HEALTH PROTECTION RESEARCH UNIT
IN GASTROINTESTINAL INFECTIONS

NHS
National Institute for Health Research

BOOK OF ABSTRACTS AND PRESENTATION OF KEYNOTE SPEAKERS

ANNUAL SCIENTIFIC MEETING
NORWICH – 7 & 8 MARCH 2018

Quadram Institute
Science • Health • Food • Innovation

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KEYNOTE SPEAKERS

Keynote speakers for the 2018 National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Gastrointestinal Infections (GI) annual conference: Professor Arjan Narbad, Professor Michael Hornberger, Professor Ian Charles and Professor Paul Hunter.

Professor Arjan Narbad: 'Understanding the microbiome of fermented foods in Africa to enhance food safety'

Professor Arjan Narbad graduated from Leeds University with a BSc in Microbiology. He then moved to Cardiff University and obtained a PhD in microbial metabolism of xenobiotic compounds. After a short postdoctoral position in the Biochemistry department of Cardiff University he joined the Institute of Food Research, Norwich in 1989 and has worked on a number of industrially funded biotechnology projects on the engineering of lactic acid bacteria and yeast for production of novel food ingredients and antimicrobials.

Currently Professor Narbad is the Translational Microbiome Group Leader at the Institute where his research is focused on understanding the role of gut bacteria in health and disease of humans and animals.

Professor Narbad's group has developed probiotic bacteria for reducing the levels of foodborne pathogens such as *Campylobacter* from the food chain. He has worked on the relationship between gut microbiota and specific gastrointestinal disorders; IBS and Ulcerative Colitis. In collaboration with clinicians at the Norfolk and Norwich University Hospital his group is actively involved in setting up a bacteriotherapy service for the treatment of *Clostridium difficile* infections, and are exploring how the exploitation of new technologies could be used to improve the diagnosis of gastrointestinal infections.

He has published more than 100 research papers and has filed 9 international patents. He has been appointed a Visiting Professor at Jiangnan University in China and has recently established a BBSRC funded UK-China joint centre for research on probiotics.

Professor Michael Hornberger: 'The gut-brain axis in dementia'

Michael is the Head of Department of Medicine and Professor of Applied Dementia Research at the Norwich Medical School, as well as the Director of Aging Research in the Norfolk & Suffolk Mental Health trust. His research focuses on improving diagnosis, disease progression tracking and symptom management in dementia. His research group employs various research methodologies (clinical, cognition, neuroimaging and genetics) as well as disease interventions (pharmacological and non-pharmacological) for their research studies. He is working in close collaboration with other scientists as well as old-age psychiatrists, neurologists, nurses, clinical psychologists and speech and language therapists to approach dementia from a multi-disciplinary angle.

Professor Ian Charles: 'At the forefront of a new era of food and health research'

Professor Charles' research interests are in the area of infectious diseases, the microbiome, and its impact on health and wellbeing. He is particularly interested in harnessing 'omics technologies to understand how microbes evolve, spread, survive and compete in the food chain to reduce foodborne illness and to counter antimicrobial resistance.

Prior to becoming the founding Director of the Quadram Institute he was Director of the ithree institute, University of Technology, Sydney, Australia.

Professor Charles has over 30 years' experience in academic and commercial research. His academic career has included being a founding member of The Wolfson Institute for BioMedical Research at University College London, one the UK's first institutes of translational medicine. He has also worked in the pharmaceutical industry at Glaxo Wellcome, and founded biotech companies in the area of infectious disease, including Arrow Therapeutics, sold to AstraZeneca in 2007, and Auspherix, a venture capital backed company founded in 2013.

Professor Paul Hunter: After dinner speaker

Professor Paul Hunter is a professor of Health Protection at the University of East Anglia. He is qualified in Medicine and specialised in Medical Microbiology and Communicable Disease Control. Paul has particular interest and experience in the diagnosis, management and epidemiology of infectious disease. His main research interests are in the area of environment and health and he has experience of conducting epidemiological studies in outbreak settings and in the investigation of sporadic disease.

Professor Hunter has run case-control studies, population surveys, serological surveys, geographical information systems and randomised control trials. He also has experience of field research in the UK, Europe and elsewhere. Paul has published over 180 papers in peer-reviewed journals, six books and numerous chapters in books and with > 3000 citations is one of the most cited European researchers working on water and health issues. In addition, Professor Hunter is an expert advisor to the World Health Organization and has sat on several UK and International advisory committees.

ORAL ABSTRACTS

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SOCIAL DIVISION & GASTROINTESTINAL INFECTIONS SESSION

Socioeconomic inequalities in risk of and exposure to gastrointestinal infections

Natalie Adams

PhD Student

People theme

Introduction: Gastrointestinal (GI) infections are a significant burden both to the NHS and to society; affecting around a quarter of the UK population each year at an estimated cost of £1.5 billion. Many infections are socially patterned however the role of socioeconomic inequalities in the risk of and exposure to GI infections is unclear.

Methods: Study 1 explores the role of SES in risk of GI infections in high-income countries through a systematic review and meta-analysis. Study 2 assesses the association between SES and GI infections in a community cohort using Cox proportional hazards survival analysis. Study 3 presents results from two NHS telephone-based services to explore the role of SES amongst individuals accessing remote health advice. Study 4 presents results of a case-study of Shiga toxin-producing *Escherichia coli* (STEC), to explore socioeconomic patterning of risk factors for infection and the role of demographic and socioeconomic factors in progression from STEC to Haemolytic Uraemic Syndrome (HUS) in a cohort of paediatric HUS cases.

Results: In high income countries disadvantaged children, but not adults, had a significantly higher risk of GI infection compared to less disadvantaged children. In England, calls for GI infections were significantly higher in disadvantaged areas compared to less disadvantaged areas. However disadvantaged adults were found to have lower risk of GI infections in the community in the UK and disadvantaged children and adults were less likely to be reported as having STEC infection and disadvantaged children were less likely to develop HUS compared to less disadvantaged individuals.

Conclusions: Disadvantaged children are at greater risk of GI infections compared to their more advantaged counterparts. The relationship between deprivation and risk of GI infection in adults is less clear. Increased risk may relate to differential exposure, vulnerability or healthcare-seeking behaviours, including symptom recognition, across socioeconomic groups.

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SOCIAL DIVISION & GASTROINTESTINAL INFECTIONS SESSION

Exploring the experiences, management and consequences of GI infections in socio-economically contrasting places: Environmental Health Officer's 'on the ground' perspectives

Dr Sarah McGarrol

Postdoctoral Researcher

People theme

There is evidence of a social gradient in most health outcomes linked to both causes and consequences of ill health. Quantitative studies have shown that around 25% of people in the UK will suffer an episode of infectious intestinal disease (IID) per year and the consequences of these infections result in a great number of days lost from school and/or work. Socioeconomic and geographical inequalities are documented in chronic conditions, such as heart disease but understandings around observed health inequalities of gastrointestinal (GI) infections, is not well known. Previous quantitative studies investigating GI infections have most often focused on risk of infection for example, rather than on examining the influence of differing social and geographical contexts in detail which can influence both causes and consequences of GI infections. Qualitative evidence is limited related to GI infections and little is known from the perspectives of practitioners involved in the formal management and monitoring of GI infections.

This paper will outline the aims of this particular 'People' theme study and will focus on preliminary insights gained from qualitative interviews with practitioners involved in 'on the ground' investigations and monitoring of GI infection – in this case Environmental Health Officers. Their perspectives are important for better understanding the impact, consequences and burden of GI infections across socially contrasting communities within which they work.

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SOCIAL DIVISION & GASTROINTESTINAL INFECTIONS SESSION

How do people and places shape gastrointestinal infections in socio-economically and geographically contrasting areas?

Suzanne Rotheram

PhD Student

People theme

Background: Gastrointestinal (GI) infections are an important cause of morbidity in the UK with around one quarter of the population experiencing an infection each year. However, health inequalities in the burden and consequences of this disease are not fully understood. Age appears to influence inequalities with children of lower socio-economic class having an increased risk of infection and the consequences of infection appear to be greater for more disadvantaged people of all age groups. Qualitative research exploring these inequalities is currently limited and little is known about why and how these inequalities might come about.

Methods: This study took an ethnographic approach to understand the complex interaction of policies, social, economic and environmental factors that might influence the management and consequences of these infections. The research was based in two geographically and socio-economically contrasting localities in the UK, one relatively affluent, and one relatively deprived. The study incorporated multiple research methods: interviews with parents, nurseries, schools and Public Health England staff; participant observational fieldwork in playgroups; GIS mapping and geo-ethnography.

Results: The places that people live and the people that live there were found to shape how GI infections are managed and the consequences of this disease. Social, economic and environmental factors interact within different places to produce different understandings, experiences and consequences of GI infections.

Conclusion: Future work examining the socio-economic inequalities of GI infections needs to understand the places that people live in, and the social and economic context of the people that live there.

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SOCIAL DIVISION & GASTROINTESTINAL INFECTIONS SESSION

‘It’s horrendous’: mothers’ narratives challenge our perception of childhood GI as ‘just one of those things’

Dr Friederike Ziegler

Postdoctoral Researcher

People theme

Background: Although there has been some research on the epidemiology of gastrointestinal infection (GI) with particular attention paid to possible socio-economic inequalities relating to risk and severity in adults and children, there is currently a dearth of evidence of families’ experiences of GI. This qualitative study has sought to broaden our critical understanding of the lived experience of GI, which can contribute to the more effective design of future interventions.

Methods: This qualitative study included 21 interviews and 6 focus groups with (largely) women from two contrasting disadvantaged areas in a Lancashire town. The semi-structured interviews explored in detail parents’ experiences of their child’s or children’s recent gastrointestinal infection. In addition, the focus groups sought parents’ validation of early findings.

A geographical relational approach to space and place has theoretically informed the data analysis which has been carried out using NVivo software.

Results: The data analysis shows that gender inequalities persist in the care of children with GI with women as the main care givers. Whilst GI is often considered by health professionals and society as a minor childhood illness, the narratives show that GI places a particularly heavy burden on women. This is the consequence of the complex interplay of factors, which involves the negotiation of a myriad of place-based relationships and conflicting social and institutional norms. It also shows how GI threatens women’s identity as ‘good mothers’, and the consequences of this burden on their mental and emotional health.

Conclusions: A relational approach to place-based analysis highlights the complexity of everyday life, and the disruption that GI causes in spatio-temporal routines and patterns. The results show mother’s primary need for reassurance from health practitioners in times of uncertainty and increased anxiety.

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THE GUT MICROBIOME AND WHOLE GENOME SEQUENCING SESSION

The importance of method standardization for microbiota studies

Anna Maria Pulawska-Czub

PhD Student

Places theme

The human intestine contains a dense and diverse microbiota with a significant role in heath and disease. Dysbiosis of these communities is associated with wide range of pathological conditions. Determining bacterial composition profiles in faecal samples through DNA sequencing is a multistep process and studies indicate that the choice of analytical procedures can influence and bias the final observations. Therefore, understanding the significance and impact these critical steps have on the outcome is crucial for the optimization of a reproducible protocol.

A systematic approach was taken in order to study the impact of sample storage conditions; choice of DNA extraction method and amplicon target for next-generation sequencing, using faecal samples donated by healthy volunteers. Aliquots of stool material were stored at various temperatures (-80°C, -20°C, 4°C, 25°C, 37°C), neat or homogenized with stabilization buffer (DNAgard, PSP or EtOH) for up to 5 months. DNA extraction was performed with four different commercially available kits (PSP, ZYMO, QIAgen or FastDNA). Amplified sequences targeting either V3V4 or V4 region of 16S ribosomal RNA gene were further sequenced on MiSeq platform (2x250bp reads).

Results demonstrated that faecal samples storage without stabilization buffer at temperatures higher than -80°C induced fluctuations in microbiota profiles. The use of DNAgard and PSP buffers contributed to bacterial community preservation at -20°C and 4°C for up to 1 month. Bacterial phyla abundances varied across DNA extraction methods with highest proportions of *Actinobacteria* and *Firmicutes* recovered with ZYMO and *Bacteroidetes, Cyanobacteria* and *Proteobacteria* with QIAamp. Finally, differences were observed between *Bacteroidetes* and *Firmicutes* ratios when alternative variable regions of 16S rRNA gene was sequenced.

These data highlight the importance of consistency of protocols among microbiota studies in order to enable cross-comparability. It also provides useful information to help interpret differences that may be observed between studies.

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THE GUT MICROBIOME AND WHOLE GENOME SEQUENCING SESSION

Using an in vitro colon model to investigate microbiota-pathogen interactions

Dr Lee Kellingray

Postdoctoral Researcher

The Microbiome theme

Research into associations between the human gut microbiota and host health is a growing field, with evidence indicating effects can be observed at various sites throughout the human body. Although animal experiments represent a useful model to test these associations, there is currently a drive to decrease the number of animals used in scientific research. The Narbad group at Quadram Institute Bioscience have developed a colon model facility to enable testing of hypotheses regarding the gut microbiota in two different models: batch culture, and continuous culture systems. This facility ensures that any interventions related to the gut microbiota have appropriate evidence prior to the potential use of animal models. I have been using the colon model facility to investigate the effects of pathogens, such as *Salmonella typhimurium,* on the human gut microbiota structure and function, using 16S rRNA gene sequencing and proton nuclear magnetic spectroscopy, respectively.

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THE GUT MICROBIOME AND WHOLE GENOME SEQUENCING SESSION

Prevalence and persistence of antimicrobial resistance genes in returning travellers

Saskia Neuert

PhD Student

The Microbiome theme

In many developing countries, the prevalence of resistance to clinically relevant antimicrobials in gastrointestinal pathogens is extremely high. Increasingly, extensively drug-resistant isolates are also being observed in developed countries. This is linked to a rise in global travel, during which exposure to unknown environments, and thus foreign microorganisms, can shift the balance of the gut microbiota and promote the establishment of bacteria carrying antimicrobial resistance (AMR) determinants. Diarrhoeal episodes and the consumption of antimicrobials when abroad further increase the risk of resistance gene acquisition.

Here we present a longitudinal metagenomics study of gut microbiota communities and their resistomes in fifty volunteers travelling outside of Europe, North America and Australia. Volunteers provided stool samples before and immediately after travel as well as six months after their return along with questionnaires about their health status and details of their travels. Taxonomic assignment of sequencing reads generated on an Illumina HiSeq instrument was carried out using Kraken and AMR genes were identified using the Genefinder algorithm, which maps the reads against a database of resistance determinants.

We observed an overall enrichment in AMR genes after travel. When stratified according to antimicrobial class, this enrichment was most pronounced for chloramphenicol, sulphonamide and fluoroquinolone resistance determinants. In some cases, newly acquired genes persisted up to six months after travel. Generic changes in microbiota composition for the entire dataset after travel could not be identified due to inherent interindividual differences and varying travel destinations. On a per-volunteer basis, however, microbiota and resistome reflected travel-associated behaviour and diseases, such as traveller's diarrhoea.

Our results show that monitoring of international travellers using metagenomics can form the basis for a better understanding of resistance gene dissemination, which is required to guide public health interventions targeted at limiting the spread of resistant pathogens.

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THE GUT MICROBIOME AND WHOLE GENOME SEQUENCING SESSION

An examination of Australian *Salmonella enterica* serovar Enteritidis in a global context

Madison Pearce

PhD Student

Pathogens theme

Salmonella enterica serovar Enteritidis is responsible for over 30 million cases of foodborne gastroenteritis per year, making it responsible for approximately 50% of cases of human *Salmonella* infections globally every year. Enteritidis is a nonendemic serovar in Australia and is not found in Australian chicken flocks, which are the natural reservoir of Enteritidis but each year cases of Enteritidis are reported within Australia. Due to it being a nonendemic serovar it is believed that these are associated with international travel or trade, particularly with popular Australian tourist destinations, which are predominantly Asian. Approximately 100 isolates of Enteritidis were collected in New South Wales (Australia) from April – May 2016 and were sequenced for further analyses. We then used a range of methodologies to examine Enteritidis isolates from across the globe in order to find the closest relatives of the Australian isolates. Further analyses were performed to compare Australian and Asian isolates specifically. Furthermore, the genetic diversity of the isolates was studied in an attempt to find the genes driving the differences between the Australian isolates and to search for commonalities between them. We have demonstrated that Australian Enteritidis isolates are highly diverse and do not belong to one distinct lineage. Several clusters of Australian Enteritidis were observed, which may demonstrate that secondary transmission occurs within Australia after the initial infection. Additionally, isolates did not appear to be more closely related to Enteritidis from Asia than from any other country. Instead Australian isolates are related to multiple different lineages of Enteritidis, which are associated with countries from multiple continents.

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THE GUT MICROBIOME AND WHOLE GENOME SEQUENCING SESSION

Genomic analysis of routine *Campylobacter* sequencing at Public Health England from 2015-2017

Clare Barker

PhD Student

Pathogens theme

Campylobacter is the leading cause of bacterial gastroenteritis in the United Kingdom, resulting in an estimated 280,000 cases each year and a considerable public health burden. The Gastrointestinal Bacteria Reference Unit at PHE Colindale typically receives isolates of *Campylobacter spp.* from outbreaks, food monitoring and complex clinical cases. Traditionally, these were typed using laboratory methods such as phage typing and heat-stable serotyping. However, the discrimination provided by these methods is insufficient for outbreak investigation or surveillance. Serotyping was therefore phased out in 2014; replaced by PCR based 7-gene multilocus sequence typing (MLST), which is recognised as a robust and discriminatory typing method for *Campylobacter*. In 2015, the service transitioned to whole genome sequencing (WGS) with bioinformatics analyses used to detect contamination, define the sequence type using MLST, and identify antimicrobial resistance determinants.

This project aims to review the three full years of sequencing data that are available as a result of this service, comprising around 900 isolates derived from humans. *Campylobacter jejuni* and *C. coli* make up 85% and 13% of the isolates respectively, with the remainder belonging to mixed isolates and less common species including *C. fetus* (n=20), *C. upsaliensis* (n=4) and *C. lari* (n=1). A range of bioinformatics tools and methods will be used to examine the population structure of *Campylobacter* received in this period. Trends in antimicrobial resistance and patient demographics will also be reviewed. These results will provide important knowledge for future public health surveillance of *Campylobacter*.

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THE GUT MICROBIOME AND WHOLE GENOME SEQUENCING SESSION

Norovirus strain types found within the second Infectious Intestinal Diseases (IID2) study: An analysis of norovirus circulating in the community

Dr John Harris and Prof Miren Iturriza-Gómara

Lecturer & Prof in Virology

Pathogens and Places themes

Background: Norovirus is the commonest cause of infectious intestinal disease in the UK. A large prospective cohort study, the second Infectious Intestinal Diseases (IID2) study, estimated community incidence of norovirus at 59/1000 population; almost four million cases a year.

Methods: In this study we analysed stool samples provided by community cases from the IID2 study. The samples were either obtained from a GP directly, or from those recruited to the study and who were ill in the community. Detection of norovirus was by use of Polymerase Chain Reaction (PCR). Norovirus cases were defined as those in which norovirus was detected with a cycle threshold (ct) value of <40.

We analysed the data to assess if any differences existed in the ct value between the genogroups or genotypes. Data were also investigated to assess if there were differences of reported length of illness between genogroups.

Results: A total of 477 samples were submitted for analysis. Cases were more greatly represented in the youngest age group (0-4 years) with significant differences in the proportion of males and females by age group (chi square=45, p<0.001).

There was a significantly higher proportion of genotype II.4 in samples obtained from GPs (chi-square=17.8, p<0.001) compared to samples taken from other community sources. Whereas in the non-GP cases GII.6 was significantly higher (chi-square=17.4, p<0.001).

There was no statistical difference in ct values by genotype. Genotypes GI.3 and GII.3 had the lowest median ct values 22.4 and 22.5 respectively. Ten percent of people reported that diarrhoea lasted between five and six days, which was longer than vomiting duration. The median reported length of absence from work or school was 2 days with 87 percent of people reporting having three or fewer days absence.

Conclusions: This study shows the prevalence of GII.4 noroviruses in the community from two community settings, GP and non-GP settings. The proportion of cases reporting diarrhea lasting five to six days is longer than expected in community cases.

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EPIDEMIOLOGY & BURDEN OF GASTROINTESTINAL INFECTIONS SESSION

Investigating the burden and transmission of acute gastroenteritis in care homes on Merseyside

Thomas Inns

PhD Student

Pathways theme

The main objective of my work so far in this second year has been to set up and operate a study to investigate the burden and transmission of acute gastroenteritis in care homes on Merseyside. The aim of this project is to pilot an enhanced surveillance system for acute gastroenteritis among the elderly in care homes. This will provide data that can then be extrapolated and used in mathematical models to calculate the burden of norovirus infections in the elderly in long-term residential care in the UK, and the potential impact of a norovirus vaccine specifically targeted to this population. The study protocol has been published in BMJ Open. The study is currently taking place in care homes in North West England; four care homes are currently recruiting participants. Recruitment started on 2 February 2017 and 163 participants have been included so far. Participants are being prospectively followed up for relevant GI illnesses.

I have also undertaken an analysis of recent care home acute gastroenteritis outbreaks in Cheshire and Merseyside, using data collected by Public Health England. This analysis has produced background epidemiological data and provide context for the main study. The manuscript is currently under review.

Additionally, I have undertaken a systematic review of the literature to provide background and context for this work. The systematic review looked at "Community-based surveillance of acute gastroenteritis" and has been published in BMC Infectious Diseases.

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EPIDEMIOLOGY & BURDEN OF GASTROINTESTINAL INFECTIONS SESSION

Understanding the incubation period distribution of *Salmonella* Typhi

Adedoyin Awofisayo-Okuyelu

PhD Student

Tracking disease in the population theme

Background: *Salmonella* Typhi is a human pathogen that causes typhoid fever. It is a major cause of morbidity and mortality in developing countries and is responsible for several outbreaks in developed countries. Studying certain parameters of the pathogen, such as the incubation period, provides a better understanding of its pathophysiology.

Methods: In order to understand the incubation period distribution of *S*. Typhi, we carried out a systematic review and developed a mathematical model.

Published literature on outbreaks and human experimental studies reporting incubation period were reviewed. Studies with limited evidence of heterogeneity between them were identified using hierarchical clustering analysis and grouped for further analysis. Factors contributing to the distribution of incubation period were also identified by applying a generalized linear model.

Separately, a biological compartmental model describing the process of *S*. Typhi infection from ingestion to onset of clinical illness was described using evidence from in vitro and in vivo literature and formalized as mathematical equation. Parameter values were derived from the literature and model was solved using Berkeley Madonna software.

Results: Analysing extracted data from the systematic review showed previous vaccination and attack rates as factors that may lengthen and shorten the incubation period respectively. Five subgroups with limited evidence of heterogeneity were identified and the mean incubation period of the subgroups ranged from 9.7 days to 21.2 days. Outbreaks reporting cases with vaccination history were clustered in a single subgroup and reported the longest incubation period.

The mathematical model was developed using two possible scenarios of *Salmonella* invasion. The output of both scenarios was similar showing the onset of clinical symptoms around 3.3 days and 5.4 days.

Conclusion: The incubation period distribution of *S*. Typhi is influenced by some host and pathophysiological factors. Clinical onset takes longer than predicted by our current mathematical model based on biological experimental data.

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EPIDEMIOLOGY & BURDEN OF GASTROINTESTINAL INFECTIONS SESSION

The epiCrypt study: Investigating household transmission of *Cryptosporidium*

Caoimhe McKerr

PhD Student

Pathways theme

Rationale: *Cryptosporidium* is a major contributor to human diarrhoeal illness worldwide and infection with this parasite causes over 4,000 cases of diagnosed illness in England and Wales every year. Outbreaks can be large but may only represent a small proportion of actual cases, and how much sporadic disease there is has not been sufficiently established.

Secondary infection may represent an underestimated and unreported amount of sporadic disease which could be prevented with tailored advice and public health messages.

There are no published household-level studies in England & Wales which ascertain likely risk factors or pathways to secondary spread. This study is a collaborative study between Public Health Wales, Public Health England, and the Heath Protection Research Units at the University of Liverpool.

Objectives:

- To calculate secondary transmission rate within households
- To estimate the prevalence of asymptomatic carriage
- Identify risks for secondary transmission

Approach: This project will be a year-long observational study to identify secondary transmission in households exposed to a case of *Cryptosporidium*, and also to elicit information on risk factors and likely mechanisms for spread.

We will aim to recruit 400 households across England and Wales where someone has had a positive diagnosis of *Cryptosporidium*, ask general questions about the household composition and behaviours, and retrieve stool samples from each household member for testing, speciation, and further molecular typing.

We anticipate that the addition of the specialist molecular typing will help to accurately describe the epidemiology of sporadic and secondary disease and identify specific risks for spread by species.

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EPIDEMIOLOGY & BURDEN OF GASTROINTESTINAL INFECTIONS SESSION

Transmission pathways of Shiga toxin-producing *Escherichia coli* resulting in Haemolytic uraemic syndrome: systematic and methodological reviews

Rebecca Inman

PhD Student

Pathways theme

Background: Shiga toxin-producing *Escherichia coli* (STEC) are gastrointestinal pathogens that cause illnesses ranging from mild diarrhoea to life-threatening haemolytic uraemic syndrome (HUS). We aimed to assess the types of STEC transmission associated with HUS, and identify the most common strains and virulence factors associated with HUS, using systematic review methodology.

Methods: We included epidemiological studies of STEC outbreaks that resulted in a high proportion (≥10%) of HUS cases (≥2 STEC cases with ≥1 associated HUS case). Structured searches were run on Medline, Scopus, Embase and Web of Science. Risk of bias assessments were carried out using a modified Newcastle-Ottowa scale; assessing study design, control measures and exposure ascertainment. Risk of bias assessments were carried out for each review question.

Results: 51 studies were included - 23 descriptive, 23 case-control and 6 cohorts (1 study included cohort and case-control). 71% of reports described outbreaks associated with foodborne transmission; of which 53% were attributed to meat products (some studies explicitly stated that meat was either raw or "pink"), 17% unpasteurized dairy products and 30% other foods (e.g. salads, unpasteurized juices). Transmission in the remaining 29% consisted of farm/animal contact, person-to-person, travel and recreational water. Risk of bias in STEC transmission vectors for most studies was high, suggesting the need for improved study methodology. O157 was the most commonly detected STEC strain, with only 9/51 studies reporting non-O157 outbreaks exclusively. 32 studies had data on virulence factors, where *Stx2* was the most frequently detected factor followed by *eae* and *Stx1*.

Conclusions: This systematic review suggests that majority of STEC transmission resulting in HUS is via meat, unpasteurized dairy products and other foods such as salads and unpasteurized fruit juices. Following these results, we are conducting methodological review to address identified problems in STEC epidemiology including publication bias, surveillance systems and reporting biases.

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15

EPIDEMIOLOGY & BURDEN OF GASTROINTESTINAL INFECTIONS SESSION

The Economics of Gastrointestinal Infections: Ways Forward and New Initiatives

Dr Mara Violato

Research Fellow

People, Places and Tracking disease in the population themes

Gastrointestinal infections are of increasing medical and health-economic significance and represent a challenge to public health care systems. After outlining the health economics collaborations developed within the Health Protection Research Unit across the research themes 'People', 'Tracking disease in the population' and 'Places' – and after summarising completed and ongoing research – ideas for consolidating existing collaborations and developing new ones will be proposed. These will include plans for a new collaboration under the umbrella research theme 'Pathogens', with a view to developing an economic evaluation of the use of whole genome sequencing (WGS) as an effective and cost-effective tool in the diagnosis and surveillance of infectious diseases.

Data collected by Public Health England within their surveillance system (which already makes use of WGS as a routine microbiological method for identifying and characterising a range of bacterial pathogens) will be linked to data on healthcare costs, patient costs, production losses and other wider societal costs with a view to providing a novel evidence base to demonstrate the effectiveness and value for money of this new approach, and of its potential for wider adoption and routine use in reducing infectious disease. Further ideas for potential collaborations in relation to the 'Microbiome' research theme might include an exploration of the relationship between intestinal microbiota and mental health. Those ideas which relate to the consolidation of existing rather than future collaborations will include extended analyses of socioeconomic determinants of, and costs associated with, gastrointestinal infections using population cohorts linked with available biological, economic, administrative and epidemiological data.

It is hoped that this short presentation will serve as a springboard for further multidisciplinary collaborations whose outcomes can inform the design of further public health interventions to reduce the clinical and economic burden of gastrointestinal infections.

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16

EPIDEMIOLOGY & BURDEN OF GASTROINTESTINAL INFECTIONS SESSION

The impact of rotavirus vaccination program in England on emergency department attendances: final study

Helen Hughes

PhD Student

People theme

Background: Rotavirus gastroenteritis is a common childhood disease, responsible for high numbers of GP consultations and hospital admissions each year. A rotavirus vaccination was introduced for infants aged 2-3 months in the UK in July 2013. Previous work demonstrated an apparent decrease in gastroenteritis in children during what was expected to be the next 'rotavirus season', March-April 2014.

Methods: The Public Health England Emergency Department Syndromic Surveillance (EDSSS) collects anonymised daily data from a sentinel network of emergency departments across England and Northern Ireland.

Using EDSSS data prior to the vaccine introduction, the association between gastroenteritis ED visits and rotavirus, identified from laboratory data, was quantified by age group, using multiple regression analysis.

An interrupted time series analysis was then used to quantify the impact of rotavirus vaccination on EDSSS gastroenteritis visit levels from January 2012 to July 2016 (2 years pre and 3 years post vaccination implementation), by age group.

Results: Rotavirus was found to be associated with gastroenteritis visits to EDs, particularly in young children (0-4years), where it accounted for up to 19% of the ED visits.

Interrupted time series analysis confirmed a 6% decrease in all age group ED visits for gastroenteritis, post vaccine introduction. For young children the largest impact post vaccine introduction was the reduced magnitude of the seasonal trends observed.

Conclusions: Gastroenteritis visits to EDs by young children prior to vaccine introduction, as measured by syndromic surveillance, were associated with rotavirus infection, demonstrating the potential for this data to be used for investigation of rotavirus vaccine impact.

The levels of gastroenteritis ED visits following rotavirus vaccination introduction decreased overall. This was particularly apparent in young children where the previously large seasonal shift in gastroenteritis attendances was greatly reduced, becoming more similar to that seen in older age groups, though still at a higher level.

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POSTER ABSTRACTS

1

Audit of Helicobacter pylori testing in microbiology laboratories in England: inform compliance with NICE guidance and the feasibility of routine antibiotic resistance surveillance

Dr Rosalie Allison

Research Assistant

Public Health England

Invited External Presenter

Introduction: National Institute for Health and Clinical Excellence (NICE) 2014 guidance recommends that laboratories provide stool antigen test, or locally validated serology for non- invasive diagnosis of *Helicobacter pylori.* Clinicians may also use carbon-13 urea breath test. *H.pylori* antibiotic resistance is increasing, but we do not know how many labs are providing antibiotic susceptibility.

Aims

- Assess microbiology laboratory compliance with NICE guidance
- Determine the number of laboratories performing antibiotic susceptibility testing to inform any future national *H. pylori* antibiotic resistance surveillance strategies.

Methods: We invited 170 accredited English microbiology laboratories in 2015 to complete a questionnaire.

Results: Of the 121/170 (71%) laboratories that responded, 96% provided *H. pylori* testing: 78% on site; 18% referred tests to another laboratory.

In line with NICE guidance 95% of laboratories test for *H. pylori* using a stool antigen or urea breath test. Five laboratories do not comply as they perform serology or biopsy urease tests first line (4/5 encourage urea breath tests in their acute trusts).

Cultures and antibiotic susceptibility performed Only 23% of laboratories perform *H. pylori* cultures on site and only two processed ten specimens/week; the others less than one. Only nine laboratories undertake antibiotic susceptibility on site.

Conclusions: The results of this audit are promising as the majority of centres provide a non-invasive option as their first-line diagnostic test.

As very few laboratories are routinely performing culture of biopsy specimens to investigate antibiotic susceptibility, an English culture based surveillance system would probably need centralised culture. However, a stool specimen based surveillance system using PCR would be very possible.

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2

Symptom profiling for acute infective gastroenteritis

Dr Anna Donaldson

Honorary Research Associate

Pathways theme

Background: Many patients with acute infective gastroenteritis are reluctant to submit stool samples, and of those submitted, no pathogen will be identified in almost half. Being able to use symptoms to make inferences as to the likely causative organism would support both individual case management and the control of outbreaks, where microbiological confirmation is either not possible or still pending.

Methods: A secondary data analysis was conducted using data from the IID2 Study. Binomial regression modelling was undertaken to examine associations between symptoms and causative pathogens. Organism-specific models were developed for pathogens with a prevalence greater than 10% of the total number of cases. Grouped organism models were used to identify symptoms which were associated, more broadly, with bacterial or viral causes of infection.

Results: A total of 844 cases of acute infectious gastroenteritis were analysed. Organism-specific models were developed for campylobacter, norovirus, rotavirus and sapovirus. Whilst there were few symptoms which differentiated the individual viral pathogens, the grouped analysis showed that viral pathogens in general were more likely where the symptom onset was in winter or spring, the patient was aged under 5 years, there was loss of appetite, and nausea and vomiting. The odds of campylobacter infection were higher in the summer months, in cases of diarrhoea in the absence of vomiting, diarrhoea lasting more than 3 days and fever. The grouped bacterial model largely mirrored the campylobacter model, which represented almost two thirds of all bacterial cases, whilst also identifying bloody diarrhoea as increasing the odds of a bacterial cause.

Conclusion: Symptomology could help distinguish between possible bacterial or viral causes of acute infective gastroenteritis, but may be limited in its ability to distinguish individual pathogens. Symptom profiles could be of value to help guide clinical and public health professionals in the absence of microbiological confirmation.

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3

The utility of internet data for syndromic surveillance purposes: a scoping review

Dr Obaghe Edeghere

PhD Student

Tracking disease in the population theme

Syndromic surveillance systems are increasingly used to detect and monitor in near-real-time outbreaks and secular trends of specific gastrointestinal diseases in humans. These systems have been found to provide a time advantage over traditional systems based on laboratory data. The range of data sources used for syndromic surveillance has expanded over time and now includes novel sources like internet search engine (Google®) and microblogging/social media (Twitter®) data. To inform the development and operationalization of an internet data based syndromic surveillance system in Public Health England (PHE), we need to systematically review the current literature on its utility and methodological underpinning. As a prelude to the systematic review, we undertook a scoping review in order to identify and describe previous reviews on this subject. We searched the Ovid MEDLINE, Embase, Cochrane library, LILACS (Literatura Latino Americana em Ciências da Saúde), PROSPERO, Global Health and CINAHL bibliographic databases. Our search query was restricted to English language studies on humans conducted between 1990 and 2017. We identified 315 papers and two reviewers (DK & OE) undertook a title and abstract screen, we then selected 27 papers that potentially met the criteria for a full paper review. Of the 27 papers, only eight papers were subsequently selected for full data extraction and quality assessment. We found that none of the eight reviews addressed all aspects of our research question, and we concluded that no review that specifically addressed our question had been identified and there is justification to proceed with a full systematic review.

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4

A method to estimate the spatial relative risk of STEC O157 using the sparr package in R

Richard Elson

PhD Student

Pathways theme

Background: The risk of infection with Shiga-toxin producing *E.coli* (STEC) O157 differs between UK countries and within England. The majority of the English population lives in urban areas, yet rates of STEC O157 are highest in rural areas, particularly in the North and South West of the country [1].

Whilst population based rates allow some comparison between geographically defined areas, and focused tests for spatial clustering can provide insight into the underlying disease process, neither account for the spatial variation of risk within a defined geographical area.

Kernel smoothing is a well-established approach to estimate the spatial intensity and forms a key component the estimation of the kernel density-ratio or relative risk surface, constructed as a ratio of estimated case and control densities [2, 3]. This technique is particularly useful when considering the occurrence of cases relative to the heterogeneous nature of the underlying at risk population that is common in infectious disease epidemiology [3]. There are methodological challenges to this approach, particularly concerning the selection of a control group where matching or stratification can complicate the interpretation of the estimated spatial effect.[4]

We present a method to estimate relative risk using a control group designed to reflect the population at risk of STEC O157 infection whilst preserving the spatial effect of interest.

Methods: We selected primary cases of STEC O157 with postcodes from the national enhanced surveillance system ESSS between 2009 and 2015. Cases linked to known outbreaks or those reporting foreign travel were excluded.

Two controls per case were randomly selected from the Office for National Statistics postcode directory for England using three methods: no matching, frequency matched by rural urban classification and frequency matched by government region and rural urban classification.

Results are reported as symmetrical log-relative risk surfaces with edge correction as recommended. P value contours are drawn at the 95 and 99% levels. All analyses were conducted using the sparr package [3] in R [5].

Results: Results of the analysis will be presented in the poster.

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5

Generation of a low passage panel of *Clostridium difficile* reference strains

Ms Catherine Ho

Technologist

Public Health England

Invited External Presenter

Clostridium difficile is classified as an URGENT Threat Level Pathogen in the USA due to a four-fold increase in mortality associated with infections and the appearance of antibiotic resistant strains. To facilitate preclinical research, BARDA considered there was an urgent need to generate a panel of well characterised, low passage, high provenance, recent clinical isolates of *C. difficile*.

Four isolates were selected from a database of 960 held by the PHE *Clostridium difficile* Ribotyping Network. Selection was based on severity of infection, recent isolation, antibiotic resistance profile, toxin production and representation of the four main PCR-ribotypes considered to be currently circulating in the UK and North America.

Master and Working stocks of four isolates were produced in batch culture. Spore viability (cfu/ml) was conducted on Fastidious anaerobe agar (FAA) and Braziers Selective medium. A distinctive pattern of different, reproducible spore germination efficiency was observed with all isolates over time using different growth media which greatly affected the predicted viable spore count on FAA. This difference was later, not found to reflect the *in vivo* rate of killing. Further details of the selection process and spore propagation methodology will be presented. Characterisation and virulence assessment of the panel was subsequently conducted and will be presented separately (Mathews *et al*, 2018).

This panel of low passage, recent clinical isolates of *C. difficile* strains will be shipped to a US holding facility for subsequent storage and dissemination for future use in BARDA grant awards.

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6

Impact of rotavirus vaccination on rotavirus genotype distribution and diversity in England

Dr Daniel Hungerford

Research Fellow

University of Liverpool

Invited HPRU Member

Introduction: Rotavirus vaccination with the two-dose Rotarix® vaccine was introduced for infants in England in July 2013. Since then, there have been significant reductions in the incidence of rotavirus gastroenteritis. We assessed the vaccine's impact on genotype distribution and diversity three years post-vaccine introduction.

Methods: Epidemiological and microbiological data on genotyped rotavirus-positive samples between August 2006 and September 2016 were supplied by EuroRotaNet and Public Health England. Multinomial multivariable logistic regression adjusting for year, season and age was used to quantify changes in genotype prevalence in the vaccine period. Rotavirus genotype diversity was compared using two established biodiversity indices, Simpson's index of diversity (D) and Shannon's index (H).

Results: We analysed rotavirus genotypes from 8,044 faecal samples. In the pre-vaccine era, G1P[8]was most prevalent, ranging from 39% to 74% per year. In the vaccine era, G1P[8] prevalence declined each season (35%, 12%, 5%) and genotype diversity increased significantly in children aged 6-59 months (H' $p<0.001$: D $p<0.001$). In multinomial analysis, G2P[4] (adjusted multinomial odds ratio [aM-OR]=9.51 ; 95% CI 7.02-12.90), G3P[8] (aMOR=2.83; 95% CI 2.17-3.81; $p< 0.001$), G12P[8] (aMOR=2.46; 95% CI 1.62-3.73; $p<0.001$) and G4P[8] (aMOR=1.42; 95% CI 1.02-1.96; $p = 0.03$) significantly increased relative to G1P[8].

Conclusions: In the context of significantly reduced rotavirus disease incidence, genotype diversity has increased and there has been a relative change in the dominant genotype from G1P[8] in the pre-vaccine era to G2P[4] in the vaccine era. These changes will need continued surveillance, especially as the number and age of the vaccinated birth cohorts increase over the coming years. The results presented here and continued genotype surveillance will help to inform whether future modifications to rotavirus vaccines may be needed.

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7

Human Microbiome in Health and Disease: Use of metabolomics approaches to investigate gastrointestinal infections

Dr Gwénaëlle Le Gall

Senior Research Scientist

Quadram Institute Bioscience

Invited HPRU Member

Background: Gastrointestinal illness is a considerable cause of morbidity in the UK and recent estimates are of up to 17 million community cases of infectious intestinal disease and 1 million GP consultations annually. Metabolomics using high-throughput Nuclear Magnetic Resonance (NMR) can provide detailed information on the function of the microbiome in diseased state.

Methods: NMR metabolite profiles were generated from 206 faecal samples of infected patients and compared to the profiles of 73 healthy individuals. The types of sample from infected patients were divided into infections from bacteria (6 *C. difficile*; 111 *Campylobacter*, 9 *Salmonella* and 1 *E Coli O157*) and protozoan parasites (4 Cryptosporidium, 2 specimens classified as Cryptosporidium/Giardia and 20 Giardia) and 53 infections of unknown origin.

Results: The ^{1}H NMR spectra of faecal waters were dominated by signals arising from acetate, propionate, and butyrate and characterised by low levels of many other metabolites (fatty, organic, and amino acids, sugars, osmolytes, amines, alcohols, phenolic compounds, nucleobases, nucleosides, nucleotides, vitamin B3 and bacterial degradation products such as 5-aminovalerate or methylsuccinate). Statistical analysis revealed distinct patterns differentiating the profiles of patients suffering from infectious intestinal diseases from those of healthy individuals, with a more marked effect in the case of bacterial compared to protozoan infection. Increased levels of known products of bacterial metabolism (amines and short chain fatty acids) suggested an increased metabolic activity of some taxa. Interestingly, the levels of those metabolites were also increased during protozoan infection. Differences in the increase of alanine and lysine levels make those compounds potential metabolic markers for distinguishing between the two types of infection.

Conclusions: NMR metabolite profiling is a culture-free high-throughput approach that could be useful for establishing signature markers for specific pathogenic genera and species.

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8

Diversity of *Salmonella* Infantis in England and Wales

Jennifer Mattock

PhD Student

The Microbiome theme

Background: In both the UK and continental Europe Salmonella Infantis is consistently the fourth most commonly identified serovar of *Salmonella* enterica isolated from humans. Despite the drop in overall numbers of Salmonella infection - largely as a result of chicken vaccination programs - there has been an increase in the numbers of S. Infantis infection reported. Despite this, S. Infantis it is a much understudied serovar, with little known about global diversity. To investigate the biology of sub-groups of S. Infantis we are establishing a database of genome sequence data linked to metadata.

Methodology: 673 whole genome sequences of S. Infantis (Illumina HiSeq) isolated between 2012 and 2017 by PHE in England and Wales were studied. 470 isolates from the National Institute of Communicable Disease, South Africa were selected for DNA extraction and Illumina NextSeq sequencing. A PHE pipeline, using MOST, PHEnix and SnapperDB was utilised to generate alignments of SNP differences within eBurstGroups (eBG); defined as multi locus sequence types (ST) linked by single locus variants. Randomized Axelerated Maximum Likelihood (RAxML) was used to generate a phylogeny.

Results: eBG31 encompassed the majority of the sequences and analysis of the phylogeny determined that they were clustered by ST. No clustering was seen by source of isolation, suggesting that host restricted S. Infantis is not seen. Conversely, obvious grouping was seen in isolates associated with foreign travel to North and South America, indicating that there may be distinct clades of S. Infantis in these continents.

A greater understanding of S. Infantis could be useful in the epidemiology of outbreaks of this serovar. This work found differences between S. Infantis isolated by PHE and those associated with other countries; further research is being carried out to determine the global population structure of this serovar.

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9

Development and characterisation of BARDA strain panel in hamster model of *C.difficile* disease

Mr Dennis Mathews

Microbiologist

Public Health England

Invited External Presenter

Background: PHE was commissioned by BARDA to develop a panel of well characterised, low passage, *C. difficile* clinical isolates for use in hamster model of *C.difficile* disease. PHE proposed the development of Quik Chek *C.diff* lateral flow and qualitative ELISA as a possible trigger-to-treat assay to assess the detection of *C.difficile* toxins A and/or B in hamster faecal samples. The strain selection and production process is presented separately (Ho *et al*, 2018). Details and results of the characterisation process and the identification and qualification of diagnostic assays will be presented.

Methods: Master and Working stocks of four isolates were enumerated for spore viability (cfu/ml) on Fastidious anaerobe agar (FAA) and Braziers Selective medium. All the strains were sequenced and tested for purity and the production of toxin A and B by ELISA assay and Vero cell cytotoxicity assays. The strain panel was tested for virulence in a hamster model. PCR and ELISA assays have been developed to detect toxins A and B in faecal samples.

Results: The production of toxins A and B was confirmed by ELISA and cytotoxicity assays in all strains. Purity was demonstrated by culture and Gram stains of selected colonies showed typical *C. difficile* morphology. Whole genome sequencing generated 95% coverage. Dual toxin ELISA and Quick Chek lateral flow appear to be reliable in the detection of toxins in faeces.

Conclusion: The panel has been thoroughly characterised and all the strains were virulent in hamsters but a reproducible difference in the rate of death was observed between strains. The dual-toxin ELISA assay proved to be advantageous to PCR in terms of assay duration and sensitivity, but the Quik Chek assay was found to be a more practical indicator of *C.difficile* disease due to being the fastest and most sensitive diagnostic assay.

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10

Whole Genome Sequencing of *Campylobacter* for Routine Surveillance

Dr Anaïs Painset

Postdoctoral Researcher

Pathogens theme

Food safety remains a public health priority as foodborne illness is a significant health service and economic burden. The Gastrointestinal Bacteria Reference Unit (GBRU) at Public Health England routinely detects and characterizes foodborne pathogens including *Campylobacter*, *Salmonella, pathogenic E. coli* and *Listeria* that are involved in outbreaks of gastroenteritis linked to the consumption of contaminated food products. With the advent of Whole Genome Sequencing (WGS), new methods have been developed to characterise these pathogens and provide the opportunity to replace many of the conventional microbiological techniques used to identify and type bacterial pathogens.

GBRU are currently using WGS for the routine identification and epidemiological investigation of *Campylobacter*. As with traditional typing a hierarchical approach is required to provide appropriate levels of discrimination depending on the clinical or epidemiological question at hand. This includes species, clone and strain identification and antimicrobial resistance characterization. We have used multiple bioinformatics approaches based on genome sequence analysis to provide characterization of foodborne pathogens at these differing resolutions implemented in an automated pipeline. Here we present data to demonstrate the applicability of different genome analysis methods including K-mer screens, traditional and core genome Multi Locus Sequence Typing, antimicrobial resistance characterization and Single Nucleotide Polymorphism analysis for the routine characterization of *Campylobacter* isolates.

The results illustrates how the implementation of WGS analysis is a viable alternative to conventional reference microbiological methods and demonstrates how WGS can enhance the detection, characterisation and investigation of *Campylobacter* outbreaks.

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11

Characterisation of *Clostridium difficile* Ribotype 332 Strains

Dr April Roberts

Senior Project Team Leader

Public Health England

Invited External Presenter

In 2013 Health Protection Scotland was alerted to a novel PCR ribotype of *Clostridium difficile*, designated ribotype 332. Three patients infected with this strain were severely ill due to other underlying conditions and died following their episode of *Clostridium difficile* infection (CDI). The Toxins Group at PHE-Porton are developing antibody based therapies for the treatment of CDI, using recombinant toxin-based fragments as the antigens for antibody production. Therefore, we wanted to purify TcdA and B from ribotype 332 to ensure that our antibodies would neutralise the toxins expressed by 332.

Dialysis sac culture in supplemented Brain Heart Infusion Broth (sBHI) was used to encourage toxin production. Several compounds were added to this medium in an attempt to improve toxin yields. The strains were further characterised for growth, spore production, toxinotype and other characteristics, using standard techniques.
Ribotype 332 strains (x4) were determined to belong to toxinotype 3, the same toxinotype as ribotype 027 strains and all the strains were positive for the binary toxin genes. Ribotype 332 strains produced low concentrations of both TcdA and B in dialysis sac culture, approximately 100-fold lower than a 'typical' hypervirulent 027 strain (NCTC 13366). Attempts to make the growth medium 'habitat-simulating' did not lead to significant increases in TcdA and B expression. Interestingly, 332 strains appeared to sporulate earlier than NCTC 13366 with all strains reaching a spore count of $2x10^7$ c.f.u./ml on Brazier's Agar after 22 days incubation in sBHI. 332 strains also had a shorter lag phase than NCTC 13366 when grown in sBHI batch culture.

In conclusion, *C. difficile* ribotype 332 strains are poor toxin producers *in vitro*. It is possible that *in vivo* toxin expression in ng/ml levels is all that is required to cause destruction of the gut epithelial cells and cause inflammation and clinical symptoms.

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12

Socioeconomic inequalities in the consequences of gastrointestinal infections

Tanith Rose

PhD Student

People theme

Background: Gastrointestinal (GI) infections are common and associated with numerous adverse consequences. Some evidence suggests those of lower socioeconomic status (SES) are more likely to present to healthcare services with GI infections. This may reflect greater need amongst more disadvantaged groups, either due to increased risk of infection or disease severity. This PhD endeavours to expand current understanding by exploring the extent of inequalities in the risk of infection, and in disease severity, sickness absence and hospitalisation as outcomes of GI infections.

Methods: Three studies were conducted. Firstly, a systematic literature review was performed to examine inequalities in the risk of symptomatic GI infections in high income countries. Secondly, analysis of data collected in the UK-based IID2 study was conducted to examine inequalities in self-reported symptom severity and sickness absence, amongst infectious intestinal disease (IID) cases. Thirdly, an ecological analysis using English Hospital Episode Statistics data was performed to evaluate inequalities in emergency hospital admissions and admission duration for IID.

Results: Examination of current literature suggested that children of lower SES, but not adults, appeared to have a greater risk of infection compared to their more affluent counterparts. Analysis of the IID2 study revealed that IID cases aged $\geq$5 years, of lower SES, were more likely to experience severe symptoms, and be absent from work or school. The association between SES and sickness absence was largely explained by greater symptom severity amongst more disadvantaged cases. Finally, neighbourhood deprivation was positively associated with IID-related emergency hospital admissions and admission duration, for adults and children. These associations were partly explained by the higher prevalence of long-term health problems in more deprived neighbourhoods.

Conclusions: The consequences of GI infections incur heavy burdens for individuals and societies. Evidence from this PhD suggests these consequences disproportionately affect socioeconomically disadvantaged groups. With this in mind, due consideration should be afforded to policies that address inequalities in the consequences of being ill with a GI infection, as well as those designed to reduce the risk of infection.

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Outbreak of *Salmonella* Adjame in England, June to July 2017: Increasing our Epidemiological knowledge-base of a rare serovar

Victoria Shah

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Public Health England

Invited External Presenter

Introduction: In August 2017, Public Health England was alerted of a cluster of three *Salmonella* Adjame cases, a rare salmonella serovar. Subsequently, more cases were identified predominantly in North West London (NWL) residents. Previously, only 9 cases were reported nationally between 2008-2016. We aim to describe this recent outbreak in order to widen the knowledge-base of *S*. Adjame.

Methods: An outbreak control team established the case definition: all confirmed *S*. Adjame reports in England with sample dates from June-July 2017. Case questionnaires collected information on demographics, travel and food exposures. Descriptive analyses were undertaken in Stata-13 to determine common exposures. Backward tracing was undertaken. Isolates were SNP-typed by whole genome sequencing.

Results: There were 14 confirmed cases, 6 female and 8 male, median age 66.5 years (range 3-85). Typing showed sub-clustering and considerable genetic variation across human samples. Thirteen cases were of South Asian descent. Four of 12 cases reported being admitted to hospital. No international travel was reported. Seven of 11 cases were vegetarian. We identified some common Indian grocers in NWL and food items, which were fruit/vegetables (lettuce, tomatoes, onions, bananas, n=8) and herbs/spices (pepper, turmeric n=9; chilli powder, coriander n=8; and cinnamon n=7). Backward tracing showed that there were multiple possible sources. Some products were sourced in the Indian sub-continent.

Conclusion: We report, for the first time in the UK, an outbreak of *S*. Adjame, building on our knowledge-base of this rare Salmonella serovar. Cases were mainly older and of South Asian descent, with the majority resident in NWL. Although the food source could not be determined, it was suspected to be a fresh product bought from common Indian grocers. Unfortunately, due to the complexity of supply chains it was difficult to determine the potential source of contamination but was likely due to an imported product.

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Family income exposure to norovirus in childhood: findings from the UK Millennium Cohort Study

Dr Mara Violato

Research Fellow

Tracking disease in the population, People and Places themes

Background: Existing empirical literature indicates that children born into families with limited financial resources are at greater risk of poorer health outcomes than their wealthier peers. Nonetheless, evidence on the relationship between family income and childhood exposure to norovirus (NoV) is still limited, with published studies pointing to conflicting results. NoV is one of the most common causes of viral gastroenteritis in all age groups worldwide, but constitutes a major disease burden especially for young children and the elderly.

Aims: To investigate the extent to which family income is associated with NoV exposure in children aged 3 years; to identify the main mechanisms through which family economic resources translate into exposure to NoV.

Methods: We assessed level of exposure to norovirus, as measured by oral fluid serology, in a unique high quality (cut-off value of 2mg/L) biomedical sample of 5,962 children from the UK Millennium Cohort Study (MCS). NoV risk factors were identified from the published literature and mapped into the MCS dataset. Univariate analysis, OLS and Quantile Regression multivariable models were estimated to study the relationship between the serology titre and family income, assessing the potentially mediating role of a wide range of family, social and environmental factors.

Results: Higher norovirus oral serology titres are associated with higher family income, but the relationship weakens after controlling for potential mediating factors. These are mainly factors which reflect increased frequency of person-to-person contacts, such as child formal care arrangements and residence in deprived, overcrowded, and polluted areas.

Conclusions: This study provides novel evidence that can help inform and prioritize policy interventions and health promotion programs policies, with a particular emphasis on improving hand-washing practices in nurseries and families with children as well as other 'behaviour-modifying' measures which can minimise occasions of NoV transmission.

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