



FELLOWSHIP REPORT



Summary of work activities

Stine Ulendorf Jacobsen
Intervention Epidemiology path (EPIET)
Cohort 2015

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;

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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 EPIET scientific guide¹.

Pre-fellowship short biography

Stine Ulendorf Jacobsen has a bachelor and master's degree in public health from University of Copenhagen. After graduating, she worked for two years at the Danish Health Authority, primarily with tasks in the fields of clinical guidelines development, health emergency management, and communicable diseases.

Fellowship assignment: Intervention Epidemiology path (EPIET)

On 15 September 2015, Stine Ulendorf Jacobsen started her EPIET fellowship at the Statens Serum Institut, Copenhagen, Denmark, under the supervision of Kåre Mølbak. 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

Title: *How PCR and serology testing can be used in surveillance of rubella in Denmark – a retrospective national cohort study*

Background

WHO in the European Region targeted at eliminating measles and rubella in the region by 2015. This goal has not been met on a regional level for neither rubella nor measles. In March 2016 WHO's Regional Verification Commission declared rubella endemic in Denmark, primarily because of the lack of comprehensive surveillance for rubella.

¹ European Centre for Disease Prevention and Control. European public health training programme. Stockholm: ECDC; 2013. Available from: http://ecdc.europa.eu/en/epiet/Documents/Scientific%20guides/EPIET%20Scientific%20Guide_C2016.pdf

Our study aimed at investigating how rubella test results can be used as a means to document the status of rubella incidence in Denmark in order to help reaching the WHO target of eliminating rubella in the European region.

Methods

We collected data from the Danish Patient Registry, LDUS (a database used at the reference laboratory), as well as the Danish Laboratory Database and the Danish Microbiology Registry – both of which are serology databases. The Patient Registry was searched for cases with rubella-related ICD-10 codes, the LDUS was searched for rubella PCR test results, and the serology databases were searched for IgM positive or inconclusive cases which were then manually excluded according to one or more of a number of criteria, including vaccination against rubella.

Results

There were no rubella RNA positive cases during the three year period. Test results from 48,092 persons were found in either one or both of the serology databases, with a minority of 187 being IgM positive or inconclusive. Four of these were left after we excluded a majority of the possible cases based on either fulfillment of one or more of the criteria, vaccination status or supplementary information drawn from the database at the reference laboratory. We found twelve cases with an ICD-10 code of rubella in the Danish Patient Registry but were able to exclude nine based on their vaccination status.

Conclusion

We showed that it is possible to establish high-quality surveillance for rubella based on existing data. It is, however, also clear that some manual data control will be necessary in particular to verify/discard the diagnosis of clinical rubella in the Patient Registry or seropositivity (IgM) in a person without known registration of recent vaccination.

No rubella cases could be found for the years 2014-2016 when applying a strict case definition requiring a positive PCR test for rubella. This indicates that active transmission has indeed been interrupted. However, applying a more sensitive case definition on the vast amount of test results for rubella serology and excluding cases manually, resulted in four possible cases that could not be accounted for. Adding the three unvaccinated cases from the Danish Patient Registry left us with a total number of seven possible rubella cases for 2014-2016. Further case-by-case investigation of these possible rubella cases seems feasible and is recommended.

Role and outputs: As the principal investigator, Stine wrote the protocol, analysed the data, and wrote the final report including recommendations.

Supervisor(s): Peter H.S. Andersen and Kåre Mølbak

Competencies developed: This project has given me hands-on experience in working with registry data and understanding its strengths and limitations. Furthermore, it has increased my knowledge on immunology and vaccinology and developed my skills in data cleaning and statistical analysis.

2. Outbreak investigations

Title: *An outbreak of gastroenteritis in Vejle, Denmark, in December 2016*

A group of people attending the same Christmas party on 25th November 2016 fell ill not long after the party. With the aim of finding the source of infection in order to take the relevant public health measures, we conducted a retrospective cohort study collecting information on exposure as well as symptoms and contact to health services. No samples were collected from the specific batch of food consumed at the Christmas party as there were no leftovers. No stool samples were collected either.

We conducted a retrospective cohort study. We designed and distributed an electronic questionnaire via a link in an e-mail to all participants. We calculated attack rates as well as risk ratios for the different food items.

The analysis showed that the outbreak was a point source outbreak peaking with the majority of cases becoming ill within 18 hours after the beginning of the Christmas party. Onset and characteristics of

symptoms fit the initial hypothesis that the illness was caused by a toxin-producing bacterium (e.g. no vomiting and short incubation period) and the infected food item was probably either the dessert ('risalamande') or patty shells. Since all cases ate both it was not possible to determine which of the items actually caused the illness.

Due to non-conclusive results and lack of information on how the food was kept after delivery to the customer, no steps were taken to sanction the responsible catering company.

Role and outputs: As the main investigator of the outbreak, Stine developed the electronic questionnaire, analysed the data, and wrote the outbreak report.

Supervisor(s): Luise Müller and Steen Ethelberg

Competencies developed: Investigating the outbreak gave me an opportunity to practice on real-world data what I had been learning during the EPIET & EUPHEM training modules. It further developed my competencies in regards to questionnaire development, data analysis and the art of formulating recommendations (or knowing when not to) based on my results.

3. Applied epidemiology research

Title: Examining determinants for reporting suspected adverse reactions in Denmark following HPV-vaccination

Background

Vaccination of 12-year-old girls against human papillomavirus (HPV) has been included in the Danish vaccination programme since 2009. In 2013 the Danish Medicines Agency (DMA) started to receive an increasing number of suspected adverse events after vaccination (AE), almost half of which were self-reported. This raised public concerns and resulted in an intense press coverage focused on vaccine safety issues, which led to a dramatic decrease in vaccine uptake from initial 88% in birth cohorts 1996-2002 to 44% in girls born in 2003. This dramatic decrease represented an alarming setback for cervix cancer prevention.

This study aimed to identify characteristics of females who interpret post-HPV vaccination symptoms as severe AE in order to provide better care for the females affected and to inform public health policies to improve vaccine uptake in the future.

Methods

We conducted a case-control study. A questionnaire focusing on demographics, life-style and health related issues was distributed to 251 cases who had reported severe AE and 1,003 controls randomly selected from the population-based Danish Vaccination Registry. All had been HPV-vaccinated and controls were matched on age, and year and municipality of vaccination. We used conditional logistic regression for the analysis.

Results

396 respondents (119 cases/277 controls) were included in the final model. There were no significant differences on measures of physical symptoms or psychiatric or somatic diagnoses before vaccination. More cases reported being physically very active prior to first HPV vaccination (OR 5.6; 95 % CI 2.07-12.34) while fewer cases than controls sometimes (OR 0.29; 95 % CI 0.17-0.55) or often or always (merged into one group) (OR 0.26; 95 % CI 0.07-0.97) felt sad.

Conclusion

This study provides insight into how females with perceived severe AE may differ from those not reporting severe AE. The finding that cases were less prone to feeling sad prior to vaccination is surprising considering the fact that a recent Danish registry-based case-control study concluded that females reporting severe AE were more likely to consult a psychologist/psychiatrist before first HPV vaccination. The same register-based study showed that cases had increased health care-seeking in regards to a number of somatic specialties. This makes the present case-control study finding that cases did not report more often having a diagnosis and/or symptoms prior to vaccination unexpected

as you would assume increased health care seeking to be the result of more sickness. These discrepancies might be due to a tendency to recollect time prior to becoming ill more positively and it emphasizes the importance of understanding the lifeworld of the affected females in order to treat them with the necessary empathy for them to recover.

Role and outputs: As the principal investigator, Stine wrote the protocol, developed and distributed the invitation letter and the questionnaire incl. the informed consent, performed the data analysis, presented the results at a conference, and submitted a manuscript to a peer-reviewed journal.

Supervisors: Palle Valentiner-Branth and Kåre Mølbak

Title: Addressing HPV vaccine hesitancy in Denmark, 2017

Background

Vaccination of 12-year-old girls against human papilloma virus (HPV) was included in the Danish vaccination program in 2009. Since 2014, increased public concerns about vaccine safety have resulted in a dramatic decrease in uptake.

In 2016, we initiated an investigation to better understand parents' and girls' knowledge, attitudes and decision patterns regarding HPV vaccination to design an information campaign.

Methods

We applied a mixed-methods approach: (1) a media analysis investigating online trends and mapping the media consumption of parents and daughters; (2) focus group interviews with mothers and double interviews with young girls looking into knowledge and risk perception; perceived credibility of national public health organizations, general practitioners, and others; household dynamics and message framing; and (3) a survey including a representative sample of 1,000 parents to validate conclusions from the focus group interviews.

Results

Mothers are primary decision makers regarding HPV vaccination of their daughters. Their primary source of information is online media, particularly Facebook. Thirty-four percent of survey respondents were vaccine hesitant. Hesitant parents indicated relatively high confidence in GPs, but less than half had discussed HPV-vaccination with them. The respondents had a lack of knowledge on several HPV-related facts.

Three main messages showed potential for convincing hesitant parents to vaccinate their daughters: 1) high prevalence of HPV infection in young women; 2) scientific consensus on HPV vaccine effectiveness; and 3) risk of cervical cancer versus risk of adverse events.

Conclusion

Based on these findings, the HPV vaccination information campaign was implemented on Facebook and a designated website. It focused on presenting facts to parents including the three above-mentioned main messages. Material targeted at healthcare personnel was developed to prime them for evidence-based conversations with parents.

Role and outputs: As the project manager, Stine planned the process and was involved in each of its steps, including: discussing and reviewing methodology, communicating results, writing and completing the tender for external help in relation to communication and press handling, discussing and implementing communication strategy, as well as producing texts for website and patient leaflet, among other things.

Supervisor: Bolette Søborg, Danish Health Authority

Competencies developed: Due to the special and alarming situation in Denmark with a dramatic decline in uptake of HPV vaccination among 12-year-old girls, work related to HPV vaccination has been taking up a lot of time in my work as an EPIET fellow. It has increased my competencies in various fields.

The case-control study was the perfect opportunity for me to develop my skills in STATA and to get an in-depth knowledge on the advantages and disadvantages of different epidemiological studies as well as a hands-on experience in interpreting and communicating findings and understanding its limits.

The project on preparing and executing the information campaign on HPV vaccination has improved my skills in scientific communication in a highly conflictual environment and opened my eyes to the research field of vaccine hesitancy in general. It has made me aware of how different methods can be used in combination in order to scientifically inform the design of a communication strategy and hopefully significantly improve its impact.

4. Communication

Manuscripts submitted to peer reviewed journals (in review process)

One manuscript submitted (1).

Conference presentations

One ePoster presentation at ECCMID, Vienna, April 2017: Uncovering determinants for reporting suspected adverse events after HPV vaccination (2).

One oral presentation at ESCAIDE, Stockholm, November 2017: Addressing HPV vaccine hesitancy in Denmark, 2017 (3).

Reports

One outbreak report (4) and one surveillance project report (5).

Other

Internal meeting at the Danish Health Authority, 2 March 2016: the Zika virus epidemic and our response in a Danish health care setting.

EPIET-EUPHEM forum², the Statens Serum Institut, Copenhagen, 25 May 2016: the 1976 Ebola outbreak in Zaïre.

EPIET-EUPHEM forum, the Statens Serum Institut, Copenhagen, 14 September 2016: the 1980's AIDS epidemic in the US.

Launch of an information campaign on cervical cancer and HPV vaccination, the Danish Health Authority, 10 May 2017: Stop HPV – stop cervical cancer (6).

Information evening on cervical cancer, hosted by the patient organization for women with abdominal cancer (KIU), Cinemateket, Copenhagen, 30 May 2017: the launch of the information campaign on cervical cancer and HPV vaccination

Meeting in an informal peer group on HPV vaccination, WHO Regional Office for Europe, Copenhagen, 27 June 2017: the launch of the information campaign on cervical cancer and HPV vaccination and our experiences so far.

5. Teaching activities

Title: Developing and executing a PhD course in infectious disease epidemiology, October 2016

² A weekly meeting at the Department of Infectious Diseases Epidemiology & Prevention. EUPHEM, EPIET, and PhD fellows take turn on presenting current projects and challenges.

With co-fellows at the Statens Serum Institut, I developed, facilitated and presented at a three-day PhD course on infectious disease epidemiology in collaboration with the University of Copenhagen. I was involved in planning the programme in detail, developing course objectives, putting together and delivering a presentation on national and international notifications of infectious diseases, facilitated case studies and was responsible for the smooth execution of the entire course. The course was given a very positive evaluation both orally and in an online questionnaire.

Supervisor: Kåre Mølbak

Educational outcome: I was very well trained in all aspects of preparing, executing and evaluating a training activity, including formulating objectives, developing the programme, facilitating case studies, and preparing a presentation while keeping the target audience in mind. Preparing and delivering a presentation on my own has developed my independency and performing skills.

6. Other activities

As part of my everyday work at the Danish Health Authority, I was involved in the following work:

- Publishing a guideline on preventing the spread of MRSA (7)
- Publishing a national guideline to health care professionals on the management of Zika virus infection in pregnant women (8)
- Drafting a guideline as a means to reduce spreading of CPO (9)

7. EPIET/EUPHEM modules attended

1. Introductory Course, 28 September – 16 October, 2015, Spetses, Greece
2. Outbreak Module, 7-11 December, 2015, Berlin, Germany
3. Multivariable Analysis, 14-18 March 2016, Vienna, Austria
4. Rapid Assessment and Survey Methods, 20-25 June 2016, Athens, Greece
5. Project Review Module, 22-26 August 2016, Lisbon, Portugal
6. Time Series Analysis, 7-11 November 2016, Bucharest, Romania
7. Vaccinology, 12-16 June 2017, Stockholm, Sweden
8. Project Review Module, 28 August – 1 September 2017, Lisbon, Portugal

Supervisor's conclusions

The fall in the uptake of the HPV vaccine in Denmark represents a major challenge for public health and a set-back for cancer prevention. Much of Stine's work was focused on addressing this crisis, including the case-control study that aimed at uncovering determinants of suspected adverse events, and the cross disciplinary study on addressing vaccine hesitancy. In this aspect, the work of Stine was important. Stine learned a lot, but public health also benefited from her work. In fact, there is now room for optimism as regards HPV vaccine uptake, partly because communication and media coverage has improved. The studies and work done by Stine contributed to this change.

Another highlight is the study on rubella. WHO categorizes Denmark as rubella-endemic. Not because there is evidence that rubella is circulating in the population, but because the surveillance only covers rubella in pregnancy and congenital rubella syndrome. The aim of the project was to use available national rubella diagnostic data and data from the national hospital register to obtain figures on the occurrence of rubella. The project was a proof-of-concept: It showed that it is doable to establish comprehensive rubella surveillance based on the national diagnostic databases. The plan is to establish

this as an ongoing surveillance activity, and thereby improve the quality and comprehensiveness of the Danish rubella surveillance. Without the efforts of Stine, we would not have reached this stage.

Finally, the fellowship has connected the Danish Health Authority more closely with SSI, which is another result of the fellow's work.

I have no doubt that Stine Jacobsen deserves her diploma, and we look forward to continue working together.

Kåre Mølbak, 17 August 2017

Coordinator's conclusions

Stine has greatly improved her epidemiological skills throughout her fellowship, especially in regards to data analysis, outbreak investigation and surveillance. She is very dedicated, hardworking and efficient in her work.

Stine is a Public Health expert by training (Bachelor and Master degree) and has been working for the Danish Health Authority (DHA) since 2013. She had a heavy work load during her fellowship being based part-time at the DHA and part-time at the SSI, but worked very independently and in a very structured way and was able to focus on relevant tasks.

During her fellowship, Stine conducted a retrospective cohort study to investigate a gastroenteritis outbreak and a case-control study to explore if girls that reported suspected side effects after HPV vaccination were different from girls who did not report side effects. She also analysed registry data and existing surveillance data for a rubella virus surveillance project. These different studies and projects gave her the opportunity to develop her skills in applied research including study protocol writing, designing a questionnaire, using online-survey tools, conducting data analysis and writing reports. She was also involved in teaching outbreak investigations to PhD students.

She was result-driven in her work and was able to communicate the findings of her projects at international scientific conferences and through a scientific peer-reviewed publication.

Stine plans to continue working for the Danish Health Authority and continue collaborating with SSI. I wish her great success in the future.

Coordinator: Christian Winter

Personal conclusions of fellow

Completing the EPIET programme has been a huge step forward towards a career in epidemiology and public health. It's been a great journey both professionally and personally and a privilege to be surrounded by such talented and engaged people, including facilitators, supervisors, and co-fellows.

Acknowledgements

First of all thanks to Department of Infectious Disease Epidemiology & Prevention at Statens Serum Institut for welcoming me so warmly and making me feel like a part of the department. An extra thanks to the people I have been working closest together with: Palle, Sofie, Luise, Steen, Lara, Peter, Lasse, and most of all Kåre, who is the coolest and most talented epidemiologist I know. Second of all, a thank you to my frontline coordinator Christian for making sure that I kept making progress and for continuously giving useful feedback on my projects. A special thanks to Bolette for getting me into this whole thing to start with and for continuously supporting and encouraging me all the way through. And finally, a huge acknowledgement of the great people of cohort 2015 whom I have come to cherish and will greatly miss.

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