INFECTION AND IMMUNITY NETWORK NEWSLETTER

University of BRISTOL
Elizabeth Blackwell Institut for Health Research

NOVEMBER - DECEMBER 2017

PhD training programme to tackle AMR

The Medical Research Foundation (MRF), the charitable foundation of the Medical Research Council, has invested £2.85M in delivering the UK's first nationwide PhD training programme to focus on the major health challenge of antimicrobial resistence (AMR).

The PhD training programme leadership comprises 16 academics from 13 universities and research institutes. The University of Bristol, known for its pioneering multidisciplinary research into AMR, will lead delivery of the programme, which will bring together PhD students from all academic disciplines to explore new ways of tackling the threat to human life posed by AMR.

The MRF's Programme will provide 4-year PhD funding for 18 students in the first cohort, with the studentships being distributed across a wide range of participating UK universities. In addition, training courses and cohort building/ networking events will be funded to benefit up to 200 PhD students studying AMR-related problems from across the UK.

Dr Matthew Avison, Reader in Molecular Bacteriology at UoB, is Principal Investigator and Academic Lead for the programme.

Read the full story

Follow Matt: @MutantBug

UoBRISTOL EVENTS

Using zebrafish to understand the genetics of joint disease
4 December 2017, 13.00 - 14.00, Chrissy Hammond (PPN), C42 Biomedical Sciences Building

Complexity and complexity theory in health services research
4 December 2017, 15.30 - 16.30, Prof Alex Clark (University of Alberta Population Health Sciences), Canynge Hall LG:08

Careers Beyond Biomedical Sciences - Creative Science Careers
6 December 2017, 13.00 - 14.00, Dr Shereen Kadir (Science Animation) / Claudia Stocker (Vivid Biology), Chemistry LT4

Introduction to Research Grant Applications: Medical Faculties
7 December 2017, 14.00 - 16.30, Senate House room 3.16

Mental Health in Academia: A review of the evidence
8 December 2017, 15.30 - 16.30, Susan Guthrie (RAND Europe), Priory Road Complex, Senior Common Room (2D17)

Statistics Clinic- 13 December
13 December 2017, 14.00 - 15.30. SM3 Mathematics Building

Introduction to Research Governance
1 - 2 February 2018, 8:30 - 15:15, Course tutors: Profs Yoav Ben-Shlomo & Rona Campbell *et al*.

NIHR Bristol Biomedical Research Centre Launch Symposium
1 February 2018, 10.00 - 17.30, We The Curious

Public lecture and debate: Can surgical research improve health?
1 February 2018, 18.00 - 19.30, Gianni Angelini (British Heart Foundation Professor of Cardiac Surgery), Prof Debbie Lawlor CBE & Prof Jane Blazeby (Professor of Surgery), We The Curious

How ethics and values impact upon being the Chair of the RCGP
8 February 2018, 15.30 - 16.30, Prof Helen Stokes-Lampard (RCGP), Canynge Hall, G:12

Dr Warwick Dunn, School of Biosciences, University of Birmingham
15 February 2018, 2.00 PM - 19 October 2017, 3.00 PMDr Warwick Dunn (Senior Lecturer in Metabolomics, Director of Mass Spectrometry, Phenome Centre Birmingham)TBC

Building Global Partnerships for Global Challenges: SAVE THE DATE
11 April 2018, 9.00 AM - 13 April 2018, 5.00 PM

Integrating molecules with taxonomy and systematics
14 May 2018, 9.00 AM - 18 May 2018, 5.00 PM

UoB EVENTS

OTHER EVENTS

NIHR HPRU EZI Annual Conference 2017
12 December 2017, 9.00 - 17.00, Dr Ana Bispo de Fillipis (Head of Laboratório de Flavivírus, Instituto Oswaldo Cruz, Brazil) and Prof Daniel Bausch (Director, UK Public Health Rapid Support Team), University of Liverpool in London, 33 Finsbury Square

NIHR Webinar: How Clinical Academic Careers can benefit the whole NHS
12 December 2017, 11.00 - 12.00, Prof Joanne Cooper (Assistant Director of Nursing, Research, Innovation and Professional Regulation, Nottingham University Hospitals NHS Trust) and Pete Thompson (Assistant Director, NIHR Trainees Coordinating Centre)

From reconstructing to using phylogenetic networks
13 December 2017, 17.00 - 18.00, Cécile Ané (University of Wisconsin-Madison)

NHS Digital and MRC Researcher Roadshow
8 January 2018, 9.30 - 16.30, TBC in Bristol

JSPS-Academy of Medical Sciences, Japan-UK Collaborative Symposium: Medical Imaging and Artificial Intelligence
23 January 2018, 9.00 - 16.00, Academy of Medical Sciences, London

Health: The design, planning and politics of how and where we live conference
25 - 26 January 2018, UWE Bristol, Frenchay Campus

Royal Society open presentation
28 February 2018, 11.00 - 12.30, Reception Room, Wills Memorial Building

NIHR Health Protection Research Unit in Gastrointestinal Infections Annual Conference 2018
7 - 8 March 2018, Keynotes: Ian Charles, Michael Hornberger, Paul Hunter & Arjan Narbad. The Assembly House, Norwich

UoB EVENTS

Infection and Immunity Annual Symposium 2018

5 January 2018, 9.30 - 13.45

Graduate School of Education, 35 Berkeley Square

Draft Programme

09:30 - 10:00	arrival and welcome refreshments
10:00 - 10:05	Opening remarks: Dr Lindsay Nicholson (Network co-Lead)

Session 1: Vaccination and Humans
Chair: TBC

10:05 - 10:25	Adam Finn (Professor of Paediatrics, Bristol Medical School) *title tbc*
10:25 - 10:40	Rajeka Lazarus (University Hospitals Bristol NHS Trust) *Memory B cell responses to Pneumococcal vaccines in adults*
10:40 - 11:05	Keynote 1: TBC
11:05 - 11:25	break

Session 2: Vaccination and Animals
Chair: TBC

11:25 - 11:40	Mick Bailey (Professor of Comparative Immunology, Bristol Veterinary School) *Mucosal immunisation and the microbiome*
11:40 - 11:55	UoB speaker 4 TBC *title tbc*
11:55 - 12:20	Keynote 2: Timothy Connelley (Roslin Institute, University of Edinburgh) *title tbc*
12:20 - 13:00	breakout sessions 1 & 2
13:00 - 13:35	lunch
13:35 - 13:45	reports on breakout sessions (5 mins each)

ATTENDANCE IS FREE AND ALL ARE WELCOME

Register Now

NEWS

Tackling challenges of African vector-borne plant diseases

Destructive plant diseases are transmitted by aphids, beetles, whitefly and other insects, which act as vectors of plant viruses and spread disease by moving between plants in a field.

Smallholder farmers in Sub-Saharan Africa grow a range of crops to feed their families. Vector-borne plant viruses are a significant constraint on staple and cash crops such as cassava, sweet potato, maize and yam. Limiting crop production causes food insecurity, malnutrition and poverty, all of which hinder economic and social development.

The emergence of new viral diseases and the environmental fluctuations of climate change together with resource limitation and population growth will also acutely impact this region of the world.
Prof Gary Foster and his team have been awarded a £2M Vector-borne Disease Network grant, funded by the Global Challenges Research Fund (GCRF) which supports research on global issues that affect developing countries.

Read more

Interventions for reducing hepatitis C infection

The first global review to quantify the impact of needle syringe programmes (NSP) and opioid substitution treatment (OST) in reducing the risk of becoming infected with the hepatitis C virus has been recently published.

Over 70 million people live with hepatitis C and there are three to four million people newly infected each year. The main risk for becoming infected in developing countries is associated with illicit drug use and sharing used needles/syringes. In many countries, at least half the people who have injected drugs such as heroin, cocaine or methamphetamine have hepatitis C.
While it is known that the provision of sterile injecting equipment through NSPs or providing OST such as methadone or buprenorphine reduces injecting risk behaviour, and there is evidence also that OST and NSP reduces HIV transmission.

There was consistent and strong evidence that current use of OST (defined as use at the time of survey or within the previous six months) reduces risk of hepatitis C infection by 50 per cent and when combined with high coverage NSP reduces risk by 74 per cent. However, there was more uncertainty on the effectiveness of NSP alone.

Read the full story

Platt L *et. al* (2017). Interventions for reducing hepatitis C infection in people who inject drugs. *Cochrane Database of Systematic Reviews.* 9 (CD012021).

The Lightning Process®

The first trial to investigate The Lightning Process® (LP) studied the effectiveness of LP in addition to specialist medical care compared to specialist medical care alone in children with mild or moderate chronic fatigue syndrome (CFS/ME).

CFS affects at least 1% of secondary school children in the UK and is very disabling, and there is limited evidence for how the condition should be treated in children. The National Institute for Health and Care Excellence (NICE) recommends three treatment approaches: cognitive behavioural therapy (CBT), graded exercise therapy (GET) or activity management; even with treatment, only about two thirds of children can be expected to recover at six months.

Around 250 children with CFS use LP each year. The programme teaches techniques for using the brain to make changes to the body's level of health. However, there have been no reported studies investigating its effectiveness, cost-effectiveness or possible side effects. The randomized controlled SMILE (Specialist Medical Intervention and Lightning Evaluation) trial investigated the effectiveness and cost-effectiveness of LP in addition to specialist medical care compared with specialist medical care alone.

Read the full story

Funding successes: Part 1

Dr Ruth Massey (CMM), a **BBSRC** Doctoral Training Programme grant which will allow Emily Stephens to undertake her PhD.

Dr Andrew Davidson (CMM), an **MRC** UK-Indonesian Consortium grant to *Identify Biomarkers Predictive of Dengue Disease Severity*, £399,257; start: 01/08/2017 for two years.

Dr Paul Race (Biochemistry), a **Royal Society** grant for Structure function and engineering of beta-barrel Diels-Alderases, £66,000; start 01/11/2017 for two years.

A **Norweigan Research Council** grant was awarded to Prof Peter Vickerman (BMS, PHS) for *Integrated treatment of hepatitis C virus infection among patients with injecting drug abuse: a randomised controlled trial (INTRO HCV),* £254, 812; start 01/06/2017 for six years.

NIHR - RFPB grant was awarded to Dr Suzanne Audrey (BMS, PHS) for *OAFI The practicality, acceptability and potential impact of self-consent procedures for schools-based adolescent vaccination programmes*, £160,878; start 01/09/2017 for two years. High coverage of HPV vaccination programmes, administered in early adolescence, can substantially reduce cervical cancer incidence and mortality. However, there are concerns about low uptake of the vaccine in some areas in the SW of England. The requirement to provide written parental consent is a barrier to some young women receiving the vaccine, and staff at Public Health England (South West) have developed a 'South West Template Pathway on Self Consent for School Aged Immunisations'. Researchers at the University of Bristol NIHR Health Protection Research Unit (HPRU) in Evaluation of Interventions will be examining the implementation of the new procedures and the impact on uptake rates.

Grant to fight antibacterial drug resistance in Thailand

UoB has been awarded a grant through the Antimicrobial Resistance (AMR) cross-research council initiative, in partnership with the Department of Health, to lead an inter-disciplinary research project to tackle the growing threat of antibacterial drug resistance (ABR) in Thailand.

ABR reduces the ability of doctors to treat infections with antibiotics. Thailand, like many countries, is currently facing a major health threat due to the high prevalence of ABR in disease-causing bacteria found in humans, animals and the environment. ABR and antibiotic use impacts the ability of the global community to meet many of its Strategic Development Goals, particularly around human health, environmental pollution, poverty and food security. In 2010, ABR was estimated to be responsible for 38,000 deaths and an economic loss of 1.2 billion US$ in Thailand, a country in receipt of Official Development Assistance (ODA) from the UK Government.

In response to the threat of ABR, the Thai Government has instigated its National Strategic Plan on Antimicrobial Resistance (2017-2022). The aim is to improve national surveillance for ABR bacteria to quantify the problem, and includes initiatives to reduce the rate of infections and the usage of antibiotics, which are known to select for ABR bacteria.

The project will enhance work already ongoing in Thailand to understand the drivers of ABR and behaviours around antibiotic use. At the outset, the project will involve a series of workshops in Thailand to share knowledge amongst Thai and UK ABR experts, to bring together a group of early career academics, and to collectively develop a research programme which will explore a number of challenges.

Read the full story

Funding successes: Part 2

Prof Peter Vickerman (BMS PHS) from the **World Health Organisation** for *Modelling the prevention benefits of a treat all policy for HCV*, £8,735; start 06/09/2017for five months.

Dr Aarti Kathrani (Companion Animal Studies, BVS) from the **Petplan Charitable Trust** for *The utility of* ex-vivo *whole blood stimulation assays in diagnosing immunological loss of tolerance to diet in dogs and cats with food responsive enteropathy.* £9,729; start 01/12/2017 for one year.

Prof Bo Su (BDS) from the **EPSRC** for *Biophysical stimulation enhanced antimicrobial surfaces to combat AMR infection*, £53,991; start 01/10/2017 for seven months.

University of Bristol 2017 **Strategic Research Fund Award** to Prof Kristen Reyher (PI, BVS) Dr Harriet Mills (Co-I, BMS-PHS) and Prof Andrew Dowsey (Co-I, BMS-PHS) for *Towards a flexible and multi-use databank for veterinary antimicrobial resistance research*.

Two Bristol Medical School staff have been awarded **NIHR Doctoral Research Fellowship**s: Barnaby Hole (PHS-kidneys) and Amberly Brigden (PHS- CFS/ME).

RCGP Research Paper of the Year award

Urinary tract infections (UTI) in young children can lead to kidney damage but are notoriously difficult to diagnose in primary care because symptoms can often be vague and unclear. A definitive diagnosis can only be achieved by a urine test but collecting urine samples from babies and children under five is a challenge.

A three-year study (Diagnosis of Urinary Tract infections in Young children–DUTY) involving more than 7,000 children resulted in the development of a technique to identify those children who need to provide a urine sample; this involved a clinical rule using symptoms and signs. The second step adds dipstick results to help identify who should be treated with antibiotics. The technique could reduce the amount of time and effort used to collect unnecessary urine samples and increase sampling among children most likely to have a UTI.

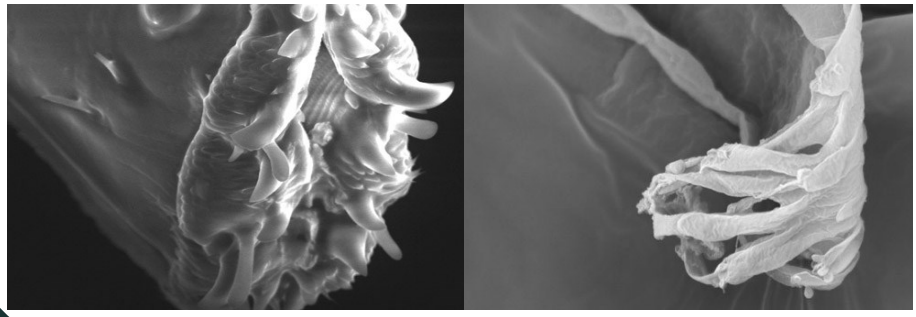
The journal article, published in the *Annals of Family Medicine*, was awarded a 2017 Royal College of General Practitioners (RCGP) Research Paper of the Year award.

How the African tsetse fly really drinks your blood

Using the new high-powered scanning electron microscope in the University's Life Sciences Building, researchers from the Trypanosome Research Group were able to see the rows of sharp teeth and rasps that the fly uses to chew through the skin when it bites. The teeth tear the delicate blood capillaries in the skin, so the fly can suck up the blood.

To stop the blood clotting, the fly squirts saliva containing anti-coagulant into the wound through a narrow tube inside the proboscis. The group found that the tip of this tube is decorated with intricate finger-like structures with suckers. Prof Wendy Gibson (Biological Sciences) led the research-

We've no idea yet what this ornate structure is for – we haven't come across anything like it in other bloodsucking insects such as midges and mosquitoes. The tsetse fly...carries human sleeping sickness and the animal disease, nagana. The needle-like proboscis is armed with a formidable array of sharp teeth and rasps.



Left: The tip of the tsetse proboscis showing teeth and rasps. Scale bar 10 µm, © Wendy Gibson and Sally Hobson, UoB. LSB environmental SEM. Right: Detail of the tip of the saliva tube showing fingers, © Wendy Gibson and Maggie Gamble; specimen prepared by Lori Peacock and Gini Tilly, Wolfson Bioimaging Facility.

Vet School changing antimicrobial (AM) use on farms

Antimicrobial resistance (AMR) is a global threat, with an estimated 700,000 people dying from resistant infections every year. 13-19 November 2017 was World Antibiotic Awareness Week, and ongoing research from the Bristol Vet School was showcased in a video produced by the Food and Agriculture Organization of the United Nations.

AMR is a crucial example of the importance of the One Health concept, which recognises that the health of humans is connected to the health of animals and the environment. People share many of the same health problems as animals; for instance, they both suffer from age-related diseases and infections, such as pneumonia.

AMR research at the Bristol Vet School is led by the AMR Force and major questions the group are addressing include:

- Can we impact the way veterinarians prescribe medicines?
- Can we encourage responsible medicines use by veterinarians by using medicines auditing and benchmarking?
- Can we assist in developing medicines use policies with policy-makers, veterinarians and farmers ?
- Does reducing antimicrobial use impact patterns of resistance?
- How can we utilise diagnostic tests more effectively to better target prescribing?
- How do microbes and AMR genes cycle in the environment?

The AMR Force, led by Dr Kristen Reyher, is working closely with farmers, veterinarians, food retailers and government bodies to encourage responsible use of antimicrobials.

Funding successes: Part 3

An **Academy of Medical Sciences** grant to Dr Sofia Theodoropoulou, £29,992 for *The role of mast cells in the pathophysiology of age-related macular degeneration*. Age-related macular degeneration (AMD) is a leading cause of irreversible blindness. Current treatments are available only for the very late stages of the wet form of AMD (caused by the aberrant growth of new vessels-angiogenesis) and only improve vision in 30% of those patients. There is a crucial unmet need to understand processes early in the disease to lead to pathways that can be exploited for new therapies. The aim of the project is to uncover such pathways, and investigate protein interleukin-33 (IL-33) that orchestrates inflammation in tissues and its role in AMD. Early data shows that IL-33 inhibits unwanted effects of the eyes response to inflammation by altering tissue remodelling (such as scarring). Experiments will deliver insight into how IL-33 exerts a protective effect, and specifically how IL-33 exerts its effect by altering the behaviour of inflammatory cells that are found in the back of the eye (retina and choroid where AMD targets), to maintain tissue health and subvert AMD progression.

Vice-Chancellor's Impact Awards

VCI Awards recognise the significant positive impact UoB research has across the world. Covering four categories, the awards were made at the annual Enterprise Reception held 23 November 2017.

The winners of the *Health and Wellbeing* category were Prof Athimalaipet Ramanan, Prof MW Beresford (Liverpool) and the Uveitis (Sycamore) Study team in recognition of their medical intervention work in visionary disease in children by facilitating access to sight-saving medication for children suffering from eye disease.

Co-I Ramanan and colleagues set up a landmark trial proving the effectiveness of and case for improving access to a novel drug (adalimumab) for treating uveitis in children. The interim successful results led to the trial being stopped early by the data safety monitoring committee with NHS England immediately approving access to the new drug across England. Pharmaceutical company, Abbvie Inc, applied and obtained license and market authorisation from the European Medicines Agency enabling access to the drug for thousands of children across Europe. This access may soon be replicated in the USA.

Group B Streptococcus infection causes stillbirths

An estimated one in five pregnant women around the world carry Group B Streptococcus (GBS) bacteria which is a major, yet preventable, cause of maternal and infant ill health globally. Led by the London School of Hygiene & Tropical Medicine and involving more than 100 researchers from around the world, including Prof Marianne Thoresen (BMS), a series of 11 research papers conservatively estimates that out of 410,000 GBS cases every year, there will be at least 147,000 stillbirths and infant deaths globally. Despite being home to only 13% of the world's population, Africa had the highest burden, with 54% of estimated cases and 65% of stillbirths and infant deaths.

This first comprehensive study of the burden of GBS includes data and estimates for the year 2015 from every country of the world, including outcomes for pregnant women, their babies and infants. Research found GBS is present among pregnant women in all regions of the world, with an average of 18% of pregnant women worldwide colonised with the bacteria, ranging from 11% in eastern Asia to 35% in the Caribbean, totalling 21.7 million in 195 countries.

Although several vaccines to prevent GBS are in development, none is currently available. This is despite the disease accounting for more than the combined neonatal deaths from tetanus, pertussis, and respiratory syncytial virus, for which maternal vaccines are already in use, or further advanced in development. This analysis shows for the first time that a maternal GBS vaccine, which was 80% effective and reached 90% of women, could potentially prevent 231,000 infant and maternal GBS cases.

Read the full story

Articles were published in a special supplement of *Clinical Infectious Diseases*, 65 (suppl_2), published 6 November 2017.

Antibiotic discovery in the abyss

The emergence of antimicrobial resistance (AMR) as a global threat to our health and wellbeing has brought into sharp focus the pressing need for the discovery and development of new antibiotics capable of overcoming the impending threat of AMR. Historically, the majority of clinically useful antibiotics have been based on molecules isolated from natural sources.

Funded by BrisSynBio, Dr Paul Race and colleagues are combining the innovations of synthetic biology with robotic environmental sampling to attempt to unblock the antibiotic discovery pipeline. The deep ocean is one of the most 'extreme' environments on Earth, and microorganisms that live there are considered to be excellent sources of novel natural products. Using a remotely operated vehicle, deployed from the James Cook research vessel, the team has been recovering environmental samples from previously unexplored regions of the Atlantic Ocean sea bed at depths >4.5 km. Following sample recovery, the bacteria present in these samples are grown in the lab and their capacity to produce new natural products with antimicrobial activity is determined. This project has only been running for 18 months but the team has already isolated >1000 previously uncharacterised microorganisms, and six new natural product based antibiotic leads.

Read the full story

Funding successes: Part 4, and media quotes

From UK charity **Medical Detection Dogs** to Dr Nicola Rooney (BVS), £8,888 for *Objective testing of efficacy of glycaemia alert dogs*; start date 1/10/2017 for three months.

From the **World Health Organisation** to Dr Katharine Looker (BMS/PHS), £11,672 for *Global estimates of genital ulcer disease due to herpes among 15-49 year olds*; start date 01/09/2017 for three months.

To Prof Peter Vickerman (BMS/PHS) from **Médecins du Monde**, £16,912 for HIV and HCV modelling to guide intervention planning amongst people who inject drugs (PWID) in East Africa; start date 01/07/2017 for six months.

To Dr Emily Blackwell (BVS) from the **Animal Welfare Foundation**, £28,653 for Risk factors associated with feline pruritus unrelated to ectoparasites (PUE); start date 01/10/2017 for one year.

'Antibiotic apocalypse': doctors sound alarm over drug resistance was the title of an article published in The Observer online on 8 October 2017. "Scientists attending a recent meeting of the American Society for Microbiology...revealed that bacteria containing a gene known as mcr-1 – which confers resistance to the antibiotic colistin – had spread round the world at an alarming rate since its original discovery 18 months earlier." Prof Alastair Hay was one of the experts whose opinion was sought.

Best moisturiser for treating eczema in children

Researchers at UoB, Nottingham and Southampton have been awarded £1.4 million by the National Institute for Health Research (NIHR) Health Technology Assessment Programme to discover which is the best emollient for treating childhood eczema.

Eczema affects one in five children in the UK and the impact on children and their families can be great, commonly interfering with their sleep, play and mood. Most children are looked after by their family doctor and treated with moisturisers to relieve skin dryness and steroid creams (e.g. hydrocortisone) for when the skin gets red and itchy.

The new study, BEE (Best Emollient for Eczema), will compare four of the most commonly used emollients (Aveeno® lotion, Diprobase® cream, Doublebase® gel and Epaderm® ointment) in a randomised clinical trial. This will involve recruiting 520 children through GP surgeries and giving them one of the four emollients to use for at least 4 months. To assess the long-term effects, there will also be follow-up after 12 months. Parents and carers of children taking part will be asked to regularly assess and record their child's eczema symptoms.

Dr Matthew Ridd at the Centre for Academic Primary Care is the lead researcher.

Primary care is key to optimising value in healthcare

Healthcare systems across the world are under immense pressure to deal with ageing populations alongside increasing numbers of patients with chronic diseases and multi-morbidity. With finite resources, and an increasing recognition of the potential harms to patients of over diagnoses and overtreatment, it is essential that resources are used optimally.

Researchers from the Bristol Medical School highlight how NHS reforms can increase or decrease value and optimality in primary care. For example, reforms which aim to increase seven-day working in primary care may have knock-on effects on continuity of care, which has been shown to be associated with reduced hospital admissions. While population level reductions in risk factors for cardiovascular disease led to large improvements in cardiovascular mortality, expanding indications for treatment to include low risk people with mild hypertension takes us beyond the point of optimality. Reforms also require adequate investment. For example, developing new multi-professional roles such as physician assistants requires senior mentoring and support and can take several years to reach full potential.

The study recommends that policy changes are evidence-based and trialled or piloted before implementation alongside improved data and primary care systems to measure the impact of policy interventions. This would help policy makers decide where to focus scarce resources, where they will deliver most benefit, helping manage increasing demand within financial constraints, and reduce over diagnosis and over treatment.

Watson J *et al*. (2017). Better value primary care is needed now more than ever. *BMJ* 359(j4944).

Genetic risk factors for asthma, hay fever and eczema

A team which included Dr Manuel Ferreira from QIMR Berghofer Medical Research Institute, Brisbane Australia and Dr Lavinia Paternoster, MRC Integrative Epidemiology Unit, undertook this first study designed specifically to find genetic risk factors that are shared among the three most common allergic conditions.

Asthma, hay fever and eczema are allergic diseases that affect different parts of the body. They are similar at many levels, for example, the three diseases share many genetic risk factors. However, it was unknown where exactly in the genome those shared genetic risk factors were located. Knowing where they are located shows which specific genes, when not working properly, cause allergic conditions, leads to the understanding of why allergies develop in the first place and, potentially, provides new clues on how they could be prevented or treated.

The genomes of 360,838 people were analysed and data pinpointed 136 separate positions in the genome that are risk factors for developing these conditions. Some of the genes implicated in the study already have drugs available that can target them, which drugs currently used for other conditions may be effective in treating allergic conditions. The next step is to test these in the laboratory.

Ferreira MA *et al*. (2017). Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nature Genetics*. Published online 30 October 2017.

Consortium to accelerate drug discovery in kidney diseases

The NEPLEX (nephron on a chip with cellular and extracellular matrix complexity) consortium, comprising institutions including the Universities of Bristol and Cambridge and Evotec AG, will combine key technologies to develop and build a novel drug discovery device ("Nephron-on-a-Chip").

The consortium's aim is to develop a functional nephron on a chip device that reflects both the filtration area as well as the resorption area of a human kidney. The functional nephrons will be based on fully characterised human cell lines and iPSC-derived human cells. It will merge state-of-the-art microfluidics technology established at the University of Cambridge with world-class expertise in iPSC technology and kidney disease from the University of Bristol, the Mario Negri Institute in Bergamo and from Evotec AG.

Prof Moin Saleem and his group will contribute human kidney cell lines focusing on the resorption unit, Dr Yan Shery Huang and her lab from Cambridge will develop the glomerular part of the chip, Dr Christodoulos Xinaris and his colleagues from the Mario Negri Institute will provide human iPSC lines and expertise.

Evotec will add its state-of-the-art iPSC and kidney disease platforms. The device will allow testing of drug candidates in a fully human nephron already in the pre-clinic and thereby improve and accelerate drug discovery in the field of kidney diseases.

Microscope and labelling technique maps DNA mutations

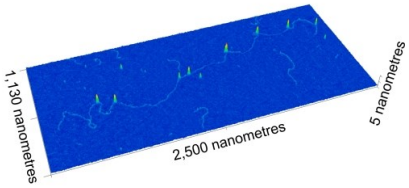
A new nanomapping microscope - powered by the laser and optics found in a typical DVD player- is being used to transform the way disease-causing genetic mutations are diagnosed and discovered.

This microscope maps hundreds of chemically barcoded DNA molecules every second in a technique developed in collaboration with a team of US scientists led by Prof Jason Reed at Virginia Commonwealth University.
His team uses CRISPR-Cas9 to label the molecules so they can be mapped almost as accurately as DNA sequencing, while also processing large sections of the genome at a much faster rate.

Using off-the-shelf DVD components, the Bristol team supercharged their atomic force microscope (AFM) to enable it to physically map the lengths of individual DNA molecules to a resolution of tens of base pairs at rates of hundreds per second. This unprecedented speed increase enables this DNA barcoding method to be used for real-world diagnostics for the first time.

A typical 3D image collected by the nanomapping microscope showing a CRISPR-labelled DNA molecule.

Read the full story



Hope of reversing antibiotic resistance

Two recent studies led by UoB provide significant new hope in the fight against antibiotic resistance. By identifying what makes some bacteria resistant to the most commonly prescribed antibiotics, and how this can be reversed, the findings have demonstrated potentially life-saving consequences and could help reverse the tide of antibiotic resistance.

Antibiotics including penicillins, cephalosporins and carbapenems (or β-lactams) are the most commonly prescribed worldwide. In the first paper, researchers defined the relative importance of two mechanisms associated with β-lactam antibiotic resistance. In one, bacteria restrict the entry of antibiotics into the cell; in the other, bacteria produce an enzyme (a β-lactamase), which destroys any antibiotic that gets into the cell. The latter was found to be the more important of the two mechanisms. These findings imply that if chemicals could be developed to inhibit β-lactamase enzymes, a significant proportion of antibiotic resistance could successfully be reversed. Building on these findings, and working in partnership with chemists at the Universities of Oxford and Leeds, in the second paper, researchers studied the effectiveness of two types of β-lactamase enzyme inhibitor in a bacterium known to be highly resistant to common antibiotics.

Calvopina TK *et al*. (2017). Structural/mechanistic insights into the efficacy of non-classical β-lactamase inhibitors against extensively drug resistant *Stenotrophomonas maltophilia* clinical isolates. *Molecular Microbiology*. 106 (3), pp492-504.

Li, G-B *et al*. (2017). Crystallographic analyses of isoquinoline complexes reveal a new mode of metallo-β-lactamase inhibition. *Chemical Communications*. 53(43), pp5806-5809.

Biology and chemistry combine to generate new antibiotics

With resistance growing to existing antibiotics, there is a vital and urgent need for the discovery and development of new antibiotics that are cost effective. Promising developments are derivatives of the antibiotic pleuromutilin, with the core pleuromutilin isolated from the mushroom *Clitopilus passeckerianus*.

Pleuromutilin derivatives are potent antibacterial drugs but often require difficult chemical modifications. A Bristol team report the genetic characterisation of the steps involved in pleuromutilin biosynthesis through heterologous expression and generate a semi-synthetic pleuromutilin derivative with enhanced antibiotic activity. This was achieved by taking the complete genetic pathway for pleuromutilin production, containing seven genes, from the mushroom, and rebuilding it in the industrially useful filamentous fungus *Aspergillus oryzae*, traditionally used to make soy sauce.

This then generated a unique platform of Aspergillus lines with combinations of the pathway genes to allow new compounds to be synthesised.

This is a classic case where nature has produced something really useful, but combining nature with chemistry through a synthetic biology approach we are able to make things even better
Prof Chris Willis (Chemistry)

Alberti F *et al*. (2017). Heterologous expression reveals the biosynthesis of the antibiotic pleuromutilin and generates novel bioactive semi-synthetic derivatives. *Nature Communications*. 8(1831).

Breastfed babies are less likely to have eczema

Babies whose mothers had received support to breastfeed exclusively for a sustained period from birth have a 54% lower risk of eczema at the age of 16.

The study examined more than 13,000 Belarussian teenagers enrolled in the PROmotion of Breastfeeding Intervention Trial (PROBIT) and found a 54% reduction in cases of eczema amongst teenagers whose mothers had received support to breast-feed exclusively. Eczema affects around 1 in 5 children and 1 in 10 adults in the developed world. The WHO recommends between four and six months of exclusive breastfeeding to aid prevention of allergy and associated illnesses. These findings add further weight to the importance of campaigns like the Baby-Friendly Hospital Initiative (BFHI), which is tackling low rates of breastfeeding globally.

The UK has one of the lowest rates of breastfeeding in the world. Only 34% of UK-born babies have received any breast milk, compared with 49% in the USA and 71% in Norway. Only 1% of babies in the UK are exclusively breastfed to six months.

Flohr C *et al*. (2017). The effect of an intervention to promote breastfeeding on asthma, lung function and atopic eczema at age 16 years. *JAMA Pediatrics*. Published online 13 November 2017.

PROBIT is the largest cluster-randomised controlled trial ever conducted in the area of human lactation during infancy.

Design of novel cell-instructive biomaterial surfaces

Engineering the interface between biomaterials and tissues is important to increase implant lifetime and avoid failures and revision surgeries. Permanent devices should enhance attachment and differentiation of stem cells, responsible for injured tissue repair, and simultaneously discourage bacterial colonization. To take first steps towards such a multifunctional surface it was proposed to merge topographical and biochemical cues on the surface of a clinically relevant material, which combines antibacterial nanotopographical features with integrin selective synthetic ligands that can rescue the adhesive capacity of the surfaces and instruct mesenchymal stem cell (MSC) response. To this end, a smooth substrate and two different high aspect ratio topographies have been produced and coated either with an αvβ3-selective peptidomimetic, an α5β1-selective peptidomimetic, or an RGD/PHSRN peptidic molecule. Results showed that antibacterial effects of the substrates could be maintained when tested on pathogenic *Pseudomonas aeruginosa*.

Read the full journal article published in *Scientific Reports*.

Atopic eczema: one size does not fit all

Doctors and patients have long known that eczema can affect people in many different ways. Now Prof Sara Brown (University of Dundee) and collaborators at UoB and the University of Groningen have shown that there are atopic dermatitis subgroups in children.

The study has confirmed that eczema is a very diverse disease and has provided evidence of distinctly different trajectories, including a group that hadn't previously been recognised, in whom eczema develops for the first time around six years of age and is often associated with asthma. They have also shown that genetic risk factors contribute to the most troublesome and long-lasting eczema, so these patients can be a focus for future research to improve care. It's also important evidence that we need to consider which subtypes of eczema may respond to which treatments in clinical trials to ensure the right children get the right treatment in future.

The team looked at 13,500 children from birth to 11 or 16 years, born in the UK or the Netherlands; around 40% of children developed eczema at some time in their life. Through statistical analysis, the researchers were able to identify different groups:

- Eczema starts in infancy and doesn't go away
- Eczema starts in infancy and lasts throughout childhood
- Eczema starts in infancy and goes away in early childhood
- Eczema starts in mid-childhood (around six years) and goes away later in childhood
- Eczema starts in late childhood (11 years-early teens) and then goes away

The largest group (~1/3) develop the disease soon after birth and mostly grow out of it by their 5th birthday. However, for the 1/8 children with eczema who are in a group where eczema does not resolve, the disease can last into adulthood. These children are also most likely to have relatives with eczema and experience other health problems, including asthma and allergies.

Read more

ELIZABETH BLACKWELL FUNDING

EBI Clinical Primer Scheme

This scheme is aimed at exceptionally motivated clinically qualified medical, veterinary and dental trainees who are at an early stage of their career and is designed to give them the chance to experience a world-class research environment for the first time.

Closing date: 8 January 2018

EBI Early Career Fellowship

The Elizabeth Blackwell Institute is delighted to be supporting one of the University of Bristol Vice-Chancellor's Fellowships in 2017. In addition to this they will be launching their own competitive EBI Early Career Fellowship scheme in early 2018.

Find a Sponsor deadline: Friday 15th December 2017

EBI Identifying Candidates for Wellcome Trust Investigator Awards

This scheme is designed to support a small number of permanent academic staff at UoB within the first five years of their appointment, who are planning to apply for an Investigator Award from the Wellcome Trust. Applications will be accepted on a rolling basis.

Heads of School are asked to nominate members of staff who can be eligible for this scheme by emailing ebi-health@bristol.ac.uk

EBI Workshops Funding

Support interdisciplinary workshops in health research at new or emerging interface between two or more disciplines. Applications reviewed all year.

Returning Carers Scheme

To support academic staff across all faculties in re-establishing their independent research careers on return from extended leave (16 weeks or more) for reasons connected to caring (e.g. maternity leave, adoption leave, additional paternity leave, leave to care for a dependant.).

The deadline for applications is 30 April and 31 October each year.

EBI Bridging Funds for Senior Fellows

This scheme is designed to support a small number of academic staff at the University of Bristol who currently hold an externally funded research fellowship. Applications accepted on a **rolling** basis.

University of BRISTOL
Elizabeth Blackwell Institute for Health Research

FUNDING OPPORTUNITIES

Set up via Research Professional (RP), a full calendar of funding opportunities for Infection and Immunity Research is available online. Subscribing to a calendar will place the entries in your own calendar, which will automatically update according to pre-specified criteria.

Staff and students have FREE access to Research Professional online from all computers on the University network. You can create your own personalised funding opportunity e-mail alerts by registering with RP. Find out all about it on the RED website.

The listing below represents a *brief selection* of available funding for the infection and immunity community. Full listings of opportunities are sent out via Schools and are available on the Research Development website.
Note that some calls may be subject to a major bids process, and all details are on the website.

National Institute of General Medical Sciences
Modelling of infectious disease agent study research projects (R01): Aids-related

Closing Date: 07-Jan-18 Award amount: unspecified

This supports innovative research that will develop and apply computational tools and methods for modelling interactions between infectious agents and their hosts, disease spread, prediction systems and response strategies. Areas of interest include infectious disease research and computational, mathematical and statistical model research.

Volkswagen Foundation | VolkswagenStiftung
Travel grants – Herrenhausen symposium on individualised infection medicine

Closing date: 10 Jan 18 Award amount: €1,000

This enables researchers researchers to attend the Herrenhausen symposium on individualised infection medicine taking place in June 2018 in Hannover. A total of 30 grants worth up to €1,000 are available.

Medical Research Council
Research grants – infections and immunity

Closing date: 10 Jan 18 Award amount: £1m

These fund focused research projects that may be short- or long-term in nature related to infec-

tions and immunity, as well as method development and continuation of research facilities.

Medical Research Council
New investigator research grant – infections and immunity

Closing date: 10 Jan 18 Award amount: unspecified

This aims to support researchers who are capable of becoming independent principal investigators and who are ready to take the next step towards that goal within the areas of infections and immunity.

Medical Research Council
Partnership grant – infections and immunity

Closing date: 10 Jan 18 Award amount: unspecified

This provides core funds to support partnerships between diverse groupings of researchers, and can be used for infrastructure support, platform activities and for bringing together managed consortia or multidisciplinary collaborations.

Medical Research Council
Programme grants – infections and immunity

Closing date: 10 Jan 18 Award amount: unspecified

These provide large and long-term renewable funding for projects related to infections and immunity. A programme is defined as a coordinated and coherent group of related projects that may address an interrelated set of questions across a broad scientific area. The expectation is that not all questions will necessarily be answered within the tenure of the award.

Eunice Kennedy Shriver National Institute of Child Health and Human Development, US
Advancing understanding, prevention, and management of infections transmitted from women to their infants (R01 – clinical trial optional)

Closing date: 05 Feb 18 Award amount: unspecified

This stimulates investigations including translational, epidemiologic and clinical studies and trials that improve the understanding, prevention and clinical outcomes of non-HIV infections transmitted from women to their offspring during pregnancy, labor and delivery and breastfeeding. The maximum period of projects is five years.

National Institute of Allergy and Infectious Diseases
Novel approaches to understanding, preventing and treating Lyme disease and tick-borne coin-

fections (R21)

Closing date: 16 Feb 18 Award amount: unspecified

Supports research that will contribute to the overall understanding of Lyme disease and co-infections transmitted by Ixodes ticks. This research opportunity encourages studies that address diverse scientific areas such as pathogenesis, host response, disease transmission, vector biology and natural history, vaccines, diagnostics, and therapeutics.

National Institute of Allergy and Infectious Diseases
Maintaining immunity after immunisation (U01 clinical trial optional)

Closing date: 21 Feb 18 Award amount: USD 2,250,000

This aims to improve understanding of how durable protective immunity is achieved by supporting studies that define components and mechanisms of the immune system. Applications proposing human cells or tissue response studies help determine the human responses elicited by immunisation, however, animal studies may also be used to extend the findings from human tissues to more mechanistic studies not easily accomplished in humans.

H2020-SC1-DTH-2019 digital transformation in health and care, single stage – topics DTH 1, 5, 9, 11, HCC 2
Exploiting the full potential of in-silico medicine research for personalised diagnostics and therapies in cloud-based environments

Closing date: 24 Apr 18 Award amount: €8,000,000

This supports projects that manage health and wellbeing while empowering the participation of citizens and facilitating the transformation of health and care services to more digitised, person-centred and community-based care models, thereby enabling better access to healthcare and the sustainability of health and care systems. The indicative budget is worth €85.5 million.

THIS ISSUE'S FEATURED ARTICLE

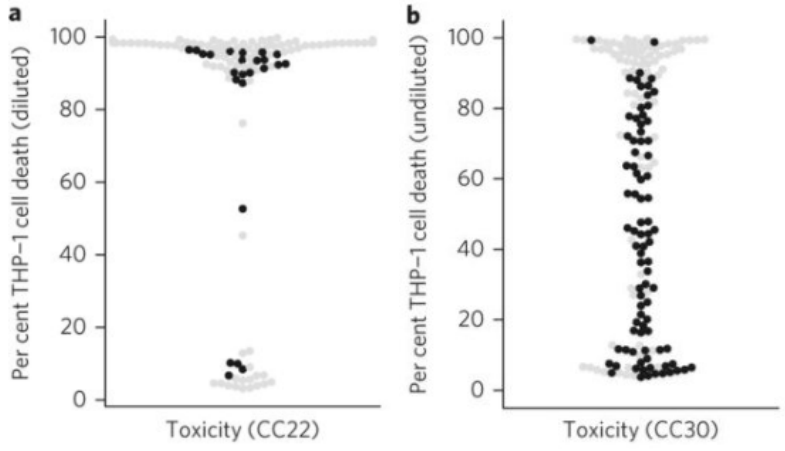
Clonal differences in *Staphylococcus aureus* bacteraemia-associated mortality

Recker M, Laabei M, Toleman MS, Reuter S, Saunderson RB, Blane R, Török ME, Ouadi K, Stevens E, Yokoyama M, Steventon J, Thompson L, Milne G, Bayliss S, Bacon L, Peacock SJ & Massey RC

Nature Microbiology 2, 1381–1388 (2017)

The bacterium *Staphylococcus aureus* is a major human pathogen for which the emergence of antibiotic resistance is a global public health concern. Infection severity, and in particular bacteraemia-associated mortality, has been attributed to several host-related factors, such as age and the presence of comorbidities. The role of the bacterium in infection severity is less well understood, as it is complicated by the multifaceted nature of bacterial virulence, which has so far prevented a robust mapping between genotype, phenotype and infection outcome. To investigate the role of bacterial factors in contributing to bacteraemia-associated mortality, we phenotyped a collection of sequenced clinical *S. aureus* isolates from patients with bloodstream infections, representing two globally important clonal types, CC22 and CC30. By adopting a genome-wide association study approach we identified and functionally verified several genetic *loci* that affect the expression of cytolytic toxicity and biofilm formation. By analysing the pooled data comprising bacterial genotype and phenotype together with clinical metadata within a machine-learning framework, we found significant clonal differences in the determinants most predictive of poor infection outcome. Whereas elevated cytolytic toxicity in combination with low levels of biofilm formation was predictive of an increased risk of mortality in infections by strains of a CC22 background, these virulence-specific factors had little influence on mortality rates associated with CC30 infections. Our results therefore suggest that different clones may have adopted different strategies to overcome host responses and cause severe pathology. Our study further demonstrates the use of a combined genomics and data analytic approach to enhance our understanding of bacterial pathogenesis at the individual level, which will be an important step towards personalised medicine and infectious disease management.

a,b: Toxicity for each isolate was determined by incubating bacterial supernatant with cultured human cells, using flow cytometry to quantify cell death (toxicity). Note that the supernatant of the CC22 isolates was diluted to 30%, and the supernatant of the CC30 isolates was used undiluted. Apart from differences in baseline toxicity between the two clones, there is a marked difference in their distribution; for CC22 isolates the toxicity was either very high or very low, but there was a more uniform distribution for CC30. No difference was observed between methicillin-resistant (MRSA, grey circles) and methicillin-susceptible (MSSA, black circles) isolates.



CONTACTS

The Infection and Immunity Network is run by a Steering Group:

Co-Chair: Lindsay Nicholson
Reader in Research

Co-Chair: Adam Finn
Prof of Paediatrics

- Andrew Davidson - Senior Lecturer in Virology
- Wendy Gibson - Professor of Protozoology
- Kathleen Gillespie - Reader in Molecular Medicine, Head of the Diabetes and Metabolism Research Group
- Alastair Hay - Professor of Primary Care
- Mark Jepson - Reader in Cell Biology
- Ruth Massey - Reader in Cellular and Molecular Medicine
- David Morgan - Reader in Immunology
- Peter Muir - Clinical Virology
- Angela Nobbs - Lecturer in Oral Microbiology
- Collette Sheahan - Research Development Network Facilitator
- Annela Seddon - Director of the Bristol Centre for Functional Nanomaterials
- Katy Turner - Senior Lecturer in Veterinary Infectious Diseases
- Peter Vickerman - Professor of Infectious Disease Modelling
- Linda Woolridge - Chair in Translational Immunology
- Catherine Brown - Research Development Administrator for the Network

e: infection-immunity@bristol.ac.uk

w: http://www.bristol.ac.uk/infection-immunity/