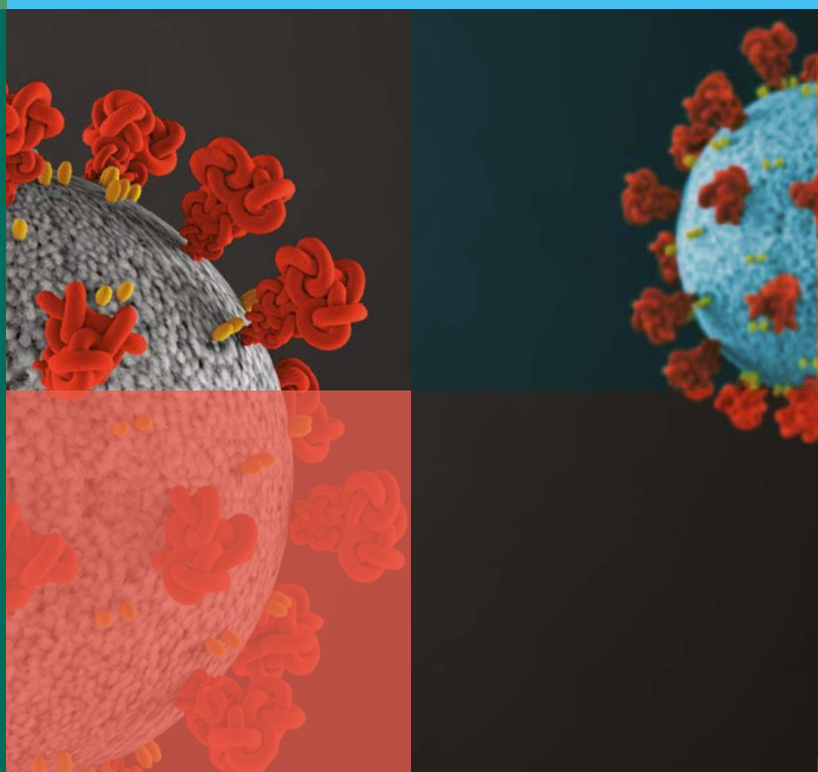
NIHR | National Institute for Health Research

EMERGING AND ZOONOTIC INFECTIONS

FIVE YEAR REVIEW



UNIVERSITY OF LIVERPOOL

WELCOME

to this 2020 review of the work of the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Emerging and Zoonotic Infections.

The Unit was established in 2014 with £5M of Department of Health funding as a collaboration between the University of Liverpool, Public Health England, and Liverpool School of Tropical Medicine. In 2020 the Unit received a further five years funding and welcomed the University of Oxford as a partner.

The HPRU supports and strengthens Public Health England in its role protecting us from emerging and zoonotic infections i.e. those which spread from animals to humans.

Since 2014 we have achieved this through:

- **World class research** on
  - emerging infections which threaten the UK, for example we played a major role in helping tackle the Ebola epidemic in West Africa (2014-16) (pXX), and the Zika outbreak in Latin America (2016-17) (pXX)
  - zoonotic infections which are already established here, such as Lyme disease (pXX) and Hepatitis E (pXX).
- **Training** the next generation of research students, plus Public Health England and university staff in the skills needed to tackle emerging infections (pXX)
- **Engaging** and involving the public to understand and assist us with what we do
- **Advising** the UK Department of Health and other national and international policy makers to mitigate the risk of current and future threats (pXX)

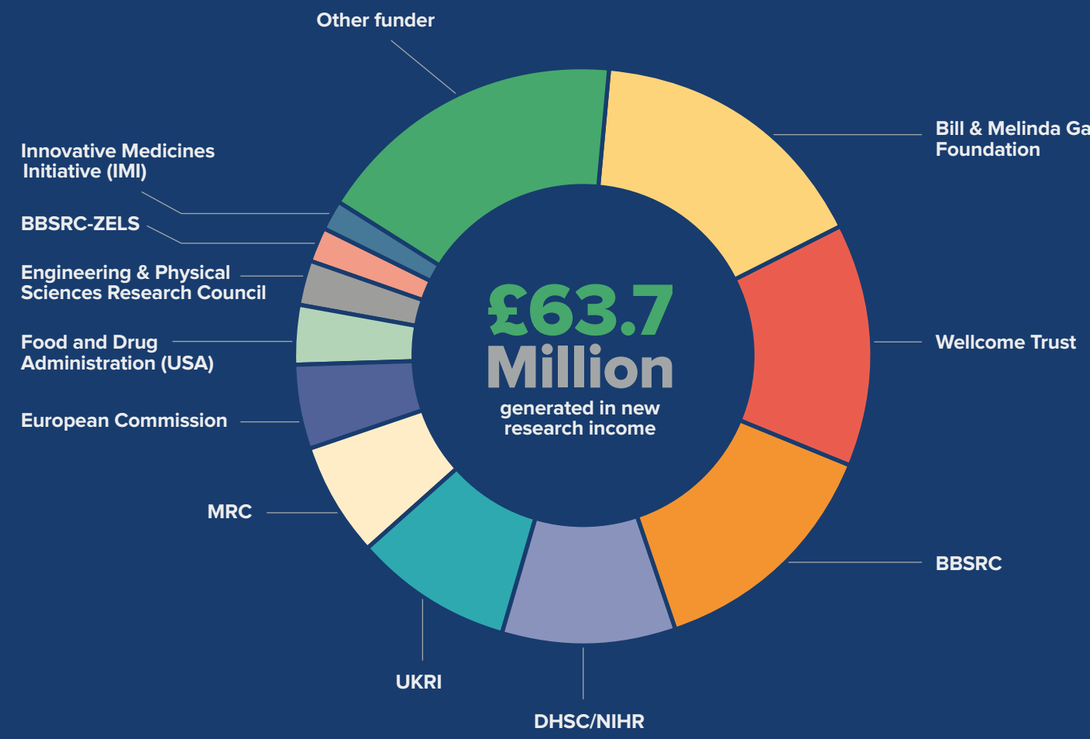
We hope you enjoy reading about our work, and look forward to receiving any feedback

Tom Solomon
Director, University of Liverpool

Miles Carol
Co-Director, Public Health England

The Health Protection Research Unit in numbers*

* figures are from XXmonth 2014 to December 2019



167
research publications

219
members
including 20 PhD students and 16 Post-Doctoral Research Associates

OUR STRUCTURE

From 2014 – 2020, our staff in Liverpool and at Public Health England's Colindale and Porton Down Sites were organised into five research themes supported by an External Advisory Panel and a Patient and Public Involvement Panel

From 2020-2025, we will build on the work of the partnership, with the addition of the University of Oxford.

We are focussing on 3 major programmes of work, delivered through four research themes and a cross cutting knowledge mobilisation and patient and public involvement and engagement theme, to maximise research impacts.

MAJOR PROGRAMMES	RESEARCH THEMES 1. Patient research for public health	2. Diagnostics and host response	3. Pathogens and vector biology	4. Epidemiology and risk analysis
High-consequence infectious diseases	1.1 Comprehensive characterisation of HCIDs	2.1 Determining molecular signatures in acute Ebola and Hantavirus disease	Putative later project/s: molecular characterisation of emergent HCID pathogens using metagenomic approaches	4.1 Modelling of MERS and other HCIDs 4.2 Nosocomial transmission of HCIDs
Emerging arthropod-borne diseases	1.2 Arthropod-borne and CNS infections study	2.2 Historic genomic analysis 2.3 Targeted assays for arboviruses 2.4 Diagnostics for flaviviruses 2.5 Flavivirus T-cell responses	3.1 Molecular tools for TBEV 3.2 West Nile Virus transmission risk 3.3 Wolbacia strategies for vector control	4.3 Vector-borne diseases in returning travellers
Endemic arthropod-borne diseases	1.3 Lyme disease study	Putative later project/s: Improving Lyme diagnostics	3.4 Monitoring tick-borne viruses	4.4 Seroprevalence of Lyme

OVERARCHING THEME: KNOWLEDGE MOBILISATION, PATIENT & PUBLIC INVOLVEMENT

A COLLABORATIVE HEALTH PROTECTION RESEARCH UNIT

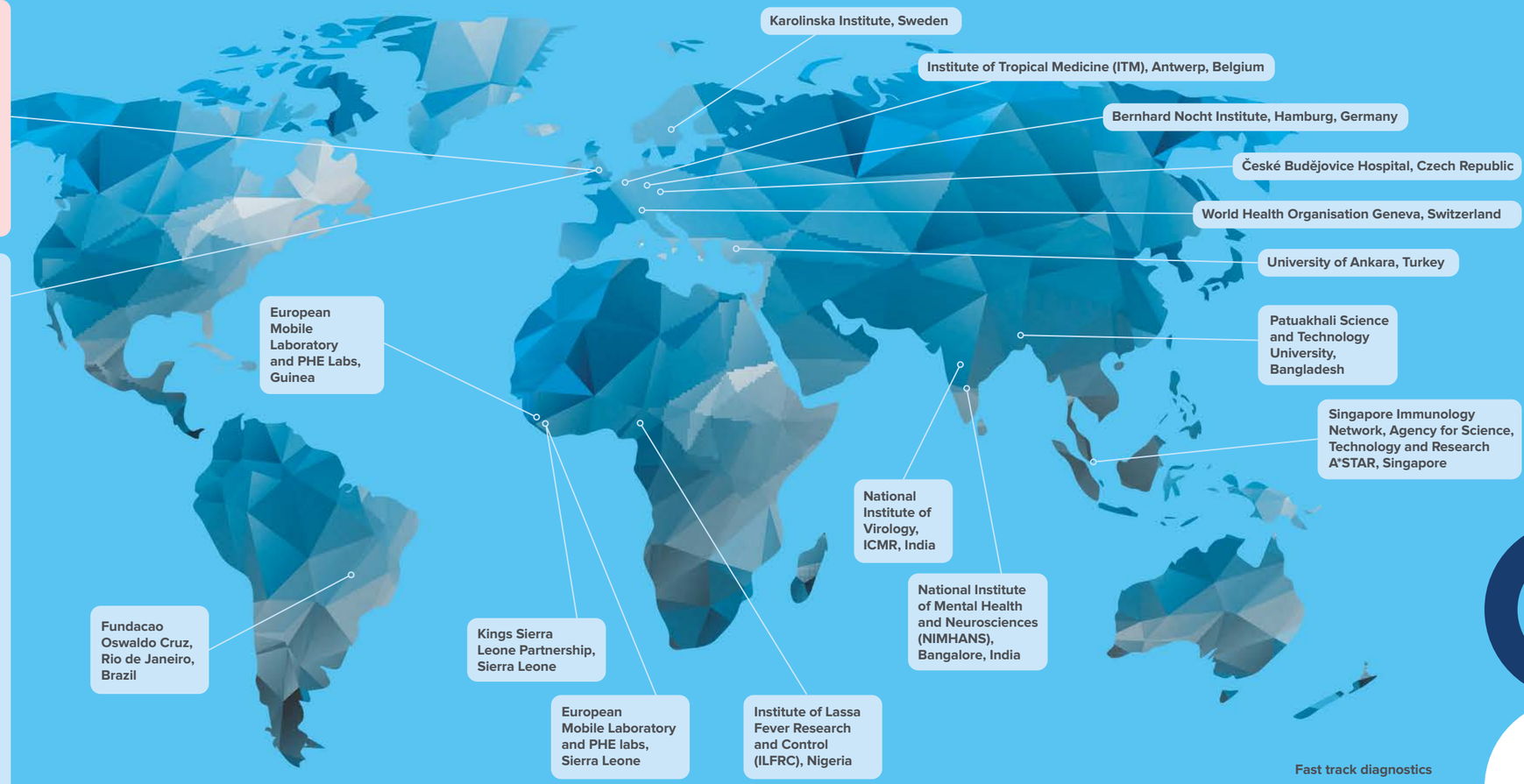
HPRU EZI PARTNERSHIP

- University of Liverpool
- Public Health England (Colindale and Porton Down)
- Liverpool School of Tropical Medicine
- University of Oxford*

* This was a collaborating institute until the additional 5 years funding was received in 2020 when they became a partner

UK

- HPRU in Healthcare Associated Infection and Antimicrobial Resistance, Nuffield Department of Medicine, University of Oxford
- HPRU in Respiratory Infections, Imperial College London
- HPRU in Evaluation Interventions, University of Bristol
- HPRU in Gastrointestinal Infections, University of Liverpool
- HPRU in Environmental Change and Health, London School of Hygiene and Tropical Medicine, London
- HPRU Emergency Preparedness and Response, Kings College, London
- Liverpool and Broadgreen University Hospitals NHS trust
- UK Public Health Rapid Support Team, London School of Hygiene and Tropical Medicine, London
- University of Warwick
- Pirbright Institute, Woking
- University of Nottingham
- Moredun Institute, Midlothian
- National Institute for Biological Standards and Control, South Mimms, Hertfordshire
- University of Salford
- University of Cambridge
- Animal and Plant Health agency, Addelstone, Surrey
- Lancaster University
- University of Southampton
- MRC-University of Glasgow Centre for Virus Research, Glasgow
- University of Keele
- University of Sussex
- Great Ormand Street hospital, London
- Met Office
- MRCVS Biobridge LTD, Cambridge
- University of Birmingham
- University of Exeter
- Royal Veterinary College



COVID-19

Since the turn of 2020, our HPRU has been working with colleagues nationally and internationally on the COVID-19 pandemic. We were very quick to realise the potential significance of the emerging virus outbreak in Wuhan, activating our rapid response team in mid-January 2020. This allowed us to direct resources to prepare the UK to respond to the virus.

Gathering data to understand the disease

One of the first actions was setting up the Coronavirus Clinical Characterisation Consortium (4C) study as part of ISARIC (international Severe Acute Respiratory and Emerging Infection Consortium), a nationwide observational study that is intended to activate in the event of the appearance or outbreak of a disease of public health importance. The 4C study was set up in every acute trust in the UK, so that when the first patients arrived at the beginning of February, we could recruit them into our study and begin characterising patients' clinical features to understand risk factors for different demographic groups. The study has, to date recruited more than 40,000 hospitalised COVID-19 patients, making it the largest study in the world; it has published data on the first 20,000, and reports weekly (through the Coronavirus Clinical Information Network, CO-CIN,) to the Department of Health and Social Care (DHSC) providing critical updates on the situation in hospitals. We are also providing vital samples for diagnostic evaluation, for better understanding of the genetic risk factors, immune response and disease mechanisms, working with various teams in Liverpool, Edinburgh, London, Oxford and around the country. HPRU members are also conducting critical studies to understand the virus' evolution and spread, and to evaluate vaccines and new treatments.

The study has, to date recruited more than 40,000 hospitalised COVID-19 patients.

Liverpool collaboration to mount a local response

More locally the HPRU teamed up with Liverpool's Centre for Excellence in Infectious Diseases Research (CEIDR), local NHS Trusts and the City Council to coordinate the regional response, including provision of diagnostics, and personal protective equipment. This programme is supported by approximately £1 million in pump priming from the University of Liverpool, the HPRU, CEIDR innovations and Alder Hey Children's Hospital Charity to support 22 research projects designed to have immediate benefits for public health, delivered by more than 200 researchers, underpinned by equipment and laboratory space across the Liverpool City Region.

One project to receive funding is the 'Liverpool Household COVID-19 Cohort Study', which plans to track and collect COVID-19 data from households across Liverpool over the coming months to provide reliable evidence of the extent of the COVID-19 pandemic in the community, how transmission is taking place, and better understand the clinical characteristics of the disease. This information is essential to better understand the necessary steps needed to move out of the current lockdown period and develop future control strategies.

Other new projects will explore areas such as disease in children and in pregnancy, new therapeutic agents, use of novel diagnostics, social media and the spread of COVID-19 misinformation and the impact of COVID-19 on mental health.

Every day there are new scientists joining the Liverpool team

The HPRU Director, Professor Tom Solomon said of the collaborative response: "This new initiative is bringing all life sciences researchers in Liverpool together in an unprecedented way. Every day there are new scientists joining the Liverpool team who are working together night and day to tackle this virus. During the Ebola outbreak we had a very good response from research community in Liverpool, but the response to the COVID-19 pandemic has been extraordinary."

Understanding the dynamics of policy development and healthcare professionals behaviour in the UK during the COVID-19 response

Following pump-priming from the HPRU, **Professor Sally Sheard** (Lead of the HPRU Knowledge Mobilisation theme) together with **Dr Nina Gobat** (University of Oxford) were awarded UKRI funding to examine the impact of policy decisions within the UK response on healthcare professionals on the frontline.

They are studying changes in UK policy, gaining unique insights through collaboration with key policy players including members of the Strategic Advisory Group for Emergencies (SAGE) that advises the Government, and Public Health England leaders and linking these to the behaviours and perspectives of healthcare professionals, feeding back findings to policy advisors to further inform decision-making. In an infectious disease outbreak public health policymakers are under tremendous pressure, especially from the media. They must respond rapidly to and take decisions which impact enormously on healthcare provision. Professor Sheard said of the project, "Our approach is novel because policy decisions are usually only studied after an event, making the findings less reliable."

Public engagement

Since the news of the outbreak in China, members of the Unit have been active across media outlets, informing the public about the disease and the response, as well as explaining the science of our own work. The work of the Unit has been featured in BBC News features, highlighting the key role of our work in the UKs dynamic response. Many members of the Unit have appeared on news programmes and other television shows, including Professor Tom Solomon appearing alongside Matt Hancock on Question Time, and published pieces in newspapers and important publications.

POLICY IMPACT

HPRU members have been advising locally, nationally and internationally on the COVID-19 response, with members being part of key WHO and UK committees, for example the Scientific Advisory Group of Experts (SAGE), the New and Emerging Respiratory Virus Threats (NERVTAG) and the Advisory Committee on Dangerous Pathogens (ACDP).

Members have submitted evidence to ongoing inquiries led by Parliament Select Committees who are reviewing various aspects of the response including management of the response, scientific and research capabilities for the response, and the delivery of other core health services during the pandemic and beyond.

In addition, many members have responded to Parliamentary surveys on the priorities of the response.

TACKLING EBOLA IN WEST AFRICA

Soon after the HPRU was launched in 2014 we began to receive reports of an unprecedented Ebola virus outbreak in West Africa. We quickly mobilised our Rapid Response Team, and diverted much of our research programme to help tackle this global public health emergency, making a major contribution to the international effort to bring the disease under control.

Control in West Africa

Our Rapid Response Team consisted of clinical and laboratory staff trained to work with dangerous Hazard Group IV Pathogens. We provided multiple personnel during and after the outbreak to the Public Health England Field Laboratories in Sierra Leone, led by **Dr Tim Brooks**, the European Mobile Laboratory in Guinea, and the clinical teams. These units provided the critical and rapid diagnosis of Ebola in patients for immediate triage and treatment.

As the epidemic grew it became apparent that although many UK Healthcare Workers said they were considering joining the control efforts in West Africa, fewer actually signed up to go. We examined healthcare workers attitudes to fighting Ebola and found that lack of information, rather than fear of infection, was the main factor holding people back.[1,2] This was reported directly to the Chief Scientific Officer, and streamlined web information made available. The overall response of UK healthcare workers was fantastic with more than 3000 personnel deployed.

These units provided the critical and rapid diagnosis of Ebola in patients for immediate triage and treatment.

[1] Solomon T, et al. BMJ 2014; 349: g6443.

[2] Turtle et al 2015 Plos one doi:10.1371/journal.pone.0120013

Protecting the UK

The transmission of Ebola to Nigeria by an unwitting airline passenger in July 2014 raised the question of where else the disease might spread. By studying airline passenger data we determined that the USA was the country outside Africa most likely to import a case, and that the UK would likely import a case before the end of 2014. The research, presented to the UK Department of Health and USA Government, helped with the development of international travel policy, although sadly both our predictions of imports proved correct. We also examined the impact of airport screening for passengers from West Africa on arrival to the UK in protecting the country.[3] We highlighted the need for all hospitals to prepare to receive patients with a haemorrhagic fever updating clinicians on the clinical features of severe Ebola,[4] and contributed to weekly teleconferences with the Department of Health Emergency Preparedness and Response to harmonise national protocols, all of which proved helpful when the first UK patients arrived.

By studying airline passenger data we determined that the USA was the country outside Africa, most likely to import a case.

[3] Read JM, et al. Lancet 2015; 385: 23-4.

[4] Fletcher TE, et al. BMJ 2014; 349: g5079.

Developing Treatments and Vaccines

There are no proven treatments for Ebola. Convalescent plasma from Ebola survivors which contains antibody to the virus, was postulated as a potential therapy, but a trial we collaborated on in Guinea, undertaken through a £2M programme with the Institute of Tropical Medicine, Antwerp and other partners funded by the Wellcome Trust and European Commission), showed no benefit.[5] Our work on the immune response to infection, supported by more than US$3M from the US Food and Drug Administration and the WHO to better understand the disease mechanisms and develop vaccines, showed a particular pattern of cellular and inflammatory cytokine response was associated with a fatal outcome.[6]

With US£1M from the UK Defence Advanced Research Project Agency we have been developing novel therapeutics to the virus. We also worked on preliminary human trials of the antiviral drugs brincidifovir and favipiravir.[7,8] These trials led the way to more definitive randomised studies, including a trial which is underway in the 2018-19 Democratic Republic of the Congo Ebola outbreak.

Before the West African Ebola outbreak there were no effective vaccines against the disease.

Before the West African Ebola outbreak there were no effective vaccines against the disease. HPRU members worked on a number of vaccine trials, including a large open-label, cluster-randomised ring vaccination trial with the Merck, vesiculo stomatisi virus (rVSV) vectored vaccine.[13] This showed the vaccine was 100% effective, and led to WHO recommendations for its use. The vaccine is currently being used in the 2018-19 Ebola outbreak in the Democratic Republic of the Congo.

[5] van Griensven J, et al. N Engl J Med 2016; 375: 2307-9.

[6] Ruibal P, et al. Nature 2016; 533: 100-4.

[7] Dunning J, et al. PLoS Med 2016; 13: e1001997.

[8] Henao-Restrepo AM, et al. Lancet 2017; 389: 505-18.

Tracking the Evolution of Ebola Virus in West Africa

Early in the epidemic one of the major concerns was around how quickly the virus was mutating and evolving. Might changes in the virus' genetic make-up explain the ferocious nature of this outbreak, and hamper molecular diagnosis and the development of treatments and vaccines? Our research, led by **Professor Miles Carroll** in collaboration with many European and African partners as part of a €1.8M programme, tracked the virus' evolution and showed reassuringly that this was not the case. "The study showed that the outbreak came from a single point of origin and that the evolutionary changes are unlikely to make diagnostics, treatments and vaccines ineffective," commented **Professor Julian Hiscox** the Deputy Director of Health Protection Research Unit and a co-author on the paper.

we tested a completely new approach to field based molecular epidemiology studies using "Minion" sequencing.

Initially, such detailed genetic studies of the virus' evolution could only be carried out in sophisticated laboratories. However during the outbreak we tested a completely new approach to field based molecular epidemiology studies using "Minion" sequencing. This revolutionary device, the size of a large USB stick, allowed rapid contact tracing of sporadic Ebola cases in Guinea and the surrounding areas, which was essential to getting the outbreak under control.[9]

In partnership with other international academic institutions, we subsequently examined the dispersal, proliferation and decline of Ebola virus throughout Sierra Leonne, Liberia and Guinea and showed that the outbreak did not spread further into neighbouring countries because although they were susceptible, there was a lower risk of virus introductions.[10] We also showed the potential importance of virus persistence in seminal fluid in maintaining the outbreak.[11]

[9] Quick J, et al. Nature 2016; 530: 228-32.

[10] Dudas G, et al. Nature 2017; 544: 309-15.

[11] Sissoko D, et al. Lancet Glob Health 2017; 5: e80-e8.

Improving Diagnostics

Diagnosis of Ebola requires taking a venous blood samples and transporting it to a biocontainment laboratory for testing by real-time PCR, causing delays that complicate patient care and infection control efforts. During the outbreak we worked with colleagues to field-test a new point-of-care rapid diagnostic antigen test; the Corgenix ReEBOV Antigen Rapid Test kit was highly sensitive and specific and was subsequently recommended by WHO for use in specific circumstance.[12]

[12] Broadhurst MJ, et al. Lancet 2015; 386: 867-74.
WHO, March 31, 2015

The Legacy

The Ebola outbreak was brought under control during 2015, and the emergency was declared over in March 2016. The legacy of the HPRU's work included training many UK and African healthcare workers in managing such outbreaks, a better understanding of the factors governing virus evolution and spread, and new approaches to diagnosis, treatment and vaccination which were developed further in subsequent haemorrhagic disease outbreaks. These included the 2018 outbreak of Ebola in the Democratic Republic of the Congo and Nigeria's largest ever Lassa fever outbreak which began in the same year, where we once again showed the value of rapid minion diagnostics in disease control.[13]

[13] Kafetzopoulou LE, et al. Science 2019; 363: 74-7.

POLICY IMPACT

In July 2015, the Commons Select Committee for Science and Technology launched an inquiry in "Science in emergencies: UK lessons from Ebola". Professor Solomon, on behalf of the unit, submitted written evidence to the Committee in September and was asked to give oral evidence in October 2015. The Committee report was published in January 2016 and included recommendations from the Unit; the Government response was published in April 2016.

The next five years

HPRU 2 programme in high consequence infectious diseases (HCID)

Building on our experiences responding to the Ebola outbreak and other outbreaks, over the next five years, projects within the HCID programme of work aim to:

- **leverage existing national infection and HCID networks and international expert consortia to address knowledge gaps**
- **provide clinical expertise and build capacity of staff to respond to HICDs**
- **develop comprehensive and coordinated UK HCID research capacity to support public health and clinical interventions for imported cases and capability to respond to emerging/novel pathogens**
- **characterise host responses and identify molecular signatures to inform triage of patients**
- **assessing the current UK risk levels based on HCIDs moving between affected countries and the UK through analysis and modelling**
- **assess and mitigate the risk of nosocomial transmission.**

LYME

Lyme is the most common vector- borne infection of humans in the UK, and our research over the last five years has shown that it is growing in importance as an emerging zoonotic disease. Despite great media and public interest, and concern, Lyme disease and other tick-borne diseases, knowledge about the incidence, diagnosis and management of Lyme disease and the emergence of other tick-borne diseases within the UK is limited. Our work has focussed on surveillance approaches, improving diagnostics, understanding the impact of climate change, and engaging with patients and the public.

Mechanisms of surveillance to inform public health approaches

Surveillance for Lyme disease and other tick-borne disease can be time and labour intensive, but research led by Dr Alan Radford has shown that passive surveillance of companion animal electronic health records through the Small Animal Veterinary Surveillance Network, provided a novel method for describing temporal and spatial tick activity.[3] Such approaches can help inform veterinary and public health programmes, and in combination with other systems already in place, the Small Animal Veterinary Surveillance Network has the potential to further inform tick and tick-borne disease risk models supporting a One-Health approach to public health messaging and tick control. It also acts as an indicator of unusual or imported tick species which may pose an issue for human or animal health in the UK. A further £719K funding for this work was received from BBSRC.

We were able to describe which Lyme disease patients access hospitals for management and treatment.

Our analysis of available data from PHE laboratories, hospitals and GPs is enabling a targeted approach to public health interventions and messages. PHE Rare and Imported Pathogens Laboratory (RIPL) data were extracted and analysis showed significant increase in the incidence of laboratory confirmed Lyme disease cases from 1.62 cases per 100 000 in 2013 to 1.95 cases per 100 000 in 2016.[4] In addition, the results also suggested that Lyme disease patients originate from areas with higher socioeconomic status and disproportionately in rural areas. Hospital data over an eighteen-year period (1998-2015) in England and Wales were analysed and we observed a six-fold increase in cases seen in hospitals.[5] The number of cases that require hospital admission are still relatively low compared to national surveillance figures as most Lyme disease cases are confirmed and treated with antibiotics by a GP without the need for laboratory diagnosis or referral to a hospital.

Through the analysis of these data we were able to describe which Lyme disease patients access hospitals for management and treatment, and for the first time, start to describe how patients enter and progress through NHS care. Further work to analyse GP data on patients with Lyme disease will provide further evidence of patients' interaction with the NHS.

[3] Tulloch et al. Epidemiological infections 2017. doi.org/10.1017/S0950268817000826

[4] Tulloch et al. BMJ Open 2019. doi: 10.1136/bmjopen-2018-028064

[5] Tulloch et al. BMC Public Health 2019. doi.org/10.1186/s12889-019-7245-8

Increasing awareness and contributing to national guidelines

There is great misunderstanding and fear around Lyme disease and its manifestations, particularly in persistent cases, which leads to distortion of the facts. We have worked closely with patients, the public and interest groups, to try to arrive at a common understanding. Through our patient and public involvement panel, we are able to liaise closely with the many interested groups. One of the key ways we have engaged with the interested groups was through a Lyme disease open day. PHE-branded materials including the Tick Toolkit and a leaflet "Lyme Disease: Signs and Symptoms" were produced and made available online on the GOV.UK, with the aim of improving awareness and ultimately leading to a reduction in the number of cases. Information in these leaflets was then adapted for use in materials aimed at primary school children with funding from the HPRU EZI Strategic Research Fund project. Teaching children how to recognise ticks, and be aware of the importance of protective behaviours, will make it more likely that parents will carry out tick checks, removing ticks promptly and reducing the risk of acquiring infection.

One of the key ways we have engaged with the interested groups was through a Lyme disease open day.

POLICY IMPACT

In addition to the varied public engagement activities, members of the Unit also contributed to the development of the NICE guidelines for diagnosing and managing Lyme disease that aim to raise awareness of when Lyme disease should be suspected and ensure that people have prompt and consistent diagnosis and treatment.[1] Following the publication of the guidance, we then contributed to the development of the NICE quality standards for Lyme disease which covers diagnosing and managing Lyme disease in people of all ages including raising public awareness about prevention and high-quality care in priority areas for improvement.[2]

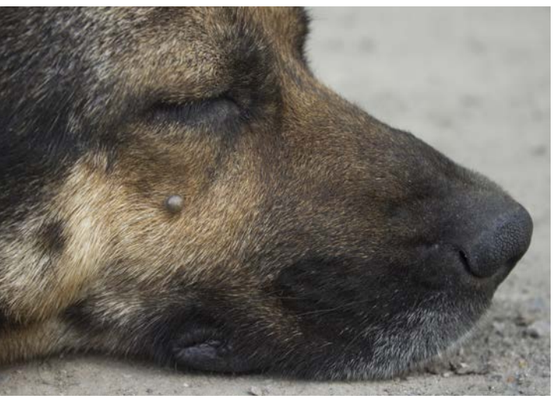
- NICE guidance
- NICE quality standards

The next five years

HPRU 2 programme in endemic arthropod-borne diseases

Our work on Lyme disease and other endemic arthropod-borne diseases will continue with projects aiming to:

- improve understanding of Lyme disease history in patients and diagnostic development
- understand drivers and distribution of Lyme disease risk around the UK to inform the provision of public health advice and improve awareness and management by health professionals
- build capacity to sample and screen tick vectors
- establish the disease burden of endemic arthropod-borne virus (arbovirus) infections in the UK
- understand host immune responses to arboviruses and develop diagnostics.



The impact of climate change on tick-borne disease

Knowledge about the tick vector, and how weather, climate and ecology factor into its activity is essential to understand the infection transmission cycle and to mitigate the human Lyme disease risk. We have carried out investigations of the influence of weather and climate on the tick vector. The research led by **Dr Jolyon Medlock** has consisted of extensive field investigation and statistical modelling of the influencers of tick activity, investigation of the prevalence of the Lyme bacteria Borrelia burgdorferi s.l. in tick populations at sites throughout the UK, and identifying seasonal trends in infection.[1] In collaboration with the HPRU in Environmental Change, we are using UK Met Office data to develop a higher resolution temperature model which may be used to better predict the distribution of this and other disease vectors in the UK.[2]

[1] Medlock et al 2018 doi: 10.3390/ijerph15102145

[2] Medlock JM , Leach SA . Lancet Infect Dis 2015 doi:10.1016/S1473-3099(15)70091-5

ZIKA

The capability of the Unit to respond to emerging outbreaks of international concern was demonstrated in the Zika emergency in Latin America in 2016. Early identification of the virus emergence in Brazil as a potential problem meant that we were well placed to respond to the emergency, and focused on improving the diagnosis of Zika, characterising the neurological manifestations and determining the risk factors. We also examined mosquito transmission to help predict further spread, and worked towards developing vaccines for future protection.

Rapid response to an emerging threat

Through early horizon scanning and intelligence gathering, we recognised that the arrival of Zika in Brazil posed a potential threat, and conducted a scoping visit to assess the situation on the ground which indicated that the situation was rapidly escalating. We diverted £100,000 of flexible Unit funding into a pump-priming call which resulted in a series of small seeding projects on diagnosis, clinical surveillance, vector biology, immunology and disease mechanism studies; these brought key researchers in the UK and Latin America together to start working on projects, and led to the acquisition of further funding to expand on the response to the emergency.

€1 million was awarded to Liverpool for our research in diagnostics and neurological manifestations of the virus.

The first award received was the MRC Zika Rapid Response Funding of £800,000 awarded for a range of projects including examining the links of Zika virus and neurological conditions, improved diagnostics, and researching vector susceptibility and the influence of temperature. Later in 2016 we joined partners in 25 countries across Europe and Latin America to form the ZikaPLAN (Zika Preparedness Latin America Network), an €11M EU Horizon 2020 project, of which €1 million was awarded to Liverpool for our research in diagnostics and neurological manifestations of the virus. The HPRU was part of a collaborative project to develop Zika vaccines, awarded £4.7M from the Department of Health and Social Care. These awards enabled us to deploy staff to work on the ground including a senior member of staff in Rio, clinical research fellows and a PhD student.

Improved understanding of neurological disease

Through clinical characterisation of Zika-associated neurological disease, we were able to understand the clinical spectrum of neuro-zika, and as a result, future threats of the disease. We were among the first to anticipate and later report on neurological complications such as Guillain-Barré syndrome, encephalitis and myelitis.[1,2] These findings were used to develop guidance for neurologists on Zika virus infection in patients returning from endemic areas.[3] This work was supported by funding as part of the ZikaPLAN network.

We were able to understand the clinical spectrum of neuro-zika

[1] Solomon et al, Lancet Infectious diseases, 2016

[2] Brasil et al, Lancet 2016

[3] Leonhard et al 2018

Further work on the characterisation of the clinical features of patients with suspected Zika and other arbovirus-associated neurological disease is ongoing in Brazil with the expected outcome of revised arbovirus diagnostic guidelines.

The impact of climate change

We developed a global model for the risk of Zika virus transmission which highlighted how a change in weather patterns, brought on by the 'Godzilla' El Niño of 2015, fuelled the Zika outbreak in Latin America.[4] Risk of Zika transmission in the UK, based on climatic conditions, was estimated to be very low.

In the laboratory, we determined that a range of UK species are competent to transmit viruses including Zika, West Nile and Japanese encephalitis; however, no tested UK vectors were competent for dengue or chikungunya viruses. For Zika, West Nile and Japanese encephalitis viruses, we have undertaken detailed assessment of the sensitivity of transmission risk to temperature and found that while the UK has indigenous vectors that are competent to transmit these viruses, the country is too cold for any substantial transmission to take place.

Risk of Zika transmission in the UK, based on climatic conditions, was estimated to be very low.

[4] Caminade et al., PNAS, 2017

Developing diagnostics and vaccines

Challenges of detecting Zika virus infection due to a high level of cross-reactivity among flaviviruses such as Dengue, coupled with demonstration of overlap of Zika virus, dengue and chikungunya meant that there was an urgent need to develop a specific serological assay to discriminate Zika virus infection from other flaviviruses.[5] An ELISA assay was developed, and was shown to have high sensitivity and specificity, as well as being a low-cost, simple and accessible for use in the response to the emergency.[6, 7] Through training, capacity for diagnostics was built in Fiocruz, Brazil and Instituto Nacional de Salud, Bogotá.

[5] Mehta R, et al 2018 PLoS Negl Trop Dis.

[6] Balsemeda et al, PNAS, 2017

[7] Tedder et al. PLoS One. 2019 Aug 2;14(8):e0215708

With no approved vaccine or treatment available, research in this area was a priority. Building on initial vaccine development research in the MRC Zika Rapid Response project, a £4.7M award from the Department of Health and Social Care, the Unit is part of a collaborative project that aims to develop a Zika virus vaccine and take two vaccine candidates through to clinical trial in humans within three years. Professor Neil French commented "Although the current Zika outbreak has slowed, there remains a significant risk of foetal abnormality when pregnant mothers become infected, and the changing climate raises the possibility of major epidemics occurring in previously unaffected parts of the world. A ready to use vaccine would dramatically reduce the threat that we face from Zika."

POLICY IMPACT

Through our work on Zika, we were able to contribute to the preparation of the UK and the wider-international response. Members of the Unit contributed to the UK Department of Health pre-Strategic Advisory Group on Emergencies (pre-SAGE), and on the World Health Organisation (WHO) Advisory Committee for Zika.

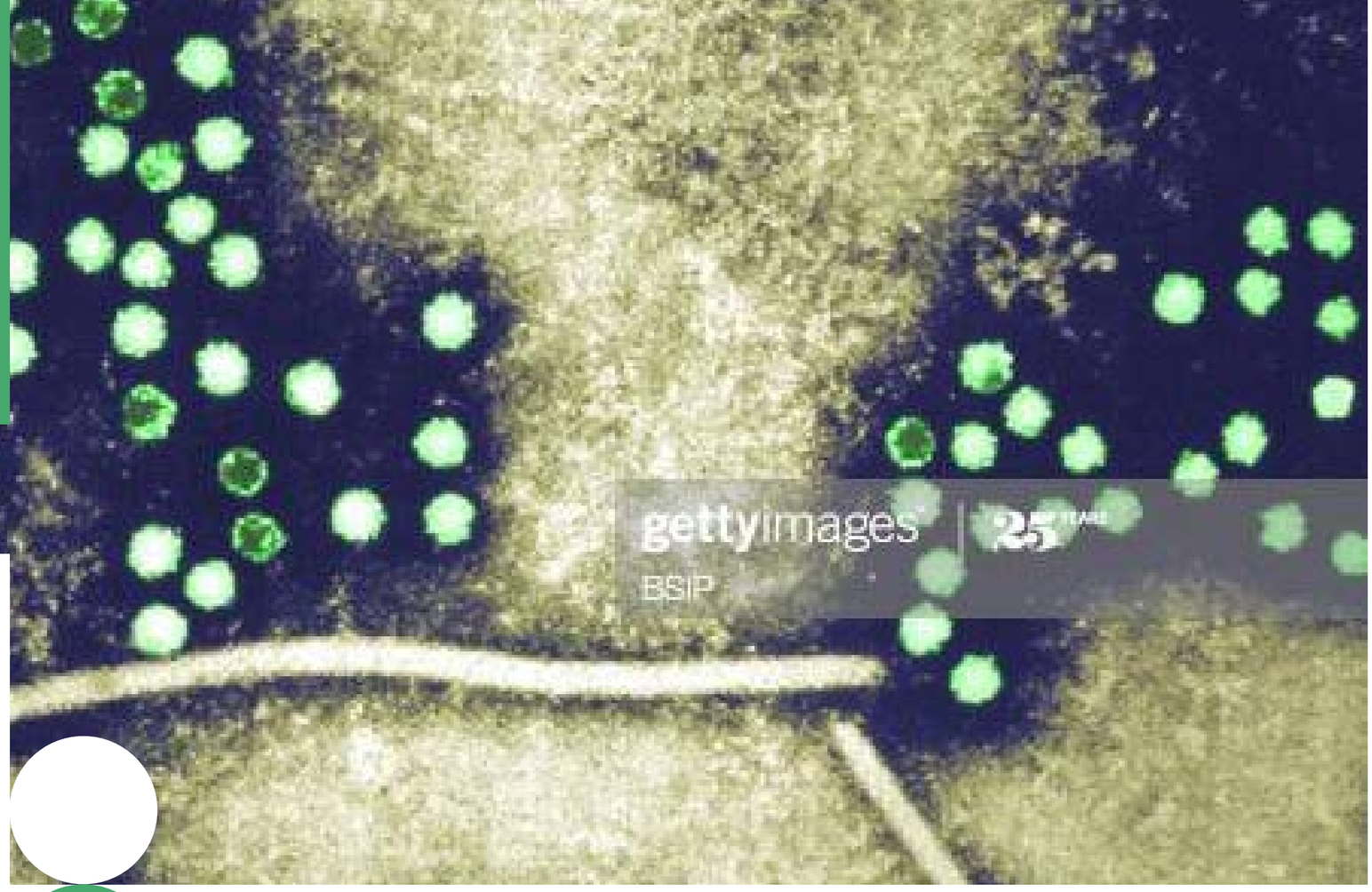
The next five years

HPRU 2 programme in emerging arthropod-borne diseases

Building on our work on Zika and other arthropod-borne viruses (arboviruses) we will aim to:

- establish the disease burden of imported arboviruses and brain infections in the UK
- develop and evaluate improved serological assays for arboviruses
- improve the capability to work with tick-borne encephalitis virus in the UK
- evaluate the transmission risk of West Nile virus in the UK and investigate strategies for vector control
- improve our understanding of the epidemiology of emerging infections from vector-borne diseases affecting returning travellers.

HEPATITIS E



Since 2010 there has been a year on year increase in the number of locally-acquired, acute Hepatitis E cases in the UK, which has been associated with the consumption of processed pork products.

In England alone, it is estimated that between 100,000 and 150,000 new cases of Hepatitis E infection occur annually. While a high proportion of Hepatitis E infections are asymptomatic, severe or chronic infections have been observed in immunocompromised individuals. Therefore, there is a need for a greater understanding of the epidemiology of this emerging disease to devise precautionary advice for Hepatitis E for such high-risk groups in order to prevent or reduce the risk of severe or chronic infection in this population.

Analysis of data from 2008-2017 has shown fluctuations in the annual incidence of Hepatitis E due to changes in risk in acquiring infection.

Our work is contributing to better understanding of both the extent of infection and risk factors for infection in the UK to inform policy and mitigate the risk to public health. A series of integrated approaches has addressed this, including data linkage studies, investigations of the association between food exposure and different virus phylotypes, surveillance studies of the changing epidemiology, and a case control study.

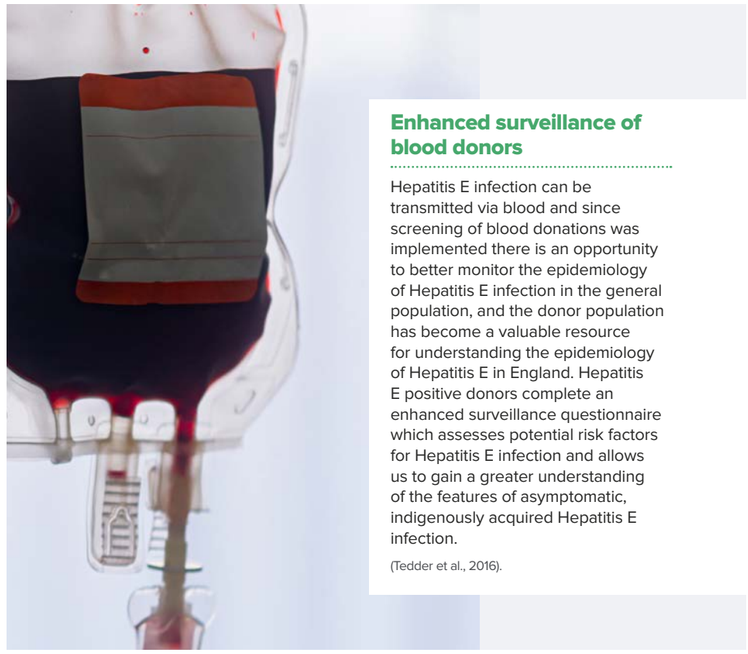
Exposure through food

Since 2010, foodborne associated human Hepatitis E infections have increased in England and Wales (Fig 1). Similar to other European countries, the increase in human hepatitis E is associated with the emergence of a new phylotype, Hepatitis E G3-group 2 (G3-2). A study on Hepatitis E-infected blood donors identified the consumption of pork products from the same supermarket as a risk factor for Hepatitis E infection.[3] Furthermore, we showed that human infections could be due to the consumption of pork products originating outside of the UK. This study has helped inform policy makers to impact changes in animal husbandry and food processing methods.[4]

(Tedder et al., 2016).

(Said et al. 2017).

[3, 4] PHE (2019). Public health operational guidelines for hepatitis E



Enhanced surveillance of blood donors

Hepatitis E infection can be transmitted via blood and since screening of blood donations was implemented there is an opportunity to better monitor the epidemiology of Hepatitis E infection in the general population, and the donor population has become a valuable resource for understanding the epidemiology of Hepatitis E in England. Hepatitis E positive donors complete an enhanced surveillance questionnaire which assesses potential risk factors for Hepatitis E infection and allows us to gain a greater understanding of the features of asymptomatic, indigenously acquired Hepatitis E infection.

(Tedder et al., 2016).

Improving surveillance data

Two national surveillance systems are used to estimate the burden of acute infection with Hepatitis E in England and Wales; the enhanced surveillance system based on national reference laboratory data and the Second Generation Surveillance System (SGSS) based on data reported by local diagnostic laboratories. We showed that linkage of reports from both comprehensive descriptions of the epidemiology of diagnosed acute Hepatitis E more comprehensively monitors trends in England and Wales.[1] Analysis of data from 2008-2017 has shown fluctuations in the annual incidence of Hepatitis E due to changes in risk in acquiring infection. Ongoing surveillance of acute cases, as well as collaboration and communication with industry and other European countries, is required to detect further changes in epidemiology and protect those most vulnerable from the severe consequences of Hepatitis E infection.[2]

Analysis of data from 2008-2017 has shown fluctuations in the annual incidence of Hepatitis E due to changes in risk in acquiring infection.

[1] Oeser et al., 2017, Epidemiol. Infect doi: 10.1017/S0950268817002047

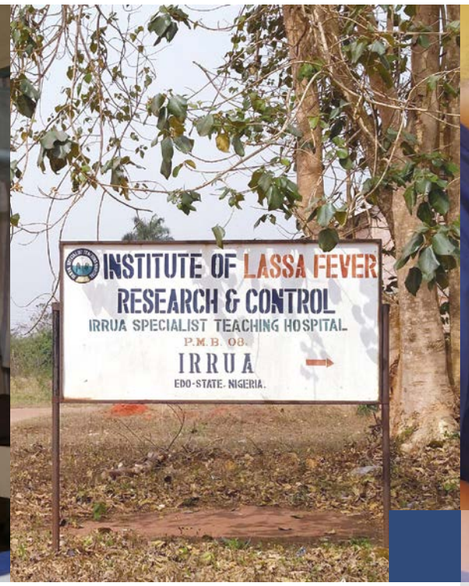
[2] Oeser et al., 2019, J Infect Dis. 2019 Jul 31;220(5):802-810. doi: 10.1093/infdis/jiz207.

POLICY IMPACT

Our findings from our work on Hepatitis E are translating through to key public health impacts, for example:

- PHE 'Public health operational guidelines for hepatitis E' written to enable Health Protection Teams (HPT) to respond appropriately to laboratory reports of HEV infection and clinical notifications of Hepatitis E infection
- UK Zoonoses, Animal Diseases and Infections (UKZADI) Group report 'Policy Options for Reducing the Risk of Hepatitis E Virus in the Food Chain' which suggests policy options to mitigate the risk to public health.

OTHER SCIENCE



Liana Kafetzopoulou in lab

CLIMATE AND VECTORS

Several vector-borne diseases have recently emerged in Europe, and some threaten the UK. Indigenous UK mosquito species may present an underestimated risk for the transmission of arboviruses. While invasive mosquitoes also present a risk of the introduction of new diseases.[1] There are major challenges to researching pathogen transmission, requiring sophisticated high containment laboratories to keep the insects and pathogens within. By pooling our collective expertise in Liverpool and PHE through the HPRU we are rapidly developing the systems to take this research forward. We are now licenced to work with nine additional viruses, including Zika virus. We determined that a range of UK species are competent to transmit viruses including Zika, West Nile and Japanese encephalitis and have undertaken detailed assessment of the sensitivity of transmission risk to temperature. An initial conclusion is that while the UK has indigenous vectors that are competent to transmit these viruses and under certain realistic environmental conditions (e.g. one very hot day), a non-vector can become a potential vector, the country is too cold for any substantial transmission to take place.

We are now licenced to work with nine additional viruses, including Zika virus.

Review of the effect of climate change on vector-borne disease highlighted the risk of changing climate, coupled with other socio-economic and environmental factors, to the maintenance of vectors and pathogens, and the impact on public health.[2,3] In addition, recent research has shown that the Asian tiger mosquito, which is able to transmit diseases such as dengue, chikungunya and Zika, and has already caused minor outbreaks in south Europe could become established over almost all of England and Wales by the 2060s.[4] This work highlights the need for continued enhanced surveillance in the UK of both endemic and non-endemic vectors, to address key emerging issues.

[1] Baylis M. Potential impact of climate change on emerging vector-borne and other infections in the UK. Environ Health. 2017 Dec 5;16 (Suppl 1):112

[2] Medlock 2017 Effect of climate change on vector-borne disease risk in the UK doi.org/10.1016/S1473-3099(15)70091-5

[3] Medlock 2018 Assessment of the Public Health Threats Posed by Vector-Borne Disease in the United Kingdom (UK) doi.org/10.3390/ijerph15102145

[4] Metleman S et al https://doi.org/10.1098/rsif.2018.0761

LASSA

Early in 2018, Nigeria was hit by its largest ever outbreak of Lassa fever. Humans become infected by Lassa fever virus by contact with food or household items that have been contaminated with rodent urine or faeces containing the virus. Like Ebola, Lassa can subsequently be transmitted between humans, especially health care workers, in nosocomial spread. As the outbreak grew it was unclear how much of the ongoing transmission was due to person-to-person spread, or how much was because people were being exposed to infection through the environment. With colleagues in Nigeria we established rapid sequencing direct from clinical isolates using MinION technology. For the first time, we were able to sequence Lassa virus using MinION set in the field. At the epicenter of the unfolding Lassa Fever outbreak, we were able to use samples from patients who tested positive for Lassa, without the need to export material outside of the country of origin. We showed multiple introductions of Lassa fever virus to humans from the environment were responsible for the large number of cases, rather than direct human to human spread. This informed the Nigerian Government response and allowed more efficient use of limited resources and prevented panic regarding the local response to the outbreak.

For the first time, we were able to sequence Lassa virus using MinION set in the field.

• Kafetzopoulou et al (2019) DOI: 10.1126/science.aau9343

Brain Infections Global annual meeting, Malawi, 2020

BRAIN INFECTIONS

Brain infections, many of which are zoonotic and/or emerging, are a major disease burden; developing improved and more rapid tests will improve health outcomes, and health economic costs. Our work has included investification of the seroprevalence of Zika, Dengue and Chikungunya in Brazil which will contribute to informing physicians and public health specialists in order to provide better clinical management. In addition, we investigated the causes of brain infections in South India.

The collaborations established through our work on neurological manifestations of Zika virus supported a successful bid for funding to establish a Global Health Research Group in Brain Infections, for which Liverpool/HPRU EZI has been awarded further NIHR funding (£2 million). This research group, to date, consists of nine organizations spread across India, Malawi, Brazil and the UK. An international multicentre study is currently being set up that aims to improve the management of acute brain infections at selected hospitals in Brazil, India and Malawi. Beyond this, the network provides a framework and networking space for all those interested in neurological infections research and training.

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SAVSNET

SAVSNET Ltd. was formed as a joint venture between the British Small Animal Veterinary Association (BSAVA) and the University of Liverpool. In April 2016, SAVSNET was awarded £700k from the Biotechnology and Biological Sciences Research Council (BBSRC) to expand its database of UK pet health records and support more ‘big data’ research into animal and human diseases. SAVSNET harnesses electronic health and environmental data for rapid and actionable research and surveillance. The research priorities are currently antimicrobial use resistance, climate and environment, and infection and zoonosis, cross-cut by enabling expertise in epidemiology, biomedical text mining and pathogen and host-pathogen interaction.

STOP PRESS: TBEV detected in the UK

In 2019, tick-borne encephalitis virus was detected for the first time in the UK through surveillance conducted by the Unit. The zoonotic virus was detected in a small number of tick samples collected by persons involved in the routine management of deer from across the UK. The detection of tick-borne encephalitis virus in the UK is important because tick-borne encephalitis virus can infect humans, causing febrile illness and neurologic complications including encephalitis. For zoonotic infections, detection of a pathogen in the animal reservoir/host, vector, or both often precedes the emergence of human infection and although no autochthonous cases of clinical human disease have been diagnosed in the UK, up to 60% of encephalitis cases reach no diagnosis. Therefore, our results indicate that tick-borne encephalitis virus should be considered as a potential cause in encephalitis patients, and the wide distribution of the natural vector in the United Kingdom indicates a need for close monitoring and a potential for geographic spread and expanding risk areas.

Following publication of these findings, the news was picked up by numerous major news outlets including the BBC, the Guardian, the Telegraph and the Huffington Post. In addition to publicising the first detection of tick-borne encephalitis virus in the UK, these articles also provided an opportunity for us to share messages about tick awareness and bite prevention.

• Holding et al (2020). Tick-borne encephalitis virus, United Kingdom. Emerg Infect Dis. doi.org/10.3201/eid2601.191085

PUBLIC ENGAGEMENT

Public engagement

From the start of the HPRU EZI, patient and public involvement has been at the heart of the public engagement strategy to maximise the profile and impact of our work. The Public Involvement Panel (PIP) established jointly by the HPRU EZI and the Institute of infection and Global Health in 2015. The Panel continues to thrive as a diverse, active and engaged panel of patients and other research users, and provided assistance on over 30 research proposals.

Public engagement activities have taken place throughout the work of the Unit, with a number of approaches taken to maximise engagement and impact, including public events, school programmes and media activities. Examples (pictured clockwise from top) include: Workshop in Brazil with families affected by Zika, Bluedot festival, Meet the scientists and Operation outbreak rucksack, school tools.

TRAINING

Training

Since the inception of our HPRU in Emerging and Zoonotic Infections we have placed great emphasis on training. The majority of scientists within our cohort are 20 PhD students and 11 PDRAs. By opening up the HPRU to associate members we have included additional 17 PhD students and 1 PDRAs from other institutions, as well as internal PHE students. Numerous training opportunities have been provided both within and out with of the HPRU/PHE/UoL and LSTM to these individuals. We have also provided training opportunities to HPRU associated and non-HPRU associated staff within PHE and other Universities and organisations within the UK.

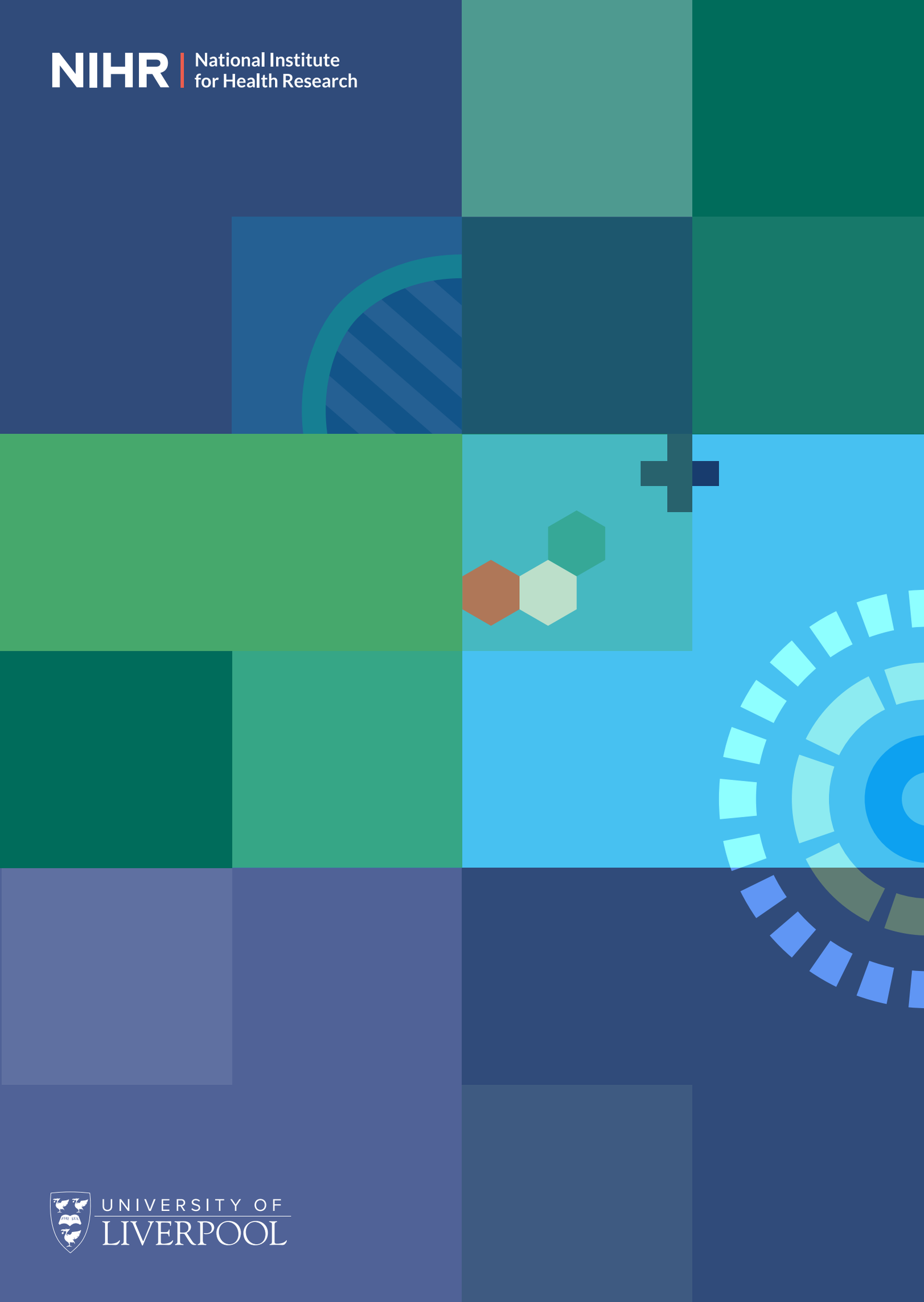
The majority of scientists within our cohort are 20 PhD students and 11 PDRAs.

All of our PhD cohort undergo specific training in helping them with the successful completion of their PhD, this has been mainly led by the UoL and has been particularly useful for PhD students based mainly at PHE. Part of this has allowed the development of networks between scientists between and within the three partner institutions. In addition, through our Strategic Research Fund and Training Calls offered each year, our researchers are encouraged to apply for funding outside their Theme budget to enable them to undertake small research projects/training.

HPRU academy

In 2017, HPRU EZI jointly with HPRU in Gastrointestinal Infections hosted PhD students from 11 HPRUs for the first HPRU PhD Academy. The purpose of the event was to share knowledge across the HPRUs and to give the PhD students a platform to present their research. The event included training opportunities from PHE on the importance of NIHR HPRU PhDs' contribution to public health, and career development in public health.

The HPRU in Emerging and Zoonotic infections support and strengthen Public Health England


NIHR | National Institute for Health Research
UNIVERSITY OF LIVERPOOL