



Fellowship summary report [6/9/16]

Helen Crabbe

Background

Pre-fellowship short bio

Environmental Epidemiologist with CRCE. Previously worked in public health intelligence; public health analysis and surveillance with PCT/LAs and environmental health and academic research. Masters in Public Health (Environment and Health) from LSHTM.

FETP assignment

FETP fellow based at both Thames Valley Health Protection Team, PHE South East Centre and in the Environmental Epidemiology team of the Centre for Radiation, Chemicals and Environmental Hazards, at Chilton, Oxfordshire.

Fellowship projects

Outbreak(s)

- 1. Foodborne illness at Wasing Park: Report of an investigation of a foodborne outbreak of norovirus among guests and staff of a wedding reception at Wasing Park, Aldermaston, Berkshire on 8/9th November 2014.**

Introduction: A wedding attended by around 100 people was held at Wasing Park, Aldermaston, Berkshire, on the Saturday 8th and Sunday 9th November 2014. This report describes the investigation of an outbreak of gastro-intestinal illness following the wedding events.

Methods: The outbreak was described by time, person and place. A cohort study, analysed by univariate, stratified and multivariable analysis was undertaken to explore the association (measured as odds ratios (OR) and 95% confidence intervals) between illness and food, drink and activity exposures over the weekend. A web based questionnaire was developed to survey both staff and wedding guests about their exposures over the weekend and illness. The kitchen and catering arrangements were reviewed, food samples taken where available and cases were encouraged to submit stool samples for testing. A case was defined as any individual who attended and ate food from the events at Wasing Park on the Saturday, 8th and/or Sunday 9th November and became unwell with diarrhoea and/or vomiting with symptom onset within ten days of the events.

Results: Of 119 individuals thought to have attended the event, we were able to contact 59. A total of 28 (47%) complete questionnaires were submitted; three were from Wasing Park staff, eight from Galloping Gourmet Catering staff and 17 from wedding guests. Two stool samples were submitted and tested positive for norovirus. A higher rate of illness was found in wedding guests responding to the survey (76%) compared to the illness rate among staff surveyed (9%) (OR of 32.5 (95% CIs 2.66-1514, $p < 0.001$)). The incubation period of the illness appeared to be short with the first case being ill during the event, and all cases being ill within 1-3 days following the events. The main symptoms experienced were diarrhoea (93%), abdominal pain/cramps (79%), vomiting (79%) and nausea (72%). Univariate analysis demonstrated that gastrointestinal illness was positively associated ($p < 0.05$) with being a wedding guest, consumption of canapé drinks, soup, red wine, prosecco, dinner sparkling water and eating from the evening buffet. None of the other items eaten during the events or other activities were statistically associated with illness. Stratified analysis by guest status and canapé drinks was limited due to no exposed cases or un-exposed non-cases. Multivariable analysis found that prosecco and red wine were the exposures with the highest association between illness; and although red wine had the highest aOR (7.42 [CIs 0.46-infinity]) this was not statistically significant ($p = 0.167$). There was no single item that was shown to be the source of contamination. The environmental investigations examined hygiene practices at both catering kitchens on site. Environmental swabs taken from the kitchen were tested for viral and bacterial contamination. This found unsatisfactory Enterobacteriaceae contamination of the yellow ready to eat (RTE) surface (chopping board). Cleaning and working practices were recommended to be improved in this area. The food samples were tested for a range of pathogens, and the blackberry and apple mix and cooked sliced beef were borderline for *Clostridium perfringens* and Enterobacteriaceae respectively. There was clear evidence of faecal contamination of the RTE board and bacterial contamination of some food items, so contamination via the kitchen could have been possible.

Conclusion: The source of the norovirus infection was not confirmed or limited to individual food or drink items. A possible source of illness was a wedding guest that reported having contact with someone having a history of diarrhoea and/or vomiting in the week before attending the event, and who was also ill on site with norovirus during the wedding events

Tasks undertaken personally: Lead epidemiological investigator. Designed exposure questionnaire. Undertook epidemiological analysis – univariate, stratified and multivariable analysis. Wrote outbreak investigation report. Consulted with members of the OCT.

Outputs: Outbreak report; to OCT, LA, food business operator, TVPHEC.

2. Outbreak of Campylobacter among participants attending a hospitality event at Twickenham Rugby Football Village.

Introduction: A hospitality event at Twickenham Rugby Football Union (RFU) Village was held on 15th November, 2014, with approximately 1,120 diners eating a set menu. Over the following week, there were at least two hospital admissions and a number of complaints of gastrointestinal illness to the local authority and PHE.

Methods: The outbreak was described by time, place and person. Two cohorts were studied, 1) of the diners attending and 2) of the staff either working at the event serving food, or as food handlers catering for the event. These cohort studies explored the association between foods consumed and illness (measured as an odds ratio and 95% confidence interval where

possible). Web based questionnaires were designed for each cohort and an email invite sent to the event organisers and catering company respectively. A case was defined as any individual who attended and consumed food at the hospitality event at Twickenham RFU village on the 15th November 2014, or handled or consumed food prepared for this event, and became unwell with diarrhoea and/or vomiting with symptom onset between one and ten days after attending.

Results: There were 51 valid responses to the staff questionnaire. This represents a response rate of approximately 41%. Responses were received from waiters/front of house, chef/kitchen staff and back of house roles. Only one person (2%) became ill after attending the event that matched the case definition. As illness was limited in the cohort it was not possible to conduct further analytical epidemiological analysis on the data. There were 30 valid responses to the diners questionnaire, giving an approximate response rate of 2.7%, although it is unclear how far the request for the survey was distributed. Of these, 21 out of the 27 valid respondents reported being ill after attending the event (78%). Onset of symptoms was between 16th to 22nd November. The most commonly reported symptoms included diarrhoea, abdominal pain/cramps, nausea, and fever/high temperature. The strongest association between illness and a food item was with duck liver parfait. A statistically significant trend was found with the amount of parfait eaten and illness rates. Univariate analysis demonstrated that individuals who ate the duck liver parfait were 10.68 times more likely to become ill than those who didn't. Five out of six faecal samples related to the event tested positive for *Campylobacter*.

Conclusions: Given the small sample size the study had low power and even the strongest observed associations were not statistically significant so that the study does not provide strong evidence on which specific food was responsible. The weak evidence it provides for the duck liver parfait needs to be interpreted with regard to which of the foods served are highest risk for this illness and results of inspection of food preparation processes.

Tasks undertaken personally: Lead epidemiological investigator. Designed exposure questionnaire. Undertook epidemiological analysis – univariate, stratified and multivariable analysis. Wrote epidemiological outbreak investigation report. Consulted with members of the OCT.

Outputs: Outbreak report; reports to Local authorities, SW London PHEC, CIEH, Twickenham Rugby Stadium event organisers and agents.

3. Foodborne illness at the Red Lion Pub, Old Marston. Report of an investigation of a foodborne outbreak of *Salmonella* among customers eating at the Red Lion Pub, Old Marston, Oxford, during June 2015.

Background: Reports of gastro-intestinal illness were received from three different parties after eating at the Red Lion pub, Old Marston, Oxford, over the period 13th-16th June, 2015. This report describes the investigation of an outbreak of *Salmonella* associated with eating at the pub.

Methods: The outbreak was described by time, person and place. A case-control study was undertaken to explore the association (measured as odds ratios (OR) and 95% confidence intervals) between illness and food, drink and activity exposures associated with the pub. A web based questionnaire was developed to survey both staff and customers about their exposures associated with the pub, and illness. Active case finding was also conducted by reviewing Enhanced Surveillance Questionnaires (ESQs) of *Salmonella* cases in Thames Valley in June 2015. Food preparation and catering arrangements were reviewed. Cases and staff were encouraged to submit stool samples for microbiological testing. A case was defined as any individual who consumed or prepared food and/or drink from the Red Lion Pub from the 13th to 17th June 2015 inclusive and became unwell with diarrhoea, fever, abdominal pain or nausea with symptom onset between one and seven days inclusive after attending.

Results: A total of 23 complete individual questionnaires were submitted; 15 (65%) were from customers, and eight (35%) were from staff attending the Red Lion pub. Twelve people were defined as cases, giving an overall attack rate of 52% among responders. A higher rate of illness was found in customers responding to the survey (73%) compared to the illness rate among staff surveyed (13%) OR 19.25 (95% CIs 1.44-943, $p=0.005$). The incubation period of the illness was short with a median of 2 days (range 1-3 days). The main symptoms experienced were diarrhoea (52%), fever/high temperature (43%), abdominal pain/cramps (39%), and nausea (39%). Univariate analysis demonstrated that gastrointestinal illness was positively associated ($p<0.05$) with being a customer, consuming drinks, and consuming some items related to roast dinners (gravy, turkey roast; potatoes, vegetables and/or gravy). Multivariable analysis was performed to control for confounding and effect modification, but due to the small sample size and low power, residual confounding remained. There was no one single item that was identified as the likely vehicle of transmission. Five stool samples were submitted by customers and four tested positive for Salmonella Enteritidis PT4. Whole Genome Sequencing of the stool samples genetically linked all four confirmed cases from three separate parties who ate at the pub, suggesting that the same contaminated source was responsible for illness. No stool samples were submitted by staff. The environmental investigations examined hygiene practices in catering on site. No environmental or food samples were available for testing due to a two week delay in notification. Possible contributory factors to the outbreak based on the Environmental Health Officer (EHO) visit concluded that the staff were not clear on the 48hr exclusion period and staff may have been working while sick, although this could not be verified. Active case finding from local authority records in the region found 22 ESQs for Salmonella infections. These were reviewed but none were connected to the outbreak. Whole Genome Sequencing helped to identify a cluster of Salmonella Enteritidis infections in Thames Valley and neighbouring HPT areas. It is unknown how the other community cases are linked, but potentially through a common food source in the community.

Conclusion: The source of the Salmonella infection was not confirmed or limited to individual food or drink items. A possible source was sickness in staff, but this could not be confirmed.

Tasks undertaken personally: Lead epidemiological investigator. Designed exposure questionnaire. Undertook epidemiological analysis- univariate, stratified and multivariable analysis. Wrote epidemiological outbreak investigation report. Consulted with members of the OCT.

Outputs: Outbreak report; to OCT, Oxford City Council, Oxfordshire County Council, FBO, PHE SEC, FES Victoria.

Surveillance project(s)

1. Capturing exceedances, clusters and outbreaks of infectious diseases in Thames Valley.

Example of routine surveillance: A need for a review of the current practices for identifying clusters, exceedances and outbreaks of infectious diseases (ID) in Thames Valley HPT occurred as a more robust system was required from an operational point of view. It was also identified from a requirement of a quality assurance indicator that was introduced in 2014. The review outlined current practice, reviewed peer best practice and availability of surveillance intelligence, and made recommendations for future work in order to improve practice locally. A protocol was produced for the work, planning work activities. A final report reviewed current

practice, made recommendations for future work programmes and a diary for the review of ID implemented. A system for the review of ID was implemented, monthly reports of exceedances was put in place, and an example is attached in the zip file uploaded to sharepoint. A template for the monthly outputs was devised and is also included.

Tasks undertaken personally: reviewed practice, wrote protocol and consulted with stakeholders on the needs of the project. Worked with the new surveillance officer to design surveillance outputs, templates and process of regular surveillance outputs. Wrote review report with findings and recommendations.

Outputs: protocol report, review report, surveillance outputs and templates. Commended for best practice by quality review panel in SE PHEC.

2. Evaluation of Laboratory-Based Surveillance of Lead Poisoning in Children Pilot for England, 2014-2015

Introduction: Exposure to lead in children may result in neurodevelopmental problems. The extent of lead poisoning in England is not currently known, and there is no national screening programme. However, a study in the mid 1990's suggested that 6% of children had blood lead levels (BLL) $>10\mu\text{g}/\text{dl}$, a level requiring public health investigation. In March 2014, a pilot Lead Poisoning in Children (LPIC) surveillance system for England was developed to improve the timeliness of reporting of LPIC cases to Health Protection Teams (HPTs) for investigation. Trace Element Laboratories report eligible cases (aged ≤ 16 years, $\text{BLL} \geq 10\mu\text{g}/\text{dl}$) via the system to HPTs.

We undertook an evaluation of the system at 12 months to determine if the pilot met its objective to provide timely information for the public health investigation of cases.

Methods: Cases were described by sex, age and blood lead levels. The timeliness of case reporting was evaluated, calculated as time between specimen date and reporting date to HPTs; the difference between the pilot period and preceding 2 years was tested using a Mann-Whitney test.

Results: Thirty-eight cases were reported in the pilot phase (2014-15), including 26 new cases previously unknown to HPTs. 28/38 (74%) of cases were male, the median age was 5 years (range 1-11); 17/35 (49%) were under 5 years old. Mean BLL was $24.6\mu\text{g}/\text{dl}$ (max= $64.6\mu\text{g}/\text{L}$) with no difference in sex ($p=0.484$). The mean number of days between specimen date of first elevated BLL and date of report to HPTs was 14 days (range 4-50, $n=20$) during the pilot, compared to 241 days (range 0-1,460, $n=16$) in the 2 years before the pilot started ($p=0.006$).

Conclusions: During a one-year pilot of LPIC surveillance, timeliness of case reporting was greatly improved. Recommendations are to continue the surveillance as routine work, enabling earlier public health investigations.

Tasks undertaken personally: Wrote protocol report, consulted with stakeholders for project needs, designed and conducted questionnaires, analysed data from systems and questionnaires. Wrote up evaluation report.

Outputs

Evaluation Report.

Presented at;

- CRCE EPH Tracking Board – Aug, Nov 2015, May and August 2016.
- US-CDC Environmental Hazards and Health Summit, Atlanta- January 2016,
- PHE Applied Epidemiology conference- March 2016.
- International Society for Environmental Epidemiology Conference, Rome, Italy- September 2016.
- NHS SAS Trace Element Laboratory Network quarterly meeting- August 2016.

Research

1. An epidemiological risk assessment for chemicals in private water supplies in Cornwall.

Introduction: Many properties in the UK are served by private water supplies (PWS) where mains connection is not possible. Chronic exposure to chemicals in PWS may have an adverse effect on health causing cancers and skin lesions, although no evidence observed in the UK. The SW of England is an area with elevated arsenic concentrations in groundwaters supplying a number of domestic property PWS. A Prescribed Concentration Value (PCV) of 10 µg/L is set by Regulations enforced by local authorities. However, there remains uncertainty as to the precise extent of the local population exposed to arsenic. We undertook to calculate exposure to arsenic in PWS in Cornwall to help estimate the health burden.

Methods: We invited known PWS users on a register to take part in a water sampling programme from 2011-13. We asked for information on the number of residents drinking PWS water and if properties shared the supply. The number of PWS in Cornwall and mean household population was estimated using GIS. We calculated population exposure to the range of concentrations found in samples.

Results: 497 PWS were sampled, serving 868 properties supplying 1,979 (95% CI 1,901-2,057) residents. An estimated 4,044 properties are served by PWS in Cornwall supplying 9,625 (95% CI 9,504-9,746) people. The proportion of the population exposed to arsenic levels ranged from 71%: <1µg/L, 24%: 1-10µg/L and 5%: >10µg/L.

Conclusions: Extrapolation estimates that 600 people are drinking water over the PCV in Cornwall. Households were given public health advice and recommendations to regularly test water for arsenic.

Tasks undertaken personally: Analysis of data to produce population exposure estimation. Designed and presented posters at conferences. Wrote protocol for risk assessment based on geology, designed methods for research project. Wrote and consulted on chapter for IWA book on exposure estimation.

Outputs

Protocol for risk assessment based on geology. Chapter in book on population exposure estimation.

Poster presentations at:

- Occupational and Environmental Epidemiology Conference, Health and Safety Laboratory, April 2016
- International Society for Environmental Epidemiology International Conference, Rome, Italy- September 2016.

2. Characteristics associated with late reporting of cases of pertussis in London and the South East from 2010 to 2015.

Background: In the UK, pertussis guidance recommends prophylaxis of all household contacts within 21 days of case symptom onset to reduce severe disease in infants and reduce likelihood of secondary transmission if there is a vulnerable contact. Prophylaxis is also offered to under-immunised infants (<1 year) or individuals likely to transmit to them (health care workers (HCW) and women who are >32 weeks pregnant) when identified as contacts by Health Protection Teams (HPTs). Contact tracing and prophylaxis of contacts will occur if cases are reported within 21 days of disease onset. We undertook a cross sectional study to examine the epidemiology of cases in 2010-2015 and to assess timeliness of reporting pertussis cases to public health teams in London and the South East of England in 2015.

Methods: We extracted information on laboratory confirmed and clinically suspected pertussis cases from case management systems. We defined late cases as late if the interval from symptom onset to report date was >21 days. We identified risk factors for reporting late compared to non-late cases on univariate analysis. We calculated adjusted odds ratios and 95% confidence intervals (aOR; CI) using a stepwise logistic regression model.

Results: 9163 cases of pertussis were notified to HPTs in 2010-2015. The incidence of pertussis was highest in the <1's at (273 cases per 100,000). Most 35% of cases occurred in the autumn (35%) and in more deprived areas. 40% of cases occurred in an outbreak year (2012), 55% were female and 77% were laboratory confirmed. Of 1649 cases reported in 2015, 86% were reported late, 11% within 21 days and for 17% timeliness was unknown. After adjusting for age, source of reporting and confirmed cases, late reporting was associated with older age groups (aged 1-3 months; aOR=1.19 [95%CI 0.11-12.4]; 4-12 months; aOR=1.48 [95%CI 0.13-17.2]; 1-9 years; aOR=7.80 [95%CI 0.79-79.1]; 10+ years; aOR=14.4 [95%CI 1.48-139] compared to newborns (<1 month)); confirmed compared to suspected cases (aOR=2.96 [95%CI 1.92-4.58]); and GP reporting; aOR=1.18 [95%CI 0.61-2.27], or the source being a laboratory report; aOR=20.5 [95%CI 8.52-49.6], compared to reporting by hospital clinicians. Being a HCW (OR=0.31 [95%CI 0.08- 1.44]), being pregnant (OR=0.20 [95%CI 0.05-0.77]), being hospitalised (OR=0.09 [95%CI 0.02-0.40]), or reports from schools (aOR=0.54 [95%CI 0.01- 0.52]) were associated with timely reporting. Odds of late reporting increased with deprivation. Of those cases investigated by HPTs, only 23% required active public health intervention; 22% had vulnerable contacts identified, most of which were HCW (42%) and infants under 1 year (27%).

Conclusions: The highest odds of pertussis are among those aged under one year. Timely reporting is associated with younger age, being pregnant, being a HCW, school and hospital clinicians reporting. Nearly 90% of cases were reported late, potentially missing opportunities for secondary prevention. We recommend further exploration of the reasons for late reporting, and feedback to local general practitioners groups to improve reporting on clinical suspicion.

Tasks undertaken personally: Wrote protocol for research work. Analysis of data to identify risk factors for late reporting. Univariate and multivariate analysis. Wrote up research for journal article.

Outputs:

Protocol for research project. Peer reviewed journal article submitted for publication. Accepted for oral presentation at ESCAIDE conference, Stockholm, November 2016.

Scientific communication

- Two posters, one at Occupational and Environmental Epidemiology conference and ISEE, 2016, another one at ISEE, 2016.
- Three oral presentations; two at international epidemiological conferences, one at a national epidemiology conference.
- 2 manuscripts drafted, 1 book chapter in press, 1 peer reviewed journal article manuscript submitted.

Teaching experience

1. Teaching 5th year medics at Oxford University on Public Health management of communicable diseases and outbreak management.

Ran two hour sessions every six weeks in conjunction with other TVHPT staff. Contribute to running sessions with c25 students on methods of outbreak investigation: scenario of Trichinosis in Paris and GI (Norovirus) in a workplace environment. Facilitate practical sessions. Lead on sections for outbreak investigation and calculating odds ratios. Check materials prepared before session. Designed feedback evaluation form and executed evaluation of session by students. Collated evaluation report and updated material accordingly (slides and practical). Considered replacing material to more relevant case study. Suggested case study and consulted on application. Drafted material for running new exercise and piloted. Continue to co-present session with Consultant. Reflective notes completed. Current redesign of session underway.

2. CPD sessions on Basic Statistics for Epidemiology for Thames Valley PHEC staff.

Two x 1.5 hour CPD sessions in July and August 2015. Preparation of material and writing slides and exercises to run in conjunction with Clinical Surveillance Officer

Identified a local training need and skills gap and suggested a training session to meet these needs to CPD co-ordinator. Planned session, conducted pre-learning needs assessment by questionnaire to colleagues gaining level of knowledge before designing material. Preparation of slides and case studies to present. Designed in-class exercises and training material. Delivered two informal seminar style sessions and group work. Reflective notes completed.

3. Facilitation on Environmental Epidemiology training course at PHE Colindale.

Facilitated group discussion on population exposure assessment for arsenic contamination of private water supplies and Broomfield Coal fire tip epidemiology study. Facilitated group discussion for 2x 2 half day group exercise sessions, in 2015 and 2016.

International mission

Title: Evaluation of the Barbados National Registry (BNR) for Chronic Non-Communicable Diseases.

Description: Three week mission on behalf of ECDC for the Barbados Ministry of Health. The BNR has been operational since 2008 with the stroke component (BNR-Stroke), followed in 2009 by acute myocardial infarction (BNR-Heart) and 2010 with BNR-Cancer. This multi-disease surveillance system had not yet been evaluated.

Aim: To evaluate the national surveillance system for non-communicable disease in order to provide information on areas for improvement.

Output: Evaluation report assessing the BNR for several criteria; usefulness, acceptability, timeliness, flexibility, simplicity, data quality, completeness and sensitivity. A number of recommendations were made to the Ministry of Health for improvements to the system.

Next steps

- I will be working on a short term contract as an epidemiological scientist in the Environmental Epidemiological Team at the Centre for Radiation, Chemical and Environmental Hazards at PHE.

References - List of the publications and communications

Manuscripts:

Crabbe, H., Saavedra-Campos, M., Verlander, N. Q., Leonard, A., Morris, J., Wright, A., Balasegaram, S. (2016) Are pertussis cases reported too late for public health interventions? Cross sectional study in London and the South East of England, 2010 to 2015. Submitted to EuroSurveillance Journal, September 2016.

Crabbe, H., Close, R., Rimell, A., Leonardi, G., Watts, M.J., Ander, E.L., Hamilton, E.M., Middleton, D.R.S., Smedley, P.L., Gregory, M., Robjohns, S., Sepai, O., Studden, M., Polya, D.A., Fletcher, T. (2016) Estimating the population exposed to arsenic from groundwater-sourced private drinking water supplies in Cornwall, UK. Chapter A3 in IWA book: Best Practice Guide on the Control of Arsenic in Drinking Water, in press.

Conferences:

Crabbe, H., Close, R., Leonardi, G., Watts, M., Ander, L., Hamilton, E., Middleton, E., Smedley, P., Gregory, M., Robjohns, S., Sepai, O., Polya, D., Fletcher, T., (2016) Estimating the population exposed to arsenic from groundwater-sourced private drinking water supplies in Cornwall, UK. In: Abstracts of the 2016 International Society of Environmental Epidemiology (ISEE). Abstract P1-384 | ID: 3838. Research Triangle Park, NC: Environmental Health Perspectives; <http://ehp.niehs.nih.gov/isee/2016-p1-384-3838/> Poster presentation.

Crabbe, H., Dabrera, G., Close, R., Morris, J., Keshishian, C., Leonardi, G., Ruggles, R. (2016) Lead poisoning in children; evaluation of a pilot surveillance system in England, 2014-15. In: Abstracts of the 2016 International Society of Environmental Epidemiology (ISEE). Abstract P2-267 | ID: 3829. Research Triangle Park, NC: Environmental Health Perspectives; <http://ehp.niehs.nih.gov/isee/2016-p2-267-3829/> Poster presentation.

Crabbe, H., Dabrera, G., Close, R., Morris, J., Keshishian, C., Leonardi, G., Ruggles, R. (2016) Lead poisoning in children; evaluation of a pilot surveillance system in England, 2014-15. Oral presentation to PHE Applied Epidemiology Conference, University of Warwick, February 2016.

Crabbe, H., Close, R., Leonardi, G., Watts, M., Ander, L., Hamilton, E., Middleton, E., Smedley, P., Gregory, M., Robjohns, S., Sepai, O., Polya, D., Fletcher, T., (2016) Estimating the population exposed to arsenic from groundwater-sourced private drinking water supplies in Cornwall, UK. Poster presentation to 10th UK and Ireland Annual Occupational and Environmental Epidemiology conference, HSL, Buxton, May 2016.

Crabbe, H., Saavedra-Campos, M., Verlander, N. Q., Leonard, A., Morris, J., Wright, A., Balasegaram, S. (2016) Are pertussis cases reported too late for public health interventions? Cross sectional study in London and the South East of England, 2010 to 2015. Accepted for oral presentation, ESCAIDE conference, Stockholm, November 2016.