EUPHEM

EUPHEM REPORT

Summary of work activities

Lotta Siira

European Public Health Microbiology Training Programme (EUPHEM), 2016 cohort

Background

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.

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 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'.

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

This report summarises the work activities undertaken by Lotta Siira, cohort 2016 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.

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Pre-fellowship short biography

Prior to her EUPHEM fellowship, Lotta worked for several years at the National Institute for Health and Welfare in Finland, with a focus on laboratory based surveillance of invasive bacterial diseases. She joined the EUPHEM programme to broaden her knowledge on public health microbiology and intervention epidemiology, to gain experience on outbreak investigation and to learn more about infectious diseases and infectious disease control in Europe.

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 projects or activities (on-job services) 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 guide[1].

1. Epidemiological investigations

1.1. Outbreak investigations

Supervisors: Katrine Borgen, Emily MacDonald

A. A gastrointestinal outbreak following a memorial service, Norway, December 2016

On 19 December 2016, the Norwegian Food Safety Authority (NFSA) reported 32 gastroenteritis cases among approximately 70 people, who had lunch during a memorial service at a venue in a Norwegian municipality, on 16 December. We investigated the extent of the outbreak and aimed to identify the mode and vehicle of transmission, in order to implement control measures.

We conducted a retrospective cohort study including all persons, who had consumed food served at the memorial service. A case was defined as a person who consumed food served at the memorial service and reported gastroenteritis symptoms with onset from 16 to 19 December. We collected data using a self-administered online questionnaire. Specimens from ingredients used for preparation of the food were collected and patients were encouraged to deliver stool samples. We calculated attack rates (AR) and risk ratios (RR) using univariate analysis.

Of all 73 participants, 44 (60%) completed the questionnaire and 33 (75%) cases were identified; symptoms included nausea (97%), vomiting (94%), diarrhoea (76%), stomach pain (76%) and fever (24%). Onset of symptoms was reported from 16 December 9 pm to 18 December 12 am. The epidemic curve suggested a point source outbreak. The median duration of illness was two days (range 0-6 hours to 4 days). Those who consumed salmon sandwich had a 44% (RR 1.44; 95%CI 0.87-2.38) higher risk of illness compared with those who did not; 80% of cases ate salmon sandwich. Specimens from two patients were positive for norovirus. No pathogens were identified in the three tested food specimens.

Epidemiological data suggested a point source norovirus outbreak without conclusive results regarding the source and mode of transmission. Neither cross-contamination of food nor person-to-person transmission could be ruled out. We recommend adherence to the current guidelines to prevent norovirus outbreaks.

[1] European Centre for Disease Prevention and Control. European public health training programme. Stockholm: ECDC; 2017. Available from: http://ecdc.europa.eu/en/publications/Publications/microbiology-public-health-training-programme.pdf

The fellow participated in all stages of the outbreak investigation, from contributing to designing questionnaires, receiving and analysing the data, to writing the final outbreak report.

B. A gastrointestinal outbreak following a music festival at hotel, Norway, January 2017

On 17 January 2017, the NSFA reported more than 20 gastroenteritis cases among approximately 210 people who had attended a music festival at a hotel, during 13-15 January. We investigated the outbreak to identify the mode and source of transmission, in order to implement control measures.

We conducted a retrospective cohort study among all individuals who consumed food served at the hotel buffet during the festival. A case was defined as a person who consumed food served at the hotel and reported diarrhoea or vomiting with onset during 14-18 January. We conducted telephone interviews using a structured questionnaire. Patients were encouraged to provide stool samples. We calculated attack rates and adjusted risk ratios (aRR) using binomial regression.

Of the participants, 67 (32%) were reached for interviews and 23 (31%) cases were identified. Symptoms included nausea (68%), vomiting (64%), diarrhoea (75%), stomach pain (57%) and fever (17%). The epidemic curve suggested a point source outbreak. The median duration of illness was two days (range 0-6 hours to 7 days). Those who consumed cold cut meats (aRR 2.03; 95% CI 1.25-3.32), crayfish (aRR 2.25; 95% CI 01.38-3.68), and gravet cod seasoned with saffron (aRR 3.05; 95% CI 2.10-4.43) had higher risk of illness compared with those who did not. Of the cases, 81% had eaten at least one of the abovementioned three dishes from the cold buffet. One patient sample was tested and was positive for norovirus. No irregularities in kitchen hygiene were identified by the NFSA. No food samples were available for testing.

Epidemiological evidence suggested that the three cold buffet dishes consumed by the majority of cases may have been the vehicles of transmission. However, neither cross-contamination of food nor person-to-person transmission could be ruled out. We recommend adherence to the current guidelines to prevent norovirus outbreaks.

The fellow participated in all stages of the outbreak investigation, from contributing to designing questionnaires, conducting interviews, analysing the data, to writing the final outbreak report.

C. A prolonged norovirus outbreak at a conference hotel, Norway, February 2017

On 17 February 2017, local health and food authorities were notified of more than 20 people reporting gastroenteritis during or after their stay at a hotel. We investigated the outbreak to describe its extent and factors associated with illness. The outbreak was presumed over when the investigation commenced on 1 March.

We conducted a cohort study among persons staying or working at the hotel during 15-24 February. Using a self-administered online questionnaire, we collected information on symptoms, meals, and exposures to meeting rooms and common areas in the hotel. We defined cases as a person, who vomited or had diarrhoea during or within 3 days after their visit to the hotel during 15-24 February. We performed univariable and multivariable data analysis. Stool samples were analysed and genotyped. We inspected the premises including kitchen facilities.

Among the 436 respondents, 161 cases were identified (attack rate 37%). Epidemiological analysis did not give any conclusive results regarding source and mode of transmission, but data suggested a point source outbreak peaking two days after a guest vomited in the hotel reception on the 15 February. Norovirus of genotype GII.P7 and with identical internal ORF1 fragments was identified in all ten tested stool samples that originated from two different time points in the outbreak. No irregularities in kitchen hygiene were identified. Use of chlorine-based disinfectant-solutions at critical control-points, enhanced hand hygiene, and cleaning/disinfection measures during a four day closure, as of 24 of February, did not prevent further cases. After a ten days closure with extensive cleaning/disinfection measures and installation of new flooring in the reception and common areas, no more gastroenteritis cases were reported.

This prolonged norovirus outbreak was only controlled through exhaustive control measures including part refurbishment of the hotel. Norovirus has a potential for continued environmental spread, especially when vomiting occurs in highly-frequented areas. We recommend that hotels have procedures and guidelines in place for preventive control measures when events with potential infectious spreading take place.

The fellow participated in all stages of the outbreak investigation, from contributing to designing questionnaires, receiving and collating the data, to writing the final outbreak report.

D. A prolonged outbreak of monophasic *Salmonella* Typhimurium with environmental contamination in Norway, August 2017

On 15 September 2017 the National Reference Laboratory (NRL) for Enteropathogenic Bacteria at NIPH sent an alert about a cluster of six monophasic *Salmonella* Typhimurium isolates sharing a rare multi locus variable tandem repeat analysis (MLVA) type (3-13-12-NA-210) from five different municipalities in Norway. An outbreak investigation was initiated by NIPH, the NFSA and the municipal doctors in the affected municipalities.

We defined a case as a person residing in Norway with a laboratory confirmed infection with monophasic *Salmonella* Typhimurium MLVA type 3-13-12-NA-210 detected after 15 August 2017. The NRL identified more cases in the coming months, with a total of 21 cases identified by 1 February 2018.

A standardised trawling questionnaire for hypothesis generation for exposures was used to interview the four first cases. A more concise questionnaire was produced based on their answers and the cases were re-interviewed using this questionnaire to obtain more specific information about the exposures. New cases were interviewed based on the concise questionnaires. Only descriptive epidemiology was undertaken in connection with the outbreak. Both NFSA and the company that operated the café inspected the premises and collected specimens. Salmonella isolates from patient samples are mandatorily submitted to the NRL for species verification and typing. Environmental swabs and food specimens were collected by NFSA and analysed for presence of *Salmonella* and *Escherichia coli*. All monophasic *Salmonella* Typhimurium isolates connected with the outbreak were analysed at NIPH by whole genome sequencing through core and accessory genome multi locus sequence typing including 4,235 genes.

Of the 21 identified cases, 13 (62%) were women. The median age was 27 years, range 17-60 years. The cases resided in 10 municipalities. The range of the date of onset was 23 August to 18 November, but was between 23 August and 23 September for the majority of the cases. The median incubation time was 6 days, range 0-16 days. The incubation time increased as the outbreak progressed. All cases reported having eaten at the same café at Oslo Airport before their onset of symptoms. The results from the interviews showed that they had eaten different foods. The inspections of the café identified several weaknesses in the hygiene routines. None of the obtained food specimens were positive for Salmonella. Monophasic *S.* Typhimurium with the same MLVA type as the outbreak strain was found in several environmental specimens. Whole genome sequencing of 21 isolates from cases, and 5 isolates from environmental specimens showed that there were ≤2 differences between the isolates. The company operating the café implemented control measures to prevent spread, and stated that specimens were obtained from all members of staff and the café was temporarily closed.

The outbreak investigation showed that all cases had visited Oslo Airport and consumed food items from a specific café at the airport during different days from 18 August 2017. The microbiological results from cases and environmental specimens obtained at the café support the hypothesis of a common source outbreak. No further cases or isolates of the outbreak strain have been identified at the NRL after 18 December, which gives reason to believe that the control measures implemented, including the voluntary closure of the café stopped the outbreak.

The fellow participated in all stages of the outbreak investigation, from contributing to designing questionnaires, receiving and analysing the data, to writing the final outbreak report. She is further writing a final manuscript (in preparation) as first author.

Training modules

The EPIET/EUPHEM Introductory Course provided participants with the basic concepts of logistical and analytical approach to outbreak investigations through three weeks of lectures, interactive sessions, case studies, group work, and writing of a research protocol as training in public health microbiology and intervention epidemiology. The course introduced fellows to the ten steps of an outbreak investigation.
The Outbreak Investigation Module was an interactive course methodologically going through the steps required in an outbreak investigation, form data entry and management, designing of questionnaires, descriptive and analytical data analyses, communication of the findings and implementation of control measures. Participants were also given practical training in when and how to perform analytical studies for an outbreak investigation, including descriptive, cohort and case-control studies.
The Multivariable Analysis Module provided a more comprehensive understanding of the principles of statistical analyses, and how to build an optimal model using linear, logistic, Poisson and Cox regression.
The Management, Leadership and Communication in Public Health Module trained fellows in many aspects of management and collaboration including time management and team collaboration.

Educational outcome:

As a co-investigator and member of multidisciplinary outbreak investigation teams, the fellow has applied microbiological and epidemiological knowledge in outbreak situations, participated and gained a good understanding of all ten steps of an outbreak investigation. The performed activities include taking part in a field

visit, designing and distributing questionnaires by e-mail/SMS/mail, conducting telephone interviews, framing case definitions, performing descriptive and analytic statistical analyses, communicating with NFSA and the municipal health authorities in person and by participation in tele/videoconferences, writing outbreak reports and meeting summaries, and performing sequence analysis and interpretation of microbiological typing data.

1.2. Surveillance

Supervisors: Are Berg, Karoline Bragstad, Susanne G. Dudman, Anneke Steens, Didrik F. Vestrheim

A. Pneumococcal antimicrobial susceptibility and clonality during a period with changes in pneumococcal childhood vaccination, Norway, 2004-2016

Following introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) into the Norwegian childhood vaccination programme in 2006 and PCV13 in 2011, the incidence of invasive pneumococcal disease (IPD) has decreased. We describe changes in antimicrobial non-susceptibility of IPD isolates in Norway during 2004-2016 coinciding with use of PCVs, in order to inform treatment guidelines.

We included isolates of all notified IPD cases from 2004-2016 (n=10,242). Isolates were serotyped and susceptibility to seven antimicrobials was determined using EUCAST 7.1 breakpoints. We genotyped isolates from the first 6 months, every second year (2005-2015) by multilocus sequence typing. Incidences and incidence rate ratios (IRR) were calculated to describe changes in non-susceptibility in the pre-PCV (2004-5), PCV7 (2006-10), and PCV13 (2011-16) periods.

In the PCV7-period, the incidence of isolates non-susceptible to ≥1 tested antimicrobial decreased overall (IRR 0.74, 95%CI: 0.69-0.91) and in age-groups <2, 20-49, 50-64, and >64 years (IRR <1). The largest reduction was in erythromycin-resistant IPD isolates, which decreased from 2.5 cases/100,000 population in 2005 to 0.58/100,000 in 2010, especially due to the reduction of IPD caused by serotype 14, ST9. The incidence of trimethoprim/sulfamethoxazole resistant isolates causing IPD increased slightly (IRR 1.1, CI: 1.1-1.2) in the PCV13-period, however, otherwise there were no significant changes in IPD non-susceptibility overall in the pre-PCV- and PCV13-periods. In the PCV13-period, the incidence of PCV13-serotype isolates non-susceptible to penicillin (IRR 0.82, CI:0.72-0.94) or resistant to erythromycin (IRR 0.77, CI:0.68-0.89) decreased. In the PCV periods, the incidence of non-susceptible or resistant non-PCV13-serotype isolates increased for all tested antimicrobials (IRR 1.2). 50% (10/20) of the genotyped penicillin-non-susceptible and erythromycin resistant isolates were serotype 15A, ST63.

PCV7 introduction coincided with a reduction in the incidence of IPD caused by pneumococci non-susceptible to ≥1 antimicrobial, especially in the youngest and oldest age-groups, while the switch to PCV13 did not significantly change the overall low incidence of non-susceptible IPD for the majority of the tested antimicrobials.

The fellow was involved in all stages of this project, from planning, reviewing literature, conducting the laboratory survey, analysing the data, to writing a final manuscript (in preparation) as first author.

B. Options for surveillance of respiratory syncytial virus (RSV) in Norway

Respiratory syncytial virus (RSV) is the leading viral cause of acute lower respiratory tract infections in infants and young children and may be a cause of substantial burden of disease in the elderly and in adults with chronic medical problems. Surveillance of RSV is important as a potentially vaccine preventable disease. Several vaccine candidates have moved into the human testing phase, and a vaccine is likely to be available in the next few years. The aim of the project was to explore the options for systematic RSV surveillance in Norway.

We used existing literature and data sources to propose surveillance objectives and outline optional surveillance systems and carried out a survey of laboratory methods used for RSV diagnostics through Questback.

The following surveillance objectives were identified: creating baseline data to determine implementation future RSV vaccination in Norway; evaluating the impact of future RSV vaccination in Norway; estimating the healthcare and disease burden of RSV infection in different demographic groups; ascertaining seasonality of RSV in Norway; tracking trends among RSV subtypes (RSV A and RSV B) and describing the genetic diversity among circulating strains; further understanding the role of RSV in respiratory disease.

The following optional surveillance systems were outlined: reporting of RSV positive laboratory tests by the clinical microbiology laboratories; hospital-based syndromic surveillance; surveillance through sentinel general practitioners; syndromic surveillance through the Norwegian Syndromic Surveillance System (NorSySS) platform; surveillance set up through selected hospital laboratories; weekly laboratory reports and sample submission.

The outlined surveillance systems are not mutually exclusive, and to fulfil all surveillance objectives several data sources and parallel systems would be required. Using existing surveillance structures or data sources are likely to increase compliance with surveillance and increase acceptance. The report, including the results from the laboratory survey, will be useful when setting up RSV surveillance in Norway, in anticipation of an RSV vaccine.

The fellow was involved in all stages of this project from initial discussions, to designing and carrying out the laboratory survey, reviewing literature, and writing the final report as first author.

Training modules

The EPIET/EUPHEM introductory course familiarised participants with the development, evaluation and analysis of surveillance systems.
The rapid assessment and survey methods module familiarised fellows with 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 skills to serve public health interventions such as surveillances.

Educational outcome:

The fellow learned the complexities involved in preparing to set up a surveillance system. The fellow developed understanding and experience on how to analyse existing laboratory surveillance data and select appropriate methods, interpret, formulate recommendations and write reports using the data.

2. Applied public health microbiology research

Supervisors: Susanne G. Dudman, Hanne Nøkleby, Dominique A. Caugant, Martin Steinbakk

A. Response to third dose of rubella vaccine among Norwegian conscripts

Rubella is an acute viral childhood disease transmitted through airborne droplets. In early pregnancy, it can cause congenital rubella syndrome that has devastating effects on the foetus. In this study, our aim was to evaluate the long-term rubella immunogenicity afforded by two childhood doses of the measles, mumps and rubella vaccine (MMR) of the Norwegian vaccination programme in a cohort of conscripts and to determine seroconversion in conscripts previously seronegative after a dose of MMR vaccine, in order to inform vaccination policy and monitor the effectiveness of the vaccination. Previously, few data exist on the immunogenicity of a third MMR dose.

Blood samples from Norwegian conscripts (n=495) before and eight months after a dose of MMR vaccine were tested using an enzyme immunoassay to measure the anti-rubella IgG. Antibody concentrations <5 IU/mL were regarded as negative, 5.0-9.9 IU/mL as equivocal, and ≥10 IU/mL as positive. We calculated the overall seroprevalence before and after the administered MMR dose for the cohort of conscripts (seropositive tests/number of performed test) with 95% confidence intervals (95% CI). Data was stratified for analysis by sex, age in years, and the following age groups: <22 year-old (eligible for two childhood doses of MMR vaccine through the national vaccination programme) and ≥22 year-old (ineligible for two childhood doses of MMR vaccine through the national vaccination programme). Differences in the proportion of seropositive samples were examined for statistical significance using the Chi-square test. Geometrical means of anti-rubella IgG were calculated, statistical significance of differences between mean antibody concentrations before and after the third MMR dose were examined with the Kruskal-Wallis test.

The majority of the conscripts were male (98%). The mean age was 19 years, range 18-26 years, with 98% of the cohort being below 22 years-old.

Overall, the seropositivity before vaccination was 85% (CI, 81-88%) and 99% (CI, 98-100%) of the conscripts had anti-rubella IgG concentrations ≥5 IU/mL. The seropositivity eight months after vaccination was 95% (CI, 92-96%) and 100% (CI, 99-100%) of the conscripts had antibody titers ≥5 IU/mL. The proportion of seropositive samples by age ranged between 80-100% before and 94-100% after vaccination, however, the differences were non-significant. The geometrical mean IgG concentration increased from 21.5 IU/mL before vaccination to 28.8 IU/mL after. Four out of five conscripts with seronegative concentrations before administrations of a MMR dose had equivocal or seropositive results following vaccination.

Administration of an additional MMR dose in early adulthood has been mentioned as a possible public health strategy for ensuring rubella immunity in adulthood in vaccinated populations, and our study provides evidence that this could be a viable suggestion, as a third dose of MMR administered in early adulthood provided increased protection against rubella. Our study shows that the cohort of healthy young adults in Norway was protected against rubella, following eligibility for two childhood MMR doses, and efforts should be made to maintain high vaccine coverage to ensure a high immunity level in the future.

The fellow cleaned and collated the data, performed the analysis, and wrote the final manuscript as first author.

B. Can gonococcal antimicrobial resistance be predicted from next generation sequencing data?

The Gram-negative bacterium Neisseria gonorrhoeae causes the sexually transmitted disease gonorrhoea. A major global public health concern is that gonococci have progressively developed resistance to antibiotics, which may lead to suboptimal treatment and treatment failures, requiring surveillance to keep track of such events and inform treatment guidelines.

In this project, we aimed to describe the resistance gene profile of phenotypically susceptible and resistant isolates of gonococci, in order to investigate the feasibility of prediction of antimicrobial susceptibility from whole genome sequencing (WGS). We described the genetic diversity of the gonococcal isolates using their multilocus sequence type (MLST), and the susceptibility patterns of isolates having the same genotype.

The first 100 isolates received at the Reference Laboratory for Gonococci at the Norwegian Institute of Public Health in 2016 were included in the study. Phenotypic susceptibility data were produced using the gradient strip diffusion method. WGS was performed on an Illumina MiSeq platform. We used the Bacterial Isolate Genome Sequence Database (BIGSdb) gene comparator tool for gonococcal antimicrobial resistance to analyse and describe 22 different antimicrobial resistance loci of the study isolates. Mutations conferring resistance described in the literature were used to guide prediction of resistance from the molecular data.

We observed a high level of genetic diversity, including 45 different MLST sequence types (STs), among the isolates and found that the phenotypic antimicrobial susceptibility pattern cannot be directly inferred from the ST. Analysis indicated that the phenotypic susceptibility patterns and the presence of described resistance mutations were not fully concordant. Sensitivity and specificity of the genetic resistance prediction varied depending on the class of antimicrobials.

As this field is rapidly changing and user-friendly bioinformatics tools are being developed, the methods used in this study will not be convenient for routine use, however, the study provided a look at the genetic diversity of the gonococci circulating in Norway, both in terms of clonality and in terms of genes conferring antimicrobial resistance, and can be used when planning use of sequence data in gonococcal surveillance.

The fellow was the principal investigator and was involved in all stages of this project, from planning to becoming familiar with the laboratory methods, and analysing, interpreting, and presenting the data.

Training modules

The EPIET/EUPHEM Introductory Course familiarised fellows with developing and presenting study protocols. The Outbreak Investigation Module introduced methods of whole genome sequencing and next generation sequencing. The Management, Leadership and Communication in Public Health Module trained fellows in many aspects of management and collaboration including time management, team collaboration, and efficient presentation deliveries according to target audiences.

Educational outcome:

The fellow was familiarised with all stages of conducting a public health research project, from identification of the public health problem, reviewing literature, writing study protocols, understanding laboratory methods, analysing data, and writing scientific manuscripts.

3. Applied public health microbiology and laboratory investigations

Supervisors: Lin T. Brandal, Umaer Naseer, José Miguel Rubio, Silvia Herrera Leon, Aftab Jasir

A. Whole genome sequencing of *Salmonella* Chester to reveal geographic outbreak clusters

Salmonella enterica subsp. enterica serovar Chester cases were rare in surveillance until 2014, when a multi-country outbreak travel-related to Morocco was revealed across Europe. In the summer of 2016, Norway observed an increase of *Salmonella* Chester cases with a travel-history to Greece.

In this study, we investigated genetic relatedness of *S.* Chester for surveillance and outbreak detection by core genome multi locus sequence typing (cgMLST) and compare the results to genome mapping.

S. Chester isolates from 51 cases of salmonellosis from years 2000 to 2016 were included. Paired-end sequencing (2x250bp) was performed on Illumina MiSeq. Genetic relatedness by cgMLST for *Salmonella enterica subsp. enterica* including 3,002 genes was compared to reference genome mapping with CSI Phylogeny version 1.4 and

conventional MLST. Resistance determinants and plasmids were studied through the online tools ResFinder and PlasmidFinder.

Confirmed travel-history was available for 80% of included cases: Europe (n=13), Asia (n=12), or Africa (n=16). Isolates were distributed into four phylogenetic clusters corresponding to geographical regions. Sequence type (ST) ST411 and a single locus variant (n=17) was primarily acquired in Southern Europe, ST1954 (n=15) in Africa, and ST343 (n=11) and ST2063 (n=8) primarily in Asia. The Southern European cluster was further divided into a Greek (n=10) and a Cypriot (n=4) cluster. The discriminatory power of cgMLST and SNP based analysis was high (0.99) and exceeded that of classical MLST (0.78). All isolates in the African cluster displayed resistance to ≥1 class of antimicrobials, most commonly trimethoprim-sulfamethoxazole resistance (n=13) and *sul2* and *dfrA14* genes, while resistance was rare in the other clusters. Overall, quinolone resistant isolates carried genes or mutations known to confer resistance, most commonly *qnrS1* (n=10) and *qnrB19* (n=5).

WGS of *S.* Chester in Norway showed four geographically distinct clusters, with a possible outbreak occurring during summer 2016 related to travel to Greece, distinct from the multi-country outbreak originating in Morocco. We recommend public health institutes to implement cgMLST based real-time *S.* Chester surveillance for early and accurate detection of future outbreaks. Norway has since implemented cgMLST in surveillance, which will enable timely outbreak detection by flagging similar geographical clusters that were detected retrospectively in this study.

The fellow was involved in isolate selection, becoming familiar with the laboratory methods, analysing, interpreting, and presenting the data, and drafting the manuscript as the first author.

B. Malaria in Europe: Detection and typing of imported and outbreak cases, ISCII, Madrid, Spain

Globally, the malaria case incidence was reduced by 41% between 2000 and 2015; however, malaria remains a public health threat with nearly half of the world's population at risk. In Europe, malaria cases are mostly imported by immigrants visiting their countries of origin or by other unprotected travellers returning from endemic countries. In recent years, local malaria transmission has been reported in Europe. In Spain, malaria is a notifiable disease and > 1,000 blood specimens from patients with suspected malaria are received each year at the national reference laboratory at Instituto de Salud Carlos III (ISCIII). In contrast to Spain, Norway has no reference laboratory for malaria parasitology, but cases are notified to the Norwegian Surveillance System for Communicable Diseases (MSIS). In the last ten years, between 30 and 120 malaria cases have been identified annually.

The aim of this project was to train the EUPHEM fellow in the surveillance of imported cases of malaria at the reference laboratory at ISCIII to learn methodology that serves as a powerful tool for malaria surveillance and allows for characterisation of possible autochthonous malaria outbreaks.

A semi-nested multiplex PCR was used to diagnose malaria and determine the *Plasmodium* species. It amplified a positive control product of mammalian 18S rRNA and a *Plasmodium sp.* specific product in the first PCR reaction. In the second PCR reaction, *P. malariae*, *P. falciparum*, *P. ovale*, and *P. vivax* specific products were amplified. The method is especially beneficial since it is able to diagnose patients infected with more than one *Plasmodium* species. Genotyping of *Plasmodium* parasites by the use of the merozoite surface protein (*msp*) genes was based on the parasite populations present in an infected individual. The *msp* genes contain polymorphic regions that were used to differentiate the populations present either through fragment size comparisons or through sequencing. The exact areas of amplification and interest differ between the species. In addition, techniques for the analysis of single nucleotide polymorphisms (SNPs) of genes associated to malaria resistance were used.

The molecular methods learnt represent an array of tools that are used to confirm malaria infection and type the cases to confirm autochthonous transmission and transmission during pregnancy. This is relevant, especially as local transmission has been suspected in several European countries. In addition to surveillance applications, the methods can be used for research purposes. Diagnostics using these or other methods are important for prompt recognition of malaria infection in order to treat the patient and to prevent further spread of infection in the community via local mosquito population, where the competent vector is present. The fellow presented the methods learnt and her visit overall at her main training site NIPH.

The fellow visited the malaria reference laboratory at ISCIII, received training and independently applied the laboratory methods, following her visit, she produced a final report and gave a presentation at her training site on the methods learnt.

Training modules

The EPIET/EUPHEM Introductory Course, the Management, Leadership and Communication in Public Health Module, Rapid Assessment & Survey Methods and the Outbreak Investigation Module broached many concepts necessary for successful completion of projects, 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. The Biorisk and Quality Management Module provided understanding of biorisk and quality control management, which are important in any laboratory investigation.

Educational outcome:

The fellow has deepened her public health microbiology knowledge in terms of laboratory investigations, including becoming familiar with parasitology. She also gained experience in the preparation of a study protocol, working with whole genome sequencing data, managing time, formulating recommendations and collaboration with different experts and disciplines.

4. Biorisk management

A. Preparedness laboratory training

Training for BSL-3 preparedness laboratory staff at NIPH included a general theoretical and a general practical part given by Tone Bjørndal Johansen and Veronica Klausmark. Topics covered were laboratory biosafety levels and microbial risk group classification, biosafety and biosecurity legislation and standards, risk assessments, physical barriers in the laboratory, personal protective equipment, safe working practices and operating procedures including following spills, illness, fires etc. The participants learnt how to put on and wear PPE, work in the laboratory, and manage laboratory waste. In addition, the fellow participated in training on Crimean-Congo Haemorrhagic Fever Virus RNA-extraction in the BSL-3 laboratory glove box; this part of the training was given by Coraline Basset.

B. Certifications

- Certificate of Achievement: Basic Security in The Field II (UNDSS)
- Certificate of Achievement: Advanced Security in The Field (UNDSS)
- International Transport of Infectious Substances (WHO)
- Online course on Clinical Biosafety Awareness for Public Health Professionals by Emory University

C. Table-top exercise in biorisk management

The fellow performed a table-top exercise using a fictional virus and laboratory scenario focusing on the biosafety risk of direct exposure to individuals in the laboratory and to the community and biosafety risk of direct exposure to individuals in the laboratory and to the community, both before and after mitigation efforts.

Training modules

The Biorisk and Quality Management Module provided understanding of biorisk and quality control management. Participants were trained in identification and mitigation of biorisks and shipment practices and protocols for infectious substances among others.

Educational outcome:

The fellow developed an understanding of the importance of biorisk management, and the requirements necessary to control risks associated with the handling, storage, and disposal of biological agents and toxins in laboratories, understanding the processes associated with BSL3 and BSL4 laboratories as well as biosafety risk assessment and mitigation.

5. Quality management

Supervisors: Susanne G. Dudman, Kristin Modalsi

A. Accreditation of rotavirus identification assay

The aim of the project was achieving accreditation of the enzyme immunoassay for identification of rotaviruses at the national reference laboratory at NIPH, in order to ensure high quality of laboratory results used to inform public health policy and vaccination programme evaluation. The work was undertaken in co-operation with colleagues Moustafa Gibory, Ildri Haltbakk, and the project supervisors. The applied standard was NS-EN ISO/IEC 17025. The national accreditation body Norwegian Accreditation Board will audit the laboratory to evaluate if accreditation will be granted.

For the validation, 45 samples obtained through external quality assurance (EQA) or samples received at the reference laboratory were analysed in three separate runs if there was enough material. In two runs, an automated setup was used; in one run, the setup was manual. The material included samples that were positive

for several common genotypes of rotaviruses, including the vaccine strain, samples positive for other viruses (norovirus, adenovirus, astrovirus, enterovirus), and samples negative for all intestinal viruses. Furthermore, the results from 265 pairs of samples comparing two sampling materials (stool samples and rectal swabs) were included in the validation report. The enzyme immunoassay was validated following the standard operating procedure in place at the laboratory. The method is an ELISA sandwich method that detects rotavirus VP6-antigens that are present in all rotaviruses that cause disease in humans.

The analysed samples gave congruent results with the known results and between the different setups, except for one sample which gave a positive result in the first automated run and the manual run, but a negative result in the second automated run. This sample was re-run and found to be positive. For the automated setup the sensitivity was 96.6%, specificity 100%, both the positive and negative predictive values were 100%. For the manual setup, all values were 100%.

The validation demonstrated that the assay is fit for the purpose of identifying rotavirus in stool and rectal swab samples that are received at the national reference laboratory, consequently providing high quality laboratory data for public health policy and national childhood rotavirus immunisation programme evaluation. The method is currently in routine use at the reference laboratory at NIPH.

The fellow become familiar with the laboratory methods used, contributed toward interpretation of the results and writing of the final validation report.

B. Quality audit of the measles, mumps, and rubella laboratory

The fellow performed an internal audit of the national reference laboratory for measles, mumps and rubella at NIPH by interviewing the head of laboratory and staff, going through protocols and methods descriptions and workflows in the laboratories. The audit focused on process management, quality control indicators, and documentation. The audit yielded a general indicator percentage of 96%. The overall quality was high and no deviations affecting the quality of the results were identified. The laboratory was advised to consider further improving quality management by making monthly summaries of quality parameters, such as process time, to track process management and workflow.

Training modules

The Biorisk and Quality Management Module familiarised participants with all aspects concerning quality management in both internal and external quality control.

Educational outcome:

The fellow learned how to apply the principles and practices of biosafety according to WHO and EU directives. Additionally, she was familiarised with and applied the concepts of accreditation procedures, quality audits, and validation of laboratory methods.

6. Teaching and pedagogy

A. Facilitation of case study at an outbreak course for municipal doctors working with communicable diseases

The one-day course on outbreak investigation with lectures in the morning and a case study in the afternoon was organised by NIPH. The fellow facilitated a case study describing an outbreak of gastrointestinal disease caused by enterotoxigenic *Escherichia coli* (ETEC) at a hotel in Norway. Prior to the facilitation, the EPIET and EUPHEM fellows went through the case study to make final edits.

B. Developing and delivering lecture on Microbiological Methods

The fellow developed and delivered internal teaching at NIPH for non-microbiologists about the role of laboratory methods in public health microbiology, including genotyping and the basics of whole genome sequencing and options for utilising the sequencing data.

D. Developing teaching materials and delivering lectures on the Norwegian Childhood Vaccination Programme and Travel Vaccinations

Teaching given as part of a one-day course on vaccines organised by the NIPH in collaboration with the University of Oslo, School of Pharmacy, for university students. The fellow developed and delivered lectures covered the Norwegian childhood vaccination programme and the role of national immunisation programmes in controlling infectious diseases, and key concepts in vaccinology; furthermore, the role of vaccines in preventing disease during or after travel was covered and participants were familiarised with the factors that should be considered when

giving travel advice related to vaccination. The fellow also designed an evaluation form, collected, and reported the results of the evaluation of the one-day course to develop the training. In addition a reflective teaching report was written following the training.

C. Lecture on Norms and Accreditation

Teaching at the Biorisk and Quality Management Module adapted and delivered together with EUPHEM fellow Laura Bubba. The lecture covered and contrasted accreditation, certification, and licensure, described the process involved in the development of standards and discussed the need for laboratory standards.

Educational outcome:

The fellow learned and gained experience on all stages of organising workshops, from outlining course objectives, developing the curriculum and lectures, giving lectures and facilitating 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 time management, communicating between epidemiologists and the microbiology laboratory, team building and coordination, research collaboration and management of cultural differences in international contexts. For all projects, the fellow described the benefit to public health microbiology and was engaged in scientific communication to peers and stakeholders. During the outbreak investigations, the fellow was involved in planning response and control measures. The fellow acquired team building and negotiation skills by working as a team member during the projects working alongside epidemiologists and microbiologists from different departments at NIPH. The fellows' communication output in terms of manuscripts, reports, and presentations are listed in section 8.

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 for which the outbreak responsible writes a summary of the outbreak situation nationally and internationally.

C. NIPH website on laboratory analyses

The fellow acted as editor in the overhaul of the NIPH website describing the microbiological laboratory analyses. The work involved making templates for collecting the information and drafting and writing articles on reference functions and specimen submission instructions, collating, and summarising information on preparedness laboratory functions and import virus work, working with the experts responsible for the laboratory analysis, the communications team and other staff responsible for the information on the website. She worked closely together with Sigrid Rasdal Eliassen in the NIPH Department for Quality and Laboratory Resources and Ingrid Holm Finseth and Harald Pors Muniz in the NIPH Communications Department.

D. Whole genome sequencing for surveillance and outbreak investigations in Norway - 3-minute presentation to ECDC leaders

For the Management, Leadership and Communication in Public Health Module, the fellow researched and then presented the laboratory capacity and current status of using microbial whole genome sequencing (WGS) for surveillance and outbreak investigations in Norway for invited ECDC leaders. The main conclusions were that Norway had a good capacity for microbial genomics across all regional health trusts and a strategic decision has been made at NIPH to integrate WGS for surveillance and outbreak investigations. For the majority of pathogens prioritised in the ECDC roadmap v. 2.1, there is already the possibility to use WGS for outbreak investigations, and a surveillance application is available for *Neisseria meningitidis, Neisseria gonorrhoeae*, carbapenemase producing *Enterobacteriaceae*, and methicillin resistant *Staphylococcus aureus.* Further testing and implementation was underway for several other pathogens. To build further competence in WGS and phylogeny, the National Consortium for Microbial Genomics and established internal and external training provided by NIPH are recommended to be utilised.

E. Outbreak team teleconferences

The fellow participated in multidisciplinary outbreak tele/videoconferences between NIPH, the Norwegian Food Safety Authority, the Veterinary Institute and involved municipal physicians by taking meeting minutes, compiling the information available to date or giving situation updates. During these meetings, joint decisions by the parties

were taken regarding whether a thorough investigation, potentially including analytical epidemiology, was warranted or not in the relevant outbreaks.

F. Nordic Mini Project Review Module

The fellow co-organised together with the EPIET fellows at NIPH and participated in this two-day module, which is held annually in one of the Nordic countries to facilitate detailed presentation and discussion of current projects among EPIET and EUPHEM fellows in the Nordic and Baltic countries. The tasks included the practical arrangements, including inviting fellows, drafting the agenda for the module and identifying and inviting local experts to facilitate sessions. A total of 15 experts participated in the review of 15 projects, which were presented by 12 fellows.

Training modules

The Management, Leadership and Communication in Public Health Module familiarised participants with understanding roles and responsibilities in public health management settings. Topics covered included the identification and application of different management styles, team roles and team evolution, the delegation of tasks and the provision of structured, clear and efficient feedback.

Educational outcome:

The fellow experienced general public health management throughout her projects, such as describing added value of PH for public health, applying principles of scientific communication to peers, stakeholders and the public, recognising the role of different agencies, identifying interdisciplinary needs between public health professionals.

8. Communication

Publications

1. Siira L, Nøkleby H, Barlinn R, Riise ØR, Aaberge IS, Dudman SG. Response to third rubella vaccine dose. Human Vaccines & Immunotherapeutics, Volume 14 Issue 10.
2. Siira L, Naseer U, Alfsnes K, Hermansen NO, Lange H, Brandal LT. Whole genome sequencing of *Salmonella* Chester from 2000-2016 in Norway reveals geographically distinct outbreak clusters. Submitted manuscript.
3. Siira L, Vestrheim DF, Winje BA, Caugant DA, Steens A. Pneumococcal antimicrobial susceptibility and clonality during a period with changes in pneumococcal childhood vaccination, Norway, 2004-2016. Manuscript in preparation.
4. Siira L, Holmbakken G, MacDonald E, Sundar T, Myklestad LM, Lange H, Brandal LT, Naseer U, Johannessen G, Bergsjø B, Espenhain L, Vold L, Nygård K. Increasing incubation periods during a prolonged monophasic *Salmonella* Typhimurium outbreak with environmental contamination, Norway, 2017. Manuscript in preparation.

Reports

1. Veneti L, Espenhain L, Siira L, Løvlie A, Borgen K, Lange H, Vold L. Outbreak report: An outbreak of gastroenteritis after a memorial service, Norway, December 2016.
2. Veneti L, Espenhain L, Siira L, Løvlie A, Borgen K, Lange H, Vold L. Outbreak report: An outbreak of gastroenteritis connected to a music festival at a hotel, Norway, January 2017 (in Norwegian).
3. Løvlie A, Siira L, Veneti L, Lange H, Borge SK, Vold L, Møller K, Guzmán B, Borgen K. Outbreak report: Outbreak with norovirus at hotel, February-Mars 2017, Norway (in Norwegian)
4. Gibory M, Haltbakk I, Siira L, Modalsli K, Dudman SG. Validation report: Rotavirus antigen detection (EIA) (in Norwegian), June 2017.
5. Outbreak report: An outbreak of *Salmonella* Typhimurium, 2017 (in Norwegian)
6. Siira L, Bragstad K, Dudman SG, Hungnes O, Berg AS. Options for Surveillance of Respiratory Syncytial Virus (RSV) in Norway, September 2018.
7. Comparison of *Neisseria gonorrhoeae* susceptibility data obtained from phenotypic testing and next generation sequencing using the Bacterial Isolate Genome Sequence Database
8. Malaria in Europe: Detection and typing of imported and outbreak cases – Report of laboratory stay, March 2018

Conference presentations

1. Lotta Siira, Umaer Naseer, Kristian Alfsnes, Nils Olav Hermansen, Lin T. Brandal. Whole genome sequencing of *Salmonella* Chester from 2000-2016 in Norway enables comparison of geographically distinct outbreak clusters (Poster ESCAIDE, 2017).

2. Astrid Løvlie, Lotta Siira, Lamprini Veneti, Heidi Lange, Kaja Sverdrup Borge, Line Vold, Karin Møller, Bernardo Guzmán Herrador, Katrine Borgen. Challenges in controlling norovirus transmission in semi-closed populations: Lessons learnt from an outbreak at a hotel in Norway (Poster ESCAIDE, 2017, presented by Astrid Løvlie).
3. Lotta Siira, Dominique Caugant, Martin Steinbakk. Can we predict the antimicrobial susceptibility of *Neisseria gonorrhoeae* with the help of next generation sequencing data? (Oral presentation, NIPH Annual conference, 2017)
4. Lotta Siira, Gry Holmbakken, Emily MacDonald, Tom Sundar, Lars Meyer Myklestad, Heidi Lange, Lin T. Brandal, Umaer Naseer, Gro Johannessen, Bjarne Bergsjø, Laura Espenhain, Line Vold, Karin Nygård. A prolonged outbreak of monophasic *Salmonella* Typhimurium with environmental contamination in Norway, August 2017 (Abstract accepted for poster presentation at ESCAIDE 2018)

Selected other presentations

1. Lotta Siira. Whole genome sequencing for surveillance and outbreak investigations in Norway (Oral presentation, ECDC, Management, Leadership and Communication in Public Health Module)
2. Lotta Siira, Hanne Nøkleby, Regine Barlinn, Øystein R. Riise, Ingeborg S. Aaberge, Susanne G. Dudman. Rubella seroprevalens hos rekrutter før og etter 3. MMR dose (Oral presentation, NIPH vaccine meeting, 2018)

Training modules

The Introductory Course and the Project Review Module familiarised participants with concepts relating to communicating efficiently and writing scientific articles, including how to present data in the form of tables and figures.
The Management, Leadership and Communication in Public Health Module familiarised participants with communication to different audiences including the public and higher authorities, and tailoring the main message depending on the audience.

9. EPIET/EUPHEM modules attended

Introductory Course, Spetses, Greece, 26 September - 14 October 2016
Outbreak Investigation Module, Berlin, Germany, 5-9 December 2016
Multivariable Analysis Module, Zagreb, Croatia, 13-17 March 2017
Rapid Assessment & Survey Methods, Athens, Greece, 8-13 May 2017
Project Review, Lisbon, Portugal, 28 August - 1 September 2017
Biorisk and Quality Management Module, Stockholm, Sweden, 5-9 February 2018
Management, Leadership and Communication in Public Health Module, Stockholm, Sweden, 12-16 February 2018

10. Other training

1. The European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE), Stockholm, Sweden, 18-30 November 2016
2. Workshop regarding the Norwegian Outbreak Notification System "VESUV" at NIPH, Oslo, Norway, 24 October 2016
3. Training visit at the reference laboratory Department of Zoonotic, Food- and Waterborne Infections, NIPH, Oslo, Norway, 25 October 2016
4. Seminar about WGS and other laboratory techniques used for surveillance organised at NIPH, Oslo, Norway, 17 January 2017
5. Nordic Mini Project Review Module, Helsinki, Finland, 3-4 April 2017.
6. EUPertstrain/EUPertgenomics meeting on pertussis research and surveillance, Oslo, Norway, 6-7 September 2017
7. Seminar on Norwegian Surveillance System for Communicable Diseases (MSIS), Oslo, Norway, 24 October 2017
8. Training visit to the NIPH Vaccine Supply Facilities, Oslo, Norway, 2 November 2017
9. The European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE), Stockholm, Sweden, 6-8 November 2017
10. National Consortium for Microbial Genomics Meeting, Oslo, Norway, 7 December 2017
11. The NIPH Annual Conference in Microbiology and Immunology, Oslo, Norway, 8 December 2017
12. Nordic Mini Project Review Module, Oslo, Norway, 5-6 March 2018
13. Smitteverndagene meeting on communicable diseases, 11-12 June 2018
14. UNDSS online courses on Basic and Advance Security in the field
15. Online vaccinology course organised by Institute Pasteur
16. Online course on Bacterial Genomes: Disease Outbreaks and Antimicrobial Resistance by the Sanger Institute
17. Online course on Bacterial Genomes: From DNA to Protein Function Using Bioinformatics by the Sanger Institute
18. Online course on Clinical Biosafety Awareness for Public Health Professionals by Emory University

Discussions

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 Lotta Siira during her two-year EUPHEM fellowship (cohort 2016) as an EU-track fellow at the Norwegian Institute of Public Health (NIPH), Oslo, Norway. The projects described in this portfolio demonstrate the depth and breath of the public health microbiology work of Lotta. Epidemiological studies included participation in a number of local and national outbreak investigations with clear public health outcomes while surveillance activities extended from study of pneumococcal antimicrobial susceptibility to the evaluation of possible options for surveillance of respiratory syncytial virus (RSV) in Norway. Her research project on the effect of a third dose of rubella vaccine among Norwegian conscripts provided valuable information on the relevance to maintain high vaccine coverage to ensure immunity in the future. The laboratory and epidemiologically based projects covered a diverse range of disease programmes working in all domains of microbiology and also exhibiting the fellow's strengths in effective multidisciplinary team work. Lotta has effectively contributed to the training site cascading her knowledge through teaching on various arguments and to a variety of audiences. Lotta has also contributed to the organisation of the Nordic Mini Project Review module and has been editor for the NIPH website on laboratory analyses. All projects here described were in line with the 'learning by doing' and 'on-the-job' training service approach of the EUPHEM programme and followed the core competency domains described for professionals in mid-career and above. Projects had a clear outcome, with results communicated in technical reports, scientific journals and at conferences. The EUPHEM Coordinator concludes that the fellow has succeeded in performing all her tasks to a very high standard and with a professional attitude, which indicates her development in leadership. We wish the fellow every success in her future career as a public health microbiologist.

Supervisor's conclusion

Lotta embarked on the EUPHEM fellowship as a microbiologist with experience from a national reference laboratory service. During her fellowship, Lotta has taken on a wide variety of tasks, activities and projects. She has demonstrated a very good understanding for the need and aim of the different tasks she has performed, resulting in outputs that have added to national and international public health activities. In her work she has balanced very well between pragmatic problem solving and scientific work according to the situation and need. Lotta has contributed to the investigation of outbreaks in Norway, she has compiled and analysed laboratory and epidemiological surveillance data for invasive pneumococcal disease and explored options for surveillance of RSV-infections. She has performed and participated in quality management, and delivered several lectures, and she has analysed complex NGS datasets. For all these activities, Lotta has established good and strong relationships with project supervisors and co-workers from several departments in the institute. During her fellowship, NGS has been introduced as a leading platform for microbiology at NIPH, and Lotta's work has been important and very useful for this process. Her work has been of value for indicating the direction of further work within public health microbiology at NIPH. The completion of the EUPHEM training programme is dependent on a broad involvement of NIPH staff, leading to an added value of broad collaboration. Lotta has masterly managed to engage her co-workers, and pulled through different projects, leading to a strengthening of public health microbiology.

Personal conclusions of fellow

The EUPHEM fellowship has provided me with the unique opportunity to work on interesting and diverse projects and attend high-quality training modules in the field of public health. Through my projects and activities, I was allowed to broaden and expand my knowledge on public health microbiology and its links with epidemiology, deepen my knowledge on bacteriology and venture into the fields of virology and parasitology. I especially appreciate how the fellowship is able to show how public health microbiology and epidemiology can benefit from bridging the gap between the disciplines by developing understanding and collaboration, as well as establishing and expanding Europe-wide networks of colleagues in public health. At NIPH, I was fortunate to be offered all the opportunities, projects, help and guidance needed to not only fulfil the fellowship requirements, but also allow me to develop into a more experienced public health microbiologist.

Acknowledgements of fellow

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insights and experience in epidemiology. My warmest thanks also to my many project supervisors, who have generously taken me under their wing and shared their knowledge, the other members of staff that I have had the opportunity to work with, and my office mates at the institute.

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