

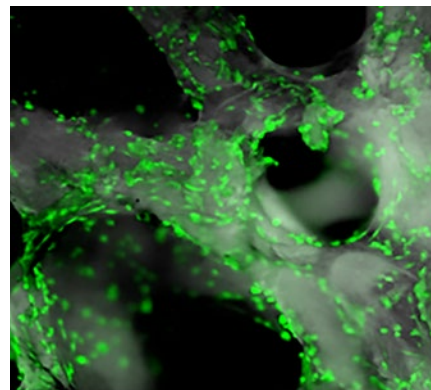


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Advancing health

The impact of UK medical
schools' research

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Introduction

The government has declared its ambition for the UK to become a “global science superpower”. Strong foundations are in place. The UK has an impressive research base, producing 7% of the world’s scientific publications¹ - behind only China and the USA. The UK was also at the forefront of the global effort to combat the COVID-19 pandemic, developing and delivering life changing treatments and vaccines. It continues to increase the understanding of the disease and its effects.

The results from the Research Excellence Framework 2021 (REF 2021) provide extensive evidence that UK universities and their medical schools produce research that is world-leading and has global impact. This publication showcases selected examples submitted to REF 2021, highlighting the impact of university and medical school research across the UK. The case studies are presented in four broad categories:

- Improving clinical practice
- Reducing the cost of healthcare
- Driving policy change
- Health beyond borders

In truth, this is an over-simplification. Many of the impacts extend across multiple categories – from reducing health inequalities, to delivering cutting edge therapies, from making treatments more efficient and cost effective to informing health strategies in developing nations.

The results of REF 2021 show that world-leading research is taking place right across our country. Increased investment building on this will be a very powerful approach to level up opportunities across the UK. Many of the case studies in this document were conducted in collaboration with industry. The growing scale and effectiveness of partnerships between academia and industry are dramatically increasing our ability to translate discoveries into benefits for patients.

The merits of medical research are clear. It advances medical treatments which result in better outcomes for patients and improved health for the nation. It also boosts the economy by creating a highly skilled and sought-after workforce and encourages investment from both public and private sectors. The economic value of medical research is enormous, with previous studies finding that for every £1 invested, society benefits by ~25p per year, every year, indefinitely².

Importantly, the UK’s biomedical research is highly collaborative internationally, and is committed to building research capacity and sharing benefits across the world.

Thus, biomedical research is very well placed to contribute to achieving science superpower status. However the UK’s hard-earned competitiveness in this key area should not be taken for granted. In order to exert the influence of a science superpower we must be able to work seamlessly with international partners. This means access to overseas funding and collaboration opportunities, including with our neighbours in Europe, and the ability to attract and retain talented researchers from across the globe.

At home there is a very strong strategic investment case for enhancing our research infrastructure, bolstering our health system, and embedding research and innovation more deeply into the NHS. Considerable research is already conducted within the health service and this can drive improvements in services and patient care. One of the biggest successes of the relationship between research and the health service can be seen during the pandemic where over a million people volunteered through the NHS to take part in essential Covid-19 studies across the UK. This contribution from the public not only helped develop our scientific response to the virus but it directly impacted millions of lives both in the UK and abroad. The studies highlighted here would not have been possible without the patients that took part in research and their contributions are crucial and highly appreciated. Further work is needed

1. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/815400/International_comparison_of_the_UK_research_base_2019_Accompanying_note.pdf

2. <https://www.brunel.ac.uk/news-and-events/news/articles/Every-1-invested-in-medical-research-returns-25p-per-year-forever>

across our sector to encourage recruitment into clinical trials from across all areas of society to ensure that all have the opportunity to take part in research, and that the results are truly representative of our society as a whole.

Another group which has contributed greatly to medical school research and the UK's science output are clinical academics, health professionals who conduct research and undertake teaching alongside their clinical duties. This dual role allows clinical academics to directly help improve patient care by generating new ways to prevent, diagnose and treat disease. Many of the studies in this publication have been led by clinical academics and they are an integral part of the UK's research workforce, but their numbers are declining. If the nation is to maintain the high quality of research it produces, then it needs to secure the pipeline of the clinical academic workforce by ensuring research careers are attractive and there is sufficient support for those in their early years.

Successful research depends on collaboration, and our collaborative approach is a striking strength of UK medical schools. I believe there is an opportunity for greater collaboration between policy makers and leaders in the research sector to work together to grow the nation's influence on the global stage, to deliver future advancements in healthcare, and to fulfil the UK's potential to be a science superpower.



Professor Patrick Maxwell
Chair, Medical Schools Council

“The merits of medical research are clear. It advances medical treatments which result in better outcomes for patients and improved health for the nation. It also boosts the economy by creating a highly skilled and sought-after workforce and encourages investment from both public and private sectors”

Improving clinical practice

The COVID-19 pandemic was a stark reminder of the importance of clinical research, with the UK playing a leading role in responding to a health emergency unprecedented in modern times.

The UK led the world in developing urgently needed vaccines and treatments, modelling the transmission of the virus and tracking the emergence of new variants. None of this vital work would have been possible had not the UK already invested in the infrastructure and systems required for the UK to be a global leader in medical research and development.

COVID-19 is but one of the many important health challenges. The cutting-edge science conducted at UK medical schools and universities uncovers the knowledge and understanding needed to tackle healthcare challenges, and produces the tools and technology required to

address them. These advances allow the clinical community to gain a better understanding of the nature of disease and ill health, building an evidence-base for which treatments work best and why.

The case studies in this chapter highlight the breadth of expertise and knowledge embedded in medical schools up and down the country. What they have in common is the potential to continually push the boundaries of clinical care delivery and understanding, deliver new treatments and refine existing ones. They also highlight the critical importance of the clinical academic workforce in delivering the cutting-edge healthcare of tomorrow.

Using suboptimal livers to save lives in transplant surgery

Liver disease is a major health problem, having increased 5-fold over the last 40 years. It is now the fifth most common cause of premature death globally accounting for 8,500 deaths annually in the UK.

Liver transplantation is a highly effective treatment for patients with end-stage liver disease, however access to life-saving transplantation is limited by a shortage of donor organs. This is a consequence of both greater demand and the quality of donated organs decreasing over the last decade due to the increasing age, obesity and co-morbidities of many donors. Today, one third of donated livers are of suboptimal quality and are considered high-risk for transplant. As a result, many are not used.

“22 livers (71%) met the viability criteria and were successfully transplanted into recipients with 100% 12-month patient and organ survival”

In 2013, University of Birmingham researchers established a programme aimed at reducing the number of donor livers discarded by testing the function and improving the quality of sub-optimal organs. Previously, donor livers were kept in icebox storage until transplant in order to slow metabolism and reduce the effects of oxygen deprivation. Previous research had suggested that passing oxygenated fluid with nutrients through an organ's blood vessels ('perfusing') prior to transplant

improves transplant efficiency and that to do this at body temperature might further enhance the quality of donor organs by preserving metabolic reactions important for liver function. If so, this could reduce the likelihood of organ damage during storage, a particular problem when transplanting suboptimal livers.

This led the researchers to perform preclinical studies to assess whether donor livers could be preserved using machines that perfuse blood at body temperatures – so-called 'normothermic machine liver perfusion' (NMLP). At the same time, they developed a panel of tests that allowed assessment of the function of the preserved livers.

Between 2013-2014, the research team used NMLP in the laboratory to preserve 12 livers that had been turned down by the transplant programmes because they were considered too damaged to safely transplant. They found that the rejected livers could be divided into two groups according to whether they could clear lactate – a metabolite produced in response to oxygen deprivation. The ability to clear lactate is an indication of reduced tissue breakdown, better metabolic recovery and better liver function — all factors that would be expected to result in better transplant outcome.

Lactate clearance and other functional tests were then incorporated into novel viability criteria capable of defining which suboptimal livers treated by NMLP are safe to transplant. In August 2014, the Liver transplant team at the Queen Elizabeth Hospital Birmingham carried out the first ever human transplant of

a discarded donor liver reconditioned by NMLP and assessed using the novel viability criteria. By 2015, the team had completed the first pilot series of five such suboptimal livers transplanted after NMLP. All livers functioned well and patients survived. The team published the protocol for the VITTAL (Viability testing and transplantation of marginal donor livers) and proceeded with a Wellcome Trust funded clinical trial incorporating their viability criteria to assess the success of NMLP prior to transplantation. The trial commenced in 2017 and, in total, 31 suboptimal livers rejected for transplant by all UK transplant centres were enrolled and subjected to NMLP. 22 livers (71%) met the viability criteria and were successfully transplanted into recipients with 100% 12-month patient and organ survival. In response to the Birmingham studies, transplant teams worldwide have changed their practice and incorporated NMLP as part of their routine practice. Nationally, the work has vastly improved transplant services by allowing a greater proportion of donated organs being transplanted into patients.

Lead researchers: Simon Afford, Darius Mirza, Thamara Pereira and Hynek Mergental



Transplant recipient, Sue Bennett, received a machine perfused liver.

Global implementation of instantaneous wave-free ratio (iFR) to diagnose coronary stenosis

Coronary artery stenoses (i.e., narrowing) limit blood flow to the heart muscle and can cause angina. Relief of a stenosis by use of a stent aims to reduce vessel obstruction, improve blood flow and reduce angina symptoms. However, unless stenoses are flow limiting, they can be safely left alone without stenting or surgery, reducing patient exposure to unnecessary procedures and potential complications.

Instantaneous wave-free ratio (iFR) is a diagnostic tool that was invented and developed by Imperial College to assess whether a narrowing in a coronary artery is limiting blood flow to the muscular layer of the heart known as the myocardium. It is used to stratify selection of patients for surgery, stenting or medical management. It has been shown to reduce patient discomfort, procedural time and costs by 10% compared to the leading alternative (Fractional Flow Reserve) in two large randomised clinical trials.

Fractional Flow Reserve (FFR) was the main technique to determine the need for clinical intervention by measuring the pressure drop across a stenosis. This assesses systolic pressure under the condition of maximal vessel dilation, which is dependent on administration of adenosine. The latter adds time to the procedure

and often causes significant chest pain. Subsequently Imperial College developed instantaneous wave-free ratio (iFR) as an alternative technique.

The idea emerged from a cardiology-bioengineer collaboration that developed a method called wave intensity analysis for assessing arterial physiology. Translating it from peripheral arteries to the coronary arteries was challenging because of the complex relationship between pressure and flow in arteries supplying the myocardium. These technical challenges were overcome in 2006 and researchers at Imperial College conducted a series of studies to understand the factors influencing coronary flow in human physiology and pathology.

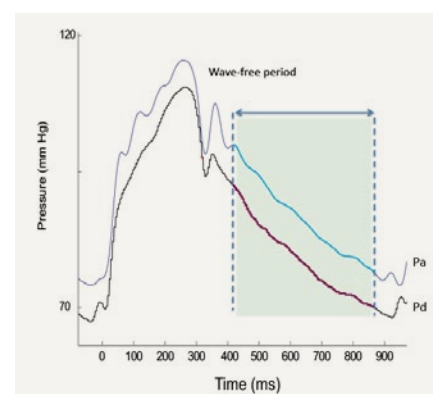
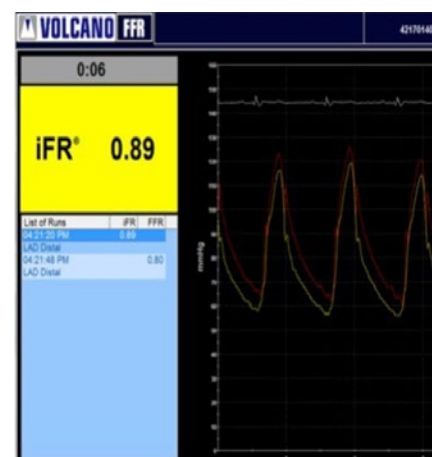
During these studies they recognised that there was a period between heartbeats when there are no reflected arterial waves influencing flow and realised that if pressure was monitored at this time point, it would provide a surrogate for flow measurement without needing vasodilation or adenosine. This led to the invention of iFR in 2010 and its development and validation as a clinical tool in the clinical cardiac catheter labs at Imperial College Healthcare NHS Trust against the then gold standard FFR.

Researchers then led an international multicentre randomised controlled trial (DEFINE-FLAIR) to compare iFR with FFR. The study randomly assigned patients to undergo iFR or FFR, and either inserted a stent or not, depending on the stenosis measurements. Patients were followed up for 12 months after the procedure. There were no significant differences between the two techniques in subsequent heart

attack or mortality, but procedural time was 10% quicker with iFR and it was associated with a 90% reduction in adverse procedure events compared to FFR. These findings were confirmed in an independent study of 2,037 patients by a Swedish group (iFR-SWEDEHEART). A subsequent study has shown that iFR can assess serial stenoses in coronary arteries, which is an important limitation of FFR.

The iFR technology was patented by Imperial Innovations and licenced to Volcano-Philips and received FDA approval in 2014. iFR is now used in over 5,000 clinical cardiac catheter labs in more than 30 countries.

Lead researchers: Justin Davies, Jamil Mayet, Darrel Francis, Alun Hughes and Kim Parker



Instant wave-free ratio across a stenosis during the wave-free period, when resistance is naturally constant and minimised in the cardiac cycle



Advancing robotic surgery in the UK

King's College London researchers have transformed urology surgery in the UK through the use of robotic surgery. This pioneering work has helped to improve the health outcomes for patients with urological cancers.

Prostate cancer is the most common male cancer with around 40,000 men diagnosed each year in the UK alone. It is often treated through standard radical prostatectomy – having the prostate removed – but this is a complex operation that has a high risk of men experiencing incontinence and impotence afterwards. Traditional open surgery is also associated with greater blood loss, more pain and longer hospital stay compared to laparoscopic (keyhole) surgery – a minimally invasive alternative with a better prognosis for patients. However, developing proficiency in keyhole surgery involves a steep learning curve for surgeons, which many find difficult to overcome. King's has been at the forefront of a technology-aided alternative, robotic radical prostatectomy, that has evolved over the last 20 years to become the most effective and common form of surgery for prostate cancer in the UK. This work to refine robotic surgery in the context of urology has also led to progress in the application of robotic surgery in other clinical specialties.

In 2004 the urology team at King's established the use of the da Vinci Surgical System, powered by state-of-the-art robotic technology. The da Vinci allows the surgeon to sit comfortably at a console that scales, filters and translates their skills into the precise movements of robotic micro-instruments within the operative site. Following this, researchers have created new robotic

tools to advance this procedure and other applications of robotic surgery such as haptic technology, which can create an experience of touch by applying forces, vibrations, or motions to the user and thus improving the practitioner's experience and surgical effectiveness. Since then, based on this technology, King's has contributed to the field of robotic surgery through a number of ground-breaking developments including conducting the first-ever randomised trial of Telerobotics – the area of robotics concerned with the control of semi-autonomous robots from a distance, chiefly using high speed networks. Subsequently, through the CORAL trial, researchers were able to show that patients had shorter hospital stays and less blood loss when surgery was performed through the robotic arm, building high quality evidence for robotic surgery.

This work has transformed urology surgery in the UK through national uptake and training of robotic surgery through The Urology Foundation which provides funding for urology research

“This work has transformed urology surgery in the UK through national uptake and training of robotic surgery through The Urology Foundation which provides funding for urology research and training”

and training. This has meant that in a relatively short space of time, the majority of urological patients on the NHS now have access to robotic surgery by skilled robotic surgeons. King's expertise has enabled Guy's and St. Thomas' Hospitals to carry out the most multi-disciplinary robotic surgery in the country, around 1,300 cases a year. The researchers have also developed the first international curriculum for safe training in robotic surgery which has been adopted and recognised globally.

Lead researcher: Prokar Dasgupta



Professor Prokar Dasgupta, pictured, led the ground-breaking research.

Development of a new class of therapy for severe asthma

Asthma is a chronic inflammatory airway disease, affecting all ages, and causes considerable morbidity and significant avoidable mortality. In the UK, 60,000 asthmatics are admitted to hospital annually, with over 1,000 dying.

Globally, 20% of children and 5% of adults are affected, with 5% of cases having severe disease. Collaboration between the University of Leicester and GlaxoSmithKline (GSK) resulted in the development, licensing, and widespread use of a new type of medicine, mepolizumab (Nucala™).

Generally, asthma can present in one of two ways: episodic breathlessness primarily due to airway smooth muscle (ASM) contraction, and exacerbations primarily due to airway inflammation. These exacerbations cause asthma deaths. The frequent need for continuous corticosteroid treatment is a risk factor for several other conditions, including diabetes, hypertension, obesity, and bone thinning. Asthmatics with inadequately controlled disease – estimated to be 250,000 in the UK – suffer significant impairments in their quality of life, mental health, and employment.

Prior to University of Leicester research, there was a major unmet need for new therapies to help this group.

Research by the Leicester Institute for Lung Health (LILH) led to the proposal of a new model of asthma, deconstructing it into the component physiological abnormalities underpinning the disease. Eosinophils are specialised white blood cells that curb infection and boost inflammation. Examining airway tissue from patients LILH researchers found that eosinophils were only responsible for the exacerbation

component of asthma, and not the ASM abnormalities which are responsible for day-to-day symptoms. Further research demonstrated that active eosinophilic inflammation was not present in all asthmatics, leading to the development of sputum tests which could predict which patients would respond to corticosteroids.

This ground-breaking research convinced GSK to commission and support LILH to undertake a Phase-2, double-blind placebo-controlled clinical trial. This consisted of twelve months treatment with mepolizumab in patients with active eosinophilic airway inflammation (measured in sputum), using severe exacerbations as the primary outcome measure. This study demonstrated that mepolizumab prevented 50% of exacerbations, without any discernible effect on day-to-day symptoms, showing that eosinophils were causal in exacerbations and suggesting that mepolizumab would be effective in severe asthma if targeted at those with eosinophilic, exacerbation-prone disease. GSK followed this trial with

“This ground-breaking research convinced GSK to commission and support LILH to undertake a Phase-2, double-blind placebo-controlled clinical trial”

a multi-dose, Phase-2 trial (DREAM) in collaboration with LILH, using the same design. This confirmed the original findings, additionally discovering that blood and sputum eosinophil counts were equally as effective in identifying treatment-responsive eosinophilic asthmatics. Subsequent Phase-3 studies (MENSA and SIRIUS) further verified LILH results.

This research collaboration with LILH led to GSK obtaining a global license in 2015 for the use of mepolizumab in adults and children, marketed as Nucala™. GSK continues to adapt Nucala for the treatment of rare conditions related to severe asthma.

Lead researchers: Andrew Wardlaw, Ian Pavord, Peter Bradding, Chris Brightling, Ruth Green, and Pranab Halder



Implementing PINCER to reduce medication errors in general practices

Prescribing errors in general practice are an important and expensive preventable cause of safety incidents, illness, hospitalisations, and deaths. This is a significant quality and safety issue that is widely relevant to all health care systems.

To address this, the research team at Nottingham conducted a study to determine the prevalence and nature of prescribing and monitoring errors in general practices in England. Their research revealed prescribing errors in 5% of prescription items, with 1 in 550 items containing a severe error – equating to 2,000,000 serious prescribing errors in general practices in England each year. A report commissioned by the Department of Health and Social Care estimated the annual hospital admission costs for primary care avoidable adverse drug events to be £83.7 million resulting in 627 deaths in England per year.

“Follow-up data from over 1,000 practices showed a decrease of 14% in the number of patients at risk of a least one medication error and a decrease of 26% in errors associated with gastrointestinal bleeding”



This led the University of Nottingham research team to develop and test a pharmacist-led, IT-based intervention to reduce medication error in primary care (PINCER), informed by the Medical Research Council's framework for complex interventions. The process involves searching GP clinical systems using computerised prescribing safety indicators to identify patients at risk from their prescriptions, and then acting to correct the problem with pharmacist support.

With an expansive reach covering 40% of England's population, PINCER has proven to substantially reduce hazardous prescribing in its implementation in general practices across England. By December 2020, 2,032 health care professionals had been trained to deliver PINCER; 2,688 general practices had implemented PINCER and 25,545,538 patient records had been searched for prescribing errors. Follow-up data from over 1,000 practices showed a decrease of 14% in the number

of patients at risk of a least one medication error and a decrease of 26% in errors associated with gastrointestinal bleeding – a common cause of medication-related hospital admissions.

The data collected suggested that PINCER is an efficient and cost-effective method for reducing a range of clinically important and commonly made medication errors in primary care. PINCER has since been recommended in the National Institute for Health and Care Excellence's (NICE) guidance and included in five NHS guidance documents. While it has already been widely adopted by general practices across England, its expansion continues, maintaining significant reductions in medication errors and subsequently medication-related hospital admissions.

Lead researchers: Tony Avery and Sarah Rodgers

The Oxford-AstraZeneca COVID-19 vaccine

The University of Oxford's Jenner Institute and the Oxford Vaccine Group have been at the forefront of scientific endeavour to develop vaccines for diseases of major global importance for more than 30 years. When a novel respiratory virus began circulating in China at the end of 2019, the team quickly started work to develop a vaccine, without yet knowing whether it would be needed.

It soon emerged that the pathogen responsible for COVID-19 was a novel coronavirus, SARS-CoV-2, and that there was a high risk that a localised outbreak in Wuhan could develop into a global pandemic. When Shanghai virologist Professor Zhang Yongzhen first decoded the virus's genetic sequence and published his results on the internet, Professor Sarah Gilbert and colleagues were already prepared to start developing a vaccine for SARS-CoV-2 using Zhang's data. When it became clear that a vaccine was going to be needed, Professor Andrew Pollard gathered a team to work on clinical development.

"The Oxford-AstraZeneca vaccine has prevented thousands of hospitalisations and deaths"

The Oxford team had already used ChAdOx1 viral vector vaccine platform technology to produce candidate vaccines against a number of pathogens including influenza, Zika and Middle East Respiratory Syndrome (MERS), another coronavirus. This platform is both highly flexible, allowing for development of new candidate

vaccines in a number of weeks and can be administered safely, as the common cold virus used to deliver the vaccine has been genetically engineered to be incapable of causing disease in humans. Viral vectored vaccines work by delivering the genetic code to the vaccine target, in this case the spike protein of SARS-CoV-2 to cells of the body which then produce and present it to the body's immune system. This primes the immune system to attack the SARS-CoV-2 coronavirus if exposed to it in future.

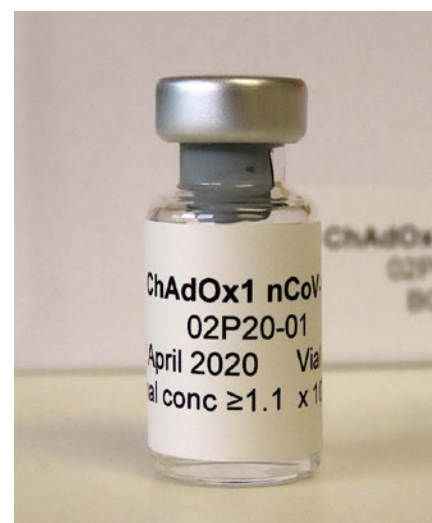
From April 2020 the Oxford-AstraZeneca team began clinical trials for the ChAdOx1 nCoV-19 vaccine to confirm this new vaccine was safe and effective. Based on the available evidence from clinical trials, the team found that two doses of the Oxford AstraZeneca vaccine were about 70% effective at preventing mild to moderate disease and almost 100% effective at preventing hospitalisation after the full course of vaccination.

However, in order to be successful it was also important that the vaccine was easy to manufacture, transport and store. Manufacturing a vaccine in sufficient quantities to tackle a global pandemic was no easy task. The solution to this problem came when the team found a way of creating up to 10 times more vaccine from a modified manufacturing process. Work which would have normally taken years could be compressed into a few months, and with a distributed manufacturing model involving manufacturers in multiple countries, production could be scaled up to deliver a vaccine for the world. The most high-profile manufacturing partnership was made with AstraZeneca to produce and scale up

distribution of the vaccine, even before clinical trials were complete. A key element of Oxford's partnership with AstraZeneca is a joint commitment to provide the vaccine on a not-for-profit basis for the duration of the pandemic across the world, and in perpetuity to low- and middle-income countries.

The Oxford-AstraZeneca vaccine has prevented thousands of hospitalisations and deaths. It has been shown to be stable, easily manufactured and can be transported and stored at domestic fridge temperature which allows the vaccine to be rapidly administered in existing healthcare settings. The vaccine was approved for emergency use in the UK in December 2020 and has now been approved in a number of countries, marking an important milestone in the fight against COVID-19. To date the partnership has manufactured over 3 billion doses of the vaccine that have been released to more than 170 countries worldwide.

Lead researchers: Sarah Gilbert, Andrew Pollard, Teresa Lambe, Sandy Douglas, Catherine Green and Adrian Hill



Eliminating Hepatitis C with effective treatment and priority screening

The Hepatitis C virus (HCV) is one of the most common forms of viral hepatitis in the UK and can cause liver scarring (cirrhosis) and failure. It has developed genetic mutations – categorised as different genotypes – over time, leading to several different manifestations of the infection.

The World Health Organisation (WHO) has issued targets to eliminate Hepatitis C Virus by 2030. Work by Professor Graham Foster, who is the national clinical lead for achieving the WHO targets, has revealed the aggressive nature of a strain of the virus known as genotype 3 HCV, which was previously thought of as being ‘easy to cure’. To address this, he led bespoke treatment trials that successfully defined optimal and effective regimes and have helped shape both national and international guidelines on a) HCV treatment and b) which subgroups to prioritise in HCV screening. In England, this led to an Expanded Access Programme, followed by general access, with Foster as national clinical lead.

The work on the natural history and prevalence of genotype 3 HCV has shown that:

- Immigrants, not previously considered a high-risk group for this virus, have a high prevalence of infection and cirrhosis
- Novel viral mutations, which reduce the effectiveness of antiviral treatments, can be identified through screening. Foster’s team has developed a test for mutations to the variant and now show that the genotype 3 mutation is associated with cellular changes associated with malignancy.

- Genotype 3 is a more aggressive strain than previously thought. In 2013, therapy for HCV infection involved injectable ‘interferon’ and tablets with a high incidence of side effects. The team found that genotype 3 HCV and cirrhosis responded poorly to standard HCV interferon-based treatments, highlighting the need for genotype-specific HCV trials.

As a result of these findings, biopharmaceutical company Gilead Sciences Inc., which holds the licence for the latest HCV treatment sofosbuvir, approached the team to lead an exploratory UK-based study into overcoming the reduced response to the treatment seen in genotype 3 HCV. This study identified possible combinations of treatments alongside sofosbuvir that could improve treatment response.

“The Public Health England HCV annual report for 2020 indicates a 20% and 44% fall in deaths and transplant listings for HCV respectively, and a 95% success rate in ‘curing’ patients of the virus”

Foster then led an international Phase-3 trial in genotype 3 HCV with a newly developed combination of sofosbuvir/velpatasvir, which achieved a far greater response rate in patients. Foster also led trials for the alternative therapeutic glecaprevir/pibrentasvir, which achieved a high response rate in patients with genotype 3 HCV without cirrhosis.



Prof Foster and colleagues at the screening camp, Aga Khan University, Karachi

The English Expanded Access Programme achieved the first real-world confirmation that these treatments are effective and can improve life expectancy in patients with severe (decompensated) cirrhosis. The policy is the largest ever single NHS investment in specialist services. The programme has mobilised 22 Operational Delivery Networks and successfully treated over 50,000 patients. The Public Health England HCV annual report for 2020 indicates a 20% and 44% fall in deaths and transplant listings for HCV respectively, and a 95% success rate in ‘curing’ patients of the virus. The team has also developed a screening test for novel mutations that reduce the effectiveness of antiviral treatments, further improving HCV outcomes.

Lead researcher: Graham Foster

DiPALS: Evidence to inform guidance on the use of diaphragm pacing for patients with amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), named motor neurone disease (MND) in the UK, is a devastating illness that leads to muscle weakness and death, usually within a few years of symptom onset.

Respiratory insufficiency is a common cause of morbidity and respiratory complications are the leading cause of mortality in ALS/MND patients. Non-invasive ventilation (NIV) is the current standard therapy to manage respiratory insufficiency, however some patients are unable to use this treatment due to mask interface problems and claustrophobia.

As a result, the Diaphragm Pacing System (DPS) was originally developed for patients with respirator insufficiency and diaphragm paralysis secondary to stable high spinal cord injuries but was approved by the United States Food and Drug Administration to be used on ALS/MND patients.

The University of Sheffield has been undertaking research in collaboration with the NIHR Health Technology Assessment Programme to examine the efficacy and safety of diaphragm pacing. The study discovered that its use was associated with decreased survival in patients with amyotrophic lateral sclerosis (ALS). The study has directly resulted in halting the use of DPS in the UK, Europe and Canada and has prevented it from becoming an accepted treatment for ALS patients.

“The Sheffield team were instrumental in shaping clinical policy on the use of DPS in ALS patients in the NHS and has highlighted the importance of undertaking rigorous safety checks”

The Sheffield team was instrumental in shaping clinical policy on the use of DPS in ALS patients in the NHS and has highlighted the importance of undertaking rigorous safety checks. The National Institute for Health and Care Excellence (NICE) have since published their recommendations on DPS following the Sheffield study, claiming that the procedure should not be used to treat ALS/MND. It is highly likely that if the Sheffield study had not been conducted, the use of DPS would eventually have become standard care; consequently within a few years, undertaking such a study on DPS would be seen as unethical.

Lead researchers: Christopher McDermott and Pamela Shaw



Improving prostate cancer detection and treatment

For the past 50 years, men at risk of prostate cancer have been assessed using a blood test for prostate specific antigen (PSA), followed by biopsy if PSA levels are high.

To obtain the sample, a needle is inserted into the prostate via the rectum – a painful procedure which provides inaccurate results and can cause bleeding and sepsis.

Led by Professor Mark Emberton, the research team at University College London (UCL) and University College Hospitals NHS Foundation Trust (UCLH) pioneered a new diagnostic pathway that includes an MRI scan to detect prostate cancers. This led to two pivotal trials which tested the effectiveness of MRI scanning and

“In case a biopsy is needed, the team developed a technology to make the procedure more precise, requiring fewer needles and improving cancer detection by nearly double”

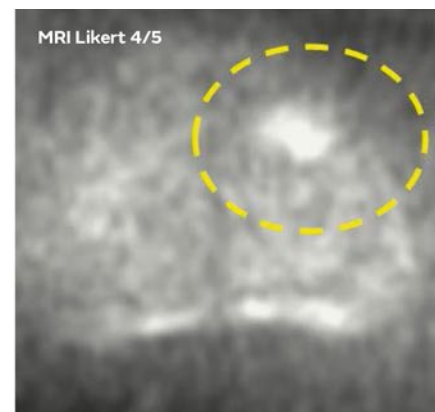
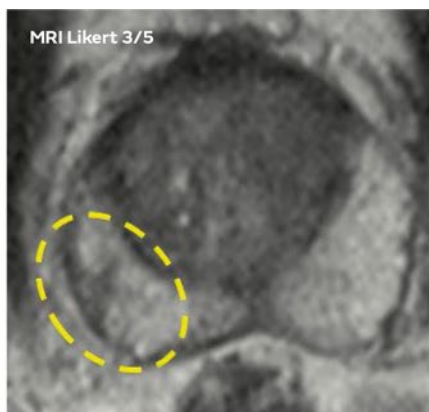
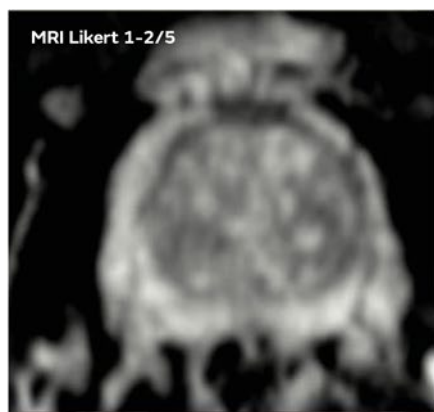
demonstrated the procedure could identify tumours without the need for invasive, risky and sometimes unnecessary biopsies. The trials provided sufficient evidence to change clinical practice; the National Institute for Health and Care Excellence (NICE) has recommended imaging in the form of MRI be offered to all patients undergoing prostate biopsy.

In case a biopsy is needed, the team developed a technology to make the procedure more precise, requiring fewer needles and improving cancer detection by nearly double. During the biopsy procedure, ultrasound is used to find the prostate, but ultrasound cannot see tumours. The UCLH system, SmartTarget, overlays tumour information from MRI scans onto ultrasound images. The chance of side effects such as blood in urine, semen or faeces are reduced by half, and pain and risk of sexual dysfunction are reduced. SmartTarget has been used to treat over 500 men in clinical trials in the UK and US and is being rolled out in Spain, Ireland and the US.

World-wide adoption is benefiting five million men every year by avoiding unnecessary biopsies and

providing cheaper, less harmful, and more accurate biopsies with fewer cancers missed. NHS savings alone are approximately £113 million per year. MRI scanning means surgery can be targeted to the tumour itself and a wide margin around it, preserving more of the prostate. Radiotherapy can be targeted more effectively to avoid harm to normal tissue. Biopsy numbers have been reduced by a quarter, allowing over one million men every year to avoid unnecessary procedures.

Lead researcher: Mark Emberton



MRI images showing low, moderate and high prostate cancer risk.

Improving cardiac arrest survival

When the heart suddenly stops, death will occur within minutes unless effective treatments are provided. There are 275,000 out-of-hospital cardiac arrests annually in Europe and it is the third leading cause of death, with a survival rate of only 12%.

There is variation in survival outcomes from cardiac arrest and a lack of data and understanding of patient outcomes following an out of hospital cardiac arrest. Evidence demonstrated that bystanders rarely know how to respond, therefore patients often do not receive CPR; with fewer than one in forty receiving public access defibrillation. There has also been little research evidence to support treatments such as mechanical CPR and the use of adrenaline.

Warwick researchers contributed to an improvement in patient care for cardiac arrest, cardiopulmonary resuscitation (CPR) and long-term health outcomes by working with international and national standards bodies, charities, patients, doctors and the public. Led by Dr Joyce Yeung, with Professor Gavin Perkins, the Emergency Prehospital Perioperative & Critical Care Group has investigated standards of care and CPR decisions with a wide range of national and international collaborators. This included charities such as the British Heart Foundation and St Johns Ambulance, international and national standards bodies such as the International Liaison Committee on Resuscitation and the Resuscitation Council (UK) and over 100 NHS Trusts.

The award winning PARAMEDIC1 clinical trial compared the effectiveness of mechanical and manual chest compression when

performing CPR. PARAMEDIC2, a placebo-controlled trial, investigated the safety and effectiveness of adrenaline in out-of-hospital cardiac arrest patients. With the British Heart Foundation and the Resuscitation Council (UK), Warwick established the Out of Hospital Cardiac Arrest Outcome registry to improve data on patient outcome and led the development of a core outcome set for reporting on effectiveness studies of cardiac arrest.

The findings have influenced policy and guidance on cardiac arrest care around the world. PARAMEDIC1 demonstrated that mechanical chest compression was no more effective than manual methods of CPR. As a result, the NHS saved £40 million by not investing in this specialist equipment. Evidence of poor community CPR response has led to the inclusion of CPR on the National Curriculum and over 1 million young people being taught lifesaving skills.

This raised the bystander response rate from 57% to 69% over the last five years, saving an additional 1000 lives.

“PARAMEDIC1 demonstrated that mechanical chest compression was no more effective than manual methods of CPR”

Following evidence of low rates of public access defibrillator use and potential number of lives that could be saved with increased uptake, the group secured a £3 million investment to work with the Department of Health and the British Health Foundation to map and install a national network of defibrillators; open to emergency use by the public and marked by clear signage.

Lead researchers: Gavin Perkins and Joyce Yeung



Reducing the cost of healthcare

In recent years many sectors have had to adjust to acute economic and budgetary pressures, and sadly health and medical research is no exception.

Indeed, factors such as an ageing population with more complex health needs can push up costs significantly at a time where budgets are constrained. Thankfully research can help to deliver the most cost-effective care through advances in technology, a better understanding of the mechanisms of disease, and better targeted use of drugs and medicines.

Medical research not only delivers major advances in patient care – it is also a sound investment for the public finances, with every £1 invested in medical research delivering a return equivalent to around 25p every year, in perpetuity^{3,4}. This is good for the UK economy, and much of this revenue remains in the NHS. In the financial years 2016/17 to 2018/19, it is estimated that clinical research supported

by the NIHR Clinical Research Network generated £8 billion in gross value added. Furthermore, for each patient recruited into commercial clinical research studies, NHS Trusts in England received an average of £9,189 in revenue from life sciences companies, as well as a pharmaceutical cost saving of between £4,143 and £7,483⁵.

As we now once again face difficult economic times it is vital that, as a sector, we continue to make the arguments for why medical research is not just a moral necessity, but is also a sound financial investment. Without continued investment in health research, we will not be equipped to respond to health emergencies, such as COVID-19, where the potential costs of being ill-prepared will dwarf those of preventative investment now.

3. Grant J & Buxton MJ (2018). Economic returns to medical research funding. *BMJ Open* 8, e022131.

4. Wellcome Trust, et al. (2018). Medical Research: What's it worth? A briefing on the economic benefits of musculoskeletal disease research in the UK. <https://acmedsci.ac.uk/file-download/54792223>

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Optimising breast cancer care by reducing treatment, side effects and costs

Breast cancer is the most common cancer in women with 55,000 new cases diagnosed in the UK each year.

While chemotherapy, hormonal and biological therapies, together with radiotherapy have doubled breast cancer survival since the 1970s, it is now clear that many patients are over-treated. This results in serious side effects, and unnecessary healthcare costs. University of Cambridge researchers have led UK-wide collaborative clinical trials to test if treatments can be reduced safely.

The IMPORT trial (Coles et al) explored less radiotherapy, limited to the region around the tumour bed (partial breast). After surgery, patients received standard full dose, whole-breast radiotherapy; or reduced dose, whole-breast radiotherapy; or partial breast radiotherapy. All three treatments produced equally excellent disease control however patients receiving partial breast radiotherapy had significantly fewer side effects. Another UK trial FAST Forward (Brunt et al), demonstrated that one week of whole-breast radiotherapy was as effective as three weeks. IMPORT Low and FAST Forward were designed in parallel to enable the smooth transition to one-week of partial breast radiotherapy for patients at lower risk of breast cancer recurrence; and this is now standard of care in the UK.

The PERSEPHONE trial (Earl et al) tested whether adjuvant trastuzumab (biological anti-cancer drug) could be reduced safely from 12-months (standard length) to six-months in patients with HER2-positive early breast cancer. The results showed that five-year disease-free survival rates were equally excellent among patients receiving six-months or 12-months trastuzumab with similar overall survival. Importantly, patients

receiving six-months experienced significantly fewer severe side effects and fewer patients stopped trastuzumab early because of cardiac damage. Widespread adoption of six-months trastuzumab could result in halving side effects and costs. The trial was funded by the NIHR HTA programme (£2.6 million), enrolled 4,088 patients over eight years and during that time saved £20 million from the NHS budget.

“This collaborative research has shown that breast cancer treatments can be safely reduced thereby decreasing side-effects and abolishing unnecessary healthcare costs”

Around 10,000 women are eligible for partial breast radiotherapy per year in the UK. This would save around 100,000 fractions of radiotherapy per year. A Markov cohort model to simulate lifetime healthcare costs and quality adjusted life years (QALYs) demonstrated that one-week partial breast radiotherapy had the least cost and greatest expected QALYs when compared with one-week whole breast radiotherapy and three-week radiotherapy. Around 3,300 patients receive single agent trastuzumab each year in the UK and reducing to six-months means an estimated annual cost-saving of £20 million to the NHS.

The collaborative research has therefore shown that breast cancer treatments can be safely reduced thereby decreasing side-effects and abolishing unnecessary healthcare costs. The findings of both trials have also impacted treatment in developing nations. IMPORT uses a simple technique and widely available radiotherapy equipment and therefore it can be implemented in any centre worldwide and the results of PERSEPHONE have directly increased the use of trastuzumab in several low-and middle-income countries, resulting in improvement in the uptake of this essential medicine.

Notes:

The researchers would like to acknowledge the patients, Patient and Public Involvement partners, principal investigators in CRN centres, and co-applicants at the Institute of Cancer Research Clinical Trials and Statistics Unit (IMPORT Low) and the Clinical Trials Unit, University of Warwick (PERSEPHONE), without whom these trials would never have been done.

IMPORT Low was funded by Cancer Research UK and sponsored by the Institute of Cancer Research. Professor John Yarnold, Institute of Cancer Research was the original Chief Investigator until retirement in 2012. PERSEPHONE was funded by the NIHR HTA and sponsored jointly by University of Cambridge and Cambridge University Hospitals.

Lead researchers: Helena Earl and Charlotte Coles



Professors Helena Earl and Charlotte Coles, pictured, led the influential work.

A new first-in-class drug transforms treatment for heart failure, improves patient outcomes, and reduces hospitalisation

The University of Glasgow has been leading research on new heart failure therapies. Its 2016 study transformed treatment by underpinning the worldwide approval of the new drug sacubitril/valsartan, becoming a major breakthrough in heart failure management.

Heart failure (HF) is a condition when the heart cannot meet the body's demands and can have devastating consequences. HF patients have a survival rate of five years post-diagnosis, reduced quality of life and an increased likelihood of premature death. As the leading cause of hospitalisations for adults over 65 years, the burden of HF on health services is vast – costing the NHS over £2 billion and the US Medicare system \$17 billion. Approximately

50% of HF patients suffer from heart failure with reduced ejection fraction (HFrEF). Prior to the study, HFrEF was treated by ACE inhibitors, which only partially improve heart failure.

In collaboration with Novartis, the Glasgow team led and directed the largest drug therapy trial in patients with heart failure with reduced ejection fraction. The data from the study revealed a significant 20% reduction in the risk of death of heart failure hospitalisation, demonstrating the efficacy of sacubitril/valsartan in patients of all ages.

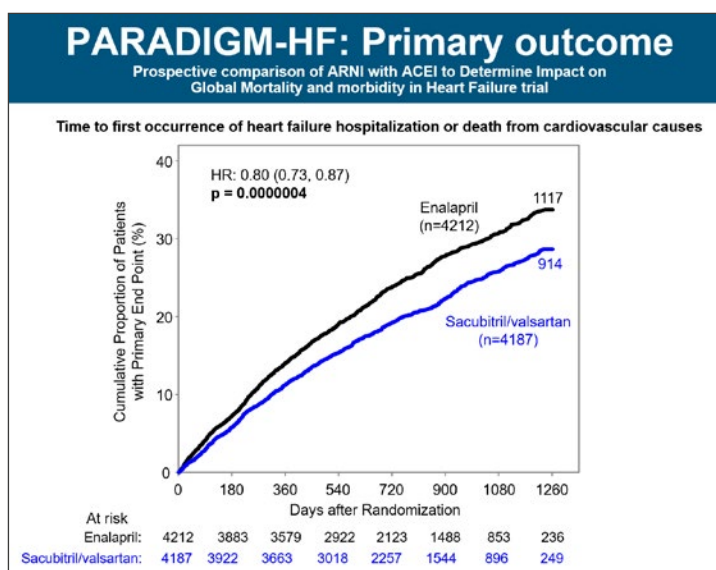
The drug sacubitril/valsartan has since been approved in 112 countries and is used to treat over 1.4 million HF patients worldwide, reducing premature death and hospitalisation rates. The drug has also been approved and recommended by influential cardiovascular societies, including the European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and Heart Failure Society of America. The UK guidelines on heart failure management have

recommended the use of sacubitril/valsartan since 2016.

The treatment of HF patients with sacubitril/valsartan, compared to treatment with the previous standard drug enalapril, has reduced the risk of dying from cardiovascular causes by 20%, heart failure hospitalisation by 21%, the risk of dying from any cause by 16%, and re-hospitalisation by 38% after the first admission. Subsequently, the University of Glasgow has been instrumental in developing a drug that both saves lives and dramatically reduces the burden on health services.

Lead researchers: John McMurray and Pardeep Jhund

“The data from the study revealed a significant 20% reduction in the risk of death of heart failure hospitalisation”



Graph comparing results of Sacubitril/Valsartan and Enalapril on first occurrence of heart failure hospitalisation or death from cardiovascular causes over time.



Improving safety, health outcomes and cost effectiveness in patients with chest pain using Computed Tomographic Cardiac Angiography (CTCA)

The University of Plymouth has been leading a study to improve treatment of patients with chest pain using Computed Tomographic Cardiac Angiography (CTCA).

Until the development of CTCA, the only way to visualise the coronary arteries to pre-empt heart attacks or angina was through a costly and invasive coronary angiography. Computed tomographic imaging is, in contrast, a safe outpatient procedure costing only £200 but had previously had technical challenges in its application to image the heart. The University of Plymouth has been working to overcome these challenges to make CTCA a viable alternative to invasive angiography. Through a series of clinical trials, the team revealed CTCA's high accuracy in clinical use.

The team came across various challenges while working to improve CTCA which included its high radiation, with known risks to causing cancer, and its poor accuracy in patients with metal stents in the vessel or high levels of coronary artery calcium. Dr Carl Roobottom, who led the research, developed new computational reconstruction methods which could overcome these limitations and provide all patient groups access to CTCA. Together with General Electric (GE) technology – the world's largest manufacturer of CT equipment – Roobottom developed the techniques and technology for performing cardiac CT.



“Through a series of clinical trials, the team revealed CTCA’s high accuracy in clinical use”

In recognising that CTCA is a technically challenging operator and requires a high level of expertise, Roobottom set up cardiac CT training courses, running five times a year, which have since trained 375 doctors, most of whom currently use CTCA in the UK. He has also integrated cross-sectional anatomy teaching for all students at the Peninsula Medical School and created the Peninsula Radiology Academy dedicated to training in imaging.

Furthermore, the National Institute for Health and Care Excellence (NICE) developed diagnostic guidance on

the use of advanced CT scanners in patients who were difficult to examine, recommending the increased use of CTCA with the appropriate CT equipment. NICE has also recommended CTCA as the first line investigation for all patients with stable chest pain. An economic evaluation of the impact of implementing CTCA in England estimated a reduced cost of £16 million per annum.

Chest pain accounts for 700,000 Emergency Department attendances per annum and 40% of hospital admissions, yet 85% of patients are still discharged without a diagnosis. With a negative predictive value approaching 100%, CTCA has the potential to save lives and reduce the cost of diagnosing a single patient in the NHS.

Lead researcher: Carl Roobottom

Harnessing skeletal stem cells to transform orthopaedic treatment

In the UK, one in two women and one in five men will suffer a fracture after the age of 50, costing the NHS billions of pounds each year.

Hip replacements are one of the most common joint replacement procedures; however, many of those surgeries need revisions. New treatments that enable the skeleton to heal better are urgently needed to meet this escalating need and save costs. Researchers at the University of Southampton have developed novel methods using skeletal stem cells to treat bone damage and disease.

The Bone and Joint Research Group at the University of Southampton demonstrated the efficacy and patient benefit of using patients' own bone stem cells together with innovative biocompatible scaffolds at the point of injury to transform approaches to orthopaedic treatment. Starting in 2002, Professor Richard Oreffo and his team demonstrated how a patient's own bone stem cells had a large capacity to form bone in vitro. Working with patient samples from University Hospital

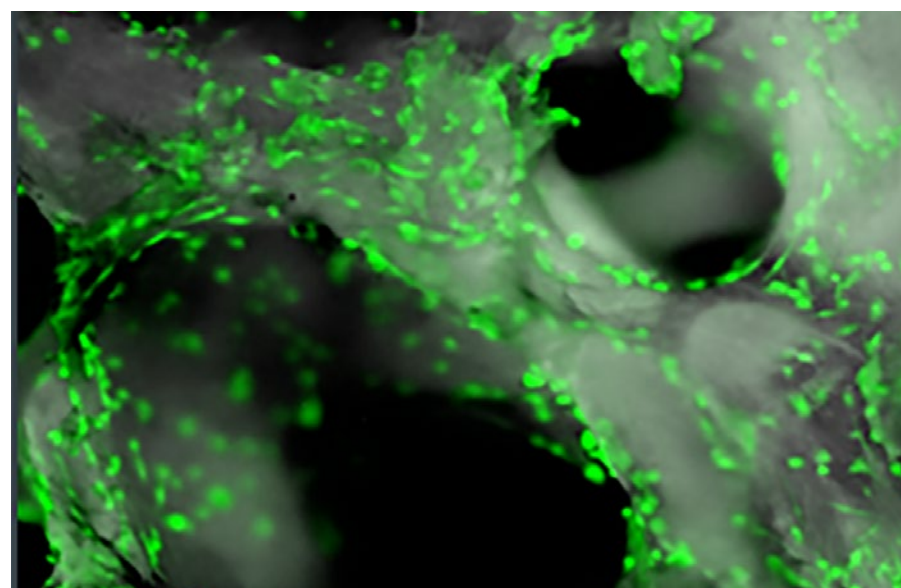
Southampton, researchers were able to isolate human skeletal stem cells and optimise the physical conditions necessary to encourage their growth.

“The work has attracted substantial investment from both the charity and private sector, which, has helped to expand the treatment to more patients and work to break the revision cycle”

Further work with Professor Douglas Dunlop led to demonstration of the applicability of using a patient's own bone cells in bone impaction grafting in animal models and in human patients. To facilitate large bone repair defects, they combined stem cells and bone graft with 3D printed scaffold templates and in 2014, the Southampton researchers translated this into clinical practice and undertook the first concentrated autologous skeletal stem cell augmentation onto the porous surface

of a 3D custom-made revision total hip replacement. Following this landmark operation in the UK, the team has followed a case series of treated patients; to date over 20 patients have been treated with this approach.

In parallel with this work, Dr Jonathan Dawson and Professor Richard Oreffo developed novel biomaterials to increase bone repair and were one of the first groups worldwide to use novel nanoclay gels as a biomaterial for bone repair. The nanoclay gel technology (Renovite®) acts as an injectable scaffold that attracts cells and localises delivered growth factors at safe, ultra-low doses. Specifically, Dawson and Oreffo have shown the ability to induce bone formation using physiological doses of bone morphogenetic protein, (BMP2), a therapy, which can stimulate bone growth. This formed the basis of University of Southampton spinout company Renovos Biologics Limited in 2017. Between 2017 and 2020, Renovos raised £870,000 from public and private sector funding, and created 3.5 full-time equivalent employment roles.



Human bone stem cells growing on bone. Oreffo and Bone and Joint Research Group, University of Southampton.

The Bone and Joint Research Group's research on biomaterials, stem cells and regenerative medicine led to ground-breaking, cost-saving approaches to clinical practice that have significantly enhanced patients' quality of life. The underpinning research led to the first patient in the UK being treated with a stem-cell augmented 3D-printed hip replacement in 2014. The work has attracted substantial investment from both the charity and private sector, which, has helped to expand the treatment to more patients and work to break the revision cycle.

Lead researchers: Richard Oreffo, Douglas Dunlop, Jonathan Dawson and Nicholas Evans

Optimising antibiotic prescribing in children

The inappropriate dosing and overuse of antibiotics has led to increased antimicrobial resistance globally. In response to this issue, St George's, University of London has been researching the dosage, duration and practice of using antibiotics, providing indicators of appropriate prescribing at a country level that can be used as targets and monitoring tools to drive down inappropriate antibiotic use world-wide.

Antimicrobial Resistance (AMR) has been identified as a huge and escalating threat to global health and prosperity, with drug resistant infections causing an estimated 700,000 deaths, and an excess cost of \$20 billion each year in the USA alone. The overuse of antibiotics is a critical driver of antimicrobial resistance, with childhood infections accounting for approximately 25% of all prescribing. The research team identified a global threat of AMR in young children and the clear need to improve the quality of childhood antibiotic prescribing in both the community and hospital setting through improved stewardship programmes. To determine the variation in antimicrobial use for serious hospital infections, the group developed a novel methodology to conduct simple web-based point prevalence surveys (PPS) of neonatal and paediatric antimicrobial prescribing.

The research highlighted the impact of low doses of amoxicillin used in UK children, leading to major changes in UK guidance in 2014. Approximately 55% of children were being under dosed until 2014 in the UK, decreasing to 6% after 2014. Since then, millions more children are now being given appropriate amoxicillin doses for common community infections in the UK. The team's study led directly to

funding for a further trial in Africa to define optimal antibiotic regimens for childhood pneumonia.

The team at St George's has also contributed an important body of work to optimise antibiotic use in children, by providing simple indicators that can be used as targets and monitoring tools to drive down inappropriate antibiotic use on a world-wide basis. The metrics developed by the research team have become an important part of global antibiotic stewardship tools and a key component of WHO efforts to combat AMR.

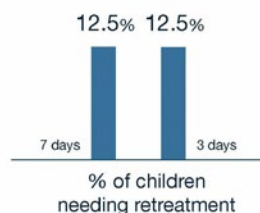
Lead researchers: Michael Sharland, Julia Bielicki and Yingfen Hsia

“The team at St George's have also contributed an important body of work to optimise antibiotic use in children, by providing simple indicators that can be used as targets and monitoring tools to drive down inappropriate antibiotic use on a world-wide basis”

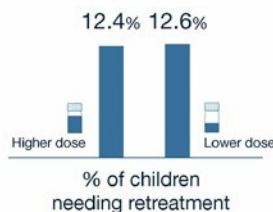
The CAP-IT results

CAP-IT looked at the number of children needing retreatment with antibiotics within 4 weeks

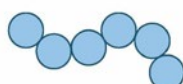
Shorter length treatment was as good as longer length treatment



Lower dose of amoxicillin was as good as the higher dose



Levels of antibiotic resistance were low in CAP-IT



The levels of antibiotic resistance were not affected by either the length of treatment, or the dose of amoxicillin used.

Driving policy change

Each year the NHS faces increasing social and economic pressures, with record-high waiting lists and an unprecedented workforce collapse.

Medical schools are now at the forefront of stimulating debate among policymakers regarding the changes needed for health and care services to meet the challenges and demands of the future.

Medical research has an important role to play in driving changes in health policy. It helps to guide priorities for public health bodies, informs resource allocation and improves public knowledge around health and wellbeing. Medical research can also have a powerful impact on the community, particularly for groups often underrepresented in health research. Understanding the complexity of disease requires research to accurately reflect the

population it is studying, as evidenced by the impact of COVID-19 on different ethnic groups. By broadening this reach, we can reduce health inequalities and lessen the burden on the health service.

The case studies that follow show medical schools conducting research into the effects of population health issues on society, shaping policy to change social behaviours as prevention strategies, and providing a better understanding of how our health system can meet the demands of the future. The research explores everything from the long-term management of frailty, to informing the UK response to COVID-19 and identifying risk factors for self-harm.

Preventing exposure to second-hand tobacco smoke

Due to a lack of data on the potential harms of second-hand smoke, homes and cars were exempt from the UK's 2006/07 smoke-free legislation.

The University of Aberdeen has been working to fill the evidence gap and assessing the potential harm of second-hand tobacco smoke on the health of non-smokers, particularly young children, in homes and cars.

The research team at Aberdeen examined concentrations of fine particulate matter – a well-recognised marker of second-hand smoke levels used by WHO – in car journeys and in homes. The team found that smoking car journeys had an average concentration 10 times higher than those in smoke-free journeys, and that window-opening and ventilation had minimal impact on reducing particulate matter exposure concentrations. Furthermore, in measuring air quality for extended periods in home settings, the study also revealed that second-hand smoke can linger indoors for up to

five hours after a cigarette. The study informed and influenced the Scottish Government's 'Take it Right Outside' campaign, having one of the highest recall of any health education advert among the target group of smoking parents. It directly supported the Scottish Government's development of a strategy to reduce the proportion of children in Scotland exposed to second-hand smoke at home by 50% by 2020 – a target which was met five years early.

Estimates have shown that prior to the changes in policy and public health campaigns by the Scottish Government, 60,000 children in Scotland were regularly exposed to second-hand smoke in cars. The Scottish Health Survey found that the proportion of children exposed at home fell from 12% to 6% between 2012 and 2015, equating to 50,000 children in Scotland who are now protected from the harms of second-hand smoke in their home.

The University of Aberdeen's research programme on preventing exposure to second-hand tobacco smoke has been incredibly influential in driving UK policy to ban smoking in cars carrying children, improving public awareness and reducing the number of children exposed to second-hand smoke. The impact of smoke-free homes and cars is likely to bring dramatic health benefits to children, particularly for those aged five and under who tend to spend more time inside the home than school-age children.

Lead researchers: Sean Semple, Steve Turner and Smita Dick

“The University of Aberdeen’s research programme on preventing exposure to second-hand tobacco smoke has been incredibly influential in driving UK policy to ban smoking in cars carrying children, improving public awareness and reducing the number of children exposed to second-hand smoke”



Introducing a meningitis B vaccine in UK infants which led to a 75% reduction in cases

Mathematical models are now a critical tool for informing decisions on vaccine policy in the UK. This is because the Joint Committee on Vaccination and Immunisation (JCVI), which advises the Government on vaccine policy in the UK, can only recommend vaccine introduction if it is deemed cost-effective.

When new vaccines are developed, new mathematical models are required to assess potential effectiveness and cost-effectiveness when implemented in populations.

Bristol-led research developed such models for novel vaccines against meningococcal B disease. Two types of mathematical models were developed, incorporating epidemiological and economic data, to predict the potential impact of introducing a new vaccine with the capacity to protect against Meningitis B, in terms of case reduction and cost-effectiveness.

“The research found that 27% of cases could be prevented over the lifetime of a birth cohort by vaccinating infants (with a vaccine preventing disease only) at 2, 3, 4 and 12 months of age”

The research found that 27% of cases could be prevented over the lifetime of a birth cohort by vaccinating infants (with a vaccine preventing disease



only) at 2, 3, 4 and 12 months of age. If the vaccine prevents transmission in addition to preventing disease, substantial disease reductions (71%) could be produced after 10 years by routinely vaccinating infants in combination with a large-scale catch-up campaign (1-17 years), due to the high levels of carriage in teenagers. This could be cost-effective at £17 per vaccine dose.

From 2011, the team further developed the models in response to the availability of new data and requests by the Joint Committee on Vaccination and Immunisation (JCVI). Model results were produced, considering several different ‘MenB’ vaccine scenarios, and the uncertainty in several of the model parameters, estimating the number of cases

averted by vaccination and in what age groups over time. The cost-effectiveness of each programme was evaluated and the maximal vaccine price estimated for each scenario to be considered cost-effective in the UK. The JCVI recommended introducing the vaccine at a cost-effective price based on the Bristol findings and MenB cases reduced by 75% by the third year of the programme.

Additionally, Bristol researchers were commissioned to tailor the models for Germany and Belgium by the health authorities in these countries; Dr Christensen led the research team, which included researchers Drs Tom Irving and Emily Nicoli.

Lead researcher: Hannah Christensen, Caroline Trotter and Matt Hickman

Improving understanding and care of postpartum psychosis in bipolar patients

Postpartum psychosis is a severe psychiatric disorder affecting over 1,400 women in the UK each year. It is characterised by sudden onset and rapid deterioration of symptoms and can lead to severe illness and suicide.

While many clinicians recognised that bipolar patients were more susceptible to postpartum psychosis, lack of evidence on the prevalence of postpartum psychosis in bipolar women, and the factors determining individual risk, meant they were unable to provide individualised, targeted care. Researchers at Cardiff university led a series of studies to address these gaps in our understanding.

“The study findings provided critical evidence that improved understanding of individual risk of postpartum psychosis in bipolar woman and has helped to improve clinical care for bipolar women in the UK”

The team conducted the largest study of postpartum psychosis in women diagnosed with mood disorders specifically, considering 1,785 women (over 3,000 deliveries), grouped by diagnosis (bipolar I, bipolar II and Recurrent Major Depression). For the first time, the study showed a considerably higher risk of postpartum psychosis in bipolar type I with symptoms occurring earlier in the

postpartum period compared to women with other forms of bipolar disorder. A further study found that women were at particularly high risk for postpartum psychosis in the first two weeks following delivery.

In further studies the Cardiff researchers investigated the contribution of previous perinatal history on risk of subsequent postpartum psychosis. They found that women with bipolar disorder who experienced postpartum psychosis during pregnancy were at risk of developing the condition in subsequent pregnancies. Length and severity of episodes, the gap between pregnancies and family history were also risk factors.

The study findings provided critical evidence that improved understanding of individual risk of postpartum

psychosis in bipolar woman and has helped to improve clinical care for bipolar women in the UK. The Cardiff research was incorporated into the National Institute for Health and Care Excellence (NICE) 2014 Clinical Guidelines and informed the development of enhanced training for clinicians and healthcare professionals. It was also used to evidence the critical need for substantial investment in new specialist perinatal mental health services across England, and the research team was part of a successful campaign alongside maternal mental health charities that led NHS England to make a commitment of £365 million for new specialist perinatal services in England.

Lead researchers: Ian Jones, Arianna di Florio, Elizabeth Forty and Nicholas Craddock



Faecal haemoglobin estimation in colorectal cancer screening and the triage of symptomatic populations

The University of Dundee's studies on faecal immunochemical tests (FIT) has significantly enhanced UK colorectal cancer screening and reduced the need for colonoscopy – a costly and intrusive procedure which is often uninformative.

Colorectal cancer is the second most common cause of cancer death in both sexes, with a prevalence of roughly 1,600 deaths in Scotland every year. Previous research led by Professor Steele at the University of Dundee demonstrated the value of faecal occult blood test in colorectal cancer screening and led to the introduction of national colorectal cancer screening programmes across the UK. Since then, the University of Dundee collaborated with NHS Scotland to develop a Colorectal Screening Research Unit to allow further research into colorectal cancer screening. The study demonstrated that population screening can detect pre-malignant adenomas, allowing them to be treated before they progress and thus reducing both the incidence of colorectal cancer and mortality.

The Scottish Bowel Screening Programme was rolled out by NHS Tayside, NHS Grampian and NHS Fife in 2007, which in turn led to the introduction of national colorectal cancer screening programmes across the UK. Over the last decade, around 2,000 deaths have been prevented annually. Since the implementation of the Scottish Bowel Screening Programme in 2007, colorectal cancer mortality has fallen by 8% and, by October 2018, 6,000 colorectal cancers had been diagnosed through screening. The team at Dundee revealed through the data how screening reduces colorectal cancer incidence against a background of increasing incidence in the unscreened population.

“Research at the University of Dundee revealed how the use of the FIT after a weakly positive occult blood test resulted in fewer false positive results, and then how FIT could replace FOBT completely”



A Faecal Immunochemical Test (FIT) kit.

The faecal occult blood test (FOBT) used in the original UK screening programmes is an indirect measure of human haemoglobin in faeces whereas the faecal immunochemical test (FIT) specifically detects haemoglobin. Research at the University of Dundee revealed how the use of the FIT after a weakly positive occult blood test resulted in fewer false positive results, and then how FIT could replace FOBT completely. Subsequently, FIT was proven to be a safe and effective ‘rule out test’ in patients with symptoms, and implementation of this approach has resulted in fewer referrals for invasive investigation without negatively impacting the rate of diagnosis of serious disease.

Lead researcher: Robert Steele

Reducing inequalities in palliative care for people with non-malignant disease

Chronic breathlessness is a debilitating syndrome which affects over 88 million people worldwide. Research by Hull York Medical School (HYMS) has characterised and improved the management of chronic breathlessness in people with non-malignant (non-cancerous) heart and lung disease.

This has been achieved by addressing the inequalities in palliative care of people with these conditions, as compared with people with cancer, by developing effective tools to identify and triage care, and providing new therapeutic interventions.

Previously few palliative care services, in the UK or worldwide, accepted patients with non-malignant conditions. This meant that many patients with such diseases had no access to specialist palliative care or evidence-based symptom control measures, even though over 90% of people with advanced heart and lung disease will have chronic breathlessness; levels similar to lung cancer patients. Most of these people died in hospital, often by default rather than by preference.

A multidisciplinary research team, led by Professor Miriam Johnson, has worked for almost two decades to rebalance this gross inequity in palliative care access. In 2000, Johnson started the UK's first integrated heart failure, primary care (HF-PC) service in Scarborough (a HYMS clinical partner site) and from the work at this centre published service descriptions in 2006, 2009 and 2012, and co-edited the world's first HF-PC clinical handbook. In 2014

the team published a UK Clinical Practice Research Database study of those dying, showing the inequality of palliative care access for people with heart failure compared with cancer (7% vs 48%). Their recent study shows that by 2014, palliative care access had increased to 25% of people dying of Chronic Obstructive Pulmonary Disease (COPD) or heart failure.

Team members published the first adequately powered, four-day placebo, randomised-controlled trial (RCT) in heart failure (HF) and the only three-month placebo RCT of oral morphine for chronic breathlessness due to HF. In addition, the team completed a ground-breaking study which underpinned a world-first (in Australia) Regulatory Licence approval for oral morphine use for breathlessness. Finally, members of the research team led international research to define the new clinical syndrome of chronic (persistent) breathlessness. In 2017 they delineated the new framework of "Breathing Space" to convey the experience of people living with chronic breathlessness. Using pooled clinical study data, researchers estimated the minimal clinically important difference (MCID) in breathlessness intensity measurement demonstrating that people with chronic breathlessness attach value to even a small improvement.

This work has led to changes in national and international guidelines and regulatory approval for morphine in the pharmacological management of chronic breathlessness.

Lead researcher: Miriam Johnson

"22 livers (71%) met the viability criteria and were successfully transplanted into recipients with 100% 12-month patient and organ survival"



"Hidden in the roses" This image is from the HYMS Breathlessness Exhibition – it depicts the experience of someone suffering from chronic breathlessness, as one exhibition viewer stated "People who have breathing difficulties often feel like they are suffocating and that they can't seem to get any air. This is depicted by the roses obscuring her view."

Influencing policy and practice for the care and management of gout in primary care

Keele University has been researching the impact of gout on patients and public health, expanding global understanding of the disease and shaping policy and practice, both nationally and internationally.

Gout is already the most common inflammatory arthritis, with its prevalence and incidence increasing in the UK due to an ageing population and higher rates of comorbidity and obesity. Gout causes excruciating flares of joint pain and swelling, long-term joint damage and a diminished quality of life. The research team at Keele University has been undertaking qualitative interviews with gout sufferers, identifying issues relating to the causes, diagnosis and treatment of the condition.

The research revealed a variety of misconceptions about the causes of gout and perceived characteristics of gout sufferers as well as the duration of the condition. As a result, the team has created public-facing materials about gout and how it affects people's lives. The website Healthtalk.org,

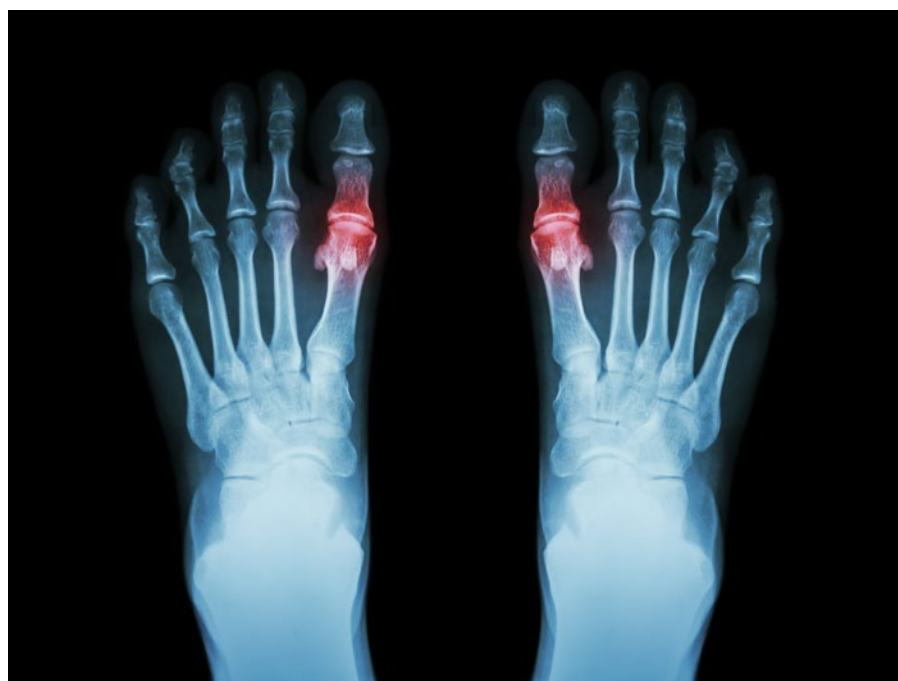
“Keele University has been immensely influential in developing national and international guidelines for gout management, improving patient outcomes, and increasing awareness on the social implications of the condition”

managed by Dipex Charity, has been hosting the team's online 'healthtalk' on gout, with each informative video reaching 4,000 views per month. Information on management and care has also been widely circulated amongst nurses in 134 practices across North Staffordshire and South Cheshire.

Using data from the Clinical Practice Research Datalink (CPRD), the research team identified clear associations between gout and comorbidities including vascular disease, sleep disorders, venous thromboembolism and sexual dysfunction. They discovered that gout was a risk factor for vascular events, with a higher incidence in women over men. The risk of chronic kidney disease (CKD) in gout sufferers is over twice that of the general population.

Furthermore, the team's CONTACT trial, comparing naproxen and low-dose colchicine for the treatment of gout flares in primary care, was the first-ever trial for non-steroidal anti-inflammatory drugs (NSAID) and colchicine, and was cited in international guidelines soon after its publication. Keele University has been immensely influential in developing national and international guidelines for gout management, improving patient outcomes, and increasing awareness on the social implications of the condition.

Lead researchers: Christian Mallen, Edward Roddy, Jennifer Liddle, Samantha Hider, Jane Richardson, Lorna Clarson, John Belcher, Mathew Roughley, Kelvin Jordan, Priyanaka Chandratre and Jane Hall



Development, implementation and impact of the electronic Frailty Index (eFI)

Frailty is a condition that is common in old age. It develops because as we get older our bodies change and can lose their inbuilt reserves.

These changes mean that older people with frailty can experience sudden dramatic changes in their health when they have an illness. International guidelines recommend frailty should be identified routinely so a more holistic approach to care can be taken, and effective treatments provided. However, the main historical difficulty with identifying frailty routinely is that available clinical tools, such as measuring walking speed or frailty questionnaires, require additional resource, and might be inaccurate.

Researchers from the University of Leeds led the development and national implementation of an electronic frailty index (eFI) that uses routine GP data to identify frailty. Professor Andrew Clegg and Dr Elizabeth Teale led the underpinning research to develop and validate the eFI in a landmark study funded by the National Institute for Health and Care Research (NIHR). The study used the cumulative deficit model, which identifies frailty on the basis of a range of variables including symptoms, signs, diseases, disabilities and abnormal laboratory values, collectively referred to as deficits. Primary care electronic health record (EHR) systems in the UK use Read Codes to categorise and log multiple patient characteristics including symptoms, signs, laboratory test results, diseases, disabilities and information about social circumstances. Primary care EHR systems therefore provide a potentially simple yet powerful mechanism for identifying cumulative deficits to identify frailty routinely.

Following eFI national implementation, over one million older people in the UK have been assessed for the presence of frailty. Examples of interventions deployed in primary care after identifying people with frailty using the eFI include:

- targeted medication reviews to reduce problematic prescribing
- proactive falls prevention
- supported self-management for people with mild frailty
- comprehensive geriatric assessment as an evidence-based frailty intervention
- advance care planning and palliative care.

The national implementation of the eFI led to major NHS policy impact as it enabled a standardised approach to identifying frailty on a national scale, providing the platform for the 2017/18 NHS England GP contract and inclusion in the 2019 NHS Long Term Plan. Impact on health and

care services is supported through inclusion in NICE guidelines and the development of new models of frailty care, cited in national frailty guidelines. Recognition of impact is through selection as an example of world-class NIHR research making a difference to patient care, and the prestigious 2017 Royal College of Physicians' (RCP) Excellence in Patient Care Award.

Lead researcher: Andrew Clegg and Elizabeth Teale

“Recognition of impact is through selection as an example of world-class NIHR research making a difference to patient care, and the prestigious 2017 Royal College of Physicians' (RCP) Excellence in Patient Care Award”



A research participant from the University of Leeds study.

Informing the UK response to COVID-19

When the COVID-19 pandemic hit, nobody knew quite how it would spread through the population or what measures could effectively contain it.

Staff at the London School of Hygiene and Tropical Medicine's (LSHTM) Centre for Mathematical Modelling of Infectious Diseases (CMMID) developed models to simulate the COVID-19 epidemic across 186 county-level administrative units of the UK. This modelling was essential to understand the transmission of the virus and avoid overwhelming the NHS during an unprecedented health emergency.

“LSHTM designed a social contacts survey designed to track the weekly reproduction number and regional differences through a representative sample of UK adults”

The team modelled various impacts; for school closures, they decreased contacts made in schools to 0, with potentially increased contact between children and older adults to reflect grandparents providing more care. They also modelled the impact of non-pharmaceutical interventions in the UK on cases, deaths, and demand for hospital services, including the likely requirements for non-intensive care unit (ICU) hospital beds and ICU beds over time. The team estimated that an unmitigated epidemic could result in 16-30 million symptomatic COVID-19 cases and 250,000-470,000 deaths. In this scenario, the NHS hospital and ICU bed capacity would be massively exceeded. A second scenario of shorter-term (1 week to 12 week) interventions, typically used to mitigate the burden

of pandemic influenza and SARS, was found likely to be inadequate in the UK for COVID-19. ICU bed requirements would exceed availability by a factor of 10 to 30. In a third scenario, longer-term (1 year) programmes of social distancing and protecting the most vulnerable, plus periodic ‘lockdowns’ with stricter measures, had the potential to prevent exceeding NHS capacity. However, the team predicted these measures would likely need to last for at least several months.

LSHTM modellers, and sociologists worked with University College London researchers to predict the impact on transmission of schools reopening in summer 2020. Scenarios included a full- and part-time rota system of alternating attendance, each within three testing scenarios reflecting various levels of contact tracing and testing. Alongside school reopening, the model included relaxing measures across society, on the assumption these would occur simultaneously. For each scenario, they estimated the number of new infections and deaths, as well as the reproductive number (R). This was complemented by modelling which demonstrated the age-dependent effects of COVID-19 transmission, showing that susceptibility to infection in under 20s was around 50% lower than in adults over 20. Interventions aimed at children were therefore likely to have a relatively small impact on reducing transmission.

LSHTM designed a social contacts survey designed to track the weekly reproduction number and regional differences through a representative sample of UK adults asked about the number of direct contacts they had on the day before each weekly analysis. Using these data, the team could predict the effect of social distancing measures, providing the first indication that the R number was driven below 1



during the first national lockdown as people observed the rules.

Combining modelling with social science insights provided evidence on measures where public behaviour was crucial to slowing transmission and reducing cases. Bonell and Curtis collaborated with experts at UCL, King's College London and Public Health England, to develop principles to inform interventions aimed at getting everyone to observe social distancing measures.

The multidisciplinary research conducted at LSHTM was at the forefront of informing the UK response to the COVID-19 pandemic. The research avoided an unmitigated epidemic scenario of 16 to 30 million symptomatic COVID-19 cases and 250,000 to 470,000 deaths and prevented the NHS from being overwhelmed. By tracking the R number to assess the rate of transmission, LSHTM research informed the safe easing of restrictions, reinforced by positive messaging to encourage people to comply with the measures. While findings were UK-focused, the research products and educational resources were influential and have been used worldwide.

Lead researchers: John Edmunds, Graham Medley, Adam Kucharski, Rosalind Eggo, Stefan Flasche, Chris Bonell and Valerie Curtis

Community-based screening boosts early lung cancer detection in deprived communities

Lung cancer is the most common cause of cancer-related death in the world. 75% of patients are diagnosed with advanced disease where treatments are ineffective and median survival rates are low.

Screening those at risk with low dose CT (LDCT) scans reduces lung cancer-specific mortality by between 20-26%. Smoking and low socio-economic status are associated with increased lung cancer risk but lower screening/research uptake. Those at greatest risk are therefore under-represented in research trials and least likely to access screening services.

In response, University of Manchester researchers in partnership with Manchester University NHS Foundation Trust addressed how, by taking lung cancer diagnostics into the greatest at-risk communities, patient lives could be saved while reducing the cost to the NHS. To help reach these communities, the Manchester team developed the Manchester Lung Health Check (LHC) to help early lung cancer

detection. The programme focused on deprived populations, a priority area for screening implementation. The holistic approach was community-based and offered a convenient 'one-stop-shop' service, including targeted LDCT screening to those at high risk with immediate access to a scan in a mobile CT scanning unit and further disease prevention strategies to improve overall health.

The programme was piloted in three highly deprived areas of Manchester with smokers aged 55-74. One person for every 23 people screened was diagnosed with lung cancer and 80% of screen-detected tumours were early stage (stages 1 and 2). The study demonstrated engaging with individuals at risk from highly deprived communities can transform outcomes from lung cancer by detecting early-stage disease, which can be curable. It also provided an important opportunity to address other common causes of premature death and co-morbidity in this population, thereby helping to reduce health inequality.

The success of the programme has led to further community-based mobile lung cancer screening pilots across the country and its results have gained international recognition. Recently the UK National Screening Committee has recommended national roll out of lung cancer screening using the LHC approach. The potential cost savings from LHC are immense, saving the health service tens of thousands of pounds per patient in cancer treatment costs through early detection and intervention.

Lead researchers: Philip Crosbie and Richard Booton

“The success of the programme has led to further community-based mobile lung cancer screening pilots across the country and its results have gained international recognition”



Utilising local community pharmacies for minor illnesses to reduce burden on hospitals and GPs

Emergency departments (ED) and general practice (GP) surgeries are facing unsustainable pressure. Treating minor illnesses in these locations is costly and reduces their capacity to treat more serious conditions. Many minor illnesses could be managed in local Community Pharmacies (CPs), but poor integration and a lack of evidence of their capacity discouraged uptake. Researchers at Newcastle University have worked to address this issue.

Newcastle researchers addressed three main areas. The first was CP accessibility. The work demonstrated that community pharmacies are the

“The work demonstrated that community pharmacies are the most accessible healthcare provider in England, and that most of the population can reach a community pharmacy within a 20-minute walk from their home”

most accessible healthcare provider in England, and that most of the population can reach a community pharmacy within a 20-minute walk from their home. In the most deprived communities, this figure increases to almost 100%, a phenomenon termed the ‘positive pharmacy care law.’ The second area of research evidenced that CPs can deliver effective public health services, for example researchers found that CP-delivered smoking cessation programmes were just as effective compared to usual care. The third area was a collaboration between Newcastle University, representatives from NHS England, NHS 111 and the Local Professional Network to develop a new pathway in the NHS 111 clinical support system. Following the success of this initial pilot, known as the Digital Minor Illness Referral Service (DMIRS), in Autumn 2018 DMIRS was extended to London, Devon and the East Midlands until March 2019, supporting up to 17.8 million people.

The Newcastle research provided clear evidence that CPs were accessible, convenient and could target hard-to-

reach groups. This work helped inform changes to the Community Pharmacy Contractual Framework (CPCF) to allow CPs to deliver a national NHS seasonal flu vaccine service targeted at eligible at-risk patients. Since the service began in 2015, there has been a rapid increase in the number of patients receiving a vaccination and the percentage of CPs involved. The DMIRS pilot directly informed a change in the NHS 111 algorithm and call handler training so that, where appropriate, callers with minor ailments were referred digitally to a CP. A large-scale evaluation of the service that ran throughout 2018 found that 13,246 patient calls to NHS 111 were referred to CP. Of these, 47% of patients attended the CP and were successfully managed in this setting, saving over 6,000 appointments in GP or ED. The success of the trial led to DMIRS being rolled into the new national pharmacy contract and launched across England in October 2019. Of note was the use of the service by patients from deprived areas: the highest number of calls and the highest number of patients referred to CP were from the five most deprived deciles. This showed that developing services from community pharmacy – aimed at treating minor illnesses and preventing disease - not only has the potential to free up time for other healthcare professionals working in other parts of the NHS, but it also has the potential to reach people who are in need of the most care.

Lead researchers: Adam Todd, Hamde Nazar, Sarah Slight, Clare Bamba, Falko Sniehotta, Katie Thomson



Informing a national approach to mental health, suicide, and self-harm prevention



Suicide is a tragedy for all concerned and a cause of distress for many people. Research evidence generated by Swansea University has shaped the development of a multi-stranded national approach to prevent suicide and self-harm.

In 2008, the issue of suicide came to prominence in Wales due to an apparent cluster of suicides in young people in the Bridgend area of South Wales. The sensationalism of the extensive newspaper coverage provoked controversy and subsequently researchers at Swansea University worked to assess the extent of the problem by determining whether a statistically definable cluster had occurred. By analysing mortality data over 10 years across Wales (a population of 3.2 million), the researchers were able to produce evidence of the existence of a suicide cluster among 15- to

35-year-olds around the time of the media attention. The team examined the quality and sensationalism of media articles on suicide in Bridgend for six months before and after the defined cluster using a tool based on guidance for responsible reporting of suicide they had developed previously. Almost half of the articles identified displayed a high level of poor-quality and sensationalist reporting during the timescale of the suicide cluster. The research highlighted the necessity for improved knowledge of the characteristics of those who die by suicide, the risk factors for suicide and patterns of healthcare contacts to better identify and support those at risk of taking their own lives.

Building on their work and funded by Health and Care Research Wales, the research group at Swansea developed a new database, Suicide Information Database-Wales (SID-Cymru), in

“The potential to bring together billions of pieces of data on to one platform has attracted a further investment of over £12 million”

2014. The largest database of its kind, it accesses and links information on prior health, the nature of previous contacts with services, and wider social circumstances for all those who die by suicide within the population of Wales using anonymised routinely collected electronic data in healthcare and social datasets from the Secure Anonymised Information Linkage (SAIL) Databank. Data from SID-Cymru has helped to direct the Welsh Government's suicide prevention strategy. In 2018, the Welsh Government pledged an additional £500,000 a year to support national and regional approaches to prevent suicide and self-harm. The success of SID-Cymru has led to similar systems being adopted internationally.

In 2016, Swansea researchers began to re-evaluate the quality of prescribing for depression (a key risk factor for suicide) in young people identified a significant gap in young people's mental health research. The potential to bring together billions of pieces of data on to one platform has attracted a further investment of over £12 million.

Lead researchers: Ann John, Keith Lloyd, Ronan Lyons and David Ford

Improving neonatal health outcomes in pregnant women with Type 1 Diabetes

Diabetes is the most common medical condition in pregnancy, affecting around one in ten pregnant women.

Type 1 diabetes, where the pancreas cannot produce insulin to regulate maternal glucose levels, adversely impacts 2,000 pregnant women and babies in England and Wales. Higher maternal glucose levels cause serious complications, such as birth defects and baby deaths, which occur in 1 in 12 pregnancies. Self-monitoring of blood sugars aiming for target glucose levels during pregnancy is vital for healthy mothers and babies. A sensor-based method called Continuous Glucose Monitoring (CGM) was available, but more expensive than existing fingerstick glucose monitoring. Moreover, the impact of sustained use of CGM on longer-term health outcomes was unclear, as were the risks and benefits of its use during pregnancy. Researchers from the University of East Anglia, in collaboration with the Centre for Mother, Infant, and Child Research in Toronto, led the Continuous Glucose

Monitoring in Women with Type 1 Diabetes in Pregnancy (CONCEPTT) trial to fill that knowledge gap.

Conducted between 2013 and 2017, the trial was based on a small sensor attached to the skin which continuously measured glucose levels, and wirelessly streamed glucose information to a mobile phone or insulin pump. The results of the trial demonstrated that pregnant women using CGM had improved glucose levels, spending on average, an additional 1.7 hours per day in the target glucose range during pregnancy. Importantly, newborns whose mothers used CGM had improved health outcomes, with fewer babies born overweight or obese, and fewer babies admitted to neonatal intensive care units or born with dangerously low glucose levels after birth.

Cost modelling of CGM use estimated by NHS Wales suggested immediate cost savings of £1,029 per pregnancy, from the reduction in babies requiring neonatal intensive care, which could lead to an estimated annual NHS savings of £9.5 million. Based on the study findings, time spent in the target glucose range is now internationally accepted as a clinically meaningful marker for glucose control in pregnancy. These results have led to changes in national and international policy and guidelines and have been endorsed by women with diabetes and leading diabetes maternity associations globally.

Lead Researcher: Helen Murphy



“These results have led to changes in national and international policy and guidelines and have been endorsed by women with diabetes and leading diabetes maternity associations globally”

Health beyond borders

The last few years have made clear that global health is a priority for all nations.

It is no longer possible or wise for countries to consider health and medicine in isolation from the world around them, particularly those in more vulnerable, lower resource settings.

With every country focused on the burden of COVID-19 on their own healthcare systems, global health initiatives were consequently put on hold. Since then, the movement to resurrect international collaboration, aid and support to tackle global health inequalities has been slow, as countries have prioritised the rebuilding and resuscitation of their economies. Medical research has the capability to improve the lives of billions of people and by improving global health we are better prepared to face any future health challenges. Now, more than ever, global scientific cooperation is essential; and the UK is well placed to be at the forefront of this work.

Medical schools have been working with a range of organisations beyond the UK to improve and inform global health. Many of the case studies in this section explore ways to improve the management and awareness of under-researched diseases. For example, neglected tropical diseases (NTDs) often affect the most impoverished areas, obstructing development, damaging economies and excluding individuals from their communities. The case studies in this section explore how health advances stemming directly from UK medical schools have benefited some of the most excluded groups, such as in the United States and sub-Saharan Africa, and how research has informed health strategies in many low-and middle-income countries across the globe.

Providing the evidence base for national policies and interventions towards eliminating podoconiosis

Brighton and Sussex Medical School (BSMS) has been conducting research into the elimination of podoconiosis (podo) – a non-infectious disease arising in barefoot individuals who are in long-term contact with irritant red clay soil of volcanic origin.

Four million people live with podo globally – a condition that has major socioeconomic implications through stigma and loss of productivity. The BSMS team has been working to fill the most urgent knowledge gaps on the condition, informing the Ethiopian and Rwandan Governments' agendas on podo control, prevention and treatment.

In gathering the data, the team conducted the first nationwide integrated mapping of the distribution and prevalence of podo in Ethiopia, identifying human and environmental risk factors for the condition and the endemic districts requiring prioritised intervention. The analysis in Ethiopia also drove the framework for modelling the distribution of podo in other endemic countries, such as Rwanda.

Additionally, the research revealed that podo sufferers were more likely to suffer from depression, caused by the stigma and negative attitudes that communities held towards people with the condition. The researchers

used the findings to advocate for the training of health professionals, as well as the inclusion of educational components in community interventions for podo, to eliminate misconceptions and stigma.

“The results from the studies have shaped policy in Ethiopia and Rwanda”

The results from the studies have shaped policy in Ethiopia and Rwanda. Working in partnership with the global NGO for podo, Footwork, and the Ethiopian government, the BSMS team helped implement important podo care management initiatives in the most endemic areas. Similarly, the data from the research has been instrumental in determining the Rwanda Ministry of Health's strategic plan, which sets strategies to reduce the burden of the disease by 2024. Such initiatives include the training of health professionals, establishing 10 podo treatment centres in the most affected areas, and educating the population to the importance of foot hygiene and shoe-wearing. Podoconiosis has since been included on the WHO Neglected Tropical Diseases' list of “other neglected tropical conditions” which was a catalyst for policy development within Ethiopia.

Lead researchers: Gail Davey, Kebede Deribe and Melanie Newport



Accurate estimates of pneumonia disease burden guide child immunisation policy, practice and global investment to reduce child pneumonia mortality



In 2013, 1.2 million children died from pneumonia globally – down from 2.1 million in 2000, but still unacceptably high.

Streptococcus pneumoniae (pneumococcus), *Haemophilus influenzae* type b (Hib), RSV and influenza are four of the major causes. More than 90% of these deaths occur in children living in low- and middle-income countries (LMICs). Coordinated action at national and global levels is required to reduce these rates of child pneumonia mortality.

Given the financial and technical difficulties of gathering health service data and conducting surveillance in LMICs, epidemiological models provide essential complementary information for national policy-making, priority setting and programme planning. These models produce regional, global and national estimates of the absolute and relative importance of pneumonia as a cause of death, and of the role of individual pathogens that cause it.

Working with international governments and agencies such as the World Health Organization (WHO), UNICEF, World Bank, the Gavi Alliance and the Bill and Melinda Gates Foundation, researchers from the University of Edinburgh have conducted 15 years (2005–2020) of international epidemiological research, modelling the burden of disease from child pneumonia, estimating the effectiveness of Pneumococcal conjugate vaccine (PCV) immunisation; and studying risk factors and burden estimates at national, regional and global levels. The estimates informed international priority-setting to scale up PCV coverage. Together, these policy and stakeholder commitments led to 60 additional low- and middle-income countries adopting PCV between 2013 and 2020, expanding the global PCV coverage from 19% in 2013 to 48% in 2020. By 2018, a total of 183 million children had been vaccinated against pneumococcus. As a direct

result of this expansion, across 170 countries globally, there was a reduction of one million child pneumonia deaths between 2013 and 2020.

More than 50 countries have used the Edinburgh team's approach to measuring national influenza disease burden using local surveillance data to inform policy, and in 2019, Bhutan began a new influenza child vaccination programme that has reached 90% national coverage.

The World Health Organisation recognised the RSV vaccine as the highest priority future vaccine in 2015, and in 2018, the Gavi Alliance prepared a Vaccine Investment Case directly informed by the team's global estimates to support the future introduction of RSV vaccine. The Bill and Melinda Gates Foundation has committed more than £84,866,760 to large new investments in RSV since August 2013. This coordinated activity of major agencies has resulted in over 40 RSV vaccine candidates being in development in 2018, from none in 2013.

Lead researchers: Harish Nair, Harry Campbell, Igor Rudan and Evropi Theodoratou

“This coordinated activity of major agencies has resulted in over 40 RSV vaccine candidates being in development in 2018, from none in 2013”

Transforming Amish healthcare services through genomic research

The University of Exeter has been transforming clinical and diagnostic services for medically underserved Amish communities in the United States.

The Exeter-led Amish translational genomic research programme “Windows of Hope” (WoH) has been designing and developing new genetic testing approaches, focusing on childhood developmental disorders and inherited neurological diseases, while improving global understanding of rare genetic disease.

The North American Amish and Mennonites are rural-living, Anabaptist Christian communities, many of whom reside in the states of Ohio, Wisconsin and Indiana where the research was undertaken. Notably, within the Amish communities the frequency of certain genetic conditions has increased. As a result of this and the lack of medical insurance, access to healthcare for Amish families has tended to be unaffordable and therefore limited.

The Exeter research group has identified the genetic basis and clinical features of over 150 conditions previously unrecognised in the communities and seven novel inherited childhood neurological disorders affecting Amish families. These included a) a brain overgrowth-seizure disorder developing in infancy, b) a DNA repair disorder similar to ataxia-telangiectasia which causes neurological degeneration and growth

failure, and c) a new form of childhood hereditary spastic paraplegia (HSP) which together with another four subtypes of HSP identified by WoH, has enabled over 95% of Amish and Mennonite patients with HSP to now receive a genetic diagnosis.

Prior to 2013, knowledge of genetic diseases was extremely limited, with approximately only 15% of affected Amish and Mennonite families receiving a precise diagnosis. The Exeter research team’s work to define the specific causes of genetic disorders affecting Amish and Mennonite families in Ohio, Wisconsin and Indiana, has meant that over 70% of families can now receive a much-needed diagnosis. In turn the genetic conditions discovered in these studies have subsequently enabled diagnoses to be provided for families worldwide affected by those same disorders, highlighting the global importance of this work.

The impact of the Exeter team’s research has been immense. Since embarking on the study, new diagnostic testing approaches have been designed, developed and embedded in regional diagnostic laboratories serving Amish communities. WoH has since worked alongside clinician-led community initiatives to develop specialist healthcare clinics in Ohio and Wisconsin. These regional clinics for genetic disease have served over 100,000 people from within the Amish population, with many patients travelling from out of state to access the specialised healthcare. Local clinicians are now much more able to recognise a patient’s disorder and order cost-effective genetic testing, improving treatment and clinical management of these disorders.

As many Amish families live below the federal poverty threshold and hold no healthcare insurance, the cost of



a clinical evaluation is unaffordable to many in the community. The new testing approaches designed by the Exeter team for Amish children has saved at least \$16,750 per diagnosis for the 950 Amish patients who have been diagnosed.

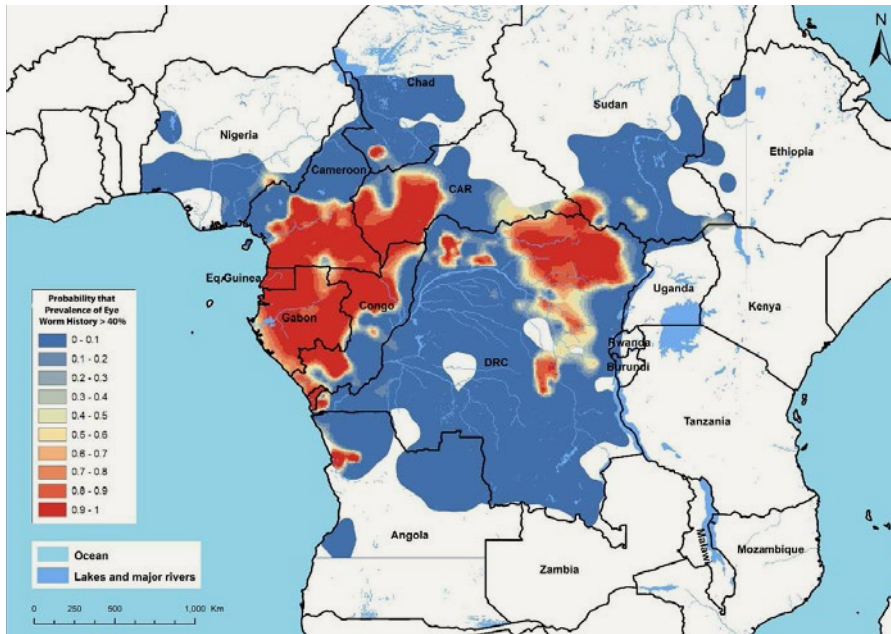
The Exeter team has also developed and implemented new education initiatives for both healthcare professionals and the wider Amish and Mennonite communities. Online courses, accredited symposia for medical professionals, and family education and support are available on the WoH website. The database provides accessible disease specific information for affected families and describes a systematic approach to defining differential diagnoses, accessing diagnostic testing and tailoring treatment.

Together, Exeter’s research and educational initiatives have improved Amish healthcare provision and outcomes, reduced hospitalisations, prevented major neurological and physical impairments, enabled estimated savings of over \$100 million in community healthcare costs, enhanced global understanding of rare genetic disease, and reduced the social stigma around genetic diseases to develop a more positive attitude towards genetic testing in the community.

Lead researchers: Andrew Crosby and Emma Baple

“As many Amish families live below the federal poverty threshold and hold no healthcare insurance, the cost of a clinical evaluation is unaffordable to many in the community”

Mapping the control and elimination of neglected tropical diseases



Spatial risk maps showing loiasis prevalence to delineate areas considered to be safe and unsafe for ivermectin treatment.

Public health mapping strategies are a vital tool for governments to plan treatment and manage resource allocation to treat disease.

Researchers at Lancaster University have developed model-based geostatistics to help treat neglected tropical diseases (NTDs) in some of the world's most adversely affected countries.

Model-based geostatistics (MBG) uses efficient, principled methods of predictive inference. It is particularly well suited to low-resource settings where, due to the lack of disease registries, the availability of comprehensive datasets is limited. In these settings, MBG provides a way of combining prevalence data with remotely sensed images of environmental variables to construct predictive maps that can be more precise than predictions based on

classical sampling methods. With funding from the WHO in 2005 the Lancaster researchers proposed a method for identifying areas that did or did not meet the WHO requirements for safe mass distribution of ivermectin in control efforts against onchocerciasis (river blindness). This was particularly important as while the drug can kill the parasites which cause onchocerciasis, it needs to be administered carefully as it can also lead to serious side effects in individuals with very severe eye-worm infections caused by the parasitic worm *Loa loa*. This presents a major obstacle to safe ivermectin treatment for onchocerciasis control. The researchers applied MBG methods to produce spatial risk maps for loiasis prevalence to delineate areas considered to be safe and unsafe for ivermectin treatment across the whole of Africa. Since 2015, the focus of

“In 2017, the team began working with the Sri Lankan Ministry of Health to provide research techniques to inform their de-worming strategy against soil-transmitted helminths (STH)”

Lancaster research on onchocerciasis control has been to develop methods for the optimal combination of mobile microscopy and a rapid diagnostic test to determine which areas are and are not safe for mass drug administration. The work in this area has led to collaborations with the NTD Centre of the Task Force for Global Health and the Gates Foundation and has been instrumental in developing a comprehensive *Loa loa* mapping strategy across Africa. The researchers have also developed novel MBG methods for malaria mapping in sub-Saharan Africa which has subsequently informed malaria control policies in Somalia and has been directly adopted by national programmes for malaria in the worst affected countries in the continent. In 2017, the team began working with the Sri Lankan Ministry of Health to provide research techniques to inform their de-worming strategy against soil-transmitted helminths (STH). This led to the Ministry to revise its approach to deworming for STH infections across the entire country.

Lead researchers: Peter Diggle and Emanuele Giorgi

Reducing infant deaths from rotavirus diarrhoea in sub-Saharan Africa

Rotavirus is the leading cause of severe gastroenteritis among infants and young children, responsible for 250,000 annual childhood deaths in Africa prior to introduction of rotavirus vaccine.

The University of Liverpool has led studies of rotavirus diarrhoea in Malawi since 1997. These studies were designed to facilitate and accelerate the introduction of rotavirus vaccines into childhood Expanded Programme on Immunisation (EPI) programmes in Malawi and other low-income African countries. Vaccines developed by GSK (Rotarix®) and Merck (RotaTeq®) were known to work well in high-income countries but their impact on protecting children in poorer countries was unknown.

A Phase-3 clinical trial of the Rotarix® rotavirus vaccine was led by Liverpool researchers and undertaken in Malawi. This pivotal trial in a low-income African country showed that severe rotavirus diarrhoea episodes were reduced by half. Together with data from trials of the RotaTeq vaccine these results led to a World Health Organisation recommendation in 2009 that all the world's children should receive rotavirus vaccine, with a particularly strong recommendation for those countries with a high burden of diarrhoea deaths.

Following rotavirus vaccine introduction in Malawi, case control studies between 2012 and 2014 demonstrated that national vaccination was more than 60% effective in preventing severe rotavirus diarrhoea episodes

among infants in urban Malawi, with rotavirus hospitalisations reduced by over 40%. A large, prospectively conducted cohort study of 48,672 live births, then demonstrated that rotavirus vaccination reduced infant diarrhoea deaths by a third in rural Malawi, the first empirical evidence from a low-income country that rotavirus vaccination saves lives. The University of Liverpool-led study also demonstrated that rotavirus vaccination provides cost-effective health protection in Malawi.

As of 2020, National rotavirus vaccination programmes had been introduced in 38 of the 54 African countries, preventing an estimated 24,200 deaths among children younger than five years in sub-Saharan Africa in 2016 alone. Based on immunisation coverage between 2013 and 2020, the 2016 data allow estimation of the impact of these programmes; since August 2013, 169,400 lives were saved across Africa, and approximately 40,400,000 cases of rotavirus gastroenteritis and 3,070,000 inpatient admissions were averted.

Lead researcher: Nigel Cunliffe

“A large, prospectively conducted cohort study of 48,672 live births, then demonstrated that rotavirus vaccination reduced infant diarrhoea deaths by a third in rural Malawi”



Improving vision care for workers in Assam, India



Presbyopia is the almost-universal decline in unaided near vision associated with ageing. Beginning at age 40 and affecting nearly all by 50, presbyopia's impact is felt at the heart of the working years.

Researchers at Queen's University Belfast have worked to improve vision care for workers, particularly those in low-resource settings.

The PROSPER (PROductivity Study of Presbyopia Elimination in Rural-dwellers) trial aimed to assess health interventions that could improve the wellbeing of people with this condition. It focused on improving care for workers in low- and middle-income countries (LMICs) in collaboration with three leading global eye health NGOs and Amalgamated Plantation Private Ltd. PROSPER studied the effect of providing glasses to correct presbyopia among 751 mostly female tea workers aged 40 or over in India who were randomly allocated to

receive free glasses to correct their refractive error. The trial found a significantly higher increase in mean productivity among workers and highlighted the minimal expense, good acceptability and wide applicability of this intervention.

“With 2.5 billion people worldwide suffering from poor vision and no access to refractive care, PROSPER demonstrated the crucial role of glasses in achieving better standards of living”

The PROSPER interventions were inexpensive, an important factor as low-cost and sustainable health interventions are needed to increase work productivity and reduce poverty in LMICs. With the global population ageing rapidly, and labour

participation rates in LMICs declining in individuals, health strategies supporting productive employment among older workers have a powerful impact. Gender equality is also highly relevant to poverty alleviation, as increasing workforce participation and productivity among women results in faster economic growth. With 2.5 billion people worldwide suffering from poor vision and no access to refractive care, PROSPER demonstrated the crucial role of glasses in achieving better standards of living.

On the basis of the PROSPER results, the project partner VisionSpring has estimated that if glasses were given to everyone who needed them in India's agricultural sector, an extra \$20 billion from productivity gains alone could be realised. The success of PROSPER provided VisionSpring with evidence to attract more corporate partners for vision programmes in India, Africa and elsewhere. The Ministry of Labour in Assam, where PROSPER was carried out, is planning a program for the distribution of glasses, catalysed by the trial's results. PROSPER also helped encourage the founding of the United Nations Friends of Vision Group, which met first on World Sight Day in October 2018. This followed a pledge from 53 member countries at the Commonwealth Heads of Government Meeting in London in April 2018 to 'take action towards achieving access to quality eye-care for all', which was the first time that so many governments had joined together in a commitment to tackling poor vision.

Lead researcher: Nathan Congdon

Developing, evaluating and implementing frugal solar-powered diagnostic tools for eyes and ears

The University of St Andrews has been developing, evaluating and implementing a lightweight, low-cost and solar-powered ophthalmoscope and otoscope called the Arclight.

The tool can be used to diagnose both eye and ear conditions with over 30,000 devices distributed in over 100 countries.

According to the World Health Organisation (WHO) over 1.5 billion people have either vision or hearing impairment with the majority of cases being either preventable or treatable. The highest incidence of disability is found in low- and middle-income countries (LMICs) where access to healthcare and educational services are most limited.

The Arclight Project team based at the University of St Andrews and

led by Dr Andrew Blaikie has been driving research into developing tools that can overcome such barriers. Traditional instruments such as direct ophthalmoscopes and otoscopes are expensive, hard to maintain in working order and can be difficult to use. Access to these important diagnostic devices in LMICs is rare outside of larger city hospitals and especially in rural areas where the need is greatest.

The team's research focuses primarily on how to empower community and district level health care workers to identify the major causes of blindness such as cataract, glaucoma and trachoma, as well as the emerging epidemic of sight loss amongst children and working age adults due to diabetes and increasingly premature birth.

To effectively implement Arclight tools in these settings, low-cost simulation eyes have also been

“Arclight has been deliberately tailored to the needs of health care users in LMICs; increasing global ophthalmic capacity and mobilising knowledge in these regions where the need is greatest”

developed. These can be used for teaching and assessment, and have proven to be particularly important in the COVID-19 era where face-to-face clinical teaching has been reduced.

The impact of the team's work has been greatest in LMICs where blindness and significant visual impairments affect educational attainment and employment, reducing long-term economic productivity. Loss of sight and hearing amongst adults can also significantly affect the socioeconomic prospects of young family members, who may have to take up caring duties instead of attending school.

Arclight has been deliberately tailored to the needs of health care users in LMICs; increasing global ophthalmic capacity and mobilising knowledge in these regions where the need is greatest. Widespread distribution alongside increased training and capacity building has led the Arclight to become the standard tool for healthcare workers to deliver opportunistic eye screening.

Lead researcher: Andrew Blaikie



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