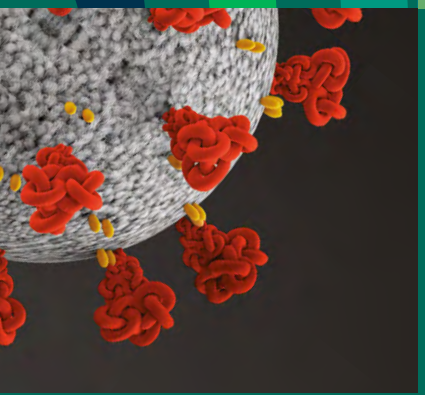
NIHR | National Institute for Health Research

HEALTH PROTECTION RESEARCH UNIT IN

EMERGING AND ZOONOTIC INFECTIONS

FIVE YEAR REVIEW: 2014–20



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), the Zika outbreak in Latin America (2016-17) (pXX), and the COVID-19 pandemic (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)

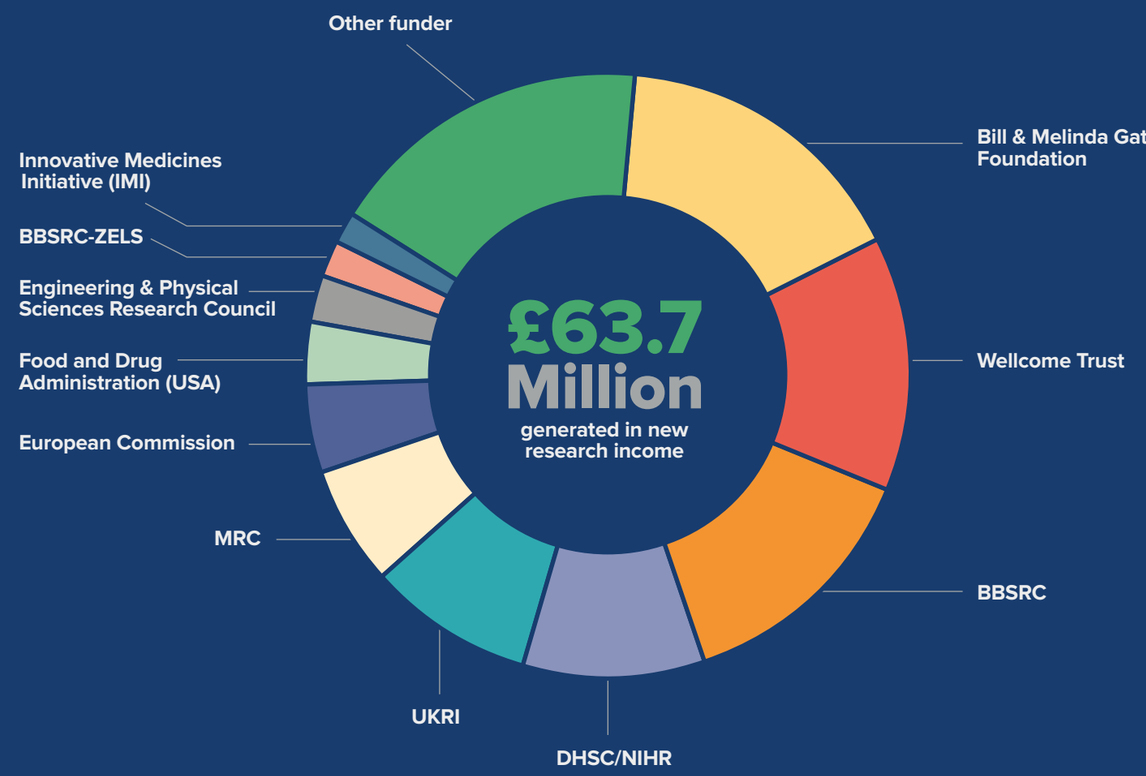
We hope you enjoy reading about our work, and look forward to receiving any feedback

Tom Solomon
Director, University of Liverpool

Miles Carol
Co-Director, Public Health England

Emerging and Zoonotic Infections 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 fully funded by the HPRU

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 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 (HCIDs)	1.1 Comprehensive characterisation of HCIDs (HCID-UK Study)	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 (ARBO/CNS-UK 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 Tick-Borne Encephalitis Virus 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 (Lyme-UK Study)	Putative later project/s: Improving Lyme diagnostics	3.4 Monitoring tick-borne viruses	4.4 Seroprevalence of Lyme

Cross-Cutting Theme: Knowledge Mobilisation, Patient & Public Involvement

A COLLABORATIVE HEALTH PROTECTION RESEARCH UNIT

Our UK and international partners are shown here

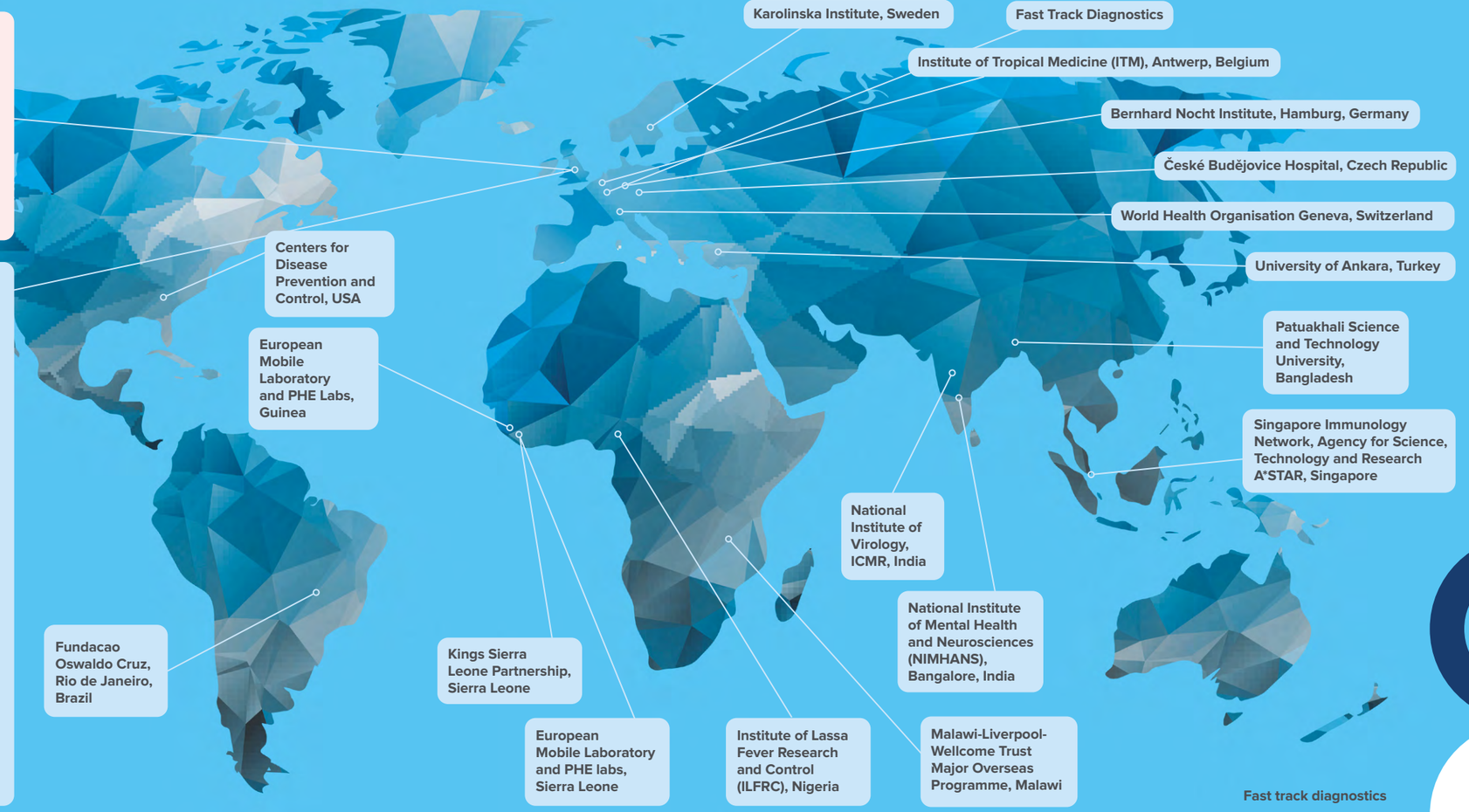
HPRU EZI PARTNERSHIP

- University of Liverpool
- Public Health England
- 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

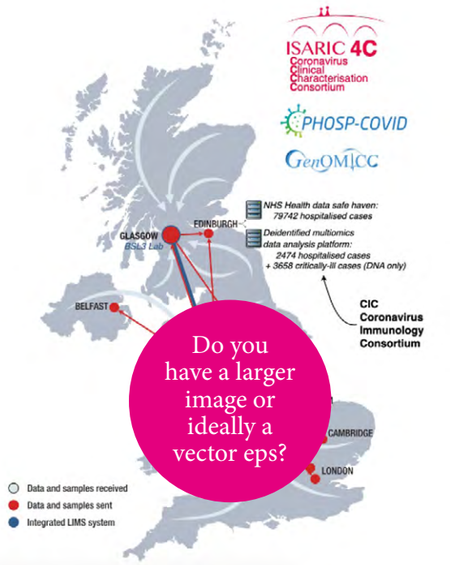
UK

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



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.



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Gathering data to understand the disease

One of the first actions of the HPRU was to support the activation of the ISARIC (International Severe Acute Respiratory and emerging Infection Consortium) WHO Clinical Characterisation Protocol in the UK (CCP-UK). This protocol was originally set up in 2012 in readiness to investigate any emerging infections of public health importance presenting to UK hospitals. The study recruited patients with MERS (Middle East Respiratory Syndrome) Coronavirus and Monkeypox at a couple of sites in 2018.

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

In January 2020, as coronavirus cases were increasing in China, and the first cases were arriving in Europe, we decided to divert HPRU efforts into opening ISARIC-CCP study sites across the UK at 260 hospitals. We were thus ready as the first UK patients occurred. With £10M from the MRC and NIHR we established the ISARIC coronavirus clinical characterisation consortium (4C) with £10M lead by Professor Calum Semple with colleagues from Edinburgh and Imperial. The study was able to recruit from the start of the UK outbreak and by October 2020 had enrolled 82,000 patients, making it the largest and most detailed study of COVID-19 in the world. It has published data on the first 35,000, superscript no 1 provided critical samples for diagnostic and immunology studies (2), 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. The ISARIC-4C study is 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 and underpinning other major national COVID-19 programmes including GenOMICC, PHOSP-COVID and UKCIC. HPRU members are also conducting critical studies to understand the virus' evolution and spread, and to evaluate vaccines and new treatments. As the pandemic evolved it became clear there are important neurological manifestations of infection. Liverpool investigators led a UK wide surveillance study showing stroke and delirium are the most common presentations (3). We also pooled international data to show a similar pattern globally (4).

1. Knight SR, et al. BMJ 2020; 370: m333 370:m333
2. Peng Y, et al. Nature Immunol 2020; Sep 4
3.Varatharaj et al, Lancet Psychiatry 2020; 7: 875-82.
4. Ellul et al, Lancet Neurol 2020; 19: 767-83.

Identifying the first treatment for COVID-19

HPRU Co-Director, Professor Peter Horby of Oxford University led the first trial that reduced the death rate from COVID-19. The RECOVERY trial showed that the relatively cheap drug, dexamethasone, reduced deaths among hospitalised COVID-19 patients by about 30%. The results of the trial were announced by Horby alongside the Prime Minister at a Downing Street Press conference. Within hours it became standard care. The trial, which has recruited more than 12000 patients continues to assess other treatments.

"It's very, very rare that you announce results at lunchtime, and it becomes policy and practice by tea time, and probably starts to save lives by the weekend."

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', led by Professor Neil French, which is tracking and collecting COVID-19 data from households across Liverpool to provide reliable evidence of the extent of the COVID-19 pandemic in the community, and providing unique samples for our studies of immune responses in asymptomatic infection.

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

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."

Every day there are new scientists joining the Liverpool team

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.

The next five years

The HPRU will continue to play a major role in the UK research response to COVID-19 through

Ongoing support for national and international studies which are lead by, or include, HPRU investigators, including

- **ISARIC-4C**
- **RECOVERY**
- **PHOSP-COVID**
- **GenOMICC,**
- **UKCIC**
- **COVID-CNS**
- **COVID-Neuro Global**

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 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.

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 subsequently streamlined information was made available on the web. 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 questions about where the disease might spread next. By studying airline passenger data we determined that outside Africa the USA was 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 shape 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 in protecting the UK.[3] We highlighted the, wrote guidance for UK clinicians (4), and contributed to weekly teleconferences with the Department of Health Emergency Preparedness and Response to, all of which proved helpful when the first UK patients arrived.

[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, showed no benefit.[5] Work by **Miles Carroll** and others 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 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 in the ongoing outbreak in the Democratic Republic of the Congo.

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 being used in the ongoing 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** 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, which was essential to control the outbreak.[9]

In partnership with other international 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 blood sample and transporting it to a biocontainment laboratory for testing, causing delays that complicate patient care and infection control efforts. 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.

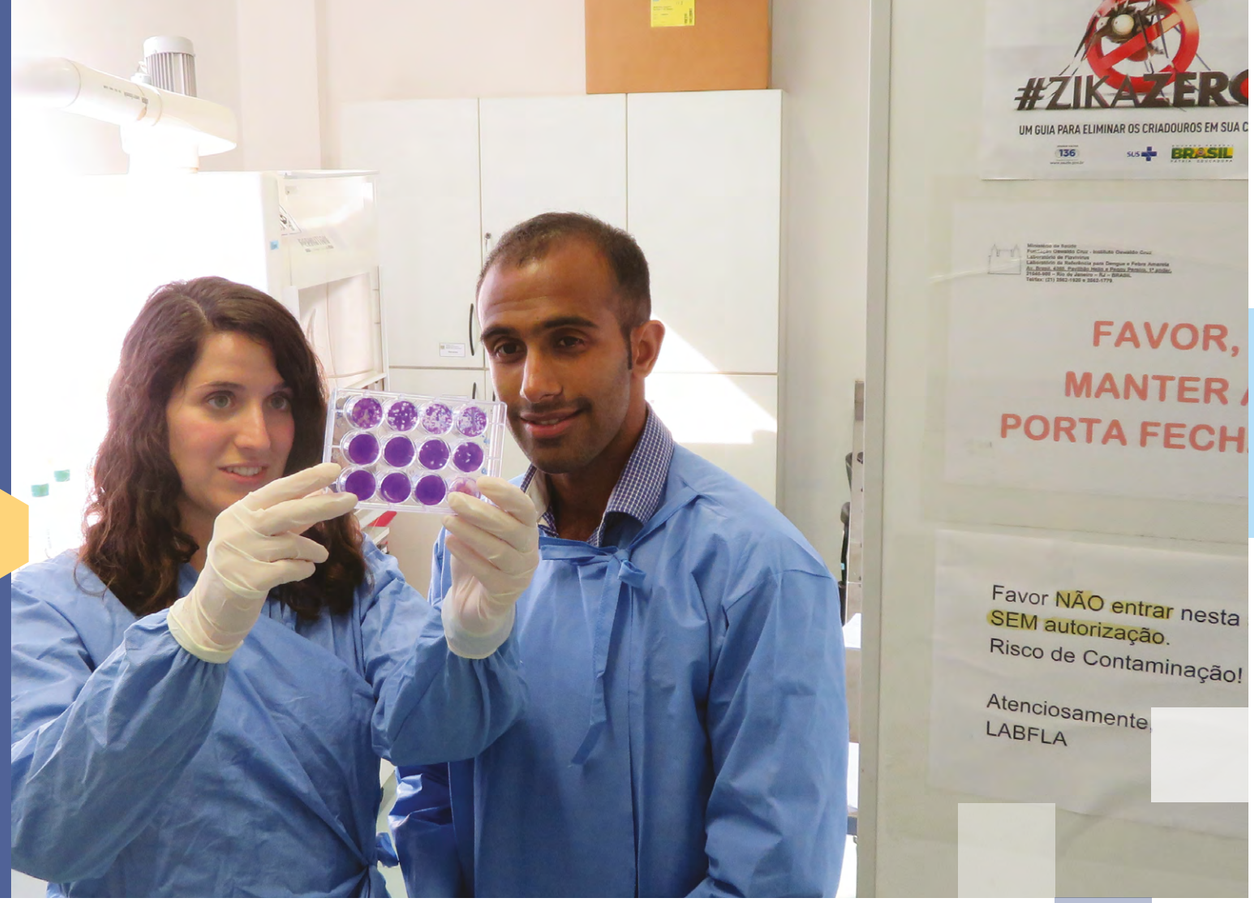
POLICY IMPACT

In July 2015, the Commons Select Committee for Science and Technology launched an inquiry into "Science in emergencies: UK lessons from Ebola". Professor Solomon, submitted written evidence to the Committee on behalf of the HPRU, and and was also asked to give oral evidence. Our recoomendations were included in the Committe report,a nd the Government response.

The next five years

The HPRU will continue to develop its programme on high consequence infectious diseases (HCIDs), such as Ebola. Through the HCID-UK study we will study patients with imported HCIDs, and model transmission risks, including nosocomial spread. Through our larger international cohorts we will develop improved diagnostics and understand disease mechanisms

ZIKA



The capability of the Unit to respond to global public health emergencies of international concern was demonstrated during the Zika epidemic 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 our 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 HPRU 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.

Through the MRC Zika Rapid Response Funding HPRU investigators were 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 climate. 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. The HPRU led investigators **Neil French** and **Lance Turtle** collaborative project to develop Zika vaccines, with £4.7M from the Department of Health and Social Care.

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 report on neurological complications such as Guillain-Barré syndrome, in which there is damage to peripheral nerves, encephalitis and myelitis (inflammation in the brain and spinal cord).[1,2] These findings were used to develop guidance for neurologists on Zika virus infection in patients returning from endemic areas.[3] We have also shown the importance of overlap between disease caused by Zika, and that caused by another mosquito-borne virus, chikungunya.[4]

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

[1] Solomon et al, Lancet ID 2016; 16: 402-4

[2] Brasil et al, Lancet 2016; 387: 1482

[3] Leonhard et al, Pract Neurol 2018; 18:271-77.

[4] Ferreira et al, Lancet Neurol 2020; 19: 826-839

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

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 mosquitoe species are competent to transmit Zika, West Nile and Japanese encephalitis, though our climate is currently too cold for any substantial transmission take place.

[5] Caminade et al, PNAS, 2017. 114:119-124

[6] Blagrove MSC et al, Proc Biol Sci 2020; 287: 20200119

Developing diagnostics and vaccines

Diagnosing Zika infection serologically by antibody detection is especially challenging because of cross reactivity with other closely related flaviviruses, especially dengue. We developed two novel approaches including the BOB (blockage of binding) assay, in collaboration with laboratories in Nicaragua, Italy, Switzerland, Brazil and the UK. 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] Diagnostic capacity was built up through training, in Fiocruz, Brazil and Instituto Nacional de Salud, Bogotá.

[6] Balsemeda et al, PNAS, 2017

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

With no approved vaccine or treatment, research in this area was a priority. Our work in this area aims to develop a Zika virus vaccine and take two vaccine candidates through to clinical trial in humans. **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 UK and international policy. Members of the HPRU sat on to the UK Department of Health Strategic Advisory Group on Emergencies (Zika-SAGE), and on the World Health Organisation (WHO) Advisory Committee for Zika as well as advising on policy in Brazil.

The next five years

Through the ARBO-UK study, which builds on our work on Zika and other arthropod-borne viruses, we will examine the disease burden of arboviral infections imported into the UK and develop improved serological diagnostic assays. We will also evaluate the future risk to the UK of endemic transmission of arboviruses as the climate changes.

LYME

Lyme is the most common vector-borne disease of humans in the UK, and our research over the last five years has shown that it is growing in importance.

Despite great public and media interest, and concern. Our work has focussed on surveillance approaches, improving diagnostics, understanding the impact of climate change, and engaging with patients and the public.

The impact of climate change on tick-borne disease

Lyme disease is transmitted by ticks. Knowledge about the impact of ecology, short-term weather and longer-term climate on tick activity is essential to mitigate the risk of human disease **Jolyon Medlock** has led extensive field investigation and statistical modelling of these factors on tick activity, looking also for the prevalence of the Lyme bacteria Borrelia burgdorferi across the UK, and seasonal trends in infection[1]. In collaboration with the HPRU in Environmental Change, we are using UK Met Office data to develop a high resolution model which will better predict the distribution of the Lyme tick, and other disease vectors[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

Mechanisms of surveillance to inform public health approaches

Surveillance for Lyme and other tick-borne disease can be time and labour intensive, but research led by **Dr Alan Radford** has shown that surveillance of electronic health records for dogs, cats and other companion animals through the Small Animal Veterinary Surveillance Network (SAVSNET), provides a novel method for describing tick activity in time and space.[3] Such approaches can help inform veterinary and public health programmes, and are a good example of the One Health approach, which emphasises that the health of humans, animals and the environment are linked. HPRU Investigators receieved further £719K funding for this work from BBSRC.

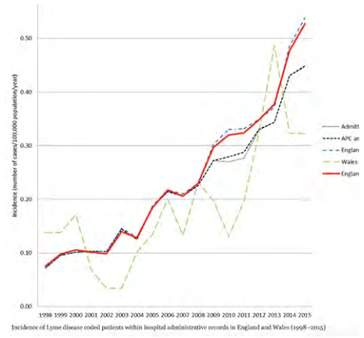
We were able to describe which Lyme disease patients access hospitals for management and treatment.

Our analysis of data from PHE laboratories, hospitals and GPs is enabling a targeted approach to Lyme disease public health interventions and messages. Data from 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] Interestingly, where-as most infectious disease are linked to poverty, the results also suggested that Lyme disease patients originate from areas with higher socioeconomic status and disproportionately in rural areas. Observed a six-fold increase in Lyme cases seen in hospitals over an 18 year period, from 1998-2015.[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.

[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



Incidence of hospital patients with Lyme disease in England and Wales (1998–2015)

Increasing awareness and contributing to national guidelines

There is great misunderstanding and fear around Lyme disease and its manifestations, particularly in cases. We have worked closely with patients, the public and interest groups, to arrive at a common understanding. Through our Patient and Public Engagement and Involvement Panel, we liaise closely with the many interested groups. For example in November 2019 we hosted a joint conference for researchers, clinicians, patients and charities to identify shared research priorities.

To improve awareness and reduce cases, we produced a PHE- "Tick Toolkit" and a leaflet "Lyme Disease: Signs and Symptoms" leaflet, which were" made available on the GOV.UK website. Information in these leaflets was then adapted for use in materials aimed at primary school children with funding from the HPRU's Strategic Patient and Public Involvement and Engagement Fund. 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.

Defining Research Priorities - a joint conference hosted by the HPRU in November 2019 for researchers, clinicians, patients and charities

Please provide excel data for graph so that we can isolate red line and make text visable. Would rearrange page to fit.

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

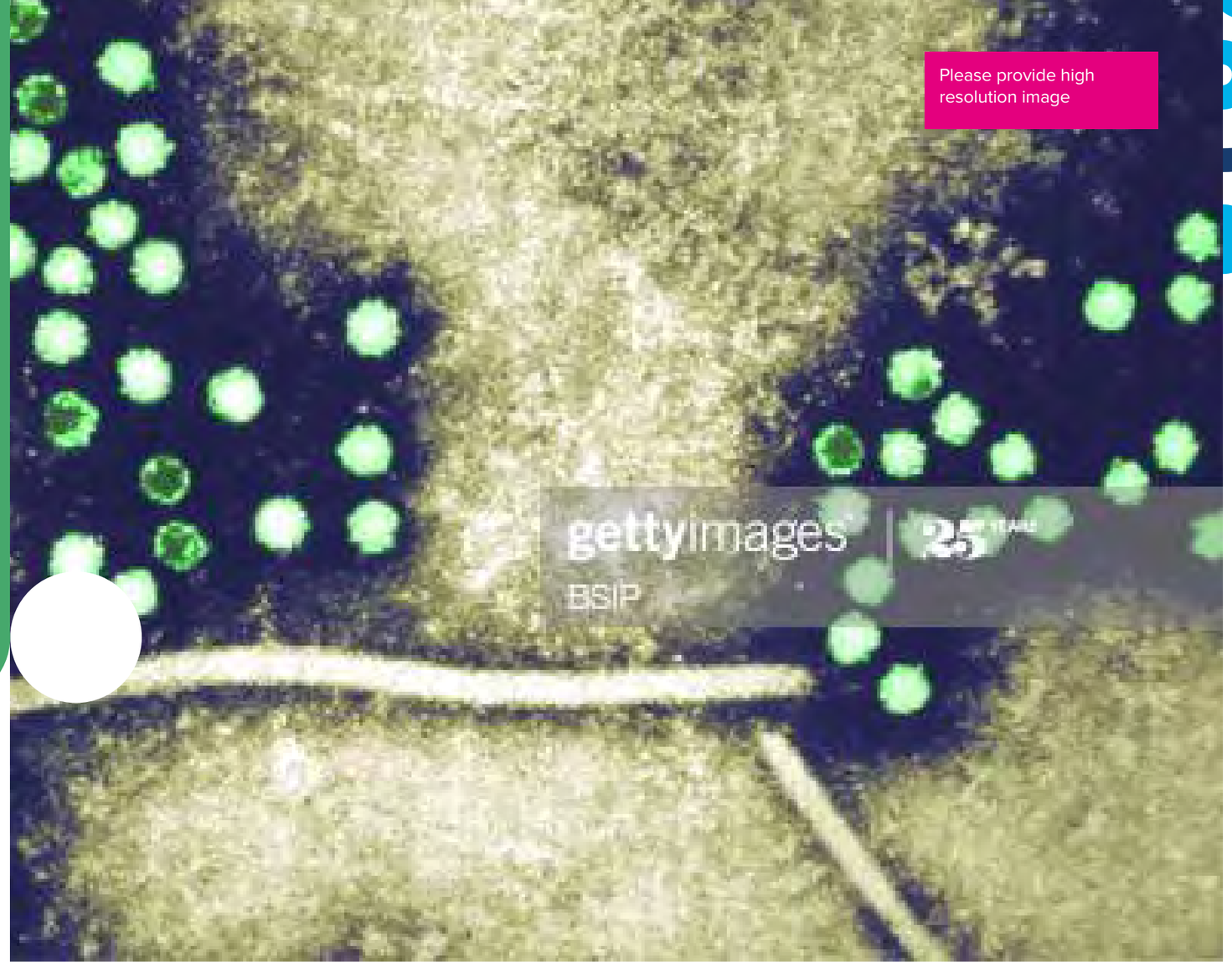
The next five years

The HPRU will continue to study Lyme and other tick-borne diseases endemic to the UK over the next 5 years.

We will set up a large prospective national study. LYME-UK, to help study the natural history of the disease, and generate samples for diagnostic studies. We will also investigate the seroprevalence and montior for other tick-borne diseases.

HEPATITIS E

Since 2010 there has been a year on year increase in the number, 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 liver disease has have been observed in immunocompromised individuals.
Our work is contributing to better understanding of both the extent and risk factors for infection 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.

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

Exposure through food

Since 2010, foodborne associated human Hepatitis E infections have increased in England and Wales (Reference 1). Similar to other European countries, this increase in 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 supermarket as a risk factor for Hepatitis E infection.[2] 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.[3]

[1] (Tedder et al., Transfusion. 2016;56:1529-36.).

[2] (Said et al. Epidemiol Infect. 2017;145:2417-2423.).

[3] 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.[4] 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.

[4] Tedder et al, Euro Surveill. 2019;24:1800386.

Improving surveillance data

Two national surveillance systems are used to estimate the burden of acute infection with Hepatitis E in England and Wales; based on national reference laboratory data and the Second Generation Surveillance System (SGSS). We showed that linkage of reports from both systems comprehensively monitors trends in England and Wales.[5] 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, 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.[6]

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

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

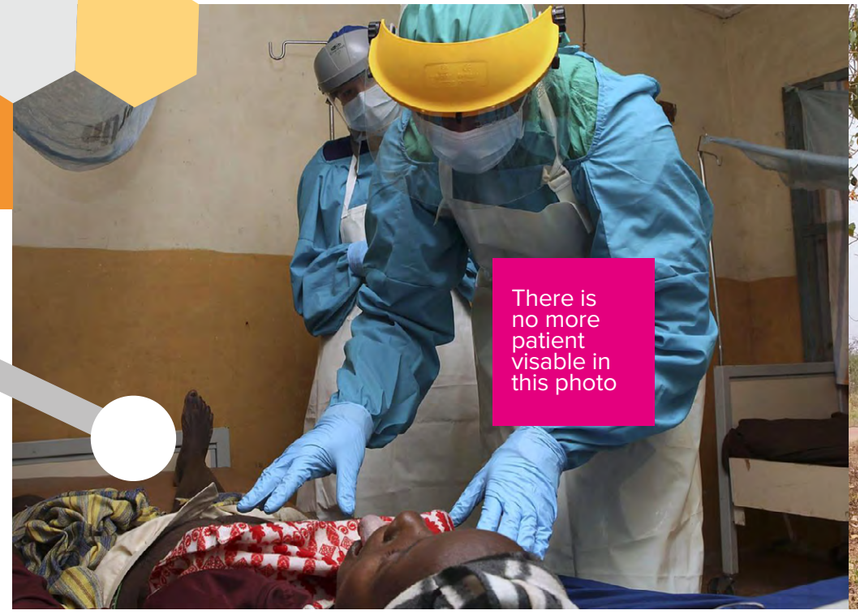
[6] Oeser et al., 2019, J Infect D is. 2019 Jul 31;220(5):802-810. doi: 10.1093/infdis/jiz207.

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 to respond appropriately to laboratory reports 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 athropod-borne viruses (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 have developed the systems to take this research forward. We are now licenced to work with nine additional viruses, including West Nile, Japanese encephalitis, and Zika viruses. We determined that a range of UK species are competent to transmit these three viruses and have undertaken detailed assessment of the impact of temperature. We found that the UK has indigenous vectors that are competent to transmit these viruses and this could occasionally happen, for example on a very hot day, 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.

Our broader 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] 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 within 40 years.[3] This work highlights the need for continuing enhanced surveillance in the UK of both endemic and non-endemic vectors.

[1] Baylis M. Environ Health. 2017 ;16 :112

[2] Medlock et al, Lancet ID 2015;6:721-730

[3] Metleman et al, J R Soc Interface 2019;16:20180761 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. 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. To sequence virus in the field. A the epicenter of the unfolding outbreak.[6]

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

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, allowed more efficient use of limited resources and prevented panic regarding the local response to the outbreak.

[6] Kafetzopoulou et al Science 2019:36374-77


Brain Infections Global **annual meeting, Malawi, 2020**

BRAIN INFECTIONS

Brain infections, many of which are zoonotic and/or emerging, are a major disease burden in the UK and around the world. They can also be important sentinels of disease emergence. To improve surveillance in the NHS, we delineated the causes of meningitis,(4) and led national guidelines to improve recognition and management.

To strengthen the HPRU work on neurological manifestations of Zika we joined 25 partners and formed the ZikaPLan (Preparedness Latin America Network) supported by €11M for the EU Horizon 2020 Programme. We described the neurological features of Zika in adults, comparing with chikungunya virus, which was circulating at the same time. We showed the former causes mostly peripheral nerve disease, whist the latter brain and spine disease. Intriguingly, patients infected with both viruses had increased risk of stroke.(5) Our international work was further strengthened by a £2M award from NIHR to form a Global Health Research Group on Brain Infections linking Brazil India and Malawi.

Our international work was further strengthened by a £2M award from NIHR

4. McGill et al, Lancet Infectious Diseases 2018; **18**: 992-1003..

5. Ferreira et al.. Lancet Neurology 2020; **19**: 826-39.

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.

TICK-BORNE ENCEPHALITIS VIRUS DETECTED IN THE UK

In 2019, tick-borne encephalitis virus was detected for the first time in the UK through surveillance conducted by the HPRU. The zoonotic virus, which is common in mainland Europe, was detected in ticks collected from deer in the Thetford Forest Area of East Anglia.7 The virus is transmitted to humans by tick bites, and is an important cause of encephalitis in some parts of Europe. No human cases have yet been detected in the UK. However, many UK patients with encephalitis have no cause found, so enhanced surveillance is needed.

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.

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

Infectious fun at
Bluedot Festival 2018

Do you have a high resolution image for this photo?

Members of the public were taught how to collect ticks, for this Tick Surveillance Project in 2017

This innovative game, developed by HPRU invetigators, teaches the role of an epidemiologist through an interactive outbreak situation

PUBLIC ENGAGEMENT

From the start of the HPRU, patient and public involvement has been at the heart of everything we do, with representation on our Steering Committee and a separate Public Involvement Panel, which reviews and advises on individual grant proposals – 30 so far.

We also involved the public in the research itself, for example they collected ticks as part of our 2017 surveillance programme. We explained our science to the public through many imaginative and creative engagement events from a hosting a workshop in Brazil with families affected by Zika, to events at festivals, including Cheltenham, Green Man, Big Bang, and Blue Dot!

Our “Bug Terror - Outbreak in a Box” game.
The Public Involvement Panel (PIP)

A joint training session for HPRU students and members of the Public Involvement Panel

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TRAINING

Three of our trainees (Charlotte Robin, John Tulloch and XXX name needed) celebrate their PhD graduation.

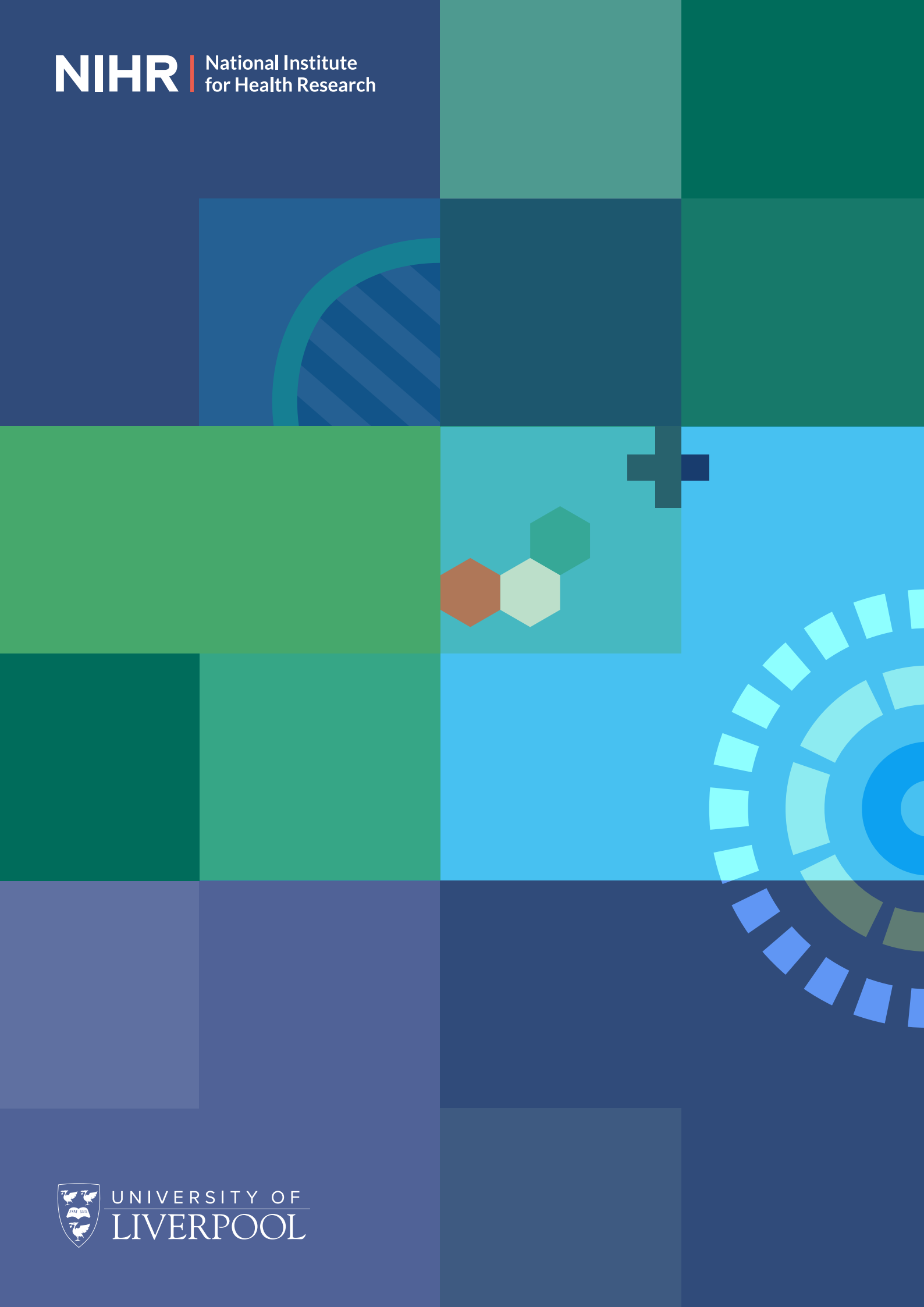
Training

Developing the next cadre of health protection researchers is an essential aspect of our HPRU, and we have placed great emphasis on training. From 2014-20 we trained 20 PhD students and 11 PDRAs , the vast majority of whom have continued with research or public health careers in emerging and zoonotic infections. By opening up the HPRU to associate members we have also supported an additional 17 PhD students and 1 PDRAs from other institutions, as well as internal PHE students. For example, we offered training to work with more dangerous pathogens in the Containment Level 3 Laboratories to all HPRU students and post-docs. And recognising the need for more UK scientists to have such training we offered this to those beyond the HPRU. This was ramped up considerably after the start of the COVID-19 pandemic. In addition the HPRU has trained researchers to work with the most dangerous High Containment Infectious Diseases, such as Ebola and Lassa Fever, in Containment Level 4 Laboratories.
We also offered training in mathematical modeling, machine learning approaches, neural networks and artificial intelligence.

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

National HPRU Academy

To strengthen training across all HPRUs, and develop the wider cadre of HPRU trainee scientists as a national cohort, we took the leadership in establishing the first “National HPRU Academy Meeting” in 2017, at the University of Liverpool in London. With 58 PhD students, from all eleven HPRUs that include PhD, the meeting was co-chaired by the Director of the HPRU in EZI (Prof Tom Solomon), and Professor Jim McLauchlin, lead Public Health Microbiologist, Public Health England. The HPRUs are now included as part of the broader NIHR Academy.


NIHR | National Institute for Health Research
UNIVERSITY OF LIVERPOOL