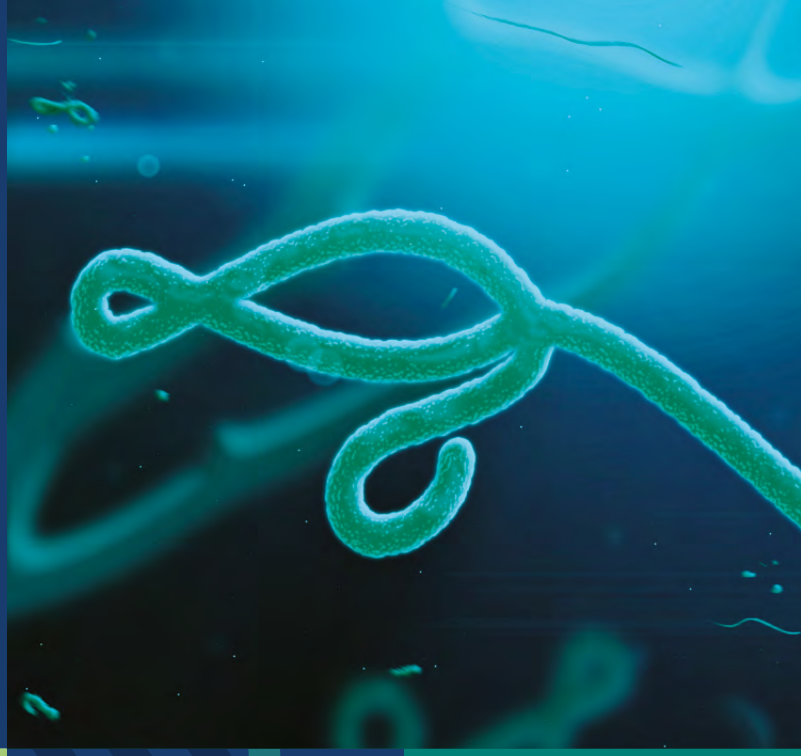
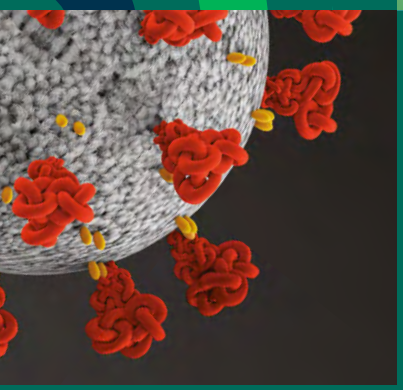
NIHR | National Institute for Health Research

HEALTH PROTECTION RESEARCH UNIT IN EMERGING AND ZOONOTIC INFECTIONS

2014–2021





UNIVERSITY OF LIVERPOOL

WELCOME

to this 2021 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 have played a major role in helping tackle the ongoing COVID-19 pandemic (p5-6), the 2014-16 Ebola epidemic in West Africa (p7-8), and the 2016-17 Zika outbreak in Latin America (p9-10).
  - zoonotic infections which are already established in the UK, such as Lyme disease (p11-12) and Hepatitis E (p13-14).
- **Engaging** and involving the public to understand and assist us with what we do (p17).
- **Training** the next generation of research students, Public Health England and university staff in the skills needed to tackle emerging infections (p18).
- **Advising** the UK Department of Health and other national and international policy makers to mitigate the risk of current and future threats.

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

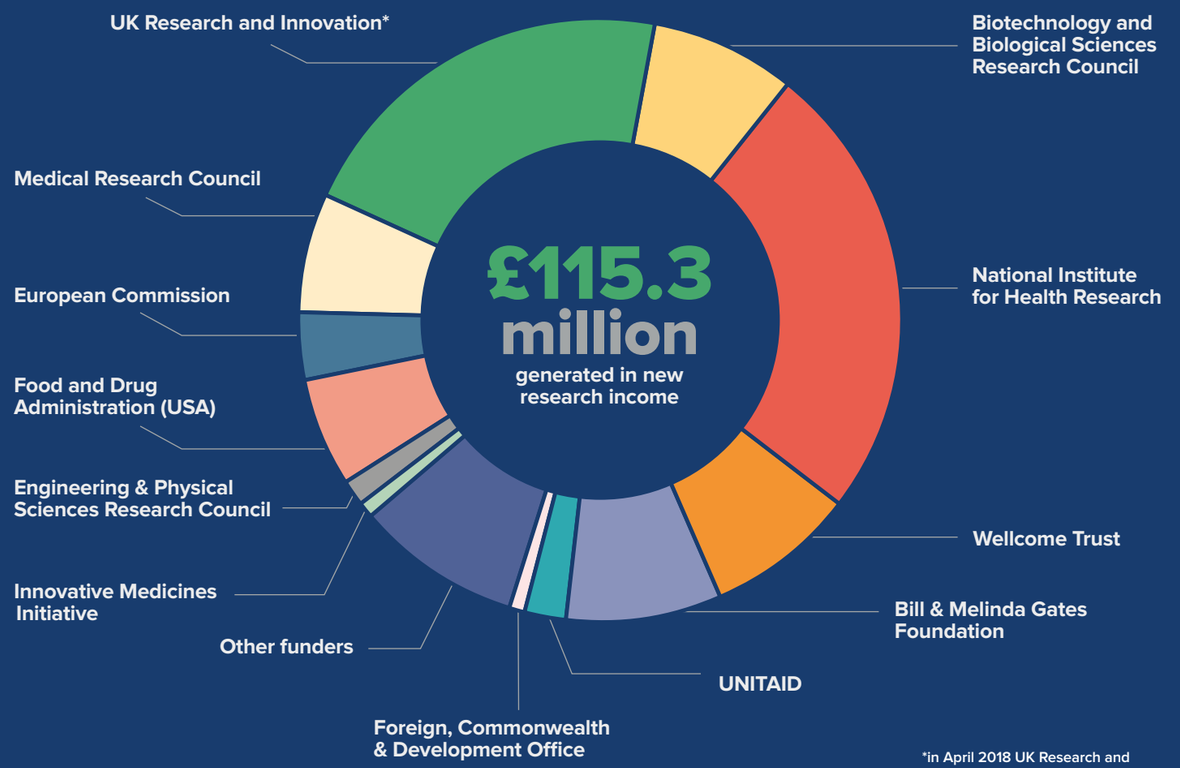
David Lalloo
Co-Director, Liverpool School of Tropical Medicine

Peter Horby
Co-Director, University of Oxford

Professor Miles Carol and **Professor Tom Solomon** at a UKRI Emergency COVID-19 funding meeting.

Emerging and Zoonotic Infections in numbers

Figures are from January 2014 to November 2020



*in April 2018 UK Research and Innovation was formed from the separate UK Research Councils

167
research publications

219
members
including 20 PhD students and 16 Post-Doctoral Research Associates fully funded by the HPRU

The Annual Scientific Meeting at Public Health England, Colindale, London, 2018

OUR STRUCTURE

Our work is organised into three major programmes, and delivered though five research themes, supported by an External Advisory Panel and a Patient and Public Involvement and Engagement Panel.

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)	Comprehensive characterisation of HCIDs (HCID-UK Study)	Determining molecular signatures in acute Ebola and Hantavirus disease	Molecular characterisation of emergent HCID pathogens using metagenomic approaches	Modelling of MERS and other HCIDs Nosocomial transmission of HCIDs
Emerging arthropod-borne diseases	Arthropod-borne and central nervous system infections study (ARBO/CNS-UK Study)	Historic genomic analysis Targeted assays for arboviruses Diagnostics for flaviviruses Flavivirus T-cell responses	Molecular tools for Tick-Borne Encephalitis Virus West Nile Virus transmission risk Wolbachia strategies for vector control	Vector-borne diseases in returning travellers
Endemic arthropod-borne diseases	Lyme disease study (Lyme-UK Study)	Improving Lyme diagnostics	Monitoring tick-borne viruses	Seroprevalence of Lyme

The graphic shows the HPRU organisation, and initial projects. In early 2020 much of the programme was repurposed towards tackling COVID-19 (see pages 5-6)

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

A COLLABORATIVE HEALTH PROTECTION RESEARCH UNIT

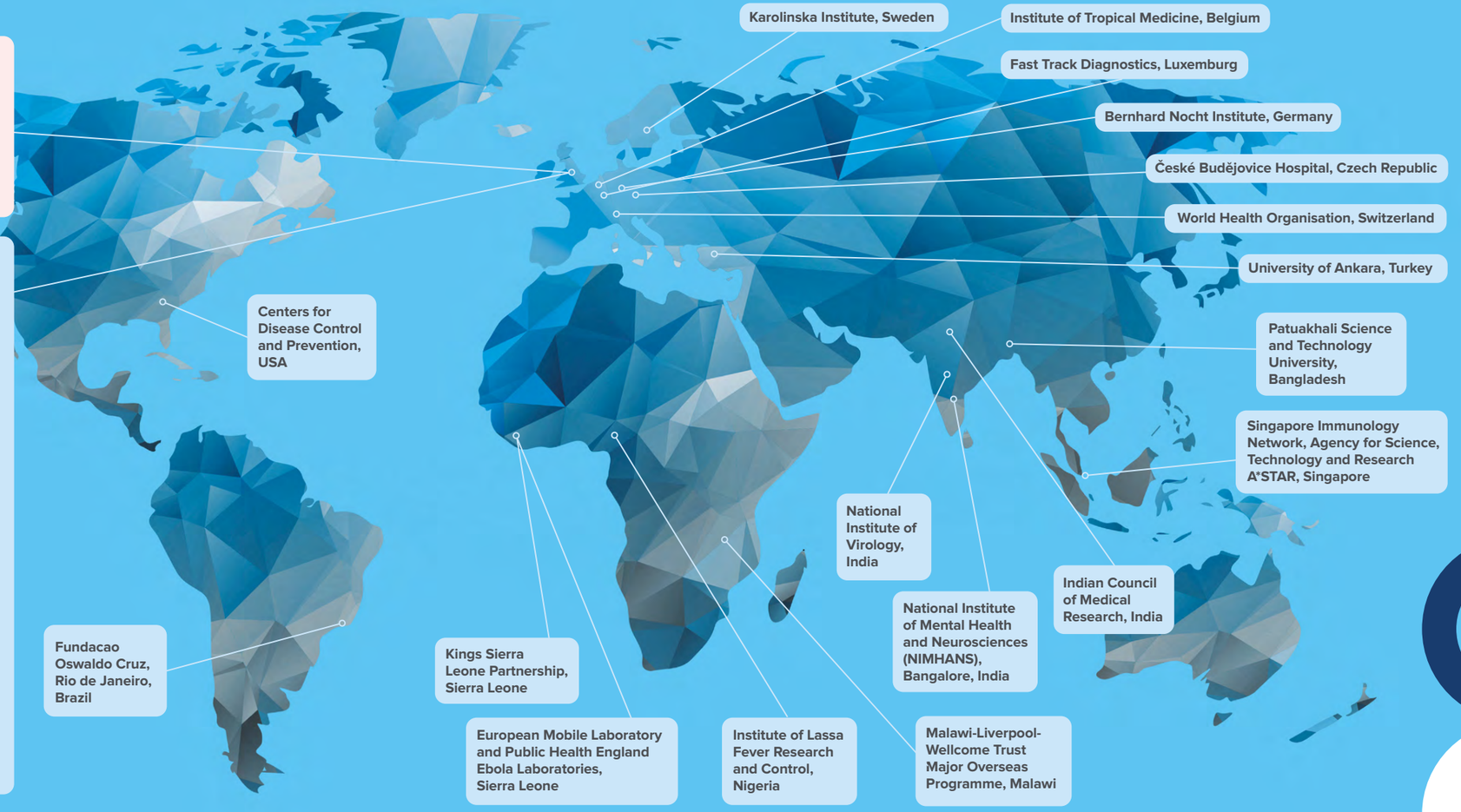
Our major UK and international partners are shown here

HPRU EZI PARTNERSHIP

- University of Liverpool
- Public Health England
- Liverpool School of Tropical Medicine
- University of Oxford

UK

- Animal and Plant Health Agency
- BioBridge Ltd, Cambridge
- Great Ormand Street Hospital, London
- HPRU in Emergency Preparedness and Response, Kings College London
- HPRU in Environmental Change and Health, London School of Hygiene and Tropical Medicine
- HPRU in Evaluation Interventions, University of Bristol
- 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 Foundation 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



THE COVID-19 PANDEMIC

Since the turn of 2020, the 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.

The major hubs for the ISARIC-4C programme and linked studies

Gathering data to understand the disease

In January 2020, as coronavirus cases were increasing in China, we decided to divert HPRU efforts to support the activation of the ISARIC (International Severe Acute Respiratory and emerging Infection Consortium) Clinical Characterisation Protocol in the UK (CCP-UK). Within days we were ready at 260 UK hospitals as the first UK patients arrived. With £10M from the MRC and NIHR we established the ISARIC coronavirus clinical characterisation consortium (4C) led by **Professor Calum Semple** with colleagues from Edinburgh and Imperial. By October 2020, 82,000 patients had been enrolled, making it the largest and most detailed study of COVID-19 in the world. It has provided essential analysis of hospitalised patients,[1,2] and reports weekly to the Department of Health and Social Care (DHSC) providing critical updates on the situation in hospitals.

The study has, to date recruited more than 80,000 hospitalised COVID-19 patients.

The ISARIC-4C study is also providing vital samples for diagnostic evaluation and for better understanding the genetic risk factors, immune response and disease mechanisms,[3,4] underpinning other major national COVID-19 programmes including GenOMICC, PHOSP-COVID, UK-CIC and COVID-CNS. Our COVID-19 work has been supported by more than £51M in new research funding, to date.

Identifying the first treatment for COVID-19

HPRU Co-Director, **Professor Peter Horby** of Oxford University led the first successful treatment trial for 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 12,000 patients continues to assess other treatments.

Liverpool collaboration to mount a local response

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, from provision of diagnostics and personal protective equipment, to the pilot of mass testing.

The Liverpool Household COVID-19 Cohort Study, led by **Professor Neil French**, is tracking and collecting COVID-19 data from households across Liverpool, providing unique samples for our studies of immune responses in asymptomatic infection. The AGILE study, led by **Professor Saye Khoo** is rapidly identifying new drugs to prevent and treat COVID-19.

"Liverpool's research response to the pandemic has been truly remarkable"
Professor Louise Kenny, Pro-Vice-Chancellor

Other projects in Liverpool explore disease in children and in pregnancy, and the use of novel diagnostics.

Neurological COVID-19 disease

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.[6] We also pooled international data to show a similar pattern globally.[7]

The work continues to be supported by more than £3M funding, with the UK consortium led by **Dr Benedict Michael** and international activities led by **Professor Tom Solomon**.

Understanding the dynamics of policy development and healthcare professionals' behaviour

Following pump-priming from the HPRU, **Professor Sally Sheard** and **Dr Nina Gobat** were awarded UKRI funding to examine the impact of UK policy decisions on front line healthcare professionals.

We are gaining unique insights into policy formation 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. **Professor Sally Sheard** said of the project, "Our approach is novel because policy decisions are usually only studied after an event, making the findings less reliable. Here we are studying them in real-time."

Public engagement

Since the news of the outbreak in China, members of the HPRU have been active across all national and international media outlets, informing the public about the disease and the response, as well as explaining the science of our own work.

POLICY IMPACT

HPRU members have been advising locally, nationally and internationally on the COVID-19 response. Our members are 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 Parliamentary Select Committees.

The next five years

The HPRU will continue to play a major role in the UK and international 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**
- **UK-CIC**
- **COVID-CNS**
- **COVID-Neuro Global**

[1] Knight SR, et al. BMJ 2020; 370: m333 370:m333.
[2] Peng Y, et al. Nature Immunol 2020; Sep 4.
[3] Pairo-Castineira E, et al. Nature 2020.
[4] Peng Y, et al. Nat Immunol 2020; 21: 1336-45.
[5] The RECOVERY Collaborative Group, NEJM 2020; July 17.
[6] Varatharaj A, et al, Lancet Psychiatry 2020; 7: 875-82.
[7] Ellul et al, Lancet Neurol 2020; 19: 767-83.

CONTROLLING 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 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 Government's Chief Scientific Advisor, and subsequently streamlined information was made available on the web. The overall response of UK healthcare workers was fantastic, with more than 3,000 personnel deployed.

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

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 wrote guidance for UK clinicians,[4] and contributed to weekly teleconferences with the Department of Health, all of which proved helpful when the first UK patients arrived.

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 **Professor 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 US$1M from the US Defence Advanced Research Project Agency we have been developing novel therapeutics for 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 subsequent 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 was used in the subsequent Ebola outbreak in the Democratic Republic of the Congo.

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? 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]

The Legacy

The West African 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.[11]

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 Tom Solomon**, submitted written evidence to the Committee on behalf of the HPRU, and and was also asked to give oral evidence. Our recommendations were included in the Committee Report and subsequent 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

1 Solomon T, et al. BMJ 2014; 349: g6443.
2 Turtle L, et al 2015 Plos one doi:10.1371/journal.pone.0120013.
3 Read JM, et al. Lancet 2015; 385: 23-4.
4 Fletcher TE, et al. BMJ 2014; 349: g5079.
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.
9 Quick J, et al. Nature 2016; 530: 228-32.
10 Dudas G, et al. Nature 2017; 544: 309-15.
11 Kafetzopoulou LE, et al. Science 2019; 363: 74-7.

TACKLING ZIKA IN LATIN AMERICA

The capability of the HPRU to respond to global public health emergencies of international concern was demonstrated again during the Zika epidemic in Latin America in 2016. We were quick to recognise the emergence of Zika virus in Brazil as a potential problem, and so were well placed to respond to the growing emergency. We 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 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 the research programme.

Through the MRC Zika Rapid Response Funding HPRU investigators were awarded £800,000 for a range of projects including examining the links between the neurological disease, 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 ZikaPLAN (Zika Preparedness Latin America Network), an €11M EU Horizon 2020 project, of which €1M was awarded to Liverpool. HPRU investigators **Professor Neil French** and **Dr Lance Turtle** led a collaborative project to develop Zika vaccines, with £4.7M from the Department of Health and Social Care.

£4.7 million was awarded to Liverpool for our research on Zika virus vaccines.

Improved understanding of neurological disease

Through clinical characterisation of Zika-associated neurological disease, we were able to understand the full spectrum. 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, and 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 were able to understand the clinical spectrum of neuro-zika

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.[5]

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 to take place.

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. An ELISA assay we helped develop, had high sensitivity and specificity, as well as being low-cost, and simple to use.[6,7]

With no approved vaccine or treatment, research in this area was a priority.

With no approved vaccine or treatment, research in this area was a priority. We are developing two Zika virus vaccines and candidates for clinical trial in humans. **Professor Neil French** commented "Although the Zika outbreak has slowed, there remains a significant risk, and the changing climate raises the possibility of future major epidemics. A 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 the UK Department of Health Strategic Advisory Group on Emergencies (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.

1 Solomon T, et al, Lancet ID 2016; 16: 402-4.
2 Brasil P, et al, Lancet 2016; 387: 1482.
3 Leonhard SE, et al, Pract Neurol 2018; 18:271-77.
4 Caminade C, et al, PNAS, 2017. 114:119-124.
5 Blagrove MSC et al, Proc Biol Sci 2020; 287: 20200119.
6 Balsemeda A, et al, PNAS, 2017; 114:8384-8389.
7 Tedder RS, et al. PLoS One. 2019 Aug 2;14:e0215708.

UNDERSTANDING LYME DISEASE IN THE UK

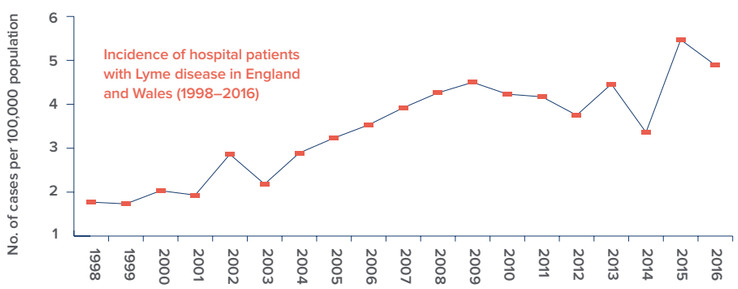
Lyme is the most common vector-borne disease of humans in the UK, and our research over the last five years has shown that it is growing in importance. Despite great public and media interest and concern, knowledge about the incidence, diagnosis and management of Lyme and other tick-borne diseases in 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.

Lyme surveillance to inform public health

Surveillance for Lyme and other tick-borne disease can be time and labour intensive. Research led by **Professor 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.[1] Such approaches are a good example of the *One Health* approach, which emphasises that the health of humans, animals and the environment are linked.

The One Health approach emphasises that the health of humans, animals and the environment are linked.

Our analysis of data from Public Health England laboratories, hospitals and GPs showed a 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.[2] Interestingly, whereas most infectious diseases are linked to poverty, the results suggested that Lyme disease patients originate from areas with higher socioeconomic status and disproportionately in rural areas. Work led by **Dr Roberto Vivancos** showed a six-fold increase in Lyme cases seen in hospitals over an 18 year period, from 1998-2015 (below).[3]



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. **Dr Jolyon Medlock** has led extensive field investigation and statistical modelling of tick activity, looking also for the prevalence of the Lyme bacteria *Borrelia burgdorferi*.[4] In collaboration with the HPRU in Environmental Change, we are using UK Met Office data to better predict the distribution of the Lyme tick, and other tick vectors.[5]

Engaging widely and increasing awareness

There is great misunderstanding and fear around Lyme disease and its manifestations. We have worked closely with patients, the public and interest groups, to arrive at a common understanding. Through our HPRU 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 define shared research priorities.

To improve awareness and reduce cases, we helped produce the Public Health England "Tick Toolkit" and a "Lyme Disease: Signs and Symptoms" leaflet, which were made available on the GOV.UK website. These were then adapted into materials for primary school children using funding from the HPRU's Strategic Patient and Public Involvement and Engagement Fund.

POLICY IMPACT

HPRU members contributed to the development of the NICE guidelines for diagnosing and managing Lyme, and the NICE quality standards for Lyme disease, which also cover measures for raising public awareness about Lyme disease prevention.

The next five years

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

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.

[1] Tulloch JSP, et al. Epidemiological infections 2017. doi. org/10.1017/S0950268817000826.

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

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

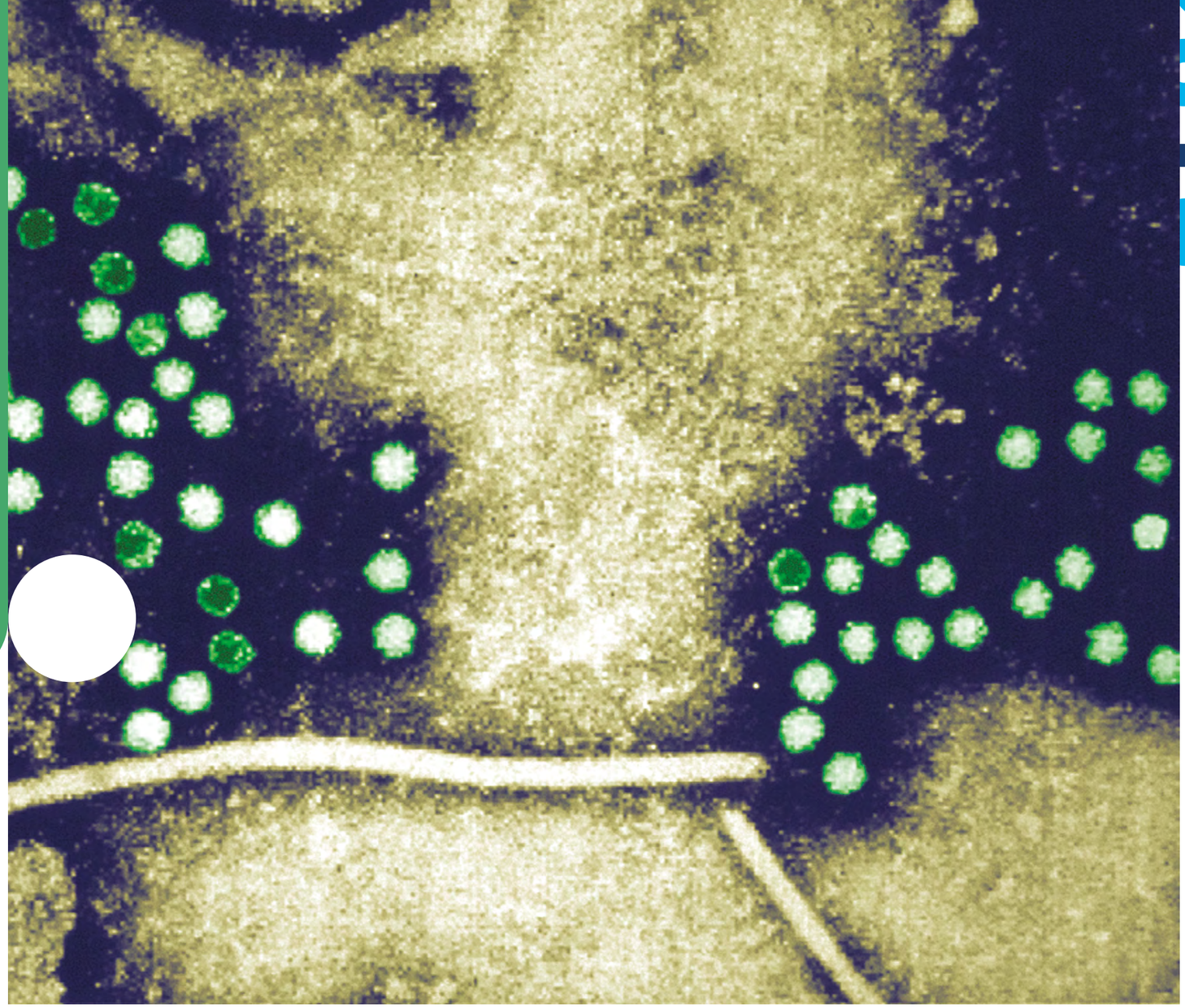
[4] Medlock JM, et al 2018 Int. J. Environ. Res. Public Health 2018;15:214.

[5] Medlock JM, Leach SA . Lancet Infect Dis 2015;15:721-30.

Defining Lyme Research Priorities – a joint conference with patient charities hosted by the HPRU in November 2019.

GROWTH IN HEPATITIS E

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

In England alone, it is estimated that between 100,000 and 150,000 new cases of Hepatitis E infection occur annually.

Exposure through food

Since 2010, foodborne associated human Hepatitis E infections have increased in England and Wales.[1] Similar to other European countries, this increase is associated with the emergence of a new phylotype, Hepatitis E G3-group 2. Our study on Hepatitis E-infected blood donors identified the consumption of pork products from the supermarket as a critical risk factor including products originating outside the UK.[2] This study has helped inform policy makers bringing changes to animal husbandry and food processing methods.[3]

Enhanced screening of blood donors

Hepatitis E infection can also be transmitted via blood. New screening of blood donations has provided an opportunity to better monitor the epidemiology of the infection in the general population.[4] Hepatitis E positive donors complete an enhanced surveillance questionnaire which assesses potential risk factors for infection and allows us to gain a greater understanding of the features of asymptomatic, indigenously acquired disease.

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. 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 of 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 the infection.[6]

Ongoing surveillance is required to protect those most vulnerable from the severe consequences of Hepatitis E infection.

1 Tedder RS, et al., Transfusion. 2016;56:1529-36.

2 Said B, et al. Epidemiol Infect. 2017;145:2417-2423.

3 PHE (2019). Public health operational guidelines for hepatitis E.

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

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

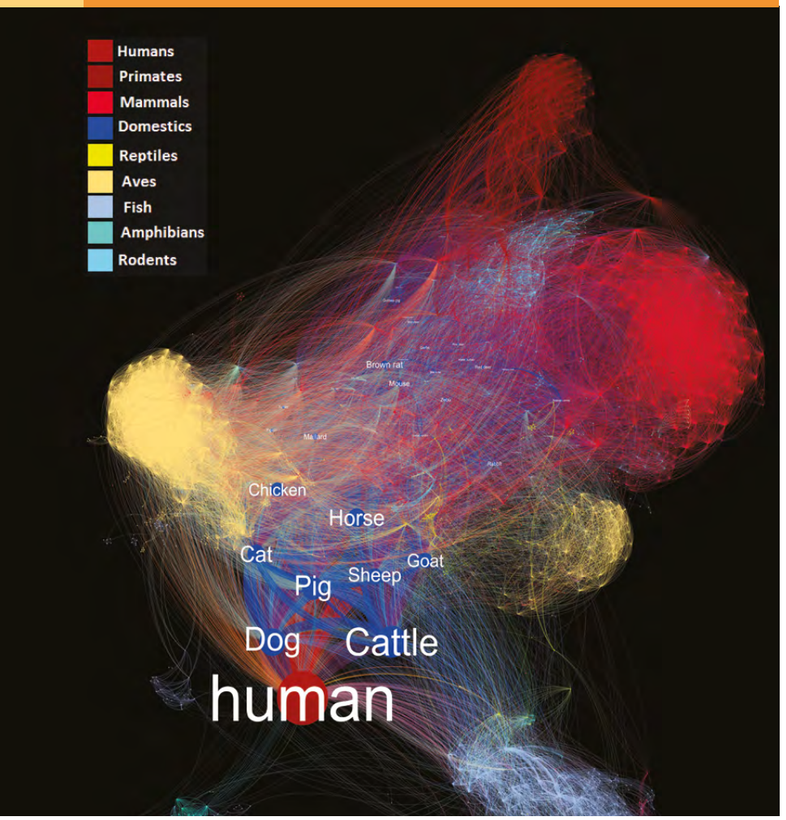
6 Oeser C, et al., 2019, J Infect D is. 2019 Jul 31;220(5):802-810. doi: 10.1093/infdis/jiz207.

POLICY IMPACT

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

- The 'Public Health Operational Guidelines for Hepatitis E' written by Public Health England to enable Health Protection Teams to respond appropriately to laboratory reports and clinical notifications of Hepatitis E infection.
- The report of the Government's UK Zoonoses, Animal Diseases and Infections (UKZADI) Group 'Policy Options for Reducing the Risk of Hepatitis E Virus in the Food Chain' which proposes policy options to mitigate the risks to public health.

EMERGING THREATS



CLIMATE AND VECTORS

Several vector-borne diseases have recently emerged in Europe, and some threaten the UK. Invasive mosquitoes may bring new arthropod-borne viruses (arboviruses) into the UK, and indigenous UK mosquito species may support their onward transmission.[1] There are major challenges to researching pathogen transmission, requiring sophisticated high containment laboratories to keep the insects and pathogens isolated. By pooling our collective expertise in Liverpool and Public Health England through the HPRU, we have developed the systems to take this research forward. We are now licenced to work with nine new viruses, including West Nile, Japanese encephalitis, and Zika. We found that the UK has indigenous mosquitoes that are competent to transmit these three dangerous viruses and this could occasionally happen, for example on a very hot day. Currently, the country is too cold for any substantial transmission to take place.

The UK has indigenous mosquitoes that are competent to transmit these three dangerous viruses.

Our broader review, highlighted that changing climate, coupled with other socio-economic and environmental factors,[2] could lead to these viruses becoming established in the UK to cause disease. We have recently shown that the Asian tiger mosquito, which transmits dengue, chikungunya and Zika causing 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.


Liana Kafetzopoulou in the Lassa laboratory

LASSA

Early in 2018, Nigeria was hit by its largest ever outbreak of Lassa fever. Humans become infected with Lassa fever virus by contact with food or household items contaminated with rodent urine or faeces containing the virus. 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 new 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 study virus in the field at the epicenter of the unfolding outbreak. 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.[6] This informed the Nigerian Government response, 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 fever virus using MinION in the field.

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 £700,000 from the Biotechnology and Biological Sciences Research Council 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 (see also page 11).

BRAIN INFECTIONS

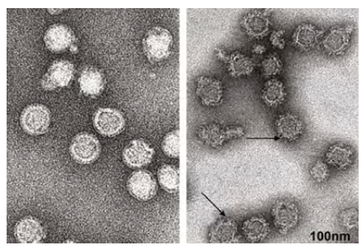
Brain infections, many of which are zoonotic and/or emerging, are a major disease burden in the UK and around the world. They can also be important sentinels of disease emergence. To enhance surveillance in the NHS, we delineated the causes of meningitis,[4] and led national guidelines to improve recognition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

To strengthen the HPRU work on neurological manifestations of Zika we joined European partners to form ZikaPLAN (see page 9). 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 our work in Brazil India and Malawi.


Bedside teaching in Vellore India through the NIHR *Brain Infections Global* programme.

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. This 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 brain inflammation and swelling (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.



News of these findings was picked up by major news outlets and provided an opportunity to share messages about tick awareness and bite prevention.

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

2 Medlock JM, et al, Lancet ID 2015;6:721-730.

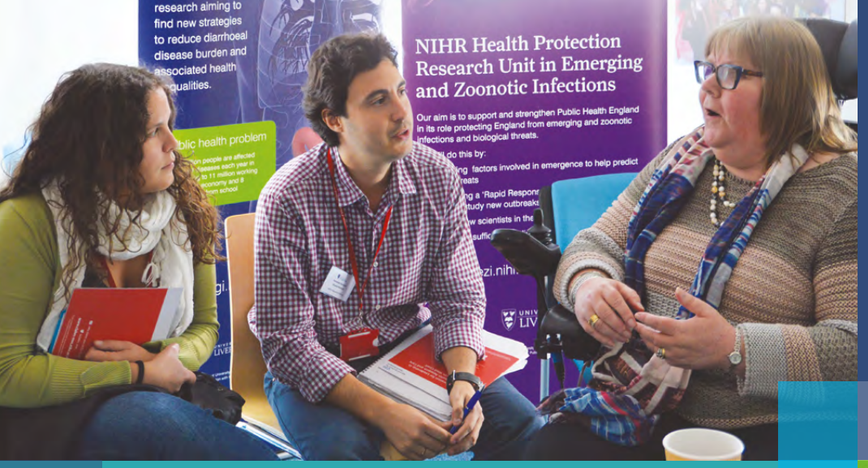
3 Metlemann S, et al, J R Soc Interface 2019; https://doi.org/10.1098/rsif.2018.0761.

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

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

6 Kafetzopoulou LE, et al Science 2019:363:74-7.

7 Holding M, et al. Tick-borne encephalitis virus, United Kingdom. Emerg Infect Dis. 2020;26:90-96.



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

PUBLIC ENGAGEMENT

Big Bang Festival

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 and Patient Engagement and Involvement Panel, which reviews and advises on all projects and grant proposals.

We also involve the public in the research itself, for example they collected ticks as part of our 2017 surveillance programme. We explain our science to the public through many imaginative and creative engagement events. These range from a hosting a workshop in Brazil with families affected by Zika, to events at festivals, including Cheltenham, Big Bang, and Bluedot, to our “Bug Terror – Outbreak in a Box” game for children.

Infectious fun at Bluedot Festival 2018

Zika Family Workshop in Brazil

STRENGTHENING CAPACITY

Three of our trainees (Charlotte Robin, John Tulloch and Ellen Murphy) 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 our training programme, led by **Professor Julian Hiscox** and **Dr Lance Turtle**. From 2014-20 we trained 20 PhD students and 11 Post Doctoral Researchers, the vast majority of whom have continued with careers in emerging infections research or public health. We offer training to work with dangerous pathogens in the Containment Level 3 Laboratories to all HPRU students and post-docs, as well as others beyond the HPRU. This proved prescient at the start of the COVID-19 pandemic. In addition the HPRU trains researchers to work with the most dangerous High Containment Infectious Diseases, such as Ebola and Lassa Fever, in Containment Level 4 Laboratories.

Our large training programme on working with dangerous pathogens proved prescient at the start of the COVID-19 pandemic.

National HPRU Academy

To strengthen training across all eleven HPRUs, and develop the wider cohort of HPRU scientists, we took the leadership in establishing the first National HPRU Academy Meeting in 2017. With 58 PhD students from all eleven HPRUs, the meeting was co-chaired by our Director **Professor Tom Solomon**, and **Professor Jim McLauchlin**, lead Public Health Microbiologist, Public Health England. All HPRUs are now included as part of the broader NIHR Academy.

NIHR | National Institute for Health Research

National Institute for Health Research (NIHR) Health Protection Research Unit in Emerging and Zoonotic Infections

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Photo credits

Page 9 – Zika Laboratory: Tom Solomon.

Page 13 – Hepatitis E Virus: BSIP/UIG Via Getty Images.

Page 16 – Tick-borne encephalitis virus: Stiasny K, et al PLoS Pathog 2007;3:e20.