HEALTH PROTECTION RESEARCH UNIT
IN EMERGING AND ZOONOTIC INFECTIONS

NHS
National Institute for Health Research

TOWARDS DELIVERING IMPACT

BOOK OF ABSTRACTS AND PRESENTATION OF KEYNOTE SPEAKERS

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UNIVERSITY OF LIVERPOOL | INSTITUTE OF INFECTION AND GLOBAL HEALTH

LSTM LIVERPOOL SCHOOL OF TROPICAL MEDICINE

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KEYNOTE SPEAKERS

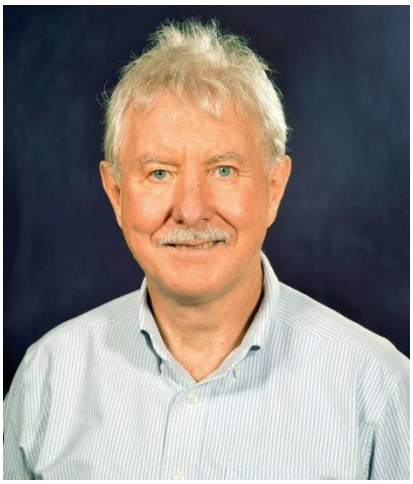
Keynote speakers for the 2018 National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Emerging and Zootnotic Infections (EZI) annual conference, on 'Towards Delivering Impact' are: Professors Marion Koopmans, Derrick Crook and Tom Solomon.

Professor Marion Koopmans: Challenges and opportunities in EID Preparedness Research

Professor Marion Koopmans, DVM PhD focuses on global population level impact of rapidly spreading zoonotic virus infections, with special emphasis on foodborne transmission. Her research focuses on unravelling the modes of transmission of viruses among animals and between animals and humans, and the use of pathogenic genomic information to unravel these pathways and to signal changes in transmission or disease impact.

She is Scientific Coordinator of COMPARE, a large H2020 funded project (20 MEuro), exploring the potential uses of next generation sequencing techniques for outbreak detection and tracking (www.compare-europe.eu), and co-PI in the FP7 funded PREPARE project (www.prepare-europe.eu) aimed at building a pan-European operational network for rapid and large-scale European clinical research in response to infectious disease outbreaks with epidemic potential.

She is Director of the WHO collaborating centre for emerging infectious diseases at Erasmus, and Scientific Director "Emerging infectious diseases" of the Netherlands Centre for One Health (www.ncoh.nl). She has received the Infectious disease award of the Dutch Association for Infectious Diseases and is the recipient of the Stevin Premium 2018. She has co-authored >500 papers that have been cited > 20,000 times.



Professor Derrick Crook: Investigating Emerging Infections through Linked Epidemiological and Whole Genome Sequence Data

Professor Derrick Crook MBBCh, FRCP, FRCPath - Director of National Infection Service, Public Health England and Professor of Microbiology, Nuffield Department of Medicine, University of Oxford.

He studied Medicine at the University of Witwatersrand, Johannesburg, South Africa; obtained the Diploma of Tropical Medicine (London), specialised in internal medicine at the University of Virginia, Charlottesville, USA, and completed a fellowship in infectious diseases at the Tufts New England Medical Center, Boston, USA. He obtained his US boards in both internal medicine and infectious diseases. He trained in clinical microbiology at the John Radcliffe Hospital Oxford and obtained both his FRCP and FRCPath. He is a practicing clinical microbiologist and infectious diseases physician at the Oxford University Hospitals NHS Trust.

He is the Director of the National Infection Service, Public Health England and oversees communicable disease control for England, UK. He is also co-director of the Oxford Biomedical Research, Infection Theme, and leads a large research consortium, Modernising Medical Microbiology, which focuses on translating whole pathogen sequencing into routine practice. He is the principle investigator of a large 15 country international research programme, CRyPTIC, which aims to comprehensively describe the genomic variation that confers antituberculosis drug resistance.

Professor Tom Solomon: 'The Health Protection Research Unit in Emerging and Zoonotic Infections - A Year of Challenges and Successes'

Professor Tom Solomon studied medicine at Oxford, did a PhD in Vietnam and postgraduate virology in the United States, before training as a neurologist.

He is Professor of Neurology at the Walton Centre NHS Foundation Trust and Director of the HPRU in Emerging and Zoonotic Infections. He studies emerging viral infections, particularly those that affect the brain, has published more than 200 scientific papers, and was awarded the Royal College of Physicians Triennial Moxon medal in 2014.

ORAL & POSTER ABSTRACTS

1

Characterisation of convalescent plasma using an EBOV GP HIV-1 pseudo-typed assay

Charlene Adaken

PhD Student

University of Liverpool

Invited HPRU Member

Poster presentation

Background

Studying survivors of the West African EBOV 2014-16 epidemic provides a unique opportunity to delineate immune responses controlling viral replication. These individuals provide a bank of convalescent plasmas (CP) that can be used to treat future outbreaks. Understanding immune responses associated with survival will indicate what an effective EBOV vaccine has to induce. We sought to develop an HIV- 1 EBOV GP pseudo-typed assay which could analyse antibody (Ab) neutralisation.

Methods

Single-round infectious EBOV GP pseudo-typed virus were produced by co-transfecting a HIV-1 envelope deficient backbone with a plasmid expressing the 2015 GEBOV GP envelope into 293T cells. Produced virus was quantified via measuring HIV-1 p24 levels and infection monitored by measuring luciferase activity within infected cells. We utilised our pseudo-typed assay in inhibition assays where limiting dilutions of CP were tested for the capacity to restrict viral entry. Sixty-five CP samples were selected for analysis where total EBOV GP binding responses had been characterised using the DABA assay.

Results

CP samples showed broad neutralisation potential against EBOV2015with an inhibitory trend ranging from low to high. Samples with high Ab titres were shown to neutralise EBOV to a greater capacity compared to lower titres ($P<0.005$). Furthermore, There was an association between the neutralizing activity of the convalescent sera against the pseudo-virus system and the live virus plaque assay ($R^2=0.7150/P< 0.0001$). Whilst we have seen differences between individual sera for their neutralizing activity against different viruses we observed an association between the 2015-west-african and the 1995-vaccine strain ($R^2=0.2215/P< 0.0001$).

Conclusion

We have developed a robust EBOV neutralisation assay that has shown to correlate with total EBOV GP Ab binding. This assay is sensitive and robust and can be used in future characterisation of EBOV Ab responses in both survivors as well as vaccine recipients.

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2

Plasma proteomic profiling of patients with haemorrhagic fever with renal syndrome from Puumala and Dobrava hanatavirus infections

Dr Stuart Armstrong

Postdoctoral Researcher

Pathogen Discovery & Characterisation theme

Poster presentation

Hantaviruses are negative strain-sense single stranded RNA viruses that belong to the family *Bunyaviridae*. Some strains of hantavirus can infect humans causing either haemorrhagic fever with renal syndrome (HFRS) or hantavirus cardiopulmonary syndrome (HCPS). Rodents are the primary host reservoir and transmission to humans occurs via inhalation or contact with virus contaminated dried urine or faeces. HFRS is endemic in parts of Europe and hanatavirus Puumala (PUUV) and Dobrava (DOBV) are associated with the disease in humans. PUUV infection is more frequent and results in a milder form of HFRS with a case fatality of <1%. HFRS from DOBV is more severe and has a mortality rate that can reach 10%. The pathogenesis behind the variance in severity of infection between individuals infected with different hantavirus genotypes is poorly understood. In an effort to gain insight into HRFS dynamics plasma samples from a total 12 individuals with either mild or severe DOBV or PUUM from 4 consecutive time points were compared with healthy controls (n=5) using a quantitative high throughput label free proteomics approach.

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3

UK dairy antibiotic policies: unravelling the practices behind the policies

Stephanie Begemann

Alumni Student

Epidemiological Approaches theme

Oral and Poster presentation

This PhD has used a qualitative study design to explore how the UK dairy industry develops and implements antibiotic policy, and how this impacts on dairy antibiotic use as public health risk. A multi-sited ethnographic has been used which involved a policy document analysis, in-depth interviews with key dairy stakeholders, participant observation of veterinarians in practice and the observation of policy transfer during farmer meetings from retailers to farmers. Adopting a Science and Technology theoretical framework, fieldwork results indicate that antibiotic policies in the UK dairy industry only partially address the complex network of people, animals and the environment in which antibiotics circulate. Although UK milk processors and UK retailers have taken up the lead to produce dairy antibiotic policies, the policies are fragmented and seem to rather benefit market purposes than address structural issues in UK dairy production systems. At the same time, the policies fail to assess the complex interplay of antibiotic exchange between veterinarians and farmers. Hence, if we want to reduce the human health risks of agricultural antibiotic use, we need to evaluate agricultural antibiotic practices beyond the achievement of antibiotic reduction targets.

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4

Using evidence-based resources to deliver health protection messages in schools

Dr Emma Bennett

Senior Epidemiologist

Public Health England

Invited HPRU Member

Oral talk

'Hands-on' resources to enrich and consolidate scientific learning in schools can often be hard to obtain. Following successful pilot outreach workshops in local primary schools and pump-prime funding from NIHR Health Protection Research Unit in Emerging and Zoonotic Infections we developed loanable rucksack resources to support teaching and learning and the delivery of public health messages to children in a fun and appealing way.

Through collaboration with local primary school science clusters and the Primary Science Teaching Trust, workshop activities were reviewed and developed into lesson plans and appropriate hands-on resources identified. Resources and lessons were piloted, observed and evaluated in schools by teachers, Public Health England (PHE) and local council colleagues. Feedback then refined the activities to ensure they were fit-for-purpose. Colleagues at Imperial College London advised on delivery of content and evaluation methods and the accuracy and scientific content of the resources was reviewed by subject matter experts.

Two rucksack resource packs have been created: "*Operation Outbreak*" (Key Stage 2) and *Tricky Ticks*" (Key Stages 1 and 2); each containing: curriculum-based lesson plans; slide packs; child-friendly summaries; non-consumable supporting equipment and digital resources. Public health messages and information form the core of these resources; hand hygiene and disease prevention are very relevant topics in the school environment and tick awareness is a particularly important intervention in areas of high-risk of Lyme disease.

The lending of rucksacks to schools and STEM ambassadors is currently managed through local school science cluster networks and STEM ambassador loaning schemes. Digital versions of the non-physical resources are available on the tes website to extend their reach and allow them to be used independently of the physical resources. Because the lessons and activities are delivered by teachers and STEM ambassadors, their potential reach and impact of these health protection messages is wide.

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5

A phase I trial of safe recombinant poxvirus-based Zika vaccine candidates

Dr Thomas Blanchard

Consultant

Royal Liverpool University Hospital Trust

Invited HPRU Member

Oral and Poster presentation

Background

This is a collaborative initiative to design, build and bring a novel Zika vaccine to phase I clinical trial. Zika has been conclusively demonstrated to cause significant defects in foetal brain development if contracted in pregnancy, causing microcephaly and other congenital abnormalities. Very occasionally Zika can also cause peripheral or central nervous system disease in children and adults, especially Guillain-Barré syndrome. Although the Zika epidemic has currently subsided, it is endemic in much of the tropics with potential to spread to areas of the USA and southern Europe within range of Aedes mosquitoes.

Methods

The vaccine is designed to elicit both antibody and T cell responses, and incorporates both structural and non-structural Zika antigens. We have modelled the desired vaccine response on that seen to the Yellow Fever 17D vaccine (the most successful flavivirus vaccine to date) whilst employing safe host-range restricted poxviruses (modified vaccinia Ankara: MVA and fowlpox virus 9: FP9) and naked DNA as vectors in order to ensure that the vaccine candidates are safe in pregnancy. GCP T cell assays are being developed in Liverpool to study the properties of the vaccine candidates in humans, with a particular emphasis on measuring CD8+ cytotoxic T cell responses.

Results

The original vaccine concept was developed in Manchester, and has been adapted to MVA and FP9 recombinants suitable for human immunisation and proof-of-concept studies in Porton Down. The original construct contained an encephalomyocarditis virus internal ribosomal entry site, but this did not generate stable poxvirus recombinants, so now contains two poxviral promoters. FP9 work is proving more challenging than MVA, so DNA vectors are being developed as a backup.

Conclusions

A planned phase I clinical trial of prime-boost dose-escalating combinations is scheduled for autumn 2019 in the Royal Liverpool Clinical Trials Unit.

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6

Longitudinal transcriptomic and viral sequencing analysis of a severe clinical case of Ebola Virus Disease

Andrew Bosworth

Alumni Student

Pathogen Discovery & Characterisation theme

Oral and Poster presentation

At the height of the West African Ebola Virus Disease outbreak, a severe case of Ebola Virus Disease arrived in the United Kingdom. The patient suffered severe disease and carried a viral load thought to be invariably lethal in West Africa, where the sustained high intensity life support the patient received would not have been available. Next generation sequencing of viral populations throughout the patients illness showed little variability, even under the selective pressure of immunotherapeutics, and no evidence of adaptation. Transcriptomic analysis, combined with clinical data of the patient's illness highlights a highly inflammatory response, and the close correlation of antiviral gene activation with viral load.

Furthermore, transcriptional changes were reflected in the clinical manifestations of disease, which culminated in a hypercoagulopathic state. Presented in this work is evidence that Ebola Virus Disease is underpinned by severe acute inflammatory response.

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7

Quantitative Analysis of the Attraction and Feeding Behaviour of UK Mosquito Species

Aislinn Currie-Jordan

PhD Student

Vector Biology & Climate Modelling theme

Poster presentation

Mosquito-borne viruses pose a global threat with increasing numbers of cases being recorded in Europe. Several mosquito species in the United Kingdom could act as vectors for viruses such as West Nile (WNV) and Japanese encephalitis (JEV). However, despite the risk posed, our knowledge of the behaviour and feeding preferences of UK mosquito species is limited. Gaining such knowledge will improve our ability to quantify risk and provide a basis for rational development of appropriate vector control strategies.

This study is focused on analysing the ecology of mosquitoes on the Wirral, particularly *Aedes detritus* which breeds in salt marches around the coast of the UK and has previously been shown to be a potential vector of pathogenic viruses. The distribution and abundance of mosquitoes has been assessed over three years using a network of traps ('Mosquito Magnets') to monitor adult mosquitoes. Additionally, drone surveys have been performed to map the potential breeding sites of *Ae. detritus* on the marsh. These surveys have been supported by sampling of these breeding sites for mosquito larvae. Further studies have quantified the relationship between trap catches and the numbers of mosquitoes biting humans. The effects of environmental temperature on the development of JEV in *Ae. detritus* has also been determined under laboratory conditions. Three years of longitudinal data has provided a detailed understanding of annual mosquito activity on the Wirral. The results have highlighted two seasonal peaks in mosquito numbers. These peaks have been linked to tidal flooding of the mosquitoes breeding sites. Drone surveys have successfully mapped the changes in the mosquito breeding sites during the year. Results of the trap comparison studies show that a mosquito magnet, and novel Human Decoy Trap, provide reliable estimates of the numbers of key mosquito species biting humans.

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8

Economic impact of delays in treatment for Herpes Simplex Virus Encephalitis patients in the U.K

Kate Ennis

Health Economics Impact Fellow

Clinical Surveillance theme

Oral and Poster presentation

The HPRU EZI has been supporting work on the diagnosis and treatment of brain infections within the UK, including Herpes Simplex Virus (HSV) encephalitis. HSV encephalitis is a rare yet severe brain infection, and even when treated with antiviral drugs, there is still a risk of death and long term sequelae. It is frequently reported in the literature that delays in the initiation of treatment is associated with poorer clinical outcomes, which is likely to result in a large economic burden to the NHS. Despite this knowledge, no studies have looked at the impact of delays in terms of healthcare costs.

This study aimed to explore the association between time to treatment with aciclovir and its impact on healthcare costs for HSV encephalitis patients. Using data from a large NIHR multi-centre prospective cohort study (ENCEPH-UK) on patient's resource use during inpatient stay and 1 year post-discharge, we analysed differences in healthcare costs based on time to treatment. Patients were split into two groups based on if they received early treatment with aciclovir (<48 hours from admission) or delayed treatment (≥48 hours from admission).

Total mean inpatient costs were significantly lower for those receiving early aciclovir treatment compared to those with delayed treatment, £20,770.25 vs £38,205.36 respectively (p=0.012). These differences were also observed during 1 year follow up post discharge. Total costs up to 12 months post-discharge for those receiving early treatment were £31,022 versus £56,916 for those with delayed treatment (p=0.043). Improvements in the management of HSV encephalitis have been observed in the UK over recent years, assisted by the publication of national guidelines encouraging early treatment. Based on the findings of this study, improvements in diagnosis to reduce the number of patients experiencing delays will have resulted in large savings to the NHS and has potential for additional savings with further improvements.

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9

Immune-complex mimetics (ICMS): adjuvant free approach to vaccination and improved immune diagnostics for the control of flaviviruses

Dr Lynsey Goodwin

Clinical Research Fellow

University of Liverpool

Invited HPRU Member

Poster presentation

Many important flavivirus diseases have no vaccine available. Zika virus caused hundreds of thousands of infections in 2015/16, as well as many thousands of cases of congenital Zika syndrome (CZS). Many vaccines are under development, but these require co-administration with adjuvants that are difficult to manufacture, are often unstable, and can have undesirable side effects. The use of adjuvants also greatly adds to the overall cost of vaccine development in low income settings.

Multimeric Fc-fusion proteins mimic immune-complexes by delivering antigens directly to antigen presenting cells, therefore ensuring that antigen processing is efficient as possible. This may allow delivery of effective vaccines that do not rely on adjuvants. The multimeric structure of the constructs allows for cross-linking and triggering of critical Fc-receptors that is not possible with monomeric Fc-antigen fusions or protein-in- adjuvant approaches.

We have developed and produced Fc-fusion proteins containing the envelope protein domain III (EDIII) epitope from Zika virus, as well as from other major flaviviruses. The EDIII was cloned into a highly engineered Fc-fusion expression plasmid and protein successfully expressed in CHO cells, demonstrating manufacturing viability. It was shown that the EDIII-Fc proteins were recognized by flavivirus-specific monoclonal antibodies and convalescent immune sera from human patients recovering from Zika and Dengue as well as being capable of binding to human immune receptors, corroborating their vaccine potential. Finally, the EDIII-Fc proteins were able to drive dendritic cell maturation in vitro, suggesting that they are capable of interacting with antigen presenting cells and further supporting their potential as vaccine candidates. Next we propose further investigation into the immunogenicity of the EDIII-Fc fusion proteins. The outcome of this work is to develop novel vaccines, not only against Zika, but also other flaviviruses.

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10

Mapping the evidence of presence of LIV and TBEV in the UK using deer as sentinels

Maya Holding

PhD Student

Vector Biology & Climate Modelling theme

Oral and Poster presentation

Louping ill virus (LIV) is the only known tick-borne virus endemic to the UK that causes disease in humans, however current data reporting the prevalence and distribution of LIV is limited. Tick-borne encephalitis virus (TBEV) has a high degree of genetic homology to LIV. TBEV has not been detected in the UK, but is present in a number of European counties and is increasing in prevalence and range. It has recently been detected in the Netherlands, the discovery of which, was aided by testing deer blood for antibodies to the virus. Deer are useful sentinels for the detection of TBEV due to their frequent exposure to ticks, production of antibodies to the virus with no clinical disease, and evidence of correlation of TBEV seroprevalence in deer and human incidence. This work aims to contribute to mapping the evidence of LIV distribution in the UK and surveillance for TBEV presence using deer as sentinels.

Between February and November 2018, deer stalkers from across the UK are being asked to collect blood samples from deer they are routinely culling, and collect ticks when present. The location the deer was shot, the habitat and deer species, sex, age, and condition are being recorded. The sera will be tested for presence of antibodies to TBEV and LIV through a commercial ELISA and confirmed by SNT and IFA. If any positives are detected against either tick-borne virus, then ticks collected from deer in the same area will be tested by PCR for evidence of virus. Over 550 samples have been collected by deer stalkers to date, from across 35 counties in England and Scotland. This work will contribute to the knowledge of the presence and prevalence of tick-borne viruses that can cause disease in humans in the UK.

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11

Metagenomic MinION sequencing for viral clinical sample investigation

Liana Kafetzopoulou

PhD Student

Pathogen Discovery & Characterisation theme

Oral and Poster presentation

Emerging and re-emerging RNA viruses cause a significant global disease burden, ranging from mild febrile illness to haemorrhagic fevers. Rapid and unbiased identification methods, such as metagenomic MinION sequencing, are vital for the identification and characterisation of emerging pathogens for which little prior knowledge is available. Portable methodologies for field use are required during such outbreaks, especially when they occur in resource-limited settings. We have investigated a range of clinical samples using a Sequence Independent Single Primer Amplification approach and have demonstrated that metagenomic MinION sequencing can elucidate full viral genomes directly from clinical samples for Chikungunya, Dengue and Lassa virus; across clinically relevant range of viral titers. Following our results we mobilized a research team and deployed in Nigeria to test and investigate the establishment of field metagenomic sequencing using the MinION. Our pilot study was expedited and utilized to support the largest reported outbreak of Lassa fever (LASV) in Nigeria.

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12

Rapid Genomic Characterisation of UK imported Monkeypox virus by Next Generation Sequencing

Dr Kuiama Lewandowski

Researcher

Public Health England

Invited HPRU Member

Poster presentation

Monkeypox (MPX) is an emerging zoonotic disease caused by monkeypox virus (MPXV), a member of the *Orthopoxvirus* genus in the *Poxviridae* family. MPXV is one of the five Orthopoxvirus species pathogenic for humans, together with variola virus, the causative agent of smallpox, now eradicated in nature; cowpox virus, vaccinia virus and buffalopox virus. Although MPXV can infect a wide range of mammalian species, its natural reservoir host is unknown. MPXV has a large double stranded DNA genome of approximately 196kb.

In early September 2018, two unrelated cases of monkeypox were reported in the UK following the return of travellers from Nigeria. A third case of nosocomial transmission to a healthcare worker followed, presenting the first recorded case of human-to-human transmission of MPXV in the UK.

Direct sequencing of clinical lesion swabs using Illumina and Nanopore sequencing platforms permitted rapid and near-complete genomic characterisation of all three MPXV cases without the need of sample enrichment or amplification. In addition, MPXV from patient lesion swabs were successfully isolated using cell culture techniques.

Phylogenetic characterisation using maximum-likelihood inferences identified the two imported virus as members of the West African clade, with the 2017 Nigerian strains being their closest relative.

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Wellcome Trust Public Engagement Grants Scheme: BUG TERROR: OUTBREAK IN A BOX! A Post-Grant Case Study

Caoimhe McKerr

PhD Student

Epidemiological Approaches theme

Oral talk

Background/Aim

The overarching aim of this activity was to introduce school-age children (secondary) and adults to epidemiology and public health, and to demonstrate how real infectious disease outbreaks might be controlled. It was anticipated that this particular piece of public engagement work would function as a route to encourage school-age children to consider this area as a career and to increase general public awareness of infectious disease work and public health response.

Furthermore, in order to support ongoing learning and build capacity within the University, the materials were collated and designed in a way that makes sessions easily re-delivered, enabling the 'outbreak in a box' to be used as an ongoing resource.

Activity description

A hypothetical Legionnaires' disease outbreak was created and materials provided in support. (see box) Participants are asked to investigate the outbreak and suggest appropriate control measures (1 to 2 hours). The activity is suitable for around four or five groups of five people (20-25) with three facilitators assisting the teams, and one playing the 'index case'.

Key resources were created specifically for this activity box, as well as extra consumables, and editable electronic templates should content need updating at a later date.

Reception

Following the sessions, feedback has been collated. Overall, the sessions are enjoyable and the groups participate well and enthusiastically. There has been a lot of interest in booking these sessions from local schools.

Future of activity

There is further potential to include more outbreak scenarios, with a choice of diseases, and to allow the complexity to be altered by including varying levels of detail and difficulty. The team are currently working on some of these resources and may access additional funding in the future to support this.

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Exposures associated with infection with *Cryptosporidium* in industrialised countries: preliminary results and inclusions of a systematic review

Caoimhe McKerr

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Epidemiological Approaches theme

Poster presentation

Cryptosporidium is a protozoan parasite of humans and other animals world-wide and is one of the greatest contributors to human diarrhoeal illness. Risk exposures are often identified from outbreak investigations, but a subset of cases remain unexplained, and sources for sporadic disease and pathways to infection are still unclear.

Given the few systematic syntheses of reported evidence in industrialised populations, the aim of this review is to consolidate the literature and describe exposures associated with human cryptosporidiosis in industrialised countries, specifically including the UK, and describe any differences between outbreak-associated and sporadic disease.

Methods/Design

Where relevant, methods followed recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. Literature were identified via; electronic database searching using PubMed, Scopus, EMBASE and Web of Science, reference list trawling, and an exploration of the grey literature. Studies conducted in industrialised countries and reporting on human subjects were included. All observational studies were included where they report exposures and relevant, quantitative results. A flowchart was produced to communicate inclusions and fit of papers. Included data were summarized, presenting the papers' main findings. Study quality was assessed using the ROBINS-I tool. Where populations are appropriate, available data will be pooled in a meta-analysis combining the significant exposures across studies.

Discussion

This review aims to consolidate the evidence for transmission routes and exposures for *Cryptosporidium* in industrialised countries, with particular reference to how these may apply to the UK. In addition, the review will seek to describe differences between outbreak and sporadic cases. This will help to identify those most vulnerable, highlighting pathways where interventions and public health response may be appropriate. This report outlines the preliminary results from stage one of the review.

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15

Investigation of an outbreak of *Cryptosporidium parvum* in pupils and teachers after a school trip to a commercial farm, South East England, April 2018

Dr Rachel Mearkle

Consultant in Communicable Disease Control

Public Health England South East

Invited HPRU Member

Oral and Poster presentation

Introduction

Public Health England were notified of gastrointestinal illness in 14/22 pupils and staff from a junior-school class following a class-trip to a commercial farm in April 2018. We aimed to describe the outbreak, and identify exposure to possible sources of infection to prevent further exposures.

Methods

A descriptive epidemiological study was conducted among pupils/staff using an online questionnaire, alongside environmental inspection of the farm and microbiological analysis of human faecal specimens.

Results

Microbiological investigation confirmed infection with *Cryptosporidium* in 6/7 faecal specimens analysed, and *C. parvum* in 5 samples forwarded to reference microbiology services, a species associated with animal contact. Genotyping in all 5 samples identified gp60 IIaA16G2R1, a rare subtype, thus strengthening the link between the cases. Survey responses were obtained on 13/22 pupils/staff, 10 of whom met the case definition (77%). Illness duration (≥3 days in 86% of cases) and symptoms (primarily non-bloody diarrhoea) were consistent with *Cryptosporidium* infection. The median time from farm visit to illness was 6 days (range 5-8 days). Survey-respondents reported holding/cuddling new-born lambs. This contact was in the lamb's pens, increasing opportunity for faecal contact. Environmental investigation identified non-compliance with Industry Code of Practice (ICoP) standards to prevent zoonotic infection.

Conclusions

The epidemiological evidence was consistent with an outbreak of illness due to *C. parvum,* following a point-source exposure. There was microbiological, epidemiological and environmental evidence that *C. parvum* transmission occurred on the farm visit. Control measures were put in place to prevent similar transmission events: the Health and Safety Executive served a prohibition notice on the farm and gave advice to the school about visit risk assessment. Working farms which open to visitors do not always have ICoP standards in place, putting visitors at risk. Agencies should work together to improve school and farm awareness of farm infectious hazards and ICoP standards to mitigate risk.

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16

Understanding the possible origin of the next pandemic using airline travel patterns and health care development

Margaux Meslé

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Epidemiological Approaches theme

Oral and Poster presentation

Pandemics may spread rapidly around the world and can have significant costs associated to them, both economic and fatalities. Early outbreak detection is key to its control and further spread, nationally and internationally. Given the significant level of global connectivity, an uncontrolled outbreak in one country may quickly reach any other country and develop into a pandemic. The aim was to determine from which countries an outbreak could develop into a pandemic.

The data regarding each country's healthcare development was equally compared against its global airline connectivity. Two indexes were used to assess health care development. An information flow matrix was generated to estimate global connectivity from the OAG airline dataset. A fictitious 'worst case scenario' (WCS) country was assigned the best connectivity value of the network and the worst healthcare development score. The Euclidian distance of each country to WCS was calculated and plotted according to each index.

The results suggest that India and Pakistan were the two closest countries to WCS for both indexes, thereby causing the greatest potential risk to the global community. Additionally, countries that have recently seen the spread of outbreaks develop into pandemics (Brazil and Mexico) were also seen as potential threats, whereas countries such as Monaco and Tuvalu posed the smallest risk.

This analysis highlights the importance of considering a country's connectivity and healthcare development when considering its potential impact in the next pandemic. In a world increasingly connected, an outbreak in one country should concern the global community. In order to reduce the global financial burden and the number of fatalities, healthcare development and global connectivity should be considered together. This analysis highlights the importance of detecting outbreaks early through strong healthcare systems, and international support could be aimed towards those countries with the potential to cause the highest global risk.

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17

Using the diurnal temperature cycle to assess current and future climatic suitability for Aedes albopictus in the UK

Soeren Metelmann

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Vector Biology & Climate Modelling theme

Oral and Poster presentation

The Asian tiger mosquito Aedes albopictus is extending its northern range in Europe. In 2016 and 2017, eggs and larvae have been found in Kent in southern UK for the first time. As this mosquito is an important vector species, able to transmit various pathogens of animals and humans there is a major interest in whether this originally sub-tropical mosquito could become established in the temperate climate of the UK. Previous studies of have analysed the mosquitoes' climatic suitability, using seasonal or daily rainfall and temperature data to drive impact models. However, none of these studies considered the impact of the diurnal temperature cycle. This cycle represents the full temperature range experienced by the mosquito in field conditions. Here, we describe a dynamical model for the life cycle of Ae. albopictus that explicitly models the mosquito's dependencies on the diurnal temperature range, precipitation, and human population density. We derive a new metric for habitat suitability and drive our model with climate data sets with different spatial resolutions. Contrary to other published studies, we find only a low suitability in the UK, except for some warmer, densely populated regions such as Greater London and the south coast of England. Mosquito surveillance and control is recommended in these southern areas, especially as the suitability in the UK is expected to increase in the future due to climate change.

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MERS and Monkeypox in England: Activation of the WHO ISARIC Clinical Characterisation Protocol

Prof MG Semple

Professor of Child Health and Outbreak Medicine

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Invited HPRU Member

Oral and Poster presentation

Background

The WHO ISARIC **Clinical Characterisation Protocol for Severe Emerging Infection (UK CRN ID12827, CPMS 14152)** permits recruitment of cases infected with pathogens of Public Health Interest presenting to acute care. This Urgent Public Health Research Portfolio Study will be given priority support in the event of emergence of a pathogen of public health interest. NHS research permissions have been granted in advance at 70 sites in England including 15 sites that host regional Intensive Care Units, Paediatric Intensive Care Units and High Level Isolation Units. The study is normally suspended in a state of maintained hibernation. It is intended to have annual test activations at 15 sites.

Method

The protocol facilitates prospective and systematic collection of data and biological samples in a format that can be rapidly aggregated, tabulated and analysed across many different settings globally with consent for research. The protocol is tiered to levels of data collection and biological sampling to optimise recruitment in outbreak settings where capacity and capability to handle high consequence pathogens will vary greatly and to allow participants to have autonomy in level of participation.

Results

On 22 August 2018, the CI was notified by PHE of a case of MERS-CoV admitted to St James's University Leeds and would be transferred to The Royal Liverpool Hospital HLIU. Verbal consent was given on 27th August, however the health status of the patient and challenges around communication delayed written confirmation of consent to 6th September. Consent was given to use clinical data and diagnostic residual material for research.

On 9th September PHE gave notice of a case of Monkeypox being admitted to The Royal Free Hospital HLIU. Written consent was given on 10th September allowing additional skin, blood, respiratory, urine and stool samples to be collected from research purposes.

On 11th September PHE gave notice a second case of Monkeypox admitted to Blackpool Victoria Hospital that was being transferred to the Royal Liverpool HLIU. Written consent was given same day for biological sampling as above and in addition sampling for a PK/PD study.

On 26th September PHE gave notice of a third case of Monkeypox that was admitted to Royal Victoria Hospital Newcastle on 25th September. Written consent was given on 27th September for biological sampling including a PK/PD study.

Conclusion

The WHO ISARIC Clinical Characterisation Protocol for Severe Emerging Infection has proven effective in facilitating rapid recruitment of pathogens of public health interest.

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HPRU EZI role in provision of the first International Standard Antibody to Ebola Virus (NIBSC 15/262)

Prof Richard S Tedder

Consultant Virologist

Public Health England

Invited HPRU Member

Oral and Poster presentation

Background
WHO International Standards (IS) for biological substances are recognized as the highest order of reference materials for biological substances and are assigned potencies in International Units (IU).

The outbreak of Ebola Virus Disease in West Africa 2013/2016 involved 28616 cases and 11310 deaths. (1)

WHO prioritised Ebola Convalescent Plasma (CP) for evaluation by clinical trials (2). Trials were conducted in Guinea(3), Sierra Leone and Liberia.

There were no standardised assays/reagents for Ebola antibody in January 2015.

Method
The study in Sierra Leone started in April 2015 and benefitted from access to a three novel ELISA assays developed by Samuel, Dicks and Tedder at the NHS B&TS PHE BBVU(4). These assays, validated under field conditions(5) allowed measurement of Ebola antibody at the point of donor selection and recruitment of a panel of CP donors with higher levels of Ebola antibody. The outbreak in Sierra Leone was contained before the trial could complete.

Six CP donations (400ml to 600ml) from Sierra Leone unsuitable for trial use were exported to PHE Colindale and confirmed not to contain EBOV RNA. At NIBSC the plasma was Solvent Detergent treated, pooled and 1203 freeze dried ampoules of 0.5 mL plasma prepared.

Ampoules of pooled CP from Sierra Leone were included in a panel of 6 candidate reference samples. 17 laboratories in the WHO Collaborative Group from 4 countries used various live Ebola virus neutralization, pseudovirus neutralisation, and enzyme immune assays (ELISA) to test the panel. Surface plasmon resonance (SPR) and Western blot assessments were also undertaken. Each laboratory performed 3 independent assays on different days(6).

The long-term stability was predicted using the Arrhenius model, using temperatures up to +56°C.

Results
Pooled CP from Sierra Leone (NIBSC 15/262) consistently had the highest titre in the various Ebola virus neutralization and pseudovirus neutralisation assays; and highest signal in ELISA and SPR assays.

It demonstrated stability at +20ºC for up to 1 year, and suitability for ambient transportation at up to +37ºC (with loss 0.5% after 1 week).

Conclusion
There was consensus in the WHO Collaborative study on the suitability of the Sierra Leone pooled CP samples to serve as the WHO 1st International Standard (NIBSC code 15/262) and assigned 1.5 IU/ml.

NHSBT/PHE BBVU working in an academic partnership with University of Liverpool facilitated production of this standard.

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Lyme disease in the UK: A proposal for future surveillance programmes

John Tulloch

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Epidemiological Approaches theme

Oral talk

In 2018 NICE published guidelines stating that 'There is a lack of robust epidemiological data on Lyme disease in the UK.' Currently incidence figures are derived from two-tier confirmatory laboratory diagnostic results, compiled by two reference laboratories. Their figures have the potential to underestimate incidence, as clinical cases managed without diagnostics are missed. To date, our work has assessed an array of UK datasets to describe the socio-demographic characteristics of Lyme disease patients, and disease incidence, in different health care settings. By comparing these data we can now propose potential future surveillance programmes.

Three datasets comprised of, laboratory confirmed cases, hospital records, and primary care electronic health records, were described and analysed for incidence and patient demographics between 1998 and 2016. Using the laboratory data as our baseline reference we investigated if there were stable multiplication factors between datasets. We explored concordance between the datasets in terms of seasonality and geography. We compared the similarity between population pyramids.

Multiplication factors remained stable for parts of the study period, however this was affected by the changing coding habits of primary care clinicians. There was significant geographic concordance in southern-central England, and the population pyramids were deemed similar. There was significant seasonal concordance. The primary care dataset appeared to offer the greatest future resource as a surveillance tool.

We therefore propose using the Read codes, identified in our primary care research, as part of the Real Time Syndromic Surveillance Team's future reporting based off a primary care sentinel network. This will allow the further assessment of the stability and reliability of using our proposed multiplication factors and may provide an additional surveillance resource to the current laboratory reporting of Lyme disease.

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Utilising social media as an adjunct to traditional zoonotic surveillance systems. A case study: Lyme disease and dogs in the UK and Ireland

John Tulloch

PhD Student

Epidemiological Approaches theme

Poster presentation

Background

Social media (e.g. twitter) has revolutionised communication, but it's potential for surveillance of veterinary diseases remains unexplored. Lyme disease is a zoonotic tick-borne disease, and it's incidence in humans is rising across Europe. However, little is known about the incidence and public perception of canine Lyme disease.

Objective

1) To compare human and canine twitter datasets to known epidemiological data.
2) Identify themes raised about canine Lyme disease.

Materials and Methods

Tweets from the UK and Ireland (July 2017 - June 2018) were searched for the word 'Lyme'. Dog and human subsets were generated. Trends in seasonality and geography were compared to published figures. Data was explored for word frequency, association, sentiment analysis, and impact.

Results

5,212 users tweeted 13,757 tweets containing 'Lyme', peaking in summer. Clustering of users occurred in the South-West of England and Highlands of Scotland**,** reflecting the known epidemiology of Lyme disease in humans.

165 users tweeted 205 tweets containing 'Lyme' and 'dog'. The data suggested some seasonality, but data was skewed by one tweet. No geographical conclusions could be drawn.

The most frequent words were 'worms', 'tape' and 'fleas', suggesting poor knowledge about disease transmission. The largest sentiment scored was 'anger'. The most impactful tweet warned people about ticks, originating from a pet charity.

Discussion and Conclusion

Twitter may be useful as an epidemiological tool to assist in Lyme disease surveillance. It can be analysed in real-time and identify potential disease hotspots; however there is a substantial risk of false positives. The canine-specific dataset was too small to provide useful epidemiological data. Such data can guide veterinary public health practitioners in the education of the public about the relative risk that Lyme poses to pets and its mode of transmission.

Perspectives

Social media can be utilised to understand the public's knowledge base and emotions about a disease; and therefore shape education and policy.

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Risks, burden and socio-biology of hepatitis E infection in England

Dr Aisling Vaughan

Research Fellow

Risk Assessment of Emerging and Zoonotic Threats theme

Oral and Poster presentation

Background

Since 2010, a substantial increase in autochthonous cases of hepatitis E virus (HEV) has been observed across Europe and has brought to light a previously unrecognised public health threat. In England, an increase in acute HEV cases has been associated with the emergence of a novel clade G3.2. Acute HEV infections in England have been shown to be associated with the consumption of processed pork products. The potential for transmission of HEV and the clinical consequences of HEV positive blood components has been recognised and screening of blood donations for HEV began in 2016. The likely burden of HEV in England has been estimated to be between 100,000 and 150,000 infections annually. While a high proportion of HEV infections are asymptomatic, severe or chronic infections have been observed in immunocompromised individuals, highlighting the need for a greater understanding of the epidemiology of this disease.

Methods

In a pilot study, donor cases identified through the screening programme were sent a link to a web-survey questionnaire. Information on a history of recent travel, food consumption, animal contact, environmental exposures, alcohol intake, medication and co-morbidities was gathered. Cases (n=100) and controls (n=300) are currently being recruited for a case-control study and recruitment is expected to be complete by October 2018.

Conclusions

In a pilot study, the epidemiology of autochthonous HEV infections in blood donors in England over an 18 month period was analysed. Donor cases were largely asymptomatic, and in those with symptoms infection was self-limiting. The majority of individuals reported consuming pork products in the nine weeks preceding blood donation. A case-control study is ongoing to further define the risk factors for acquisition of HEV infection.

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