FELLOWSHIP REPORT

Summary of work activities

Soledad Colombe
Intervention Epidemiology path (EPIET)
Cohort 2018

Background

The ECDC Fellowship Training Programme 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 curriculum paths are part of the ECDC fellowship programme that provides competency based training and practical experience using the 'learning by doing' approach in acknowledged training sites across the European Union (EU) and European Economic Area (EEA) Member States.

Intervention Epidemiology path (EPIET)

Field epidemiology aims to apply epidemiologic methods in day to day public health field conditions in order to generate new knowledge and scientific evidence for public health decision making. The context is often complex and difficult to control, which challenges study design and interpretation of study results. However, often in Public Health we lack the opportunity to perform controlled trials and we are faced with the need to design observational studies as best as we can. Field epidemiologists use epidemiology as a tool to design, evaluate or improve interventions to protect the health of a population.

The European Programme for Intervention Epidemiology Training (EPIET) was created in 1995. Its purpose is to create a network of highly trained field epidemiologists in the European Union, thereby strengthening the public health epidemiology workforce at Member State and EU/EEA level. Current EPIET alumni are providing expertise in response activities and strengthening capacity for communicable disease surveillance and control inside and beyond the EU. In 2006 EPIET was integrated into the core activities of ECDC.

The objectives of the ECDC Fellowship - EPIET path are:

- To strengthen the surveillance of infectious diseases and other public health issues in Member States and at EU level;
- To develop response capacity for effective field investigation and control at national and community level to meet public health threats;

The views expressed in this publication do not necessarily reflect the views of the European Centre for Disease Prevention and Control (ECDC).

This portfolio does not represent a diploma. Fellows receive a certificate acknowledging the 2-year training and listing the theoretical modules attended. Additionally, if all training objectives have been met, they receive a diploma.

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- To develop a European network of public health epidemiologists who use standard methods and share common objectives;
- To contribute to the development of the community network for the surveillance and control of communicable diseases.

Fellows develop core competencies in field epidemiology mainly through project or activity work, but also partly through participation in training modules. Outputs are presented in accordance with the EPIET competency domains, as set out in the ECDC Fellowship Programme Manual.

Pre-fellowship short biography

Soledad is a veterinarian by training (National Veterinary School of Lyon, France) and has a master in public health and epidemiology of infectious diseases (Yale School of Public Health, USA) and a PhD in parasitology (Leiden University, The Netherlands). Prior to the fellowship, she was working as an epidemiologist researcher in the field of international health with a strong interest in One Health. She worked on brucellosis and Q fever in Thailand as well as the epidemiology of co-infections of HIV and *Schistosoma* spp. in Tanzania.

Fellowship assignment: Intervention Epidemiology path (EPIET)

On 11 September 2018, Soledad Colombe started her EPIET fellowship at Folkhälsomyndigheten, Stockholm, Sweden, under the supervision of Moa Rehn. This report summarizes the work performed during the fellowship.

Fellowship portfolio

This portfolio presents a summary of all work activities (unless restricted due to confidentiality regulations) conducted by the fellow during the ECDC Fellowship, EPIET path. These activities include various projects, and theoretical training modules.

Projects included epidemiological contributions to public health event detection and investigation (surveillance and outbreaks); applied epidemiology field research; teaching epidemiology; summarising and communicating scientific evidence and activities with a specific epidemiology focus. The outcomes include publications, presentations, posters, reports and teaching materials prepared by the fellow.

This portfolio also includes a reflection from the fellow on the field epidemiology competencies developed during the 2-year training, a reflection from the supervisor on the added value of engaging in the training of the fellow, as well as a reflection by the programme coordinator on the development of the fellow's competencies.

Fellowship projects

1. Surveillance

Evaluation of a surveillance system in the context of national elimination: the case of rubella in Sweden.

In Sweden, rubella is a notifiable disease through a passive surveillance system. Since 2013, only 2 suspected cases were notified in the Swedish notification system for notifiable diseases (SmiNet) by clinicians. However, the absence of notified cases can only be considered as evidence supporting elimination if the surveillance system can ensure the detection of all sporadic rubella cases. The aim of this project was to evaluate the quality of the surveillance system in Sweden for detection of potential sporadic cases of rubella by estimating the number of clinically suspected rubella cases in Sweden in 2018 and assessing the ability of the five microbiological laboratories performing anti-rubella IgM in Sweden to detect acute rubella infections. For each test of anti-rubella IgM performed in 2018, the fellows collected information on demographics of the patient, test performed by the lab, and any free text given on the referral form in order to define a clinically suspected rubella case. They also performed interviews with the collaborating laboratories. They estimated a rate of clinically suspected and discarded acute rubella cases of 0.25/100,000 inhabitants. This rate does not meet the WHO target of 2 discarded cases/100.000 inhabitants. It is however likely that additional clinically suspected and discarded cases of acute rubella occur each year, but could not be identified in this study due to the limited clinical information available. In addition, a high number of anti-rubella IgM tests are performed yearly in Sweden (1600-1900 tests) by proficient laboratories and the investigators believe that if there were to be a case of acute rubella, it would be detected.

Role and outputs: Co-principal investigator (project in collaboration with Maximillian Riess EUPHEM C2018)

Soledad and Maximillian wrote the protocol, created the data collection form, coordinated the data collection from the laboratories, created an algorithm to define a clinically suspected case of rubella, analysed the data, and wrote a report that was shared as an annex to the yearly report to WHO[12].

Supervisor: Hélène Englund

Competencies developed:
Soledad was able to update her knowledge on rubella, and understand the complexities of case definitions both laboratory wise and clinically wise.

Daily surveillance of food-borne, vector-borne, and zoonotic diseases

Notifiable diseases are reported both by clinicians and laboratories into a system called SmiNet. Daily, notifications are checked and interpreted at Folkhälsomyndigheten. Different diseases have different exporting, processing, and analysis systems, but all have the same goal: to detect abnormalities in the number of cases reported. Surveillance of food-borne and water-borne diseases also require regular coordination with the regional County Council Departments of Communicable Disease Control and Prevention (CDC-Department), the Swedish Board of Agriculture, the National Food Agency, and the Swedish Veterinary Agency. The aim of this project was to understand the functioning of SmiNet, highlight the specificities of the surveillance system for different food-borne diseases in terms of case definition, reporting sources and limitations of the system, and improve processing and analysis of surveillance data when needed. For campylobacteriosis, EHEC, yersiniosis, shigellosis, tick-borne encephalitis, leptospirosis, Q fever, brucellosis, echinococcosis, hepatitis A, hepatitis E, and giardia, the fellow checked new notifications every day, analysed the new incoming data according to the described routine, discussed cases if necessary internally, collaborated with the laboratory for diseases requiring further testing, and coordinated with the CDC-departments, the Swedish Board of Agriculture, the National Food Agency, and the Swedish Veterinary Agency. Findings were reported weekly during internal surveillance meetings, and meetings across agencies. The fellow also contributed to answer to the media, and responded to EWRS and EPIS requests for these diseases. For Giardia, the daily processing and analysis of surveillance data was initially done manually, in a non-reproducible and time-consuming manner. In order to save time and reduce errors, the daily surveillance files were automatized. It now requires first to export the data into excel from SmiNet. Then a STATA do-file cleans the surveillance data and creates an excel file with all data automatically summarized in an interpretable way, by age, sex and region.

Role and outputs: Principal investigator

Soledad created and ran when necessary the automation files. She wrote the yearly report for giardia surveillance in Swedish, which goes into a public report published by Folkhälsomyndigheten on their website[13].

Supervisors: Elsie Ydring, Anette Hansen, Marie Jansson-Mörk and Moa Rehn

Competencies developed:
Soledad could reflect on the most adapted descriptive strategy for diseases with and without seasonality and with potentially large variations in the number of reported cases on a daily or even weekly basis.

Automation of the daily processing and analysis of surveillance data for COVID-19

The first case of COVID-19 was reported in Sweden on the 31st of January 2020. There was no reporting system in place since it was an emerging disease. The surveillance system and notification system for SARS was initially used in SmiNet in which both clinicians and laboratories report cases. Once a new reporting form was created for SARS-CoV-2/COVID-19, the old notifications needed to be merged with the new ones, and daily processing and analysis of the data needed to be produced in order to inform fast decision making, and to regularly communicate on the most up-to-date situation to the public. The aim of this project was to create daily summary of COVID-19 data issued from surveillance in both an automatized and easily interpretable way. STATA files were created to clean the data, run descriptive analyses and to automatically create reports for different purposes: internal updates and discussion, public website and press conferences. This work also involved daily coordination with the regional medical officers.

Role and outputs: Co-investigator

Soledad created a routine for processing of the data, created the STATA files and improved the system on a daily basis, to adapt to the urgency of the situation. Results were published on Folkhälsomyndigheten website and presented daily at press conferences.

Supervisors: Annasara Carnahan, Moa Rehn

Competencies developed:
Emergency situations require a balance between "perfection" and "timeliness". This was particularly obvious in this situation, where the files had to be re-adapted and improved every day for several months. Each day there was a "good enough" threshold that would allow us to deliver on time. The next day this threshold would be all new again. This was a job by the minute, where the information was changing several times within an hour, and where communication was key but complicated.

Evaluation of CASE (Computer Assisted Search for Epidemics), the early warning system for infectious diseases at Folkhälsomyndigheten

CASE (Computer Assisted Search for Epidemics) is a computer-based tool that was set up at Folkhälsomyndigheten in 2008, with the goal of supporting outbreak detection through linkage to SmiNet. CASE is set up for all notifiable diseases, and unusual signals are sent to epidemiologists involved in daily surveillance. Threshold values, the Farrington algorithm and SatScan are the algorithms used, alone or in combination depending on the disease. Parameters and time aggregation are also set according to the disease and to the preference of the responsible epidemiologist if necessary. The initial purpose of CASE was to provide a tool for the less experienced epidemiologists, to find outbreaks quicker and ultimately to make the organization more reactive. CASE has been evaluated twice: once in 2011 and once in 2013, both times among epidemiologists conducting daily surveillance at Folkhälsomyndigheten. No evaluation of CASE has been done since, despite changes in diagnosis techniques (ex. Whole Genome Sequencing), in detection tools, and in data sources. In order to improve CASE as an early warning system at Folkhälsomyndigheten, the investigators identified a need for a new evaluation of CASE that would specifically aim to (1) estimate its usefulness in terms of how much and how it is currently used by epidemiologists and microbiologists involved in daily surveillance, (2) evaluate the ability to interpret the signals among epidemiologists and microbiologists involved in daily surveillance (3) calculate the sensitivity and timeliness of the signals.

Role and outputs: Principal investigator

Soledad designed the study, wrote the proposal, and wrote the protocol. The study is planned to be initiated by the next EPIET fellow.

Supervisors: Pär Bjelkmar and Henrik Källberg

Competencies developed:
This project allowed Soledad to understand the key aspects of an early warning system and the need for constant improvement of these systems as methods and software tools improve.

Rapid Risk Assessment for endemic Q fever in Sweden

On September 21st 2018, Folkhälsomyndigheten was alerted of posts on social media from a pregnant female veterinarian who stated not being taken care of by the Swedish healthcare system after potentially having been exposed to Q fever. This alerted the Public Health Agency of Sweden, the Swedish Veterinary Association, the Swedish Board of Agriculture and the Swedish Work Environment Authority of a need for updated recommendations to veterinarians, farmers, and clinicians regarding exposure to Q fever. In addition, the head of the department and the state epidemiologist requested a rapid risk assessment to be conducted about the risk of endemic *Coxiella burnetii* for the public and for pregnant women in close contact with livestock.

Role and outputs: Contributor

Since Soledad is a veterinarian and had worked specifically on *Coxiella burnetii* before her fellowship, she participated by providing expertise on the epidemiology of *Coxiella burnetii* among livestock and transmission to human populations. Two internal rapid risk assessment tools were filled in.

Supervisor: Pontus Juréen

Competencies developed:
This was the first time Soledad participated in a Rapid Risk Assessment (RRA). She was able to learn the tool used by the Agency to conduct these RRA, including its advantages and limitations. This RRA also allowed Soledad to experience the making of a RRA in the context of a rare disease.

Epidemic intelligence for COVID-19

COVID-19 emerged in December 2019 in China. Sweden confirmed its first imported case on January 31st 2020, and the epidemic started in Sweden on the 28th of February. The role of the epidemic intelligence team and the fellow changed drastically between these different periods. Weekly risk assessments were conducted to measure the risk of importation and implantation of SARS-CoV-2 in Sweden. A daily summary email was prototyped and sent daily internally and to the CDC-departments. The current epidemiological situation worldwide was summarized as well as new recommendations from ECDC and WHO. A group was in addition set up to screen all new published scientific articles and select important information for decision-making at the agency. New peer-reviewed articles were entered in a list every day and articles were triaged into needing to be read or not. The team then read the articles, discussed them and summarized them. Summaries were sent to the decision makers within the agency. The team also provided input to the modellers working on a model to get hospitals ready for a potential pandemic.

Role and outputs: Contributor

Soledad participated in all activities mentioned above. More specifically, she provided insight as an epidemiologist, and reviewed the current data necessary to the newest rapid risk assessments. She was also in charge of summarizing the worldwide data, initially three times a day, then daily as the number of cases increased. She wrote Standard Operations Procedures for the daily summarizing and sharing of worldwide information. She also reported this information twice a week at agency-wide meetings. In addition, Soledad set up the system for daily review of the literature. Finally, the fellow was in charge of listening in to ECDC and WHO press conferences and taking notes.

Supervisors: Maria Axelsson and Anders Wallensten

Competencies developed:
This set of tasks allowed Soledad to be part of the COVID-19 response and observe crisis management and its evolution in times of a pandemic.

2. Outbreak investigations

Outbreak of *Salmonella Enteritidis* MLVA 2-10-7-3-2, Sweden, October-November 2018

From October 9th to November 3rd 2018 an outbreak of *Salmonella enteritidis* with a Multiple Locus Variable Number Tandem Repeat Analysis (MLVA) profile 2-10-7-3-2 occurred in Sweden. An outbreak investigation was conducted by Folkhälsomyndigheten in collaboration with the regional County Council Departments of Communicable Disease Control and Prevention (CDC-Department) of the affected counties and the National Food Agency. A total of 33 cases were identified, symptoms were mild to severe, and no death was reported. Cases were mostly adults and resided in 15 different counties. A case-control study was undertaken to investigate the source of the outbreak. Results of the case-control study suggested that being a case was associated with having eaten at a restaurant, and bacon and lettuce were the main suspected sources. No food item was available for source tracking and the environmental investigations were inconclusive. Folkhälsomyndigheten timely informed the public of the outbreak via its official website. Further public health measures such as counselling patients on food handling were of the responsibility of the CDC-departments and the National Food Agency.

Role and outputs: Co-investigator

Soledad wrote the protocol for the case-control study, participated in creating the questionnaire, processed and analysed the data and created an internal report[10].

Supervisors: Moa Rehn, Marie Jansson Mörk, Sharon Kühlmann-Berenzon

Competencies developed:
This was Soledad's first ever outbreak investigation. She learned the responsibilities of each person in an outbreak investigation team, and the role of the public health agency in regards to the regional medical officers. She was introduced to the trawling questionnaire. She also could reflect on the timeliness of outbreak investigations. In this case the outbreak died off without any source being found.

Cross-border outbreak of *Yersinia enterocolitica* O3 associated with imported fresh spinach, Sweden and Denmark, March 2019

In early April 2019, Folkhälsomyndigheten and Statens Serum Institut (SSI) independently noted an increase in *Y. enterocolitica* and *Y. enterocolitica* O3 biotype 4 cases as part of routine surveillance. In Sweden, whole genome sequencing revealed that isolates were closely related on a genetic level. On 10 April, Folkhälsomyndigheten contacted and shared a representative outbreak sequence with public health institutes in Denmark, Finland and Norway to inquire whether a matching cluster had also been observed. SSI reported a similar signal and started sequencing their *Y. enterocolitica* O3 biotype 4 isolates. Swedish and Danish sequences were compared and found to be of sequence type 18 and genetically closely related. A cross-border outbreak was declared on 24 April 2019. The two countries' national public health agencies collaborated closely from thereon in the outbreak investigation but conducted separate analytical studies (case-control studies). Folkhälsomyndigheten investigated the outbreak in collaboration with the CDC-departments and the National Food Agency. Combined investigations with Danish authorities in this cross-border outbreak suggested that the likely source of this outbreak was fresh spinach sold at major retail chains in both countries. No other European countries reported having cases connected to the outbreak.

Role and outputs: Co-investigator

Soledad participated in writing the protocol for the case-control study and in analysing the outbreak data. She participated in the discussions with SSI and wrote a scientific article together with the team at SSI[1]. She also contributed to the internal report[11].

Supervisors: Marie Jansson Mörk, Cecilia Jernberg, Sharon Kühlmann-Berenzon

Competencies developed:
This outbreak taught Soledad the challenges in cross-border outbreaks and the necessity of transparency in data sharing. It also allowed interesting discussions on the interpretation of case-studies results when in that case two separate case-control studies were conducted in Denmark and Sweden with very different results. Finally, this outbreak highlighted the need for whole genome sequencing to confirm cases being part of the same outbreak.

Outbreak of atypical monophasic *Salmonella Typhimurium* strain associated with small tomatoes, Sweden, August-October 2019

Between 28 August and 18 October 2019, Sweden experienced a nation-wide outbreak of monophasic *Salmonella Typhimurium* sequence type 3478 (78 cases). Cases were in majority female (63%) and on average 52 years-old. A matched case-control study (8:1) was implemented on cases with controls matched for sex, age, and region selected from a national survey panel. The case-control study suggested small tomatoes as a source of the outbreak (adjusted Odds Ratio=10.8[4.15-112.68], p<0.001) and a trace-back investigation led to one single non-Swedish producer in Europe. Both the *Salmonella* strain and the source of the outbreak are rarely encountered in Europe.

Role and outputs: Principal investigator of the case-control study

Soledad participated in outbreak meetings with the CDC-departments and the National Food Agency. In the fall of 2019, Sweden experienced several outbreaks of *Salmonella* spp. Knowing that all cases of *Salmonella* receive the same trawling questionnaire, Soledad investigated the feasibility of doing a case-case study instead of a case-control study and wrote an internal report for it. In the end, it was decided to conduct a case-control study, and

Soledad wrote the case-control study protocol, created the questionnaire and the data entry form. She also processed and analysed the data, interpreted the results, and wrote internal reports to communicate ongoing results of the study to collaborators. She wrote and published an outbreak report in Eurosurveillance to make other European countries aware of this unusual strain[2].

Supervisors: Anette Hansen, Cecilia Jernberg, Moa Rehn, Emma Löf

Competencies developed:
Contrary to previous outbreaks, the team had a strong hypothesis for the source of the outbreak from the beginning, which meant the case-control questionnaire could be more targeted, but that the team still needed to keep all options opened. Soledad learned how to communicate results of analyses to other actors in the outbreak investigation.

A large *Campylobacter* outbreak in Sweden, 2016-2017: cross-agency challenges and the importance of surveillance and molecular epidemiology

Between July 2016 and August 2017, Sweden experienced its largest outbreak of *Campylobacter* to date. The source was suspected to be one domestic chicken abattoir, which had been the source of two previous outbreaks, but the scope for an epidemiological investigation was limited. In February 2017, the abattoir found an installation defect in the system for cleaning chicken transport crates set up the summer before. A posteriori investigation at retail, abattoir and farm level, as well as Whole Genome Sequencing of human and chicken isolates allowed to retrace the whole story and supported the finding that the outbreak strain had been circulating between different chicken farms delivering to the abattoir and confirmed this abattoir as the source of the outbreak. This outbreak challenged the system in place. Despite the collaboration of the public health, veterinary, and food agencies throughout this outbreak, communication and sharing of data was hindered and the agencies also faced difficulties in acting to decrease the risk on the market. The goal of this project was to summarize the investigation of this outbreak and highlight the lessons learnt from this outbreak, especially the difficulties in the surveillance around *Campylobacter* cross-agencies as well as the importance of acting at the industry level to prevent further human cases of campylobacteriosis.

Role and outputs: Contributor

Soledad helped gather the results of the past outbreak investigation, put together the timeline of the communication at the time of the outbreak, coordinated with other agencies in writing a summary report, and analyse what went wrong and what could be done in the future to improve it. Soledad contributed to writing a scientific article[4].

Supervisors: Cecilia Jernberg and Rikard Dryselius

Competencies developed:
Many parallels could be drawn between this outbreak and the beginning of the COVID-19 epidemic in Sweden. Despite happening at different scales, they were both highly mediatized and criticized and triggered a different handling within the agency than regular food-borne outbreaks do. Communication and coordination with other national agencies was also key in both outbreaks. A posteriori summarizing and evaluating how an outbreak was investigated and handled allows to learn to be better suited for future crises, both at the individual and at the Agency level.

3. Applied epidemiology research

Burden of disease and cost-of-illness associated with domestic campylobacteriosis during the 2016-2017 outbreak in Sweden

In 2016-2017, a large outbreak of domestic campylobacteriosis occurred in Sweden, with over 5,000 more cases than expected, and apparently unusual severity. The investigators compared all notified domestic cases of campylobacteriosis from July 2016-May 2017 (the outbreak period) to cases from March 2009-February 2014 (the endemic period) in terms of age, gender, hospitalization length, directly standardized hospitalization and mortality rates, burden of disease (in Disability-Adjusted Life Years, DALY) and cost-of-illness. Cases notified during the outbreak period were significantly older and were more likely to be female. The median hospitalization length for

campylobacteriosis was 3 days [IQR: 3] for both periods. The standardized hospitalization and mortality rates were not significantly different between both periods. The excess burden of disease was 107.7 [range 92.1-117.1] DALY during the outbreak period, compared to an expected 56.9 [range 47.5 – 72.6] DALY. The excess cost of illness was 7.8 [range 6.7-8.5] million euros during the outbreak period, compared to an expected 4.1 [range 3.4 - 5.2]. Although severity was not greater, DALY and cost of illness associated with campylobacteriosis tripled during the outbreak, due to the large number of cases. Quantifying the economic and public health impact of foodborne outbreaks provides additional evidence for the value of preventive measures.

Role and outputs: Principal investigator

Soledad updated the protocol written by Fanny Chereau (EPIET C2016), wrote the analysis plan, processed and analysed the data, submitted a manuscript to a peer-reviewed journal[3] and presented a poster on the topic at ESCAIDE[8]. She also presented the results at the yearly zoonotic meeting between Nordic countries [9].

Supervisors: Moa Rehn, Cecilia Jernberg, Sharon Kühlmann-Berenzon

Competencies developed:
This project had a large component of health economics measurements, which Soledad was unfamiliar with before this project.

Times series analysis of domestic tularemia in Sweden, 2000-2018

Tularemia is endemic in Sweden, with a usual peak in late summer or early autumn. In 2019, Sweden experienced its largest outbreak of tularemia in over 50 years, lasting from June until October with over 1000 cases. The description of trends in endemic cases is needed to give a contextual background for the outbreak in 2019 and to further evaluate this outbreak. The investigators thus aimed at creating a baseline time series model to describe the temporal patterns of tularemia cases from 2000 to 2018. The fellow extracted data on all domestic tularemia cases notified through the Swedish electronic system for notifiable diseases between 1-January-2000 and 31-December-2018. A negative binomial regression model was fitted to the yearly number of reported cases in order to explore trends, periodicity, auto-correlation and impact of sex on tularemia counts. Between 31-05-2000 and 19-12-2018, 5378 domestic cases of tularemia were notified to the Public Health Agency of Sweden. Among those, 2201 (40.9%) were women. The majority of cases was from the northern central part of Sweden. There was a constant average level of 101 (95% CI 80-130) cases per year for the years 2000 to 2018, and a strong cyclical periodicity of 4 years and a weaker one of 2.5 years. Furthermore, the difference by sex was statistically significant, with 50% (95% CI 10%-110%) more male cases than females. The number of domestic tularemia cases between 2000 and 2018 was mostly predicted by periodicity of the disease and sex of the cases. This baseline model was further used to evaluate the 2019 outbreak. This baseline model was not enough to explain the large increase in the number of cases, and additional external parameters such as changes in climate and vector data might need to be taken into account to elucidate the outbreak.

Role and outputs: Principal investigator

Soledad analysed the data and wrote an internal report using R markdown[16].

Supervisors: Pontus Juréen, Marika Hjertqvist, Rikard Dryselius, Sharon Kühlmann-Berenzon

Competencies developed:
This project allowed Soledad to reinforce her knowledge about time series analysis.

Investigation of seasonality in severity of campylobacteriosis cases in Sweden

Little is known about factors influencing the clinical course of campylobacteriosis. Since prevalence of different species as well as resistance to antibiotics has been shown to differ in the summer and the winter, the fellow investigated if there was also a seasonality in severity of the disease. She compared severity of domestic campylobacteriosis cases occurring during the summer to cases occurring during the winter in an endemic period in terms of demographics, hospitalization, and mortality. The investigators extracted data on domestic cases notified during these periods and linked cases to registers on hospitalization and death. For each period, the following values were calculated: 1) mean age and standard deviation (SD), compared by t-test; 2) proportion of

each sex compared by X^2-test; 3) median and interquartile range (IQR) of hospitalization duration compared by non-parametric test; 4) hospitalization and mortality rates with 95% Confidence Interval (CI), directly standardized by age and sex based on national hospitalizations for infectious diseases, and compared by calculating rate ratios and their 95%CI. Data from 15529 domestic campylobacteriosis cases were included. Overall, 8104 (52%) cases occurred during the summer period. The mean age of campylobacteriosis cases was 41.39 years (SD=21.96, range=0-95) in the summer and 41.65 (SD=22.28, range=0-99) in the winter (p=0.45). In both periods, the majority of cases were male (summer period: 57% and winter period: 54%, p=0.0022).
Median hospitalization length was 3 days for both periods with an IQR of 2 days in the summer and 3 days in the winter. The directly standardized hospitalization and mortality rates in the summer were 23.5[21.2-26.0] and 0.6[0.2-1.3] per 100 cases, respectively. The hospitalization and mortality rate ratio of summer time compared to winter time were 0.99[0.87-1.14] and 1.07[0.36-3.23], respectively. There was no difference in severity of campylobacteriosis cases between the summer and the winter in Sweden in endemic times. Understanding the risk factors associated with severity of campylobacteriosis cases helps evaluating the public health impact of foodborne diseases during endemic times and stands as an important reference in order to evaluate changes in long term trend patterns.

Role and outputs: Principal investigator

Soledad analysed the data and wrote an internal report [15] using R markdown.

Supervisor: Rikard Dryselius

Competencies developed:
This project allowed Soledad to verify an assumption made for another research project, at the same time as using R Markdown.

Mathematical modelling of the prevalence of genital chlamydia in Sweden

Genital chlamydia is the most reported bacterial Sexually Transmitted Infection in Sweden. Since 2009, the number of reported positive cases has been decreasing while the number of screened patients has been increasing. One potential explanation would be that the overall prevalence of genital chlamydia in Sweden has been decreasing. However, no estimate of the prevalence of genital chlamydia is available for Sweden. The team aimed at estimating the prevalence of genital chlamydia in Sweden over time, by counties, and by age groups. They used a model developed by Joanna Lewis and Peter J. White to simulate the dynamics of chlamydia infections among men and women aged 15-29 in Sweden. Data on natural history, treatment-seeking behavior, partner notification, and numbers of chlamydia tests and diagnoses were included to obtain estimates of local prevalence using a compartmental stochastic model. The model developed by Lewis and White is a three-compartment model (uninfected, infected symptomatic, and infected asymptomatic) where uninfected individuals become infected with a constant incidence, and move to either the asymptomatic or symptomatic-infected stages. Infected individuals may return to the uninfected stage by spontaneous clearance of their infection or by detection and treatment after screening or active testing. The model was edited and calibrated according to data available for Sweden and to key behaviors and interventions specific to Sweden. Data in aggregated format (sex, age group, region) on chlamydia cases and number of tests was obtained from SmiNet at the Public Health Agency of Sweden. Other relevant transmission data and behavior data was obtained from the published literature and data from behavioral surveys. Prevalence was first estimated at the national level by age groups and sex over time (2009 to 2015) and then by region for 2015 and 2018.

Role and outputs: Co-investigator

Soledad worked on understanding and summarizing the initial mathematical model from which this project was based on. She wrote a protocol and discussed the analysis plan with a mathematical modeller. The mathematical modeller adapted the model to the national context for Sweden and discussed the results with Soledad and the rest of the team. Soledad adapted the main model from national level to regional level. She wrote an internal report[18], and contributed to the writing of two scientific articles [5,6].

Supervisors: Inga Velicko, Sharon Kühlmann-Berenzon and Disa Hansson

Competencies developed:
This project was challenging for Soledad both because it was not a disease she was familiar with, and it required to understand a mathematical model based on other authors' articles and appendices. It was a chance to understand how as an infectious disease epidemiologist, she could contribute to building up a mathematical model. This project also underlined both the importance and difficulty of data visualization when comparing several multileveled factors at once.

The path to elimination of hepatitis B and C in Sweden: estimation of WHO core indicators for 2015 and 2018

In order to monitor the progress towards the WHO target of eliminating viral hepatitis as a public health threat by 2030, the investigators estimated the incidence, prevalence, and mortality for Hepatitis B and C in Sweden in 2015 and 2018. They identified cases of hepatitis B and C reported to the National System for Notifiable Diseases since 1969 and 1990, respectively, and obtained their treatment status, vital status, and cause of death. At the end of 2015 and 2018, they defined (domestic) incidence as the number of yearly reported (domestic) cases divided by the Swedish population; prevalence as the number ever diagnosed, excluding those who died, migrated or cleared the infection (spontaneously or after treatment) divided by the Swedish population; and hepatitis-associated mortality as the proportion of all diseased cases who died specifically of hepatitis-related liver disease. They calculated Poisson 95% confidence intervals around incidence and Wilson 95% confidence intervals around prevalence and mortality estimates. In 2015 and 2018, incidence (domestic incidence) of hepatitis B in Sweden was 13[12-14] (1.3[1.1-1.5]) and 7.7[7.2-8.3] (0.5[0.4-0.7]) per 100,000, respectively. Prevalence was 0.20[0.19-0.20]% and 0.21[0.20-0.21]%, respectively. Hepatitis B-associated mortality was 20[15-26]% and 18[13-24]%, respectively. In 2015 and 2018, incidence (domestic incidence) of hepatitis C in Sweden was 16[15-17] (10.2[9.6-10.9]) and 13[12-14] (8.5[8.0-9.1]) per 100,000 persons, respectively. Prevalence was 0.20[0.24-0.25]% and 0.18[0.18-0.19]%, respectively. Hepatitis C-associated mortality was 27[25-30]% and 27[24-30]%, respectively. All indicators decreased or stayed stable between 2015 and 2018, indicating encouraging progress in the elimination of domestic hepatitis B and C. The investigators recommend that these indicators be calculated regularly to measure the effect of current interventions on the elimination of viral hepatitis in Sweden.

Role and outputs: Principal investigator

Soledad wrote the protocol, the ethical application, she designed the analysis plan, developed the data extraction form, performed data extraction, data processing, data analysis, and designed an automated report for regular internal use [14] using STATA. She also wrote an abstract for ESCAIDE, and a scientific publication [7].

Supervisors: Josefine Lundberg Ederth, Viktor Dahl

Competencies developed:
The main challenge of this project was the data management and data linkage. This also allowed Soledad to learn how to create automatized reports in STATA.

Factors affecting transmission of SARS-CoV-2 in Households of COVID-19 patients in Sub-Saharan Africa

Control measures against COVID-19 in higher income countries have focused on physical distancing and lockdowns. However, in lower resourced countries with populations that live day by day, lockdown is unsustainable. Drug therapy of COVID-19 patients with mild disease may prevent progression to severe disease, but may also reduce the viral load in the upper respiratory tract, the duration of symptoms and the duration of virus shedding. To understand the overall extent of transmission of SARS-CoV-2 within a household and to estimate the effect of treatment on the secondary attack rate of SARS-CoV-2 infection and illness in household contact, the researchers designed an epidemiological ancillary study of a randomized control trial (RCT) of the safety and efficacy of several therapies (Hydroxychloroquine and Lopinavir/Ritonavir) used in mild cases compared to the use of standard of care in controls. This RCT will be conducted in several African countries. The ancillary study will be a prospective study of household contacts (HHC - defined as sharing same cooking area) of COVID-19 patients enrolled in the RCT. Index cases (defined here as the patients enrolled in the RCT) and their HHC will be followed up for 1 month with day 1 (D1) being the start of the index case treatment. Symptoms will be collected daily. Respiratory samples will be collected weekly for RT-PCR for SARS-CoV-2 to assess presence of virus and viral load. Blood will be collected weekly for serology. Risk factors for infection and illness (such as hand washing, mask-wearing, types of contact with index case, time spent in the community) will also be gathered on a weekly basis. It is planned to enroll up to 700 index cases with up to 2100 household contacts after obtaining informed consent in 4 different countries. Household transmission studies are key to informing policy and decision-making.

Role and outputs: Co-investigator

Soledad contributed to the protocol, coordinated with the other actors of the RCT, participated in the ethical review submission and subsequent revisions, and developed questionnaires and data entry forms. She also wrote Standard Operating Procedures for the on-site teams.

Supervisors: Marc-Alain Widdowson (Institute of Tropical Medicine, Antwerp, Belgium)

Competencies developed:
This was Soledad's first time working with a randomized control trial and discovering the complex logistics behind it, especially in the urgent and daily changing context of a pandemic. As a multi-country study, Soledad also had to make sure that the questionnaires and their answers would be comparable between sites.

4. Communication

Publications in peer reviewed journals

1. Espenhain L, Riess M, Müller L, **Colombe S**, Ethelberg S, Litrup E, Jernberg C, Kühlmann-Berenzon S, Lindblad M, Hove NK, Torpdahl M, Mörk MJ. Cross-border outbreak of Yersinia enterocolitica O3 associated with imported fresh spinach, Sweden and Denmark, March 2019. Euro Surveill. 2019 Jun;24(24):1900368. doi: 10.2807/1560-7917.ES.2019.24.24.1900368.
2. **Colombe S**, Jernberg C, Löf E, Angervall AL, Mellström-Dahlgren H, Dotevall L, Bengnér M, Hall I, Sundqvist L, Kühlmann-Berenzon S, Galanis I, Lindblad M, Hansen A, Rehn M. Outbreak of unusual H2S-negative monophasic Salmonella Typhimurium strain likely associated with small tomatoes, Sweden, August to October 2019. Euro Surveill. 2019 Nov;24(47):1900643. doi: 10.2807/1560-7917.ES.2019.24.47.1900643.

Manuscripts submitted to peer reviewed journals

*Shared first authorship

3. **Colombe S**, Chereau F, Wolff E, Larsson S, Wallensten A, Rehn M, Jernberg C, Kühlmann-Berenzon S. Burden of disease and cost-of-illness associated with domestic campylobacteriosis during the 2016-2017 outbreak in Sweden. *In process*
4. Jernberg C*, **Colombe S***, Dryselius R, Ågren P, Pääjärvi A, Skarin H, Lahti E. A large Campylobacter outbreak in Sweden, 2016-2017: cross-agency challenges and the importance of surveillance and molecular epidemiology. *In process*
5. Veličko I, Hansson D, **Colombe S**, Berglund T, Axelsson A, Sparén P, Kühlmann-Berenzon S. Estimation of Chlamydia trachomatis prevalence among individuals 15-29 years of age in Sweden: a mathematical modelling study. *In process*
6. **Colombe S**, Hansson D, Berglund T, Axelsson A, Sparén P, Kühlmann-Berenzon S, Veličko I. Estimation of Chlamydia trachomatis prevalence among individuals 15-29 years of age at the regional level: a mathematical modelling study using surveillance data, Sweden, 2015-2018. *In process*
7. **Colombe S**, Axelsson M, Ederth JL, Dahl V. The path to elimination of hepatitis B and C in Sweden: estimation of core indicators for 2015 and 2018. *In process*

Conference presentations

8. Burden of disease and cost-of-illness associated with domestic campylobacteriosis during the 2016-2017 outbreak in Sweden. Poster presentation. ESCAIDE 2019.

Other presentations

9. Burden of disease and cost-of-illness associated with domestic campylobacteriosis during the 2016-2017 outbreak in Sweden. Oral presentation. Nordic Zoonoses Meeting 2019.

Reports

10. Colombe S, Riess M. National outbreak of Salmonella Enteritidis MLVA 2-10-7-3-2 in Sweden, 2018. Internal report.
11. Riess M, Colombe S. Swedish investigation of the cross-border outbreak of Yersinia enterocolitica O3 associated with imported fresh spinach, Sweden and Denmark, March 2019. Internal report
12. Colombe S, Riess M, Englund H. Estimation of the number of suspected but discarded cases of acute rubella in Sweden, 2018. Annex to the annual rubella and measles report to WHO.
13. Colombe S. Yearly surveillance report on the national situation for Giardia spp in Sweden, 2019. Public report(https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistik-a-o/sjukdomsstatistik/giardiainfektion/)
14. Colombe S. Evaluating the elimination of viral hepatitis: estimation of prevalence of diagnosed infections, reported incidence, morbidity at time of diagnosis, and mortality related to Hepatitis B and C in Sweden over time. Internal report.
15. Colombe S. Investigation of seasonality in severity of campylobacteriosis cases in Sweden. Internal report.
16. Colombe S. Times series analysis of domestic tularemia in Sweden, 2000-2018. Internal report.
17. Expert Meeting On "Innovative Control Approaches Of Rodent-Borne Epidemic Diseases And Other Public Health Consequences Of Rodents' Proliferation". 2019. WHO Meeting Report (https://ecorodman.nri.org/images/WHO_rodent_meeting.pdf)
18. Colombe S. Chlamydia Prevalence County Level. Full Report

Other

19. Colombe S, Jancloes M, Rivière A, Bertherat E. A new approach to rodent control to better protect human health: first international meeting of experts under the auspices of WHO and the Pan American Health Organization. WHO Weekly Epidemiological Record. 2019.

    https://apps.who.int/iris/bitstream/handle/10665/312102/WER9417.pdf?ua=1

5. Teaching activities

Facilitation of a case study for veterinary students, Uppsala, Sweden

On January 29th 2019, Soledad facilitated a case study on an outbreak of Trichinosis in horsemeat in France, for 2 groups of about 8 veterinary students in the last year of their training. Each group had 2 hours to complete the case study. The students had had previous basic training in epidemiology, including study design and measures of association. The session was evaluated by the course director at the end of the term as quite positive.

Educational outcome:
This activity allowed Soledad to work on the balance between engaging discussion, giving clues and keeping time when facilitating a case study.

Introduction to surveillance and outbreak investigation: lectures and case-study organized for master students of Södertörn University, Sweden

On January 14th 2019, Soledad, Maximillian Riess (EUPHEM C18) and Emma Löf (EPIET C17), organized a day of teaching on the principles of surveillance and outbreak investigation for 20 first year master students in infectious disease control. This class is usually given every year by the EPIET and EUPHEM fellows but was adapted this year to fit on one day rather than 2. The director of the course contacted the team with specific requirements on what needed to be taught. The students' background was assessed based on previous fellows' experience as well as on the course syllabus. Previous years' slides and case studies were adapted. After a short introduction about the public health agency given by Emma Löf (EPIET C2017), three hours of teaching on surveillance, outbreak investigation, and microbiological investigations were given. Soledad taught the first two. Each lecture was building on the previous one, to remind them of the previously seen concepts. The teaching sessions were made to be very interactive and to have students think and already play around with the concepts that would be re-used during the case study. A summary sheet about the ten steps and how to calculate odds-ratios and risk ratios was given to them at the end of the lectures so that they could re-use it during the case-study. In the afternoon, the class was divided into two groups and discussed a case study about an outbreak investigation of cryptosporidiosis. Each participant read a paragraph out loud and was given a chance to give an answer or to explain a concept or a calculation to his/her peers. The

training activity was evaluated by paper questionnaire at the end of the day. Overall the students found the lectures somewhat interesting and the case study very interesting. All lectures and the case study were rated useful for their training and future career path and the complexity was just about right. The students felt like they learnt a lot from the case study.

Educational outcome:
The class was very participatory, testing the teachers' reactivity on some topics, and ability to explain on the spot concepts they were not expecting to explain. In teaching situations, this is when one learns the most.

Seminar on outbreak investigation in a disaster setting for medical students, Karolinska Institute, Sweden

On January 14th 2020, Soledad delivered a seminar on outbreak investigation in a disaster setting. The audience was 20 medical students in their 4th year of training, participating in an elective on disaster setting medicine. Students had a basic understanding of the concepts of epidemiology. Soledad prepared some pre-course material to read and listen to. She started the seminar with an hour long lecture on outbreak investigation in disaster setting, to remind the students of the concepts seen in the pre-course material, and to revisit these concepts in the specific context of disaster setting. Then Soledad facilitated a case study for 3 hours on the first known outbreak of Ebola in ex-Zaire. The case study had been previously created by an EPIET fellow. An evaluation was conducted by the course organizer. The students appreciated the preparatory material. They found the course interesting and liked the case study. They also gave constructive feedback and suggested to shorten the case study to 2 hours and to start with the case study and integrate the lecture within the case study.

Educational outcome:
Soledad really enjoys teaching and preparing this seminar was especially enjoyable as it linked her previous experience in low resource settings with the skills she had been learning during EPIET. The fact that the students gave constructive feedback on how to restructure the course to fit their needs was especially educational.

Capacity building – use of R for epidemiologists

Through several workshops, Soledad participated in providing epidemiologists with the basic knowledge on the use of R for public health and epidemiological analysis of data in their own work setting. The first workshop was an introduction to R and was organized for Soledad's colleagues within the unit of surveillance at the Public Health Agency of Sweden. The same workshop was then delivered to EPIET and EUPHEM fellows. A second workshop focused on multivariable analysis in R was delivered to EPIET and EUPHEM fellows. The third workshop was facilitated under the umbrella of RECON and targeted R beginner users who would attend the ESCAIDE conference. Finally, a guide to R was created for the next cohort of EPIET and EUPHEM fellows.

Educational outcome:
Teaching the use of a software allowed Soledad to learn more tools within this software, and to make sure she understood the processes behind its coding.

6. Other activities

Rodent control – a global strategy for international and cross-sectorial initiatives

Rodent control, like vector control, is the key to preventing infectious diseases and damages that they cause. Rodents represent a global and multisectorial threat towards public health, through diseases, malnutrition, bites, accidents, and destruction of the living environment. Their control also requires a global approach, that would be evidence-based, in the context of « One Health ». There is an urgent need from experts in public health and rodent control to collaborate, to promote integrated rodent control, and to facilitate the information flow between the sectors involved. The absence of consensus, as well as the disappearing of expertise on this topic internationally, especially at a public health level, urge us to promote an initiative that would facilitate an ecological and socioeconomic equilibrium between humans and rodents. In this context, the WHO is leading the creation of a new initiative that would technically assist international organizations concerned with rodents and improve prevention and control strategies for rodent-borne diseases. A kick-off meeting for the initiative took place in Peru in March 20th-21st, that the fellow helped organize, and that saw rodent experts from research and public health from around the world debate a possible approach to the initiative. After the meeting, the fellow contributed to the

meeting report[17], and drafted a roadmap for the initiative, defined by 3 main axes, being the development of integrated control programs, the reinforcement of capacities through intersectorial cooperation, and operational research. This global initiative will be led by a Scientific Committee, and will organize logistical, financial, and educational support. This initiative will also be a platform for structured discussion and sharing of case studies. This initiative would be a significant step forward in public health and for the most vulnerable populations. The fellow also wrote a position paper in the Weekly Epidemiological report of the WHO[19].

Supervisor: Eric Bertherat (World Health Organization, Geneva, Switzerland)

7. EPIET/EUPHEM modules attended

1. Introductory course, 24th September to 12th October 2018, Spetses, Greece.
2. Outbreak Investigation module, 3rd to 7th December 2018, Berlin, Germany.
3. Multivariable Analysis module, 25th to 29th March 2019, Madrid, Spain.
4. Rapid Assessment and Survey Methods module, 13th to 18th May 2019, Zagreb, Croatia.
5. Project Review module 2019, 26th to 30th August 2019, Prague, Czech Republic.
6. Time series analysis module, 4th to 8th November 2019, Bilthoven, the Netherlands.
7. Vaccinology module part I, 18th to 25th May 2020, online MOOC organized by Institute Pasteur, France.
8. Vaccinology module part II, 22nd to 24th May 2020, online.
9. Project Review module 2020, 24th to 27th August 2020, online.

Supervisor's conclusions

It has been a true honour to work with Soledad at the Public Health Agency of Sweden. Soledad came into her fellowship with a large technical skillset and was highly motivated to develop them and learn about the public health sector. All along, she made an effort in meeting her own learning needs. The EPIET learning objectives were all completed through several projects covering a wide range of different infectious diseases, using a variety of methods and approaches with varying level of difficulty. Being involved in several surveillance activities and outbreak investigations has made her confident to collaborate with many parts of the Swedish Public Health sector. Her contribution to the COVID-19 epidemic intelligence and setting up the surveillance analysis has made great impact on the ongoing activities at the Public Health Agency. Some of the projects she has been involved in, such as the hepatitis burden-study and rubella elimination evaluation, has also contributed to reports to WHO and set the ground for the agencie's future follow-ups.

Soledad has been committed to share her own knowledge to colleges, e. g through workshops in R for epidemiologist and by implementing automatized data management and analysis in routine surveillance. These efforts have contributed to an improved efficiency and quality for the surveillance work at the unit.

Soledad has many personal qualities making her a great team player and a much-appreciated co-worker. She made a true effort to integrate in the team with a positive attitude. She has shown an impressive balance between solving problems independently, asking the right questions and making use of the feedback. She has proven her ability to juggling several projects at the same time and still be positive to take on more tasks, a quality that is highly appreciated in a busy work situation that could change quickly. By the end of the fellowship she had successfully learned to speak Swedish.

Soledad's fellowship has been a great success both from her own professional achievements, and from the contributions she made to the agency and the field of public health. I am confident that Soledad will continue to contribute to developing the future public health work in Europe and elsewhere.

Coordinator's conclusions

Soledad started her fellowship with strong epidemiological research background, and she had conducted work in international health in Thailand and Tanzania. She maximised use of the two fellowship years, being involved in eleven field assignments in the surveillance and research area, along with five outbreak investigations, including the COVID-19 pandemic. Through her knowledge and experience from veterinary medicine and epidemiology of infectious diseases, excellent skills and a high commitment, she has completed all of these, achieving all EPIET objectives and producing large amount of routine and scientific outputs of high quality. Her teaching of fellow-colleagues and contribution to the fellowship training material had been also highly appreciated.
She is highly skilled and organised, able to work independently and effectively. Supported by excellent supervision and project availability at the site and internationally, her fellowship has been highly successful. She improved her competencies mainly in surveillance and outbreak investigation, working with many public health topics, and using novel methods. I believe that Soledad has excellent professional and technical skills needed for epidemiological and public health related work.

Personal conclusions of fellow

I enrolled in the program with the hope to understand how to apply epidemiological skills in a public health setting, to learn how to conduct outbreak investigations, and to perform evaluations of surveillance programs. Within the fellowship I met these hopes, while working on a diversity of infectious diseases and having the opportunity to compare how different methods can be applied to different diseases. Doing my fellowship at Folkhälsomyndigheten also allowed me to perform the daily work that epidemiologists within governmental public health agencies are required to do, from the daily interpretation of new notifications to the daily communication with other agencies. It was a unique opportunity to pin-point what exactly excites me most in the work as an epidemiologist, namely the team work and collaboration across fields of expertise and the data management and analysis. Having an academic research background, it provided me a unique insight into the type of research done at the governmental level, and into how academic research can benefit applied public health. Finally, the fellowship gave me the chance to push myself outside of my comfort zone, both personally and professionally, by having to learn a whole new language and navigate through a different culture, and by conducting projects that were intellectually challenging.

Acknowledgements

I am deeply grateful to my main fellowship supervisors and coordinators Moa Rehn, Alicia Barrasa and Frantiska Hruba, for the excellent scientific support and for being ever so patient with my many emails, questions and ideas.

I also want to thank from the bottom of my heart all my project supervisors and colleagues, for the many project opportunities, and for always being available no matter what. Thank you for the many teaching moments, and for being ready to be challenged. I hope to collaborate with you again one day.

I was very lucky to be warmly welcomed by the Surveillance and Coordination (SH-ÖS) unit at Folkhälsomyndigheten and thank everyone for helping me navigate the system, teaching me the intricacies of Swedish culture, and being so patient with my learning Swedish. I have greatly enjoyed working with all of you.

Finally, I want to thank the whole EPIET/EUPHEM team at Folkhälsomyndigheten for the strong support and the friendships.