigations in a timely manner. This project is currently on standby as the number of asylum seekers decreased throughout the winter months of 2015, and has remained low to this date.

The fellow participated in all stages of the project, from initial discussions on which symptoms/combinations of symptoms should be included in the surveillance, how to set it up (i.e. paper based versus electronic), and also in the elaboration of the working protocol that was sent to the district medical officer in charge of the camp.

Training modules

The EPIET/EUPHEM introductory course familiarised participants with the development, evaluation and analysis of surveillance systems. In addition, the rapid assessment & survey methods module familiarised fellows on the use of sampling methods adapted to study populations and on how to contribute to the multidisciplinary and international response to complex emergencies situations, and apply their epidemiological skills to serve public health interventions such as surveillances.

Educational outcome: Natacha learned the complexities involved in setting up and evaluating surveillance systems, tending to the requirements of the health events under surveillance, from analysing existing and/or incoming laboratory surveillance data, selecting appropriate methodologies learned in the modules, developing evaluation frameworks, and writing reports where interpretation of data and formulating recommendations as needed.

2. Applied public health microbiology research

Supervisors: Dominique Caugant, Åshild Andreassen, Susanne Dudman

A. Molecular characterization of pharyngeal *Streptococcus pyogenes* in Norway

Streptococcus pyogenes, or group A streptococcus (GAS), is responsible for around 600 million pharyngitis cases reported globally each year. It causes a diverse range of diseases, from relatively mild to life threatening infections. The aim of this study was to describe the molecular epidemiology and antimicrobial susceptibility of non-invasive GAS (non-iGAS) isolates in Norway, in 2010 and 2012, and compare with invasive GAS (iGAS) isolates from the same time period. We found that the most prevalent *emm* types were *emm1* (18%), *emm4* (10%),

emm12 (25%), *emm28* (7%), and *emm89* (13%), with sequence types, ST28, ST39, ST36, ST52, ST101, respectively. In addition, antimicrobial resistance was detected for tetracycline in 7.1% of the isolates, erythromycin (1.5%), clindamycin (1.3%), and trimethoprim sulfamethoxazole (0.3%). Associations were found between *emm* types, age groups and clinical manifestations, such as *emm12* and under 10 year age group, and skin and soft tissue infections with *emm4*. The comparison between non-iGAS and iGAS isolates showed common *emm* types and similar increasing or decreasing trends, such as decrease of *emm1* and *emm89*, and increase in *emm12*, from 2010 to 2012. The results of this study served to enhance the importance of surveillance and characterisation of non-iGAS isolates, as these can help to elucidate the epidemiological pattern of iGAS infections. The fellow was involved in all stages of this project, and was the main author in a manuscript (in submission).

B. Puumala virus distribution in Norway

Hantaviruses (family Bunyaviridae) comprise an emerging global threat for public health, infecting thousands of people worldwide in both developing and developed countries. Puumala virus (PUUV) is the most prevalent hantavirus in Western and Northern Europe, and is responsible for hemorrhagic fever with a renal syndrome, often called nephropatia epidemica (NE) in humans. In nature, the main host of PUUV is the bank vole (*Myodes glareolus*), widely distributed throughout Europe. Transmission of PUUV to humans occurs mainly indirectly, through inhalation of excreta from infected carrier rodents and insectivores, but can also occur by biting. In Norway around 50 human cases of NE-like disease are reported annually, mainly during late Summer-Autumn seasons. The aim of this study was to perform a descriptive analysis of PUUV circulation in Norway, by comparing the dynamics of human NE and rodent population densities from 1988 to 2015; and also to implement PCR methodology to improve timeliness of NE diagnostics. We found a general parallel trend of peaks in rodent densities and human NE from 1988 to 2015; and established a real-time and a nested PCR for future use as a diagnostic tool at NIPH, providing an important complement to the current serological methodology of NE diagnostics in Norway.

The fellow was the principal investigator and was involved in all stages of this project, from planning and performing the laboratory work, to writing a final manuscript (in preparation) as first author.

Training modules

The EPIET/EUPHEM introductory course familiarised fellows with developing and presenting study protocols, and in the 'Initial management in public health microbiology' fellows became familiar with many aspects in the laboratory setting, such as time management, team collaboration, efficient presentation deliveries according to target audiences, among others. The Biorisk and Quality management module was also important in familiarising the fellow in biorisk/biosafety procedures, as well as in performing laboratory risk assessments, essential for good laboratory practices.

Educational outcome: Natacha was familiarised with all stages of theoretical (through the modules attended) and empirical (hands-on experience) methodology, from identification of the health problem, revising literature, designing the study and detailed protocols for its execution, applying and learning new laboratory methods, collecting and analysing data and writing scientific articles.

3. Applied public health microbiology and laboratory investigations

Supervisors: Ulf Dahle, Didrik Vestrheim, Ingeborg Aaberge, Anne Torunn Mengshoel

A. Multiple loci VNTR analysis: a potential tool for *Salmonella* Chester discrimination?

Salmonella Chester is rarely reported as a causative agent of foodborne outbreaks. However, from August 2014 onwards an unexpected number of *Salmonella* Chester cases were notified from several European countries, the majority travel-related to Morocco. This serovar is usually characterized using pulse-field gel electrophoresis (PFGE). Since *S. Chester* belongs to the same group as *S. Typhimurium*, and as result from an inquiry from ECDC, we investigated whether or not the standard multiple locus variable number of tandem repeat analysis (MLVA) used for *S. Typhimurium* could serve as a useful tool in the current as well as future *S. Chester* outbreak investigations. As such, sixteen isolates of *S. Chester* from 15 individuals hospitalised in Norway from 2012 to 2014 were characterised with *S. Typhimurium* MLVA. This technique is based on PCR amplification of five variable number of tandem repeats (VNTR) loci and identification of fragment sizes by capillary electrophoresis, each of which is assigned an allele number. As a result, seven MLVA profiles were obtained, one of which included a cluster of seven cases with a travel history to Mediterranean countries. The six remaining profiles were from individuals with different travel destinations i.e., to other global regions. The MLVA amplification profile was however, incomplete, as only two of five loci amplified, using the *S. Typhimurium* specific primers, for all isolates tested. Nevertheless, the standard *S. Typhimurium* MLVA allowed a certain degree of discrimination between *S. Chester* strains thus identifying a geographical cluster, albeit the resolution was low due to the incomplete profiles obtained. As MLVA is a more timely and comparable method than the PFGE currently in use, MLVA development by identification of VNTRs unique to *S. Chester* could be pursued allowing investigation of future outbreaks. The

current *S. Typhimurium* MLVA may serve as a potential tool for identification of appropriate *S. Chester* VNTRs. The results of this investigation were shared at an international level through an online ECDC platform. The fellow was the principal investigator and was involved in all stages of this project. A final report was prepared, and the results of this project were presented at the 9th European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE), November 2015.

A. Bridging study for carriage studies of pneumococci in Norway

Monitoring of *Streptococcus pneumoniae* in carriage and surveillance of invasive pneumococcal disease has been paramount to evaluate the impact of the introduction of pneumococcal conjugate vaccine into childhood immunisation programmes. Since 2006, three pneumococcal carriage studies have been performed in Norway, using serum broth for transport of nasopharyngeal swabs. This method has been sensitive for detection of carriage of multiple serotypes as detected by latex agglutination from the incubated serum broths. However, the method differs from the standard method for carriage studies as recommended by WHO, where specimens are transported and stored in a medium containing skimmed milk, tryptone, glucose, and glycerin (STGG). In order to adhere to this recommendation and still be able to compare retrospective and prospective Norwegian carriage studies, we established a study to compare pneumococcal recovery from both media.

Recovery of serotypes 19F, 4 and 3 of *S. pneumoniae* was compared in each transport medium (serum broth and STGG), by counting colony forming units (CFU), by latex agglutination for detection of capsular polysaccharide and by quantification of pneumococcal DNA by real-time PCR targeting the autolysin gene (*lytA*). The results for DNA quantification were comparable ($p > 0.05$, F-test) between both media, however small differences in CFU counts were observed. All serotypes were detected by the pneumococcal latex agglutination test in both transport media. We found STGG to be as sensitive as the serum broth for detection of *S. pneumoniae*, however a limitation to this study was that only a few serotypes were tested. Nevertheless, based on these results, a subsequent carriage study was performed using both transport medium for an *in vivo* comparison, and were shown to be comparable. The bridging study was thus important for establishing the STGG transport medium for future Norwegian carriage studies, and conforming to WHO guidelines.

The fellow was the principal investigator in this project, performing laboratory work, data analysis and final report. A manuscript co-authored by Natacha has been submitted. The results of this project were presented at the 9th European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE), November 2015, and to the 10th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD 2016).

C. Correlation between culture-based and molecular methods in detection of rifampicin-resistant *Mycobacterium tuberculosis* strains in Norway from 1997 to 2014.

Tuberculosis (TB) is an infectious bacterial disease of major public health concern worldwide. It is caused by *M. tuberculosis*, and affects mainly the lungs (pulmonary tuberculosis), but can also affect other organs. Around 350-400 TB cases are reported annually in Norway, with an increasing incidence observed in recent years.

The aim of this study was to perform a comprehensive analysis of the available data on rifampicin (RIF) and isoniazid (INH) susceptibility results of Norwegian TB strains received at the National Reference Laboratory at NIPH from 1997 to 2014, by comparison of the phenotypic and genotypic methods, as well as to characterise the mutational profiles in both mono-resistant and MDR-TB isolates. A high correlation (96.8%) between phenotypic and genotypic resistance to RIF was found, which was to be expected as the common mutations in *rpoB* gene included in the MTBDRplus test are found in approximately 95-98% of TB isolates resistant to RIF. A lower correlation than that observed for RIF resistance was verified between the phenotypic and genotypic resistance for INH. In this case, the conventional culture-based drug susceptibility testing was the more sensitive of the two methods for detecting resistance. In terms of MDR results, 6.6% of the isolates analysed from 1997 to 2014 were found to be resistant to both RIF and INH, and a general increase in proportion of cases was observed for the latter years. In conclusion, the results of this study highlighted the importance of considering both phenotypic and genotypic methodologies for diagnosis of TB and detection of MDR, until more advanced genotypic tests covering a higher percentage of mutations for isoniazid genes *katG* and *inhA* are developed. An early but also accurate detection and treatment of TB is paramount not only to cease transmission of the disease, but also to avoid increase and spread of resistant bacteria, which require longer, as well as more expensive, treatment.

The fellow was the principal investigator in this project, along with another EUPHEM fellow from cohort 2014, Umaer Naseer. Natacha worked on the RIF part of the project and Umaer on INH, and both worked on the final MDR section. Natacha was involved at all stages of collection of data, analysis, and drafting of a final report.

Training modules: The introductory module, the 'Initial management in public health microbiology' module, and the outbreak module (STATA instruction) broached many concepts necessary for the fellow to complete her projects successfully, such as understanding and applying the role and responsibilities of effective management within a Public Health environment relating to a variety of situations and circumstances, communicating efficiently and writing scientific articles, and learning how to use STATA for data analysis.

Educational outcome: The fellow has deepened her public health microbiology knowledge in terms of laboratory investigations and collaborating and engaging with different disciplines throughout the three projects

undertaken. She also became well versed in the preparation of study protocols, time management and collaboration within a team.

4. Biorisk management

A. Puumala virus distribution in Norway

As part of the project (described above), the fellow worked under Biosafety level 2 conditions. Prior to commencing the study, biosafety training was provided concerning safe laboratory procedures.

The fellow had previous experience in biorisk/biosafety procedures, having worked in BSL3 laboratories for many years, therefore this core competency was considered as completed by the coordinators.

Training modules

The Biorisk and Quality management module familiarised fellows with biorisk and biosafety, such as management, assessment, mitigation, performance, including WHO recommendations on biosafety management in laboratories. A full day was dedicated to the international regulations for dangerous goods, determined by the International Civil Aviation Organisation, and awarded fellows with WHO certified documentation for shipping infectious goods. A visit to the BSL4 lab as part of this module illustrated all concepts learned throughout the module.

Educational outcome: Natacha understood the principles and practices of biosafety levels 3 and 4 according to WHO and EU directives, and practised safe laboratory procedures, decontamination and personal protective equipment according to the Norwegian directives when working on practical parts of her projects.

5. Quality management

Supervisors: Regine Barlinn, Karoline Bragstad, Olav Hugnes, Ingeborg Aaberge

A. Annual Norwegian Accreditation Board visit to NIPH

A visit to NIPH from the Norwegian Accreditation Board occurs on a yearly basis, and the fellow participated and became familiar with the entire accreditation process which included, analysis of two specific protocols for in-house methods for HIV detection and identification (06ME-32-029 and 06ME-32-030), within the Department of Virology at NIPH. The fellow followed all stages of the accreditation process, and produced a final report.

B. Influenza external quality assurance (EQA)

The fellow participated in two influenza EQA: a national ringtest, where samples were prepared at the National Reference Laboratory for Influenza at the Department of Virology of NIPH and dispatched to all laboratories in Norway performing influenza diagnostics; and the WHO External Quality Assessment Project, where samples were sent to all laboratories as part of the WHO Global Influenza Surveillance and Response System (GISRS). The fellow became familiar with all stages of an EQA, from the application of external quality standards, assessment and final report writing.

Training modules

In the Biorisk and Quality management module the fellow was familiarised with all aspects concerning quality management in both internal and external quality control.

Educational outcome: Throughout her projects undertaken for both biorisk and quality management competencies, the fellow learned how to apply the principles and practices of biosafety according to WHO and EU directives, to describe all aspects concerning PPE and understand principles and practices regarding infection control, equipment decontamination. Additionally, she applied the concepts of EQA and accreditation procedures, analysed results of EQAs, and participated in drafting final EQA reports.

6. Teaching and pedagogy

A. Organisation of a workshop 'EPI for Micros: Outbreak investigation' held for laboratory researchers at NIPH, with facilitation of a case study "Oswego Mazowszanka: An outbreak of gastrointestinal illness following a christening party", with EPIET fellow from cohort 2015 Lamprini Veneti. The workshop was comprised of an introductory lecture focusing on the ten steps of an outbreak investigation, followed by the practical approach with the case study. The purpose of the workshop was to introduce epidemiological concepts behind outbreak investigations to microbiologists.

B. Facilitation of a case study "An outbreak of gastro-enteritis in Kalundborg, Denmark", with Thea Fisher, Heli Harvala and Nina Stock. Heli Harvala, fellow EUPHEM from cohort 14, organized the workshop, which was organized in the context of a trainee session for microbiologists at the 18th Annual Meeting of European Society for Clinical Virology, in Edinburgh, Scotland. There were 32 registered participants, divided into two groups based on

their background, ranging from clinical scientist and virology specialist trainees to public health microbiologists and scientists; country (Korea, France, Turkey, UK, Slovenia, Belgium, Portugal, Israel, Sweden, Switzerland and China), and previous experience on outbreak investigations (from none to some). One group was facilitated by Thea Fisher and myself, and the other by Nina Stock and Heli Harvala.

C. Organisation and delivery of laboratory briefing sessions for WHO epidemiologists and laboratory personnel arriving in Conakry, Guinea, as part of the duties of the fellow in the international Ebola response mission. The purpose of these briefings was to familiarize newcomers with the organization and operating of the mobile laboratories in Guinea, including sample collection and delivery to laboratories, type of laboratory analyses performed and PPE requirements, sequencing of positive samples and analysis and interpretation of resulting phylogenetic trees in the context of epidemiological chains of transmission.

Educational outcome: The fellow learned and gained experience on all stages of organising workshops, from outlining course objectives, developing the curriculum, and delivering/facilitating lectures and case studies to multidisciplinary audiences.

7. Public health microbiology management

A. Management during outbreak investigations and projects

All projects and outbreak investigations undertaken throughout the fellowship involved public health management, including laboratory and time management, communicating between epidemiologists and the microbiology laboratory, team building and coordination, research collaboration and management of cultural differences in international contexts.

B. Epidemic intelligence activities

As part of a biweekly rotation, the fellow acted as the outbreak responsible, performing duties such as daily monitoring the incoming email in the outbreak mailbox, the outbreak reporting system, and the international surveillance network (EWRS/IHR) and forwarding information to the relevant personnel. Weekly outbreak meetings are held at the NIPH, where the outbreak responsible updates on the ongoing outbreaks.

C. Participation in a National Committee meeting

Natacha presented the results of the evaluation of the AFP surveillance system project to the key surveillance system stakeholders during the annual national committee meeting held at NIPH, and participated in the ensuing discussion regarding the management of the current system, to be included in the final report.

Training modules

The module 'Initial management in public health microbiology' familiarised fellows in terms of understanding roles and responsibilities in public health management settings. Topics included the identification of different management styles, team roles and team evolution, the delegation of tasks and the provision of structured, clear and efficient feedback.

Educational outcome: Natacha experienced general public health management levels during her projects such as describing added value of PH for public health, applying principles of scientific communication to peers and stakeholders, recognising the role of different agencies, identifying interdisciplinary needs between healthcare professionals and front-line responders and identifying basic laboratory requirements in the field.

8. International missions

A. Surveillance of Ebola virus disease in Guinea

I was deployed by the GOARN/WHO mechanism as a WHO consultant to work at the National Coordination level in Conakry, Guinea, from 9 July-20 August 2015. My main roles were:

- To assist the sequencing laboratory team in identifying priority specimens for sequencing; integrating epidemiological data with sequencing results; interpretation of phylogenetic trees and recommendations on further actions
- To monitor incoming data on transmission chains and work with teams at the prefecture level to ensure data quality, timely submission and data completeness.
- To improve data quality for non-active transmission chains in preparation for submission to the international database.
- To collect and assess the daily reports for each prefecture via the online system, email final report to key personnel in the surveillance team for next day briefing meetings.

A final report was submitted to WHO in September 2015, and a publication in Nature letters.

Educational outcome: The fellow had the chance to put into practice many of the concepts acquired during the modules undertaken throughout the fellowship, specifically during the outbreak, RAS, 'Initial management in public

health microbiology' modules.

9. Communication

Publications

1. Joshua Quick, Nicholas J. Loman, Sophie Duraffour, Jared T. Simpson, Ettore Severi, Lauren Cowley, Joseph Akoi Bore, Raymond Koundouno, Gytis Dudas, Amy Mikhail, Nobila Ouédraogo, Babak Afrough, Amadou Bah, Jonathan H. J. Baum, Beate Becker-Ziaja, Jan Peter Boettcher, Mar Cabeza-Cabrerizo, Álvaro Camino-Sánchez, Lisa L. Carter, Juliane Doerrbecker, Theresa Enkirch, Isabel García-Dorival, Nicole Hetzelt, Julia Hinzmann, Tobias Holm, Liana Eleni Kafetzopoulou, Michel Koropogui, Abigael Kosgey, Eeva Kuisma, Christopher H. Logue, Antonio Mazzarelli, Sarah Meisel, Marc Mertens, Janine Michel, Didier Ngabo, Katja Nitzsche, Elisa Pallasch, Livia Victoria Patrono, Jasmine Portmann, Johanna Gabriella Repits, Natasha Y. Rickett, Andreas Sachse, Katrin Singethan, Inês Vitoriano, Rahel L. Yemanaberhan, Elsa G. Zekeng, Trina Racine, Alexander Bello, Amadou Alpha Sall, Ousmane Faye, Oumar Faye, N'Faly Magassouba, Cecelia V. Williams, Victoria Amburgey, Linda Winona, Emily Davis, Jon Gerlach, Frank Washington, Vanessa Monteil, Marine Jourdain, Marion Bererd, Alimou Camara, Hermann Somlare, Abdoulaye Camara, Marianne Gerard, Guillaume Bado, Bernard Baillet, Déborah Delaune, Koumpingnin Yacouba Nebie, Abdoulaye Diarra³⁴, Yacouba Savane, Raymond Bernard Pallawo, Giovanna Jaramillo Gutierrez, **Natacha Milhano**, Isabelle Roger, Christopher J. Williams, Facinet Yattara, Kuiama Lewandowski, James Taylor, Phillip Rachwal, Daniel J. Turner, Georgios Pollakis, Julian A. Hiscox, David A. Matthews, Matthew K. O'Shea, Andrew McD. Johnston, Duncan Wilson, Emma Hutley, Erasmus Smit, Antonino Di Caro, Roman Wölfel, Kilian Stoecker, Erna Fleischmann, Martin Gabriel, Simon A. Weller, Lamine Koivogui, Boubacar Diallo, Sakoba Keita, Andrew Rambaut, Pierre Formenty, Stephan Günther Miles W. Carroll (2016) Real-time, portable genome sequencing for Ebola surveillance. *Nature* 530: 228-32
2. Steens A, Milhano N, Aaberge IS, Vestheim DF (2016) In vitro and in vivo comparison of transport media for detecting nasopharyngeal carriage of *Streptococcus pneumoniae*. *Peer J* 4:e2449
3. Milhano N, Nasser U, Steinbakk M, Sandnes R-A, Nilsen E, Opland GS, Noraas S, Caugant D (2016) Molecular epidemiology and antimicrobial susceptibility of clinical isolates of *Streptococcus pyogenes* in Norway, 2010 and 2012. (submitted to *European Journal of Clinical Microbiology and Infectious Diseases*)
4. Milhano N, Korslund L, Evander M, Ahlm C, Vainio K, Dudman S, Andreassen Å (2016) Puumala virus distribution in Norway. (in preparation)
5. Milhano N, Vainio K, Christensen A, Kofstad T, AMB Kran, Borgen K, Dudman S (2016) Molecular epidemiology of enteroviruses in Norway, 2014-2015. (in preparation)

Reports

1. Multiple-locus variable number repeat analysis a potential tool for *Salmonella* Chester discrimination?
2. Correlation between culture-based and molecular methods in detection of rifampicin and isoniazid-resistant Mycobacterium tuberculosis strains in Norway from 1997 to 2014
3. Evaluation of the acute flaccid paralysis surveillance system in Norway
4. A gastrointestinal outbreak among high school pupils on a school trip to Frøya, Sør-Trøndelag, May 2015
5. A foodborne outbreak after a wedding party in Stavern, Norway, June 2015
6. Goarn/WHO mission report: Surveillance of Ebola Virus Disease in Guinea

Other presentations

Posters

1. Milhano N, Vainio K, Christensen A, Dudman S Circulating enterovirus genotypes in Norway 2014-2015: A reason for concern? Accepted for the 19th Annual Meeting of European Society for Clinical Virology, Lisbon, Portugal, 14th-17th September 2016.
2. Vestheim DF, Milhano N, Aaberge IS, A Steens A. In vitro and in vivo comparison of transport media for detecting nasopharyngeal carriage of *Streptococcus pneumoniae*. 10th International Symposium on Pneumococci and Pneumococcal Diseases, Glasgow, Scotland, 26-30 June 2016.
3. Milhano N, Løbersli I, Brandal LT, Aaberge I, Dahle UR (2015) Evaluation of the standardised S. Typhimurium multiple locus variable number of tandem repeats analysis (MLVA) as a tool for investigating S. Chester outbreaks. Årskonferanse i mikrobiologi 2015, Folkehelseinstituttet, Oslo, Norway, 3-4 December 2015.

4. Milhano N, Steens A, Vestrheim D, Aaberge I (2015) A comparative study of transport media for upper respiratory tract carriage of *Streptococcus pneumoniae* in Norway. Årskonferanse i mikrobiologi 2015, Folkehelseinstituttet, Oslo, Norway, 3-4 December.
5. Milhano N, Løbersli I, Brandal LT, Aaberge I, Dahle UR (2015) Evaluation of the standardised *S. Typhimurium* multiple locus variable number of tandem repeats analysis (MLVA) as a tool for investigating *S. Chester* outbreaks. European Scientific Conference on Applied Infectious Disease Epidemiology, Stockholm, Sweden, 11-13 November 2015.
6. Milhano N, Steens A, Vestrheim D, Aaberge I (2015) A comparative study of transport media for upper respiratory tract carriage of *Streptococcus pneumoniae* in Norway. European Scientific Conference on Applied Infectious Disease Epidemiology, Stockholm, Sweden, 11-13 November 2015.
7. Milhano N, Bragstad K, Pfeiffer HC, Vainio K, Bjørnholt J, Kran AMB, Dudman SG (2015) Acute flaccid paralysis surveillance system in Norway detected two cases of enterovirus D68 infection. 18th Annual Meeting of European Society for Clinical Virology, Edinburgh, Scotland, 9th-12th September 2015.

10. EPIET/EUPHEM modules attended

- EPIET/EUPHEM introductory course, Spetses, Greece (three weeks)
- Outbreak investigation: From data analysis to communication of findings, Berlin, Germany (one week)
- Biorisk and quality management module, ECDC, Stockholm, Sweden (one week)
- Mini module project review Copenhagen, Denmark (two days)
- Mini module project review Stockholm, Sweden (two days)
- Initial management in public health microbiology, ECDC, Stockholm, Sweden (one week)
- Multivariable analysis (MVA), Vienna, Austria (one week)
- Vaccinology, Public Health England, Krakov, Poland (one week)
- Bioinformatics and phylogenetics (BIP), Stockholm, Sweden (two days)
- Rapid health assessment and sampling module, Athens, Greece (one week)
- Project review module, Lisbon, Portugal (two weeks)

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 Natacha Milhano during her two-year EUPHEM fellowship (cohort 2014) as an EU track fellow at the Norwegian Institute of Public Health, Oslo, Norway. Natacha is the first appointed EU track EUPHEM fellow in Norway. The projects described in this portfolio demonstrate the breadth of public health microbiology. Outbreak and surveillance activities extended from regional to national mainly foodborne with participation in all ten steps of an outbreak investigation; to national surveillance of polio in Norway which contributed significantly towards international surveillance (WHO) of this vaccine preventable disease. The work undertaken resulted in changes to the current acute flaccid paralysis (AFP) surveillance system in Norway in compliance with WHO guidelines. The international mission undertaken to Guinea during the Ebola outbreaks was important to both the fellow, her organisation and on an international level with the organisation of laboratory briefing sessions and workshops for WHO epidemiologists and laboratory personnel. The laboratory and epidemiologically based projects covered all 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 contributions made by this EUPHEM fellow in Guinea as with all other fellows has highlighted the importance of developing a future critical mass of highly skilled field public health microbiologists within Member States to contribute towards national preparedness as well as being available for international responses in the interest of the EU. The EUPHEM Coordinator Team concludes that the fellow has succeeded in performing all her tasks 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

Natacha was the first EUPHEM EU-track fellow at NIPH. She was an experienced scientist, just completed her PhD when arriving at NIPH and starting the EUPHEM fellowship. During the two year fellowship Natacha gained thorough understanding and experience in Public Health Microbiology including field epidemiology, outbreak investigation and surveillance activities. Collaboration with both EPIET and EUPHEM fellows has strengthen the

collaboration between Public Health Microbiology and epidemiology at NIPH. Natacha has taken part in several projects and activities at different laboratories at NIPH and has worked as an excellent team collaborator with other fellows and laboratory personnel (technicians, scientist and medical doctors). Natacha has contributed to work with results of great importance for NIPH. It is our conclusion that Natacha adapted quickly to routines at NIPH, showed great enthusiasm and interest in our work and contributed in several aspects of Public Health Microbiology.

Personal conclusions of fellow

The EUPHEM fellowship has offered me a unique opportunity to embark on an extremely diverse and complete Public Health endeavour, broaching a wide variety of project types and various disease groups, many of which were unfamiliar to me in my previous working experience. As such, participating in this fellowship has greatly expanded my knowledge of Public Health Microbiology, and the 'learning-by-doing' approach was invaluable to facilitate the incorporation of new concepts and procedures. Another fundamental aspect of this training programme was the networking component, which greatly enriched not only the working environment and capacity to advance and complete many projects but also on a personal level. The close collaboration with the EPIET fellows and the Epidemiology department at NIPH was an excellent opportunity to further strengthen the connection between these two disciplines, i.e., Epidemiology and Public Health Microbiology, thus covering one of the goals of this training programme. Working at the NIPH has been an extremely enriching experience, allowing me to get exposed and adapt to a whole new working environment, colleagues and supervisors.

Acknowledgements of fellow

I would like to thank my main local EUPHEM supervisors, Ingeborg Aaberge and Susanne Dudman, and my EPIET supervisor, Katrine Borgen, for their supervision, unwavering support, engagement and enthusiasm throughout all projects embarked during these two years. I would also like to thank my project supervisors, as listed above for each project, who were always available and very encouraging at all stages of the projects. I also extend my deepest acknowledgements to all laboratory personnel who were always there to support and guide me through many practical stages of the projects.

I would also like to thank all my cohort EUPHEM and EPIET colleagues, and in particular Umaer Naseer, Hinta Meijerink, Lamprini Veneti and Rikard Rykkvin, with whom I had the pleasure to work closely with in these two years of fellowship.

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