NIHR Health Protection Research Units
Celebrating five years of health protection research
Introduction

In April 2014, 13 Health Protection Research Units (HPRUs) were established as partnerships between Public Health England (PHE) and eight UK universities, with funding from the National Institute for Health Research (NIHR).

The NIHR HPRUs provide evidence in key priority areas to support PHE’s remit to protect the public’s health, and contribute to realising the vision of the NIHR to improve and protect the health of the nation.

The HPRUs are helping to create an environment that encourages world class, multidisciplinary health protection research to thrive in England. This includes providing high-quality research to inform decision making by public health professionals, and translating these advances into benefits for patients and the public.

This document provides details of the health protection issues and challenges addressed by the clinicians and scientists working within NIHR HPRUs. The methods used are set out here, alongside the evidence provided and its contribution to useful solutions.

HPRUs remain responsive to emerging threats and incidents by retaining a level of capacity and providing emergency staff in the event of major health protection incidents, allowing them to address emerging health protection research requirements.

The collection includes research to:

- Reduce and control the transmission of life-threatening viruses such as Ebola and Zika, as well as meningitis and sexually transmitted diseases (STDs)
- Reduce the incidence of severe gastroenteritis in children with the introduction of a new vaccine to the immunisation schedule
- Support environmental studies that promote the benefits of green spaces for the health and wellbeing of the public, which can support planning at a local level
- Trace food contamination pathways through Europe back to a single source of the disease
- Provide clinicians with the necessary information to treat patients and inform the public about the possible consequences of taking legal highs.
Priority areas for NIHR HPRUs

Key priority areas have been identified that will have the greatest impact on public health. Each HPRU has a substantial portfolio of internationally-leading research: the majority (11) focus on priority topics and two are cross-cutting. The initiative as a whole is marked by collaborations within and across units that add significantly to a body of achievements, beyond what could be realised by units operating separately.

Topic-based priority areas:
- Blood-borne and sexually transmitted infections
- Chemical and radiation threats and hazards
- Emergency preparedness and response
- Emerging infections (including zoonoses) and biological threats
- Environmental change and health
- Gastrointestinal infections
- Healthcare associated infections and antimicrobial resistance
- Health impact of environmental hazards
- Immunisation
- Respiratory infections

Cross-cutting priority areas:
- Evaluation of interventions
- Modelling methodology

Together, the NIHR HPRUs use multidisciplinary research methods that provide evidence to improve the existing knowledge base and inform decision makers, translating knowledge into benefits for patients and the public while being responsive to emerging health protection threats and incidents.
Case study 1:
The West African Ebola virus epidemic

NIHR HPRU in Emerging and Zoonotic Infections and NIHR HPRU in Emergency Preparedness and Response

Zoonotic threats (those that spread from animals to humans) can be unpredictable, so rapid responses to emerging threats are required. Ebola virus disease was regarded as a potential risk, but an outbreak of the size that began in 2014 was unprecedented.

When the Ebola outbreak began in West Africa, the NIHR HPRU in Emerging and Zoonotic Infections and NIHR HPRU in Emergency Preparedness and Response assessed the risk of it spreading through airline travel. Research predicted that the USA was the most likely country outside Africa to report the first case, and that the UK would probably report a case before the end of the year. Both predictions proved correct.

To help control the disease in West Africa, UK healthcare workers were needed. The HPRU highlighted that the lack of information, rather than a fear of infection, was the main factor preventing UK staff from signing up to help. New information improved understanding and increased the number of volunteers. In the UK, the HPRU raised awareness that all hospitals should prepare to receive patients with Ebola-like illness and updated clinicians’ knowledge of the disease.

To improve diagnosis of Ebola, PHE deployed three field diagnostic laboratories in Sierra Leone, and worked with blood products from patients who had survived in order to develop treatments. Research staff and students in the HPRU were rapidly trained and travelled to work in the laboratories. Work in Africa and the UK included evaluation of new rapid diagnostic tests, supporting the trialling of a new antiviral drug, and developing understanding of how the Ebola virus genome evolved during the outbreak.

One factor that prolonged the Ebola epidemic was a lack of appropriate means to treat and dispose of contaminated waste material, particularly that containing blood from patients in the later stages of the disease. A patient in a West African Ebola treatment centre could produce up to 300 litres of fluid and other medical waste per day, all of which can carry the virus. It was essential to minimise the risk of transmitting disease through the waste.
Assembling an international working group with expertise (including hazard control, virology, safe water and engineering sanitation, infection control, public health and humanitarian aid delivery in low resource settings), the HPRU in Emergency Preparedness and Response scrutinised the entire bodily waste-handling chain, from patient bedside via temporary storage (buckets, latrines, vehicles) to the final disposal site.

Researchers used Hazard Analysis of Critical Control Points (HACCP) to identify when the risk of disease transmission was high, medium or low. Thirteen critical control points were identified and recommendations were made for reducing the risk at each one.

The successful conclusion of this work depended on scientific understanding of the virus, and a realistic appraisal of what was feasible for waste disposal personnel in West Africa. This balanced ‘real world’ approach is also desirable in devising risk reduction strategies, procedures and policies in well-resourced settings such as the UK.

Case Study 2: Zika virus in Brazil
NIHR HPRU in Emerging and Zoonotic infections

In 2015, the NIHR HPRU in Emerging and Zoonotic infections was working alongside other national and international health emergency response teams in Brazil, preparing to combat a potential epidemic. A series of small research projects was initiated by researchers in the UK and Latin America, looking at diagnosis,
clinical surveillance, vector (mosquito) biology, immunology and disease mechanism studies.

The researchers’ expertise and rapid analytic abilities – pre-empting rather than merely responding – meant that they were the first to establish the association between the neurological complication Guillain-Barre Syndrome and acute Zika virus infection. The Unit also investigated the risk factors for Zika infection, examined mosquito transmission to help predict further spread and contributed to development of vaccines for future protection.

Case Study 3: Severe infection in surgery patients

NIHR HPRU in Respiratory infections

In 2014, six cases of severe bacterial infection were reported in cardiac surgery patients in Zurich, Switzerland. These were followed by similar cases in the Netherlands, Germany and the USA, raising concerns that surgery patients in multiple hospitals and countries were at risk of infection from an organism known as Mycobacteria.

Working to confirm the source of the infection and look for a solution, the NIHR HPRU in Respiratory infections launched an urgent investigation in the UK to assess risk of infection in surgery. A possible association was found with the heater-cooler units (HCUs) used during cardiopulmonary bypass surgery.

The investigation followed a number of routes:
- patients diagnosed with Mycobacterial infection who had undergone heart bypass surgery in the previous four years;
- patients who had an infection consistent with the bacteria entering the body during an operation; and
- patients due to undergo heart surgery.

The HCUs themselves were also studied, which eventually led the HPRU to the solution. It directly informed cardiac centres of the risk from the heater-cooler units, and advised them on how to seal the HCUs in order to minimise the risk to patients receiving life-saving heart surgery.
Case Study 4: Salmonella infection in poultry and eggs
NIHR HPRU in Gastrointestinal Infections

In the summer of 2014 there was a major outbreak of Salmonella, with over 350 cases reported across Europe (the UK, Germany, Austria, France and Luxembourg).

Researchers in the NIHR HPRU in Gastrointestinal Infections, in collaboration with public health colleagues globally, used whole genome sequencing (WGS) to analyse the DNA of over 400 Salmonella samples. Because the WGS results are digital, they could be exchanged efficiently between four institutions in different countries. The combined results allowed the contamination to be traced through the food chain, and showed a clear statistical correlation between the distribution of eggs and the areas of Salmonella outbreak; the source of infection was a single supplier. The level of insight into the outbreak provided by international collaboration on WGS supported legal activities, and the egg producer was prosecuted.
Case Study 5: Predicting resistance to antimicrobial drugs
NIHR HPRU in Healthcare Associated Infections and Antimicrobial Resistance

Carbapenems are a type of antibiotic administered to a patient when all other drug options have failed: an antimicrobial of last resort. However the number of patients infected with Carbapenem-resistant Enterobacteriacea (CPE) has risen. Patients with CPE infection have only a 50% chance of survival.

Using data about the consumption of antimicrobial drugs, the NIHR HPRU in Healthcare Associated Infections and Antimicrobial Resistance developed methodology in the form of an online tool to forecast the emergence of CPE. The tool enables not just the detection of epidemics but also allows them to be predicted. This research can have a hugely beneficial impact on health policy and practice for patients in healthcare settings.

Case Study 6: Managing antimicrobial drugs
NIHR HPRU in Healthcare Associated Infections and Antimicrobial Resistance and NIHR HPRU in Modelling Methodology

Infections caused by the Clostridium difficile (C. difficile) bacteria are traditionally seen in elderly, hospitalised patients who have already been given antibiotics, and severe cases have a high mortality rate. An outbreak in the mid-2000s caused concern about serious failings in infection control, but then rates of infection declined dramatically.

Researchers from the NIHR HPRU in Healthcare Associated Infections and Antimicrobial Resistance and NIHR HPRU in Modelling Methodology from many different specialities – laboratory scientists, biostatisticians, statistical geneticists and clinicians – worked collaboratively on the project. They processed enormous amounts of information about the incidence of C. difficile infection (CDI),
antimicrobial prescribing data and data from whole genome sequencing (WGS) of over 4,000 *C. difficile* samples.

They aimed to understand why the UK incidence of CDI declined so rapidly since 2007, aware that the UK was almost unique in accomplishing this. They found that the incidence of CDI was most closely linked with national levels of prescribing fluoroquinolone antibiotics. The use of fluoroquinolones had allowed resistant strains of *C. difficile* bacteria to flourish. Cases of CDI fell when fluoroquinolone use was restricted as part of the effort to control the outbreak. This led to a decline in infections caused by resistant *C. difficile*, and an 80% fall in total infections in the UK.

Research findings are informing policy on how to avoid further outbreaks in the UK, where levels of fluoroquinolone prescribing are increasing again, as well as informing healthcare professionals in countries where rates of CDI remain high.

![C. difficile infections in the UK](image)

**Case Study 7: Cost effectiveness of universal meningitis vaccination**

**NIHR HPRU on Evaluation of Interventions**

Meningococcal disease refers to a group of infectious diseases caused by the bacteria *Neisseria meningitidis*. It is a leading cause of disease and death in infants in the UK, and a major public health concern. The disease progresses very rapidly even with appropriate medical intervention, and survivors can be left disabled. Vaccination is the key to prevention. A vaccine against group C meningitis (MenC) was introduced in 1999, and successfully and substantially reduced cases of this type. In 2013 Bexsero was licensed for use in Europe against group B (MenB). In the UK, vaccines can only be introduced into the routine schedule if recommended by
the Joint Committee on Vaccination and Immunisation (JCVI), and then only if the vaccine is deemed cost-effective.

Researchers at the NIHR HPRU on Evaluation of Interventions developed mathematical and economic models to assess the potential reductions in meningococcal disease cases of different vaccination strategies, and the cost-effectiveness of these interventions. The models predicted that introducing routine Bexsero vaccination in infants would be the most effective way to reduce infections in the short term, and would be value for money for the NHS. Additionally, 26% of cases could be averted in the first five years of the programme.

The HPRU’s work was critical to the JCVI’s recommendation to introduce an infant vaccination programme. In September 2015, the UK became the first country in the world to routinely offer this vaccine, which is now made available free on the NHS to more than 700,000 babies a year.

**Case Study 8: Treating Hepatitis C virus infections**

**NIHR HPRU in Blood Borne and Sexually Transmitted Infections**

The use of direct-acting antiviral drugs (DAAs) has revolutionised treatment of hepatitis C virus (HCV). However their prohibitive cost means their use will be limited, at least in the near future. Infections with HCV have increased among HIV-positive men who have sex with men (MSM), and this is an increasing public health concern as HCV is a leading cause of death among HIV-positive people.

It is not clear what proportion of people living with both HIV and HCV will be able to receive DAAs, nor how people with HCV will be prioritised to receive this treatment. Modelling work has suggested that treating HCV in people who inject drugs could prevent the onward transmission of HCV in this group but there is no evidence to support a preventive role of treatment in HIV-positive MSM.

Researchers from the NIHR HPRU in Blood Borne and Sexually Transmitted Infections modelled the likely impact of different interventions on HCV prevalence in MSM co-infected with HIV and HCV. They showed that substantial reductions in HCV transmissions in MSM could be achieved through a combination method: scaling-up the use of DAAs in this group, increased use of behavioural interventions
such as increased training among sexual health/HIV clinic staff, and the distribution of safe 'chemsex' kits. This work will allow treatment to be prioritised for groups where the potential benefit is greatest.

**Case study 9: The UK Infant Rotavirus Immunisation Programme**

**NIHR HPRU in Immunisation**

Rotavirus is the most common cause of severe gastroenteritis among young children worldwide, with nearly all children experiencing at least one episode by the age of five, resulting in considerable morbidity and healthcare utilisation.

The UK introduced the oral rotavirus vaccine (Rotarix®) immunisation programme in July 2013, which resulted in rapid and large reductions in hospitalisations for acute gastroenteritis across the population through a combination of direct protection for vaccinated infants and indirect (herd) protection for older, unvaccinated children and adults.

The **NIHR HPRU in Immunisation** estimated the reduction in health care utilisation for acute gastroenteritis and the associated healthcare costs averted in the first year of the vaccination programme.

HPRU researchers used anonymised, routinely collected NHS contact data from general practices, hospitals and emergency departments in England, and age-stratified time-series analyses to compare rates of acute gastroenteritis for children up to five in the first year after rotavirus vaccine introduction (July 2013-June 2014) with rates in the pre-vaccination era (up to June 2013). They estimated the number of cases averted, by comparing the observed numbers of acute gastroenteritis cases in 2013-2014 to the numbers predicted from the time-series models. Costs per visit were calculated from a number of NHS data sources to estimate the costs averted in each healthcare setting.

Across all three settings (general practice, emergency departments, and hospitalisations) an estimated 87,376 (95% prediction interval: 62,588-113,561) acute gastroenteritis visits by children younger than 5 years were averted during the first year of the programme (2013-14), which was associated with an estimated £12.5 million reduction in healthcare costs.
These findings highlight yet another success of the UK national immunisation programme and provide additional evidence to support the oral infant rotavirus vaccine.

**Case Study 10: Effective decontamination in mass casualty, chemical emergencies**

**NIHR HPRU in Emergency Preparedness and Response**

When groups of people are exposed to potentially hazardous chemicals on the skin, emergency decontamination may involve showering or spraying them with water – interim wet decontamination (IWD). However many people do not feel comfortable disrobing in public. If people kept their clothes on, might the transfer of chemicals to the skin be increased?

The [NIHR HPRU in Emergency Preparedness and Response](#) investigated whether allowing chemically-contaminated people to keep their clothes on would reduce the effectiveness of the decontamination process. They found that for chemicals that mimic chemical agents such as sulfur mustard (mustard gas), where IWD was highly effective at reducing absorption through the skin, casualties in most circumstances could be showered fully clothed without a significant impact on absorption into the skin. The IWD should be done promptly and, importantly, involves little specialised equipment beyond what is routinely fitted to fire appliances.

*Mass casualty decontamination test*
Case Study 11: Managing Novel Psychoactive Substances (NPS)

NIHR HPRU in Chemical and Radiation Threats and Hazards

The emergence of NPS (often called ‘legal highs’) is a public health concern, with numbers of users increasing, alongside related hospital visits and fatalities. The substantial number of new substances emerging each year, and the lack of information about their pharmacology and toxicology, is also an issue – the lack of information on the content of commonly used substances delays the treatment of patients and wider public health actions.

The NIHR HPRU in Chemical and Radiation Threats and Hazards launched the Identification of Novel Psychoactive Substances (IONA) Study to provide analytical confirmation of which substances were present in cases of severe toxicity. The side effects of each identified substance were also mapped. The IONA Study data enabled research on specific chemicals to provide clinicians, public health professionals, the police and members of the public with robust evidence about the clinical consequences of exposure to different NPS.

Information from IONA is accessible through the National Poisons Information Service and will allow monitoring of the impact on NPS of actions taken, including the 2016 Psychoactive Substances Act.

*Novel Psychoactive Substances (‘legal highs’)*
Lack of physical activity is a major determinant of ill health. Regular physical activity is associated with decreased risk of obesity, coronary heart disease, diabetes, some cancers and mental ill health. In England, only 34% of adults report meeting the minimum recommended 150 minutes of activity per week. Natural environments (green and blue space) allow physical activity among those who are reluctant or unable to participate in organised sports or gym-related activities. Many local authorities are experiencing financial challenges, with detrimental cuts to green infrastructure investment. Evidence of the benefits of green spaces is essential to support decision-making by planning and public health officers at local government level.

Researchers from the NIHR HPRU in Environmental Change and Health analysed data from the world’s largest study on recreational visits to natural places such as parks, woods and beaches, and estimated that over 8 million adults in England engage in green exercise each week. (The Monitor of Engagement with the Natural Environment survey has over 280,000 participants and has been running for the last six years.) Green exercise was defined in the study as nature-based activities of moderate/vigorous intensity and lasting over 30 minutes, including dog walking, running, horse riding, outdoor swimming and cycling.

Using two separate costing methodologies – from the National Institute for Health and Care Excellence (NICE) and from the World Health Organisation (WHO) – over 1.3 billion annual green exercise visits were recognised, delivering health benefits worth up to £2.2 billion a year. The findings provide evidence to justify maintaining and investing in the quality and accessibility of parks and wild places that may be under pressure from development and reduced resources.
Case Study 13: Composting facilities and respiratory hospital admission risk
NIHR HPRU on Health Impact of Environmental Hazards

In the UK, increasing amounts of waste and the desire to relieve the pressure on landfill sites and reduce greenhouse gas emissions has led to increases in alternative, environmentally friendly waste disposal methods, such as composting. With proper control, composting is an effective and sustainable method for waste disposal. However, large scale composting can release biological species into the air (bioaerosols) that have the potential to cause or exacerbate lung diseases such as asthma and bronchitis.

Working with researchers both nationally and internationally, researchers at the NIHR HPRU on Health Impact of Environmental Hazards examined the risk of respiratory hospital admissions within 2,500m of all 148 English large-scale composting facilities in 2008/10.

Statistical analysis models were adjusted for age, sex, deprivation and tobacco sales. Analysing almost 35,000 respiratory hospital admissions, there were no significant trends at defined distances of 250-750m, 750-1500m or 1,500-2,500m from the composting sites. Using a continuous measure of distance, a small association was seen (p = 0.054) with total respiratory admissions corresponding to a 1.5% (95% CI: 0.0–2.9%) decrease in risk if moving from 251m to 501m. However that was not statistically significant and neither was there any significant association for subgroups of respiratory infections, asthma or chronic obstructive pulmonary disease.

Working on potential environmental hazards
Case Study 14: Priorities for action on the social determinants of health

NIHR HPRU in Modelling Methodology

Population health is crucially affected by determinants outside of the health care system, known as social determinants, but there is little agreement on which ones have the greatest impact. It is difficult for policymakers to identify priorities for action to improve life expectancy in the poorest countries. Statistical techniques (multiple regression analyses) can test the association of determinants with life expectancy, and indicate their relative importance. However, conventional techniques fail because there are too many determinants to be evaluated at the same time.

The NIHR HPRU in Modelling Methodology used data on 45 determinants of health to estimate life expectancy at birth for 54 low-income countries over the years 1990-2012. Each determinant was subjected to a robustness test to observe the stability of its estimated impact on life expectancy. For 20 robust and significant determinants, the magnitude of association with life expectancy was determined.

The largest average increase in life expectancy (14.5 months per person) is associated with a reduction in HIV prevalence among children, followed by advances in gender equality (9.4 months). Improved life expectancy of between six and nine months is associated with agricultural production, political stability, access to clean water and sanitation, good governance, and primary school enrolment.

Improvements below six months are associated with increases in private health expenditure and overseas development assistance, and control of armed conflict and HIV prevalence among men. There is no evidence that national income, public spending on healthcare and education, secondary schooling, terms of international trade, employment, debt service and relief, out-of-pocket expenditures, agricultural exports or imports, livestock production, foreign investment, urbanisation or environmental degradation are robustly associated with population health.

The results will help policymakers to prioritise scarce funds for areas that will have the greatest impact on life expectancy.