Emerging Diseases
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**Correction** – In the April issue feature ‘The gut microbiome in Myalgic Encephalomyelitis’ by Maureen R. Hanson and Ludovic Giloteaux the last mention of ME on line 5 of the introduction on p10 should read CFS not ME.
Vaccination: still a challenge, always a hope

by Freddie Theodoulou, Science Editor

Which is the greater threat to humankind: animal disease or plant disease?

We asked this question in a quiz compiled by the Biochemical Society for Fascination of Plants Day 2017. The answer of course, is that both are potentially devastating. Whilst innumerable lives have been lost globally to infectious diseases such as smallpox, around a million people starved in 19th Century Ireland when potato blight decimated their staple crop. Hunger kills as efficiently as viruses and bacteria. Thanks to vaccination, the World Health Organisation declared smallpox eradicated in 1980, but as diseases are eliminated or controlled, new ones arise: now researchers and medics confront Ebola and multidrug resistant bacteria, while plant scientists and farmers scramble to avoid losing the world’s wheat crop to virulent forms of rust fungus. Whatever the pathogen, successful solutions to emerging diseases will depend not only on scientific inquiry, but also on how well the fruits of research are communicated and delivered to society.

The battle with smallpox can be traced to antiquity: Egyptian mummies bear witness to the disease which eventually spread to India and Europe and possibly contributed to the downfall of the Roman Empire a thousand years later. Introduction to the Americas by the Conquistadors had similarly devastating consequences. But it was realized as early as 430 BC that survivors had immunity to smallpox and although evidence is sparse, the practice of variolation- inoculation of non-immune individuals with smallpox virus- appears to have arisen independently in several countries.

Much as the scientific community faces resistance from “anti-vaxxers” today, variolation met with considerable opposition. Jenner owes a debt to a lesser-known smallpox hero, English aristocrat Lady Mary Wortley Montague, a passionate advocate who (unlike Tony Blair during the UK MMR triple vaccine controversy) persuaded Royal physicians to trial the practice by having her daughter publicly variolated in 1721. Across the Atlantic, the Rev. Cotton Mather’s attempts to prevent the Boston epidemic of the same year resulted in his house being bombed, but his ground-breaking statistical analysis of mortality rates influenced the widespread adoption of variolation. Jenner himself was immunized a quarter of a century later at the age of 8 and survived to spend a lifetime being both honoured and abused for his vaccination work. The 1800s saw extensive vaccination but despite unquestionable success stories, modern day objections still mirror those of 19th Century antivaccinationists. Some problems have scientific solutions- producing vaccines in plants, for example, may satisfy anti-vivisectionists. Much harder to address are moral and philosophical issues, particularly the tension between individual choice and common good. With a limited repertoire of anti-viral therapies and the inexorable march of evolution, the promise of vaccines and the case for advocacy remain as strong as ever.

Emerging viruses – is there an emerging pattern?

The Ebola outbreak in West Africa in 2014 and the spread of Zika across the Americas in 2016 have thrust previously obscure viruses into the media spotlight. But is something new really going on? What can we expect in future? Is there anything we can do?

How to frighten children

One of the formative experiences of my childhood was Terry Nation’s TV series Survivors, which aired on the BBC in April 1975. Even today, the first episode is still chilling in its portrayal of a London overwhelmed by a new infectious disease until, in the words of one character: “the dead outnumber the living.” Nation was best known as the creator of Dr Who’s perennial adversary, the Daleks, but Survivors was a far more serious project, growing directly from his own conviction, about which he had “no doubt”, that “the disaster – in whatever form – will come” (Radio Times interview, 10 April 1975). Survivors’ dramatization of the helplessness of humanity in the face of a relentless and virulent pestilence, instilled my lifelong fascination with pandemics.

Sex, drugs and blood transfusions: the first trio of pandemics

The next media health scare was genital herpes. This was not by any means a new disease, and its causative agent, herpes simplex virus type 2, had been known since the 1960s. However, there was a considerable expansion in the incidence of genital herpes in the mid-to-late 1970s and the press were quick to portray it as a disease of sexual promiscuity. Media fascination with genital herpes has long waned, but its incidence continues to increase to this day.

Part of the reason for genital herpes losing the limelight was that a far more serious disease appeared in the US gay community in 1981, named the following year as AIDS. The isolation of the causative agent, HIV-1, in 1983 revealed a previously unknown virus. Once diagnostic tests were developed, it quickly became apparent that AIDS was by then well established in Africa, with footholds in several other continents. The AIDS pandemic had simply not been noticed until it entered a Western population. In the 21st century, Bayesian phylogenetic techniques have now revealed that HIV-1 had been spreading...
in the Congo Basin in central Africa since around 1920, having entered human populations from chimpanzees, and probably arrived unheralded in New York around 1972. The process of animal-to-human host transfer, by which chimp SIV-1 became human HIV-1, is referred to as zoonosis, and it has become a recurring theme in the pandemics of the last three decades. A further recurring theme is the lateness at which pandemics are often recognized, even when the virus is previously known.

Hepatitis C virus (HCV) was finally identified in 1989, although its existence had been suspected since the mid-1970s. HCV, a blood-borne and sexually transmitted virus, spread through many of the same social networks as HIV-1, and also probably had its origins in Africa, but subsequent phylogenetic analyses have revealed a much earlier origin. HCV was not decades old like HIV-1 when it first came to public attention, but centuries old. This perhaps explained why HIV-1’s zoonotic source was readily identifiable as chimp SIV-1, but HCV’s ultimate origins have faded in the 500 years or more it has been spreading slowly around the planet. Nevertheless, historical timescales aside, the emergences of HIV-1 and HCV showed many parallels in geographical origins, modes of transmission and routes of travel.

**Virology’s meteorite near-miss**

Astronomers are fairly certain that a meteorite impact 65 million years ago led to the extinction of the dinosaurs. In January 2017, the 35 metre diameter asteroid AG13 passed between the earth and the moon, becoming the latest in a long line of near-miss events, potentially devastating if only a little nearer and larger, but otherwise simply joining the list of disasters that never quite happened.

Virology’s equivalent occurred in 2003, when a new and virulent flu-like illness, severe acute respiratory syndrome (SARS), began to spread in Hong Kong, having begun at the end of the previous year in mainland China. Initial observation of superspreader events – one case in a Hong Kong hotel led to 16 new cases – and high mortality, raised fears that SARS might cause a rapid pandemic with many millions of deaths. The confirmation that SARS was a coronavirus, a family into which some common cold viruses fall, only served to deepen the conviction that SARS was at least as dangerous as HIV-1 in terms of the total number of deaths it could cause, and was likely to cause them a lot quicker. In the end, some heroic public health efforts over several countries helped contain the disease, and the final tally of cases and fatalities revealed a death rate of just under 10% of patients – not as bad as had been initially feared.

Then, SARS suddenly disappeared and has not been seen since, like a meteorite heading off into the blackness of space. The zoonotic origins of SARS may be in bats, where several related viruses are found, via palm civets, where the virus was detected at the time of the outbreak, and SARS is just one of several diseases where the sale of wild animals for domestic consumption – the bushmeat trade – may represent the best candidate for the point of zoonotic entry.

In 2012, another new coronavirus, Middle East respiratory syndrome (MERS), appeared in Saudi Arabia. With a mortality rate exceeding 35% of patients, SARS paled by comparison, but fortunately MERS is not readily transmissible and most cases have occurred in a hospital setting. Travel-associated cases have appeared fairly regularly in several countries, but almost always without onward spread. The exception was in 2015 in Korea, when a traveller returning from the Gulf seeded a hospital outbreak of a magnitude similar to those previously seen in Saudi Arabia. MERS would seem to have relatively little pandemic potential in the general population but coronaviruses, with their fast evolution and easy respiratory transmission in some cases, always make virologists uneasy. Unlike SARS, the zoonotic source of MERS is clear – camels – but again several closely related viruses in bats may indicate its deeper origins.
Ebola tears up the textbooks

Although the 2003 SARS episode was one over which virologists lost more sleep than the general public, the 2014 outbreak of Ebola in West Africa provoked global alarm. Since its discovery in 1976, Ebola had been an exhibit in virology’s ‘chamber of horrors’ – appalling but fortunately very rare and confined to isolated parts of the Congo Basin and surrounding regions. In the recriminations following the series of events that allowed Ebola to produce its first truly mass outbreak, one of the crucial factors identified in its early spread was that Ebola was not supposed to occur in West Africa. When the teams from the Guinean Ministry of Health and Medecins Sans Frontières reached the epicentre in the second week of March 2014, performing the crucial confirmatory test, the outbreak was in its fourth month and affected patients had already spread out over several localities, including two hospitals. If it had occurred to the provincial health authorities to request an Ebola test in the first two months of the outbreak, it might have been possible to contain the disease within its initial focus in Meliandou village. Such patterns of early diagnosis and quick quarantine have long been the practice in Congo, including another unrelated Ebola outbreak that occurred in northern Congo in mid-2014. But not everything was necessarily down to human error – retrospective analysis of how the Ebola virus evolved over the course of the outbreak also identified some mutations which may have assisted transmissibility.

Some determined efforts to locate the zoonotic source of the West African outbreak have so far failed to provide conclusive evidence. Nevertheless, bats remain the best candidate for Ebola’s natural reservoir. Exactly why so many efforts to trace the zoonotic sources of human emerging viruses, from SARS through MERS to Ebola, end at the same destination, is not clear. Bats may well, because of their inverted roosting position, be more likely to have urine or faecal material on their bodies, and this inherent lack of hygiene may be a factor.

Viruses take wing

Just as there is a possibility that the West African Ebola epidemic may have been super-charged by a mutation occurring early in the outbreak, the rapid spread of chikungunya in the present century has also been linked to genetic changes in the virus. However, chikungunya is not the only mosquito-borne virus – collectively known as arboviruses – to have gone pandemic. Beginning with the spread of dengue into the Americas in 1977, followed by West Nile virus (WNV) in 1999, chikungunya in 2013 and Zika shortly afterwards, diseases spread by mosquito bite have moved out of their previous African and South-East Asian ranges to achieve global distribution in the
tropics and sub-tropics. WNV's transmission by cold-adapted midges means that it has spread as far north as the US–Canadian border and central Europe.

Dengue, WNV and chikungunya were all known pathogens that were on the surveillance radar following expansions elsewhere – most notably chinkungunya's spread across the Indian Ocean from Africa to South-East Asia beginning in 2005. By contrast, Zika had a mere dozen or so cases described in the medical literature prior to the beginning of its own trans-Pacific spread in 2007, and its mildness compared with the others only intensified the sense of shock when it became apparent that it was the cause of thousands of cases of birth defects across Latin America. Indeed, although death rates from Zika are lower than from the other members of the pandemic arbovirus quartet, its long-term economic and social impact is potentially larger.

The common themes

Despite the diversity of emerging viruses, several issues link many of them together. Zoonosis – the transfer of a virus from an animal reservoir to a new home in humans – is the origin of HIV-1, SARS, MERS, WNV, Ebola and probably HCV and Zika, even if the ultimate animal origin is unknown. Bushmeat consumption is probably a key point in the zoonotic process for SARS, Ebola, MERS and HIV-1. The need for bushmeat reflects increases in human population which cannot be sustained via traditional agriculture. Urban overcrowding into unhygienic shanty town slums provides the ideal environment for the spread of close-contact diseases like Ebola. Providing water supplies in shanty towns requires open storage tanks which then invite infestation by mosquitoes bringing dengue, chikungunya and Zika. Absence of adequate health services ensures the continuing spread of HIV-1. The immunodeficiency brought on by AIDS renders populations vulnerable to further infection and means that they cannot adequately respond to vaccination campaigns against established viruses like yellow fever, measles and polio.

We need not necessarily share the fatalism of the late Terry Nation, penning Survivors in anticipation of a dramatic pandemic end to civilization, but optimism is difficult. Children no longer need fiction to frighten them.

The bigger picture

This article has focused on viruses affecting humans over the last 40 years. Although this is the part of microbiology that fills our television screens and social media channels, we should remember that viruses also affect pets, livestock and plants, and that bacteria, fungi and parasites may cause just as much trouble in their own slower, more persistent way. If all we do is treat disease, then it will return. We need to change the conditions – ecological, social, economic and political, and all the way along the food chain – that are increasingly fostering the spread of new diseases through the human environment. Solutions that deal with a single aspect of the problem will merely deflect the problem elsewhere. There are no easy answers so far, but the first step in dealing with a problem is to recognize that it exists.

Further reading

  Penned almost as a work of reportage in the early days of the West African Ebola outbreak, this article has become something of a minor classic in its concise and compelling description of a disaster waiting to happen.

- Two papers are essential reading in understanding the origins of AIDS.

  This detailed dissection of the strange appearance of an obscure African virus on a remote Pacific island, was the first indication of the intercontinental invasion that was to follow. It can hardly be read now without hindsight producing a slight unnerving frisson.

Derek Gatherer has been a lecturer in Lancaster University’s Division of Biomedical & Life Sciences since 2013, and was previously a lecturer at Liverpool John Moores University from 1996–1999. During the intervening period he worked in the pharmaceutical industry and then for the MRC Virology Unit. Originally a molecular embryologist, he moved from the lab to bioinformatics in 1995 and has focused on computational analysis of viral genomes since 2003. Since 2014, he has become a regular media commentator on emerging viruses with over 200 appearances on radio or TV. Email: d.gatherer@lancaster.ac.uk. Twitter: @viroscope
Can we identify viruses with pandemic potential?

Mark E.J. Woolhouse and Jordan L. Ashworth (University of Edinburgh, UK)

There are believed to be thousands of as yet unknown viruses ‘out there’, circulating in wildlife and possibly our domestic animals too. Which of these viruses might have, or might acquire, the potential to cause the next global pandemic in humans?

Over the past two decades alone the world has experienced multiple major epidemics of emerging infectious diseases, including severe acute respiratory syndrome (SARS), chikungunya, H1N1 and H7N9 Influenza A, Middle East respiratory syndrome (MERS), Ebola and Zika. These epidemics have two things in common: they were all caused by viruses, and all these viruses originated in non-human mammals or birds.

There have been various attempts to identify the viruses most likely to emerge in humans. A particularly important initiative is the World Health Organization’s R&D Blueprint List of Priority Diseases, now updated annually. Many different criteria are associated with pandemic potential, and some of the most important of them are intimately linked to the molecular interactions between the virus and its host.

Pandemic potential

There are three capabilities a virus must have to pose a large-scale threat to human health: it has to be able to infect humans, it has to cause disease in humans and it has to be able to spread from one human to another (possibly indirectly, e.g., mosquito or tick vector). Each of these capabilities is functionally related to the cell types and tissues the virus can enter and replicate in and this, in turn, is determined by the molecular interactions between the virus and host cells.

Cell entry is a prerequisite for viral infectivity. Viral surface proteins or glycoproteins must bind with one or more host cell surface molecules, the cell receptors (Figures 1 and 2). Cell receptors may be proteins, carbohydrates or glycolipids, and may be single molecules or complexes (see Table) and have a strong influence on the host range of a virus. Viruses that can infect a broad range of mammalian hosts invariably use cell receptors that show a high degree of similarity – at least 90% amino acid sequence homology if the receptor is a protein – across different mammalian orders.

Cell receptors also determine the tissue tropism of a virus. Some cell receptors, such as CD4 or the...
acetylcholine receptor, are confined to specific cell types; others, such as heparin sulphate and sialic acid, are distributed much more widely. Tissue tropism is a key determinant of both viral pathogenesis and transmissibility.

Cell entry is necessary for infection but it is not sufficient. The virus must also be able to overcome host defences known as restriction factors, constitutive or inducible host proteins with antiviral activity. The M lineage of HIV-1 had pandemic potential because its Vpu protein disables human tetherin, a host protein that inhibits the release of virions from cells infected with other HIV-1 lineages.

Virus infections can harm the host in multiple ways, including tissue damage, inflammation and fever, metabolic dysfunction and immunopathology (Figure 3). Unsurprisingly, the nature and severity of viral illnesses are strongly influenced by which organs are affected. Viruses that are systemic (i.e. affect the whole body), and especially those that invade the nervous system, may be particularly pathogenic; the rabies virus is a good example. Clinical symptoms of viral infections, such as sneezing or diarrhoea, may be functionally linked to virus transmission (Figure 4). To be transmissible, a virus must be able to access a restricted set of host tissues, particularly the upper respiratory tract, the lower gastrointestinal tract, the urogenital tract, the skin or blood. Human influenza viruses bind to a form of sialic acid known as α2,6-SA, which is found in the upper respiratory tract, and so these viruses can be transmitted by humans. By contrast, avian influenza viruses bind to α2,3-SA which, in humans, is confined to the lower respiratory tract and lungs – these viruses can cause severe respiratory illness, but human-to-human transmission is very rare.

Prediction

An important area of study is the impact of natural or artificially generated mutations on virus traits relevant to pandemic potential, trying to identify single or multiple nucleotide substitutions that alter these traits in well-characterized viruses, either in vitro or in vivo. We could make much more rapid progress if knowledge of a virus genome sequence allowed \textit{in silico} prediction of human infectivity, pathogenicity and transmissibility. Merely being able to predict the cell receptor would be a good start. At present, such efforts depend on an extensive prior history of experimental study that will only ever realistically be available for a limited number of well-researched viruses such as Influenza A or HIV-1. \textit{In silico} predictions could help prioritize viruses for more detailed molecular and experimental characterization.

### Table 1.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Entry protein</th>
<th>Receptor</th>
<th>Co-receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A virus</td>
<td>Haemagglutinin</td>
<td>Sialic acid</td>
<td></td>
</tr>
<tr>
<td>HIV-1</td>
<td>Gp160 (gp120)</td>
<td>CD4</td>
<td>CCRS and CXCR4</td>
</tr>
<tr>
<td>SARS-CoV</td>
<td>S (S1)</td>
<td>ACE2</td>
<td>Vimentin</td>
</tr>
<tr>
<td>HSV-1</td>
<td>Glycoprotein D (gD)</td>
<td>Nectin-1 or HVEM</td>
<td></td>
</tr>
<tr>
<td>Enterovirus 71</td>
<td>Capsid Shell (VP1, VP2, VP3)</td>
<td>SCARB2</td>
<td></td>
</tr>
<tr>
<td>Rhinovirus A</td>
<td>Capsid Shell (VP1, VP2, VP3)</td>
<td>ICAM-1</td>
<td></td>
</tr>
<tr>
<td>Ebola virus</td>
<td>Glycoprotein</td>
<td>NPC1</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Illustration of Ebola virus. Ebola virus is a cylindrical virus belonging to the family Filoviridae. Transmitted between humans through direct contact with infected faeces, blood or organs, Ebola virus causes a number of severe symptoms including diarrhoea, vomiting, stomach pain, impaired kidney and liver function, and occasionally internal and external bleeding. Ebola disease is fatal in 50% of cases. Glycoprotein spikes on its surface (shown in green) mediate cell entry by binding to Niemann-Pick C1 (NPC1) proteins expressed most abundantly on dendritic cells. (Maurizio De Angelis, Wellcome Images)
Advances in machine learning are beginning to suggest that predictions such as these may be achievable. Most people associate machine learning with spam filtering emails and suggesting what you should watch next on Netflix, but its applications span far beyond your inbox. Recent studies have found that from a protein's amino acid sequence alone, it is possible to predict which proteins it will likely bind to, given an adequate training set. Methods vary, but usually involve transforming a pair of protein sequences into a feature vector, which represents the physiochemical properties of each amino acid (e.g. net charge, polarity, side chain volume and hydrophobicity). By assessing which features pair frequently in a training set of known protein interactions, predictions can be made about which other proteins may bind. These methods have successfully predicted intra-species protein interactions in many model organisms including yeast, Escherichia coli and Caenorhabditis elegans. The results for yeast were particularly promising, displaying better than 90% accuracy, sensitivity and specificity. This is largely due to the quality of the training set, with size and protein diversity being the main drivers. Interactions between human and virus proteins are less well known than for yeast and attempts at prediction have been less successful. However, it is encouraging that an online database of viral protein interactions (VirusMentha) has nearly doubled in the past 3 years, currently detailing over 12,000 viral–human protein interactions for 100 species of virus. As training sets continue to grow, accuracy should improve.

**Surveillance strategies**

Advances such as these raise the possibility of new disease surveillance strategies based on virus genome sequencing; we call this predictive genomic surveillance. If we could predict which viruses have pandemic potential from sequence data alone then perhaps we could detect them before they are found in humans. Such capability would add a huge amount of value to future surveillance programmes. One proposal currently being discussed is a 10-year, multibillion-dollar initiative to identify almost all the viruses in wildlife and to ascertain their pandemic potential, the Global Virome Project (www.globalviromeproject.org/). A range of methods are available to detect viruses, but metagenomic sequencing is nowadays the method of choice when a sample contains unknown and possible novel viruses. Metagenomic sequencing allows all genomic material in a sample to be turned into readable nucleotide sequence that can be assembled into whole or partial genomes. Almost any biological sample can be sequenced and a snapshot of the microbial community revealed, even when the sequences are novel. Knowledge of virus genome sequences from a global-scale study would undoubtedly be valuable, but to exploit such a resource fully a parallel bioinformatics research programme on predicting virus phenotype from genome sequence data will be needed too.
Effective surveillance is the first line of defence against emerging infectious diseases; early detection is key to managing outbreaks. Surveillance can be more efficient if we know what we are looking for and where best to look for it, even more so if we can do this in animal populations before humans are infected, a strategy known as ‘getting ahead of the curve’. As the cost of genome sequencing technologies comes down, data on virus–host protein–protein interactions accumulate and bioinformatics analyses become more powerful, this goal is looking more and more attainable.

Our work on emerging viruses is funded by the Wellcome Trust. We thank the Wellcome Collection (https://wellcomeimages.org/) for making available the images shown in this article. We are grateful to Theo Bakker for his assistance.

Mark Woolhouse is Professor of Infectious Disease Epidemiology at the University of Edinburgh. His interest in emerging viruses came about from reading Laurie Garrett’s 1994 book The Coming Plague. Since then he has been conducting systematic, hypothesis-led studies of emerging infectious diseases. The subject demands a broad approach, the answers will be found at the interfaces of many different disciplines: molecular biology, public health science, ecology, anthropology, entomology, sociology, agriculture, veterinary science and more. Email: Mark.Woolhouse@ed.ac.uk.

Jordan Ashworth is a Global Health PhD student working with Professor Mark Woolhouse and Dr Sam Lycett at the University of Edinburgh. She recently made the transition from wet to dry lab, graduating with a Master’s in Bioinformatics from Newcastle University. Her research currently focuses on mining genomic data extracted from faecal samples of Vietnamese hospital patients for zoonotic viral signals using computational methods. Email: Jordan.Ashworth@ed.ac.uk.

Further Reading

Oropouche virus (OROV) is a midge-borne human pathogen that causes periodic outbreaks of a flu-like illness predominately in the Northern parts of Brazil. However, despite its significant public health importance in Central and South America the virus remains rather obscure to the rest of the world.

Oropouche virus (OROV) is a virus in the order *Bunyavirales*, a large group of RNA viruses with segmented genomes. Here, it falls into the genus *Orthobunyavirus* along with several other pathogens of human and veterinary significance (example: La Crosse and Schmallenberg viruses). Like the vast majority of viruses in this order, OROV is an arbovirus, meaning it requires an arthropod vector for its transmission to a susceptible host. Prior to the emergence of chikungunya and Zika viruses in Brazil, OROV was regarded as the second most important arbovirus in the country after dengue virus, with an estimated total of over half a million human cases to date. As far as we know OROV is not fatal in humans, and the symptoms are similar to other viruses transmitting in the country (high fever, joint and muscle ache, light sensitivity, vomiting, dizziness). Neurological symptoms associated with meningitis and encephalitis have also been documented during some outbreaks (example: 1980 outbreak in Para state, Brazil), and OROV has been detected (PCR, and one virus isolation) in the cerebrospinal fluid of some patients.

The first reports on OROV go back 62 years to Trinidad, West Indies. Here, in 1955, OROV was isolated from the blood of a febrile forest worker. The 24-year old male was from a village called Vega de Oropouche on the Oropouche river from which the virus acquired its name. Although no other febrile cases were reported, serological surveys did find neutralising antibodies (suggesting previous exposure) against OROV in three out of 46 people that were tested, as well as in the surrounding primate population. In 1960 OROV was picked up again in Trinidad, but this time from mosquitoes (*Mansonia venezuelensis*). The same year OROV was isolated from a dead sloth (cause for death not reported) and mosquitoes (*Ochlerotatus serratus*) in Northern Brazil for the first time. In 1961, just a year after being discovered in Brazil, OROV caused its first outbreak in the country with an estimated 11,000 cases (Belem city, Para). Between 1978 and 1981 about 220,000 OROV cases were reported in Para, Amazonas and Amapa states. In 1988 the virus then spread to the states of Maranhao and Goias where about 200 people were reported ill. OROV outbreaks were soon being reported in cities all along the Amazon River, and between 1961 to 1996 more than 30 outbreaks were recorded with an estimated 500,000 cases. Outside of Brazil, OROV outbreaks were reported for the first time in Panama in 1989 and Peru in 1992.

The geographic distribution of OROV today includes Brazil, Panama, Peru and Argentina. Serological evidence suggests that the virus may also be circulating in humans in Ecuador and Bolivia, and in non-human primates in Colombia (Figure 1A). A list of all known OROV outbreaks to date can be found in the Table provided.
## Recorded Oropouche fever outbreaks in South America

<table>
<thead>
<tr>
<th>County</th>
<th>State</th>
<th>Location</th>
<th>Year</th>
<th>Month</th>
<th>Estimated cases</th>
<th>Viral Isolation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>Para</td>
<td>Belem</td>
<td>1961</td>
<td>Feb - May</td>
<td>11000</td>
<td>15</td>
<td>Pinheiro et al. 1981b</td>
</tr>
<tr>
<td>Brazil</td>
<td>Para</td>
<td>Caratateua</td>
<td>1967</td>
<td>Feb - Mar</td>
<td>400</td>
<td>2</td>
<td>Pinheiro et al. 1981b</td>
</tr>
<tr>
<td>Brazil</td>
<td>Para</td>
<td>Braganca</td>
<td>1967</td>
<td>Mar - Jul</td>
<td>6000</td>
<td>8</td>
<td>Pinheiro et al. 1981b</td>
</tr>
<tr>
<td>Brazil</td>
<td>Para</td>
<td>Belem</td>
<td>1968</td>
<td>Feb - Jul</td>
<td>n/a</td>
<td>101</td>
<td>Pinheiro et al. 1981b</td>
</tr>
<tr>
<td>Brazil</td>
<td>Para</td>
<td>Baião</td>
<td>1972</td>
<td>Jun - Sept</td>
<td>85</td>
<td>n/a</td>
<td>Pinheiro et al. 1981b</td>
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<tr>
<td>Brazil</td>
<td>Para</td>
<td>Santarem</td>
<td>1974</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Pinheiro et al. 2003</td>
</tr>
<tr>
<td>Brazil</td>
<td>Para</td>
<td>Itupiranga</td>
<td>1975</td>
<td>May - Jun</td>
<td>420</td>
<td>9</td>
<td>Pinheiro et al. 1981b</td>
</tr>
<tr>
<td>Brazil</td>
<td>Para</td>
<td>Alter do Chao</td>
<td>1975</td>
<td>Jul - Aug</td>
<td>280</td>
<td>16</td>
<td>Pinheiro et al. 1981b</td>
</tr>
<tr>
<td>Brazil</td>
<td>Para</td>
<td>Moju dos Campos</td>
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(n/a; data not available)
Emerging Diseases

Circulation of Oropouche virus

We are still not certain of the natural reservoir(s) for OROV, but the virus has been isolated from the pale-throated three-toed sloth (Bradypus tridactylus) and the black-tufted marmoset (Callithrix penicillata) (Figure 1B). It is probable that the virus is maintained in circulation amongst these mammals, although vector(s) here remain unknown. Once in an urban setting, OROV appears to be transmitted amongst people by biting midges (Culicoides paraensis). Though midges have been established as the efficient vector for human OROV transmission, laboratory-settings also show that various mosquito populations are susceptible to infection (Aedes serratus, Aedes scapularis, Aedes albopictus, Culex fatigans, Culex quiquefaciatus, Coquilettidina venezuelensis and Psorophora ferox). Interestingly, both wild and domestic birds have tested positive for OROV antibodies during outbreaks, but whether this has any significance for OROV spread remains to be determined.

The biology of Oropouche virus

OROV is an RNA virus and the first genome sequences for it were reported almost 16 years ago. The OROV genome is split amongst three single strands of RNA of negative polarity (opposite orientation to eukaryotic messenger RNA) (Figure 2). The large (L) genome segment encodes the viral polymerase (L protein), which is responsible for transcribing and replicating the viral genome. The medium (M) segment encodes the viral glycoproteins (Gn and Gc) which allow attachment and entry of the virus into a host cell. Whilst, the small (S) segment codes for a nucleocapsid (N) protein, which amongst other functions helps protect the viral RNA by encapsulating it, it additionally encodes a protein called NSs (non-structural small protein) from the same N mRNA transcript. The NSs protein works against the host cells innate immune system thereby allowing the virus to replicate efficiently inside that cell.

Unfortunately, there isn’t a lot that we know of in terms of OROV pathogenesis and mechanistic functions inside a host cell. Dr Eurico Arruda’s lab in Brazil have carried out in vitro studies and found that OROV enters cells using the
endocytic pathway (specifically clathrin mediated), whilst in vivo work by Prof Michael Diamond’s lab have identified key components of the innate immune system (interferon pathway) that play a crucial role in OROV pathogenesis. I was fortunate to have had the opportunity to be mentored during my PhD studies by the late Prof Richard M Elliott, who’s life work was centred around studying different bunyaviruses (viruses in the family Bunyaviridae, which is now an upgraded order called Bunyavirales). Prof Elliott back in 2012 was one of only a handful of people working on OROV outside of Brazil. Together, and along with colleagues, we sequenced the virus and established reverse genetic tools (viruses can be generated in vitro using cloned complementary DNA copies of their genome) that will now allow OROV to be dissected and studied at a molecular level.

**Conclusions and perspective**

Infectious diseases have a huge impact on human, animal and plant health causing significant morbidity and mortality, as well as placing a costly burden on global economies. The more we encroach into wildlife habitats the more likely we are to encounter new viruses. Before OROV caused an outbreak in Brazil it was discovered in a dead sloth found near a construction site for the major Belem-Brasilia highway. This highway construction took place between 1958 and 1960 and resulted in considerable loss of the Amazon rainforest. This brought a naive human population into close proximity to natural OROV reservoirs. The original Trinidad case was also from a highly deforested area around Melajo forest. An interesting publication by Prof Pedro Vasconcelos from the Evandro Chagas Institute in Northern Brazil (also a World Health Organisation arbovirus reference centre) describes the ecological changes that took place in Brazil in the early 60s and 80s and reports the identification of 187 different viruses, all isolated between 1954 and 1998. OROV happens to be one that managed to gain a significant foothold in human transmission.

Now, will OROV follow the likes of dengue or Zika? Well this is hard to say, but sporadic cases are being picked up outside of its original epidemic zone. Habitat destruction, urbanization and climate change are only likely to favour transmission, and though the last recorded outbreak in Brazil was 2009, last year Peru showed us that OROV isn’t going away. On June 3rd 2016, the World Health Organisation reported 57 Oropouche fever cases in the Cusco region of Peru. OROV had never been detected in Cusco before this. Additionally, a number of OROV M segment reassortants (reassortment is common in viruses with segmented genomes) have been identified and of them Madre de Dios and Iquitos viruses (isolated in Venezuela and Peru) can cause febrile illness in people (Figure 3). The genome of these reassortant viruses contain an L- and S- segment from OROV, and an M segment from an unknown virus. Since the M segment encodes for viral attachment and entry proteins it could potentially change the virus tropism and potentially expand the host range of OROV. On that note, OROV is an emerging viral zoonosis worth paying a bit more attention to.

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**Figure 2.** A schematic representation of a bunyavirus virion. Electron microscopy of OROV data estimates that OROV virions are ≈70 nm in diameter (Personal communication, Dr. Gustavo Olszanski Acrani, Federal University of the South Frontier, Brazil). On the right is the coding strategy used by OROV along with its genomic segments and expressed proteins. The size of the segments and proteins are given in brackets. vRNA; viral RNA, mRNA; messenger RNA, NSm; non-structural medium (non-structural protein encoded on the M segment).

**Figure 3.** Phylogenetic tree of the Simbu serogroup (a group of viruses from the genus *Orthobunyavirus*). The tree shows the distribution of viruses based on the M segment protein-coding region. The different coloured branches highlight the different clades. Oropouche, Iquitos, Madre de Dios and Perdoes viruses all share similar L and S segments. The tree was created using a maximum-likelihood method based on the general time reversible model (GTR) with discrete gamma distribution. Bar, number of nucleotide substitutions per site. Positions with lower than 95% site coverage were eliminated. Alignment and analysis were conducted in MEGA6 (Tamura et al., 2013) and the final tree was created using FigTree v.1.4.2.
This article is dedicated to the memory of my PhD supervisor Richard M. Elliott who passed away on the 5th of June 2015. Richard was not only an excellent virologist, but he was also an excellent mentor. His dedication and passion for virology was motivating, and his good humour meant there was never a dull day in the Elliott lab! We miss you Richard.

Further Reading

The complex relationship between the emerging flaviviruses: dengue and Zika

Many flaviviruses cause important and serious human diseases, including yellow fever, West Nile, Japanese encephalitis and tick-borne encephalitis viruses. Two further flaviviruses, the closely related dengue and Zika virus, have emerged as significant threats to global health with their potential to inflict severe disease to millions of people. Here, we look at some of the molecular similarities and differences between these two emerging diseases, as this is key to the development of novel preventions and therapeutics.

History and pathology

Flaviviruses are a group of enveloped viruses containing a positive stranded RNA genome of approximately 11 kilobases in length encoding three structural and seven non-structural proteins. The virion is comprised of the nucleocapsid, consisting of the RNA genome and encapsulating capsid (C) proteins, surrounded by a lipid membrane that integrates the other two structural proteins: the envelope (E) and membrane (M). There are some 70 different members within the Flaviviridae family, a major sub-group comprising those that are transmitted by mosquitoes (mosquito-borne flaviviruses; MBFVs). Dengue and Zika viruses belong to this group, with *Aedes aegypti* and *Aedes albopictus* mosquitoes as their primary vectors (Figure 1). Though suspected dengue virus outbreaks have been reported as early as the 17th century, changes in human travel, climate change and unsustainable vector control strategies have allowed the recent establishment or resurgence of its vectors in the tropics and sub-tropics around the globe. Each year, there are an estimated 390 million dengue virus infections with 96 million apparent manifestations around the world. In comparison, Zika virus is newer, having been first identified in Uganda approximately 70 years ago, and has caused few apparent clinical problems as it spread in Africa and Asia. However, it has become a pathogen of real concern in the past few years, as it spread with explosive outbreaks with severe sequela into naive populations first in Oceania and then South and Central Americas. The requirement of a competent vector in principle defines the geographical spread of these viruses, but it is not the only factor in the case of Zika virus, since recent reports indicate direct human-to-human transmission of Zika virus via contact with bodily fluids of infected individuals.

Both dengue and Zika virus infection typically lead to the development of mild, febrile illness, but infection with these viruses can lead to vastly different severe clinical manifestations. While dengue virus infection can induce disabling disease by causing leakage from the circulatory system that leads to acute haemorrhagic fever and shock, Zika virus infection has been shown to cross the placenta and is implicated in the development of multiple neurological diseases during development involving congenital microcephaly and Guillain–Barré syndrome. Finally, Zika virus undergoes a prolonged infection associated with the testes that leads to sexual transmission, which is unique among the MBFVs. Whilst the presence of Zika in the blood is low in these cases, it does markedly separate it from other *Aedes* clade viruses.

Early phylogenetic studies of MBFVs divided them into epidemiologically and clinically distinct groups based on their vector, reservoir host and disease associations. Two principal clades emerged (see Figure 1): one transmitted by *Aedes* mosquitoes, the other by *Culex* mosquitoes. However, it is not just the transmission vectors that are different. The *Aedes* clade uses large terrestrial mammals as reservoir hosts and is associated with haemorrhagic disease, in contrast to the *Culex* clade that associates with rodents and birds, and causes encephalitic disease. Both Zika and dengue viruses are members of the *Aedes* clade, along with yellow fever virus, Spondweni virus and several veterinary viruses. Dengue and yellow fever viruses are permanently established in the New World, with the latter currently causing an outbreak in Brazil. The emergence of Zika virus in the New World is ominous, given the track record of uncontrolled spread of dengue and yellow fever viruses on this continent and especially...
as Zika displays devastating consequences following maternal infection.

**Dengue and Zika sero-cross-reactivity: a blessing for the viruses but a curse for their human hosts**

Zika virus is serotypically similar to dengue virus, as demonstrated by strong cross-reactivity of the Zika virus E protein with monoclonal antibodies against the dengue virus E protein. Moreover, both viruses possess very similar epidemiological characteristics and their global expansions show remarkably similar rates of transmission in humans. Although phylogenetic analysis places Zika virus in the *Aedes* clade, some reports suggest it can be transmitted by *Culex* spp., but this association is not supported in all studies. Furthermore, Zika virus is not associated with haemorrhagic disease, and whilst it does not cause encephalitis infection, it is associated with neurological conditions.

There are four types of dengue viruses and they have co-existed in the face of strongly cross-reactive antibodies between them. Indeed, by exploiting antibodies from a primary infection, that are non-neutralizing to a secondary infection, subsequent infections often display increased viral replication in macrophages. This phenomenon is known as ‘antibody-dependent enhancement’ and is mediated by antibody interactions with the viral protein E (see Figure 2). While for the virus, increased viral titre in the blood increases the likely success of transmission; for humans, this can lead to increased risk of severe disease. While cross-reacting antibodies between Zika virus and dengue virus currently remain under-researched, such a phenomenon has also been proposed to lead to the development of severe Zika, as incomplete neutralization of the Zika virus by dengue virus antibodies may cause enhanced Zika virus replication and thus increased chances of fetus infection.

![Figure 1. Maximum likelihood amino acid phylogeny (LG matrix), reconstructing the evolutionary relationships between the mosquito-borne flaviviruses, showing West Nile virus (WNV), Japanese encephalitis virus (JEV), Spondweni virus (SPONV), Zika virus, dengue virus serotypes 1 to 4 (DENV1–4), yellow fever virus (YFV) and rooted by tick-borne encephalitis virus (TBEV).](image)

**Dengue and Zika: very similar and yet so different**

Despite their similarities in vector transmission and recognition by the human immune system, there are substantial differences between dengue and Zika viruses (see Table 1). This is most readily evident from the above-mentioned differences in severe clinical manifestations. These differences are probably due to distinct and complex molecular mechanisms of dengue and Zika virus infection, ranging from cell tropism to interactions of dengue and Zika viruses with the host during the course of virus infection.

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**Table 1: Mosquito-borne flaviviruses have common and unique characteristics**
The elucidation, followed by a comparison, of these interacting host proteins will be crucial to further our understanding of the dengue and Zika viruses.

The three structural proteins and seven non-structural (NS) proteins encoded by the flavivirus genome all play a wide variety of crucial roles during all phases of virus infection. These proteins exert their influence on the host cell processes by disrupting existing interactions or making new connections. Although each individual protein has high protein sequence similarity as well as enzymatic functional conservation to its homologous protein in other flaviviruses, they often interact with unique sets of human host proteins. Both the dengue and Zika virus NS5 proteins have methyltransferase and RNA-dependent RNA polymerase functions, and target the interferon-regulated transcriptional activator STAT2 for degradation. However, the molecular mechanism of degradation is different between the two NS5 proteins. While dengue virus NS5-mediated STAT2 degradation is dependent on the E3 ubiquitin ligase UBR4, Zika virus NS5-mediated STAT2 degradation does not require UBR4.

The unique interactomes of each individual flavivirus could account for the differences observed between the flaviviruses. Hence, a systematic elucidation and comparison of these flavivirus–host interactions would be integral to our understanding of flavivirus infection. Dengue–host interactions have been extensively studied for the past decade, and their elucidation has contributed significantly to our understanding of dengue infection and pathogenesis. In particular, the dengue NS1 protein has been recently shown to induce inflammation and vascular leakage associated with severe disease via binding to a host protein toll-like receptor 4 (TLR4). In addition, NS1 stimulates immune cells to release cytokines that fuel an over-active pro-inflammatory response, and hence essentially acts like a bacterial toxin. This discovery has opened a new avenue for the development of dengue antiviral drugs, as preliminary studies have begun to re-purpose existing drugs used in the treatment of sepsis that target TLR4 to treat dengue infection. These drugs could be highly specific for dengue virus treatment, as the NS1 protein of the closely related West Nile virus does not have the same effect as the dengue virus NS1 protein on vascular leakage. This finding is not particularly surprising considering West Nile virus infection does not induce vascular leakage, but it highlights how the different interactions of flavivirus proteins with host proteins can help account for the clinical outcomes of virus infection. Our knowledge of the clinical outcome of Zika virus infection would suggest that Zika NS1 would behave like West Nile virus NS1, but this remains to be demonstrated, as the Zika NS1 is largely uncharacterized. The fact that both Zika and West Nile virus can cross the blood–brain barrier to infect the brain makes it particularly interesting to uncover whether their NS1 proteins are involved in a common pathway for this process.

**Future directions**

The discovery and comparison of flavivirus-interacting host proteins, such as NS1 and NS5, will be crucial in both understanding the differences in pathology and targets for therapeutic intervention. In the Zika field, we are only beginning to uncover these Zika–host interactions and proteins, but a comparison of these interactions with those of dengue viruses will be particularly illuminating. The discovery of unique and common interactors of Zika and dengue will be instrumental in deepening our understanding of the infection and pathogenesis of these viruses, and bring hope by directing the development of antiviral drugs.
Dr Min Jie Alvin Tan received his PhD in Virology from Harvard University in 2013. He is currently a National Medical Research Council Young Investigator at the Genome Institute of Singapore. Viruses have always fascinated him, especially how they interact with their host during infection. His current research focuses on taking a systems approach to elucidate these interactions, with a particular interest in flaviviruses. By combining genomics and proteomics studies, he seeks to uncover host proteins that are crucial for virus infection and hence are potential targets for host-directed antiviral therapeutics. Email: tanmja@gis.a-star.edu.sg.

Dr Michael W. Gaunt is currently funded to study the Zika virus in collaboration with Andrew K. Falconar through the EU2020 consortia ‘ZikaPlan’. Molecular evolution is his approach and he exclusively focuses on infectious disease in Latin America. He previously worked on the Zika virus as part of his PhD on flavivirus evolution with Ernie A. Gould (Oxford), before embarking upon postdoctoral training, a Wellcome Trust fellowship, RCUK fellowship and then as Assistant Professor at the London School of Hygiene and Tropical Medicine. Email: Michael.Gaunt@lshtm.ac.uk.

Professor Martin L. Hibberd is Professor of Emerging Infectious Diseases at the London School of Hygiene and Tropical Medicine and has adjunct positions at the Philippine Genome Centre and the Genome Institute of Singapore (where he was previously associate director from 2003 to 2016). He graduated from Brunel University in 1985 and received his doctorate from King’s College, London in 1994. He has a broad scientific background spanning both microbial and human determinants of infectious and inflammatory diseases. His current research interests utilize genomic applications to cover both pathogen and host aspects of infectious disease. Email: Martin.Hibberd@lshtm.ac.uk.

Dr Nicholas Furnham is an MRC Methodology Research Fellow and Associate Professor in Computational Molecular Biology at the London School of Hygiene and Tropical Medicine. Prior to this, he held a research scientist position in the group of Professor Dame Janet Thornton at the European Bioinformatics Institute. He graduated from King’s College London and subsequently undertook an MSc at Exeter University before moving to Cambridge University to undertake a PhD in computational crystallography under the supervision of Professor Sir Tom Blundell. His research is interdisciplinary, combining biology and chemistry with computer science, which is applied to important questions in infectious diseases. Email: Nick.Furnham@lshtm.ac.uk.

Further reading

- Grant, A., Ponia, S.S., Tripathi, S. et al. (2016) Zika virus targets human STAT2 to inhibit Type I interferon signaling. Cell Host Microbe 19, 882–890
Rift Valley fever virus (RVFV) is a mosquito-borne Bunyavirus that currently affects livestock and humans, causing a wide spectrum of symptoms. RVFV was confined to the African continent for many decades and spread to the Arabian Peninsula in recent history. The potential for widespread emergence into new regions and populations is possible and likely, as many outbreaks are driven by human behaviour and livestock trade. While many imported human cases have been detected, establishment of the virus in new geographic areas will depend on amplification in dense animal populations. Western and European countries have identified a substantial risk for the emergence of RVFV, as agricultural industries constitute a large percentage of the global economy.

Recent emergence

Throughout the last decade, the unanticipated emergence of viruses has caused significant immediate and long-term hardships for people worldwide. West Nile virus emerged in the Americas in the early 2000s and was marked by the onset of severe neurological symptoms in thousands of patients. The rapid spread of chikungunya virus to populations throughout South America, the Caribbean and the Mediterranean in 2013 and 2014 led to the infection of hundreds of thousands of individuals, some of which are still suffering from long-term sequelae. By 2015, South America and territories in the Caribbean were experiencing an explosive outbreak of Zika virus that was presenting with previously unreported symptoms and consequences, such as severe congenital effects and neurological complications. There are many viruses which have been isolated to specific regions or ecosystems for decades, such as RVFV, that, with the right conditions, may emerge in larger sections of the world and cause extensive disease burden. The development of this disconcerting trend of sudden and broad emergence of viruses is due to a number of human-related factors, and is not anticipated to slow in the future.

Emergent history of Rift Valley fever virus

The first report of RVFV was published in 1931, and documented disease in humans and livestock in the Great Rift Valley region of Kenya. Cases of RVFV were limited to the African continent, primarily affecting sub-Saharan Africa, until the early 2000s, when outbreaks were detected in Saudi Arabia and Yemen. Madagascar has been endemic for RVFV since its introduction to the island in 1979, followed by significant outbreaks with devastating loss in livestock populations in 1990 and 2008. Imported cases have been reported in the UK, Europe and more recently in China. It is thought that the recent Zika virus outbreak in Brazil that spread throughout the Americas was caused by imported cases tied to large sporting events.

One Health and factors influencing disease transmission

There are four major categories of factors that influence local and widespread transmission of a virus. The first category is the vector, or a living organism that physically transmits the infection from one individual to the next. In many of the more recent outbreaks, mosquitoes are responsible for transmission. In many cases of mosquito-borne disease, the vector is species specific, meaning that only one or a few species of mosquitoes are able to carry and transmit the virus, and that the virus is dependent on the presence of the vector to continue the cycle of infection to new populations. RVFV is transmitted by many species of mosquitoes, and conserved in populations by vertical transmission, wherein a female mosquito transmits the virus to her offspring during egg laying.

The second category is the possible host, which is also species specific. For viruses that infect humans, factors that may contribute to the risk of infection
Predicting Rift Valley fever can include biological sex, age, socioeconomic status (SES), occupation, behaviour and the type of access to fundamental resources, such as water, nutrition and sustenance, and sanitation. Mobility and ease of travel, specifically with air travel, has had a significant impact on disease transmission and viral emergence because humans can carry the pathogens in their blood to a new place where the vectors exist. Additionally, human proximity to animals, through human encroachment into forest or natural areas for personal or industrial use, increases risk of exposure, as many viruses are zoonotic, and have evolved to infect both humans and certain species of animals. RVFV infects both humans and domesticated livestock, and occupational exposure, especially for individuals who work in abattoirs and handle a large amount of animal carcasses and blood products, has been proven to increase the risk of infection.

The third category is climate and environmental conditions, which directly impact where and how humans, animals and vectors live and thrive. The impact of our immense human population on the planet has reduced the availability of natural resources, and promoted irreversible changes to climate conditions. Gradual changes to climate contribute to overlaps in vector environment and human environments. Past outbreaks of RVFV have been linked to periods of heavy rainfall. Fluctuations between drought and heavy rains leads to water collection near homesteads, whether for specific use in cooking or bathing, or as passive water collection in structures and man-made containers around the home. Water collection near the home provides mosquitoes with new places to breed within close proximity to humans, making it easier to feed without flying too far from their breeding sites.

The fourth category is comprised of the molecular elements of the virus. Mutations in the viral genome drives the evolution of viruses into new vectors, reservoirs and hosts, and thus increases the chance of outward spread. The viral genome of RVFV has been mostly conserved, despite its prominent history throughout Africa and movement to the Arabian Peninsula.

These four categories impact disease transmission on a personal level, and are directly related to the health of the planet, or the 'One Health' concept. The interconnected nature of these four categories is built on dependence, in such that changes to one category drives a response or an adaptation in another. For example, vertical transmission in mosquitoes preserves new generations of mosquito populations with RVFV intact. Heavy rains can reanimate eggs preserved during a drought or dry season, not only increasing the mosquito population as larvae hatch and develop, but also increasing the likelihood of an outbreak.

These images illustrate how native Kenyan and NASA-funded scientist Assaf Anyamba and a team of collaborators from NASA Goddard Space Flight Center, the Walter Reed Army Institute of Research, the World Health Organization, the United States Army Medical Research Unit-Kenya, and the United States Department of Agriculture used satellite data to predict an outbreak of Rift Valley fever in late 2006. The top image shows vegetation growth in December 2006 compared to average growth in previous Decembers from 1998 through 2006 as seen by France’s SPOT satellite. Areas where plants were growing far more than average are dark green, while less-than-average growth is represented in brown. This information served as a proxy for the conditions that accompany an outbreak of Rift Valley fever. The lower image shows the risk map Anyamba and his colleagues created based on satellite data of rainfall and vegetation. Regions where an outbreak of Rift Valley fever might be expected based on high rainfall and higher-than-average plant growth are red. Adjoining regions, where the disease was less likely to appear based on satellite data, are green. The locations of reported human cases between September 2006 and May 2007 are marked with circles on the risk map. Those cases that fell into the risk area are yellow, while those that fell outside the risk area are blue. Credit: NASA images created by Jesse Allen, using provided by the United State Department of Agriculture Foreign Agriculture Service and processed by Jennifer Small and Assaf Anyamba, NASA GIMMS Group at Goddard Space Flight Center. Caption by Holli Riebeek. Source: https://earthobservatory.nasa.gov/
The effects of emergence

Human RVFV infections may present with a wide range of symptoms and sequelae. Many patients report mild fever and non-specific flu-like symptoms, joint and muscle pain, diarrhoea, jaundice and delirium. Mild forms of Rift Valley fever (RVF) are often misdiagnosed as meningitis, as muscle pain and stiffness concentrated in the neck with delirium are too general to differentiate without differential diagnosis. Approximately 8–10% of cases experience severe disease, which can include ocular lesions and partial or complete loss of vision, meningoencephalitis and significant neurological complications, and haemorrhagic fever. RVF has also more recently been linked to spontaneous abortion. While the mortality rate of RVFV infection is only 1% overall, experience of severe disease can increase the risk of death to 50% if proper monitoring and symptomatic treatment is not received. Asymptomatic cases are common with RVFV infection, yet are an important factor in disease transmission, as mosquitoes can pick up RVFV from an infected person who is not experiencing disease symptoms, and spread the virus to other individuals. Some theorize that asymptomatic cases of infections are often the most dangerous, as asymptomatic individuals are the least likely to access treatment or enforce precautions to limit further spread of the infection, due to the lack of diagnosis.

Animals experience sudden and widespread RVF disease, making livestock populations ideal amplifying hosts, and increasing risk for transmission to humans. RVF cases in animals, especially common in species of sheep, goats, camels and cattle raised as livestock, appear rapidly with distinct symptoms. Spontaneous abortion is the most significant and indicative experience of RVFV infection in animals. Sudden deaths and large population die-offs are common, with younger animals extremely susceptible to death because of infection. Febrile disease and prostration are more common in adult animals, with a possibility of acute hepatitis and jaundice. The loss of livestock may be devastating for families that are dependent on their stock for sources of food and milk.

RVFV outbreaks in both humans and animals have devastating impacts on economies dependent on livestock. The loss of yield of in utero animals and younger generations of animals can be difficult to recover from, causing decreased income for years. Cases in adult animals introduce a high risk for humans, as many of these animals are sent to slaughter, and infected products, such as meats, milk and blood, can be distributed widely through trade and sales. Livestock trade between regions has been a driving force for past RVFV outbreaks, assisting the virus in travelling to new regions to infect naïve populations of animals and humans without immunity to RVFV.

One of the best measures used to control the spread of RVFV has been the enactment of trade restrictions and sanctions when infected animals are detected. The duration of limitations and temporary bans after the detection of an infected animal or stock depends on the local restrictions associated with import and export. Strict limitations and fines can decrease the spread
of RVFV through animal trade and other livestock economies, but has devastating consequences on local economies leading to illegal trade and use of products from infected animals.

**Rising risks in the West**

With the unanticipated spread to the Arabian Peninsula in 2000, Europe and the United States have increased livestock importation restrictions with regulated surveillance checkpoints and bans on imports from countries with reported cases of RVFV. Establishment of RFVF in the United States or Europe would require considerable populations of amplifying hosts (livestock), and environmental conditions to support thriving populations of the vector. The United States already has several mosquito species that could support autochthonous, or local transmission of RVFV.

While the spread of RVFV doesn’t pose a huge threat of infection in the human population, it would have explosive impacts on animals in the United States. The USDA has identified RVFV as a significant threat to the expansive agricultural industry in the United States, as introduction of RVFV to the United States could cause catastrophic damage to individual farmers and the country’s economy. As seen with prior outbreaks, RVFV is difficult to control and contain once livestock populations are exposed. Additionally, the livestock industry in the United States has been designed for high volume population rearing, for the maximization of product and economic benefit leading to decreased resistance to diseases. Many industrial farming facilities also confine animals in restricted pens, which increases the risk for extensive disease spread within a facility. The common use of prophylactic antibiotics in factory and industrial farming facilities to reduce the risk of exposure to bacterial infections in animal populations illustrates the emphasis on product volume.

An animal vaccine is currently available in Africa, yet the efficacy and ultimate pay off of vaccinating is not widely recognized. Vaccine boosters are required regularly, and can be costly and hard to justify if the perceived risk is low. Additionally, side effects of the vaccine mimic symptoms of the disease and spontaneous abortion can still occur. Often, perceptions of the risks of administering the vaccine outweigh the perceived risk of disease in a healthy herd.

Given the recent increase in disease emergence, many reports have warned of the risk of RVFV emergence. RVFV is a potential candidate for more frequent outbreaks and movement into naïve populations. The imported case identified in China earlier this year highlights the vast distance that viruses can travel with ease, and suggests that further spread is imminent. We all need to be on high alert for emergence of this significant One Health threat.
Guarding the granary

The introduction of microbial plant pathogens can cause tremendous damage to crops, food security, the economy and ecosystems in very little time. What do we know about these invaders? And what can be done to defend our crops and respond quickly to new threats?

Imagine being a farmer with a field of crops. One day you notice one of your plants is looking a bit under the weather. Upon closer inspection, you notice some brown patches on the leaf and some white fluff. As the rest of the field seems healthy, you remove the plant in question and go to bed. The next morning you wake up, and a much larger patch of plants show the same symptoms as the plant you removed the day before. You frantically try to remove these infected plants, but there are too many of them. Over the course of 5 days your entire crop is gone and the losses are so severe you wonder how your family will manage in the coming year. As you go home, defeated by this invisible enemy, rumours come in that your farm is not alone, other farmers tell similar stories. It quickly becomes apparent the entire country is being ravaged by an invisible enemy that is eating the very food you need to make a living. Seven years later, one million people have died of starvation and another one million people have emigrated. After 150 years, the population of your country will still not have recovered from this culling. Science fiction? Not really, this is exactly what happened to the people of Ireland in the period of 1845–1852. The cause was an invasive microbial species (not a fungus as often thought, but a microorganism closely related to algae called an Oomycete) that hitch-hiked on a ship from Mexico. The aptly named Phytophthora infestans (phyto = plant and phthora = destroyer) has left its mark on the world forever.

**Infectious invaders**

The incursion of *P. infestans* does not stand alone, in 1868 a fungal pathogen called coffee leaf rust (*Hemilea vastatrix*) wiped out coffee crops in Sri Lanka. As a consequence, the UK is now a country of tea drinkers. The pathogen is still a major pest for today’s coffee growers in South America. Fusarium wilt of banana is caused by the fungus *Fusarium oxysporum f. sp. cubense*. It attacks the roots and vascular system of banana plants and wiped out banana plantations in the 1920–1950s. This led to the replacement of the then popular cultivar ‘Gros Michel’ by ‘Cavendish’, which was resistant to this pathogen. In 1990, a new race of Fusarium wilt, called tropical race 4 (TR4) has overcome the native resistance that is present in the Cavendish banana. As this fungus colonizes the vascular system of bananas, fungicides that are sprayed on the plant surface are ineffective. The rapid spread of TR4 may lead to a total collapse of the banana industry.

The 1990s also saw the introduction of Papaya Ring Spot Virus in Hawaii; fortunately, genetic modification of papaya has been extremely successful and has saved the Hawaiian papaya industry. In 1999, a new variant of stem rust was discovered in Uganda (called Ug99). By 2007, Ug99 had spread via wind movement out of East Africa, into Yemen and as far as Iran. Ug99 is a threat to current wheat production as it is able to break the resistance gene S31, enabling it to infect most high-yielding wheat varieties.

In the 2001–2002 growing season, Asian soybean rust (caused by the fungus *Phakopsora pachyrhizi*) was found in Brazil. Few fungicides were needed in Brazil before this pathogen arrived, but currently growers have to spray on average 2.8 times per season at an estimated cost of US$2.2 billion per year (Figure 1). Despite extensive spraying, grain losses still average around $500 million per year as the fungus impacts yield rapidly. In 2005, Citrus Greening disease was detected in Florida. Since then, this insect-transmitted bacterium has spread and production is predicted to plunge from 61 million metric tons in 2005 to 11 million metric tons by 2026. The cumulative loss during the 2006–2007 and 2010–2011 periods alone are estimated at $4.5 billion, and more than 7500 lost jobs. No known cure is currently available.

Finally, in 2016, wheat blast, a disease native to Brazil was detected in Bangladesh, and has caused total crop failure for many farmers. In a frantic effort to halt the disease, crops have been set on fire before harvest and several districts that are affected no longer grow wheat (Figure 2, pictures courtesy of Professor Tofazzal Islam). Unfortunately, this has not stopped the spread of this disease and earlier this year it was detected in India.

From the number of examples available, it is clear that plant pathogens are very much on the move and new incursions happen more frequently than in the
past. Globalization and climate change are major drivers as habitats of pathogens or their vectors shift. Similarly, global trade and travel enables rapid spread of microbes from one habitat to another. Microbial plant pathogens reproduce in large numbers and can quickly adapt to novel challenges such as fungicide treatments (Figure 1) and single resistance genes that are introduced via breeding programmes. In addition, fungicides are often harmful to the environment, as well as to the growers and consumers who are exposed to them. There is not a single ‘silver bullet’ solution, therefore fundamental insights on how different plant pathogens cause disease and how plants defend themselves against these invaders is essential to rise to this challenge. The discipline called plant pathology (a multidisciplinary mix of genetics, microbiology, biochemistry, cell biology, mathematical modelling and informatics) deals with these questions. Thanks to this scientific discipline, we now know that plants have a sophisticated, genetically encoded, immune system that is able to recognize and ward off most potential invaders. In turn, pathogenic microbes have an arsenal of molecular tools that enable them to disable this immune system and cause disease.

**Defensive strategy**

Within the plant’s immune system, there are two major types of immune receptors that are involved with the initial perception of a microbe and the subsequent activation of defence responses. These immune receptors are either on the cell surface to monitor the extracellular environment, or are intracellular receptors that monitor the cytoplasm and organelles. Different compounds can be recognized. Conserved pathogen molecules such as flagellin from bacteria and chitin from fungi are typically perceived in the extracellular environment and trigger an effective defence response that wards off most microbes. Pathogens, in turn, produce effector proteins that effectively suppress this basal defence response. In addition, effectors are used to secure nutrients and manipulate the host in various ways.

Plants have adapted by being able to recognize effectors, both in the extracellular and intracellular environment. Once an effector is detected, the plant will mount a more rapid and strong immune response, so-called effector-triggered immunity. As different pathogen species and even specific lineages of pathogens have their unique and highly variable effector complements, plant immune receptors often ‘guard’ essential cellular processes by monitoring the status of plant proteins instead of directly recognizing pathogen components. This enables plants to sense different pathogens that all need to modify key target proteins to cause disease.

Although there are still many unknowns in this complex arms race, it is clear that plants with multiple receptors have a more durable pathogen resistance, compared with plants with only a single immune receptor. Similar to a hacker trying to crack a password, pathogens are constantly trying to crack the plants’ defences. The longer the password and the more characters are used, the more difficult it is to crack. Despite this simple concept, combining the genes coding for immune receptors (R genes) using classical breeding is a challenge.

Modern-day cultivars are highly optimized to provide high yields and other agronomic qualities. Plant breeders typically source resistance genes from related wild species, however, these R genes are often closely linked to negative agronomic traits which cause reduced crop quality and yields. This is called linkage drag and with classical breeding
Although modern technologies such as marker-assisted breeding and next-generation sequencing technologies greatly accelerate the breeding process, these programmes typically take more than seven years for many crops. Furthermore, some important food crops such as bananas are sterile, preventing introduction of novel resistance in currently known cultivars such as Cavendish.

Introducing plant R genes via genetic modification does not suffer from these limitations and resistant cultivars for most crops can be introduced within 3–7 years. In addition, in one single step, multiple resistance genes can be introduced together thereby providing greatly enhanced durability. Moreover, as the R genes would all be introduced at one genomic location, there is a negligible risk that they would be separated in subsequent breeding efforts. These genetically modified plants would be engineered to detect a specific pathogen and activate their native immune systems. This enhancement would greatly reduce the need for chemical control methods and provide a durable solution for pest control. In some cases, pathogen effectors attack plant proteins that are no longer required in an agricultural setting, but do cause enhanced susceptibility of the host. In these cases, the genes encoding these proteins can be targeted via genome-editing technologies such as TALENs and CRISPR-Cas9. This is a highly complementary strategy to the use of R genes.

Plant pathogens are the ultimate hackers, however, and eventually resistance will break down. Therefore, careful monitoring of pathogen populations is another key element in plant disease management. In the end, an integrated management approach of classical breeding, genetic modification, chemical control and high-tech farming will be required to manage many important agricultural pests.

**Outbreak management**

A comprehensive disease management strategy requires a detailed understanding of the interaction between pathogens and their host or hosts. As pathogens are diverse, the above outlined strategies require fine-tuning and rethinking for each individual situation. Therefore, novel incursions are particularly dangerous, as they can hit unexpectedly, spread rapidly and can thus cause a great deal of damage, long before we can even begin to understand the pathogen and determine an effective plan of action. The rapid identification of a novel pathogen is the first step to mount an effective and informed response by scientists, breeders and farmers.

![Figure 2. Wheat blast infects spikelets and entire heads of wheat resulting in severe yield losses (top). A wheat blast infected field in Bangladesh (middle). Burning of a wheat field in Bangladesh before harvest in an attempt to stop the spread of the pathogen (bottom). All pictures courtesy of Professor Dr Tofazzal Islam, Bangabandhu Sheikh Mujibur Rahman Agricultural University.](image)
After the outbreak of wheat blast in Bangladesh, a new coordinated strategy was implemented to reduce the time it takes to identify a new plant pathogen. Using the latest in sequencing technology, scientists from the UK and Bangladesh started to analyse infected leaves together. A key feature of this effort was that all analyses and raw data were released publicly and without restrictions. This generated an instant hub for information gathering, collaboration and feedback. Using this approach, the team and many volunteer scientists were able to perform genome analyses of the pathogen 6 weeks after the first samples were collected in the field. It was this data that provided the key information that the pathogen likely originated from Brazil. This piece of information allowed growers to use the knowledge acquired to manage wheat blast in Brazil and apply it directly to the situation in Bangladesh. This includes information on disease-resistant cultivars, cultural practices and effective fungicides.

Could what happened to crops in Brazil and recently in Bangladesh, happen in the UK? The short answer is: yes. Although it was not a pathogen of a major crop, ash dieback was identified in the UK in 2012. Caused by the fungus *Hymenoscyphus fraxineus* it has spread rapidly via spores that are carried by air, on clothing or by vehicles. To secure a long-term solution for the British ash tree, scientists are currently breeding ash trees that are tolerant to the disease. With increased trade, movement of people, climate change and intensification of farming, the appearance of ash dieback is a taste of the challenges that lie ahead for farmers, government agencies and scientists in the UK.

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**Further reading**


**Additional reading:**

- 2 Blades Foundation website http://2blades.org/
- The Sainsbury Laboratory website www.tsl.ac.uk/
- Open Wheat Blast website http://s62071531.websitehome.co.uk/owb/
- Royal Horticultural Society website – Ash dieback section www.rhs.org.uk/advice/profile?PID=779

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Untreatable gonorrhoea, are we there yet?

Collette Bromhead and Heather Hendrickson (Massey University, New Zealand)

Gonorrhoea is a relatively common and easily spread bacterial sexually transmitted disease that can cause a wide spectrum of symptoms from none to severe outcomes. Through its penchant for modifying its own genetics, Neisseria gonorrhoeae has gradually evolved to become one of modern medicine’s greatest adversaries. In most countries we have only one antibiotic left to treat it with, and even that option is rapidly running out. So how do we stop this train wreck? What do we do when the treatments run out altogether?

“I am very sorry”, says your doctor, “your gonorrhoea infection cannot be treated with antibiotics. It might clear up on its own in 3–6 months. In the meantime, take painkillers for the discomfort and, please don’t have sex...”

This scenario may seem dystopian, but it is an almost certain future outcome for many of the 27 million cases of genital, oropharyngeal, ocular or rectal N. gonorrhoeae infection each year (2012, World Health Organization (WHO) estimate). And this wily organism isn’t even the most critical risk we face according to the WHO, which has published its first ever list of antibiotic-resistant ‘priority pathogens’ – a catalogue of 12 families of bacteria that pose the greatest threat to human health in 2017 (see Figure 1).

Nonetheless, many people with untreatable gonorrhoea may see 3–6 months’ abstinence as the end of the world, and the Neisseria species of bacteria is equipped with many weapons of resistance and spread that make it stand out for the microbiologists, clinicians and pharmacists who have taken up the fight.

So how did we get here?

The sad answer to that question is ‘with unexpected speed’. Indeed, N. gonorrhoeae has swiftly and mercilessly developed ways to resist every single class of antibiotics introduced for its treatment since the mid-1930’s. In some cases, antibiotic treatments for other sexually transmitted infections, such as chlamydia, have provided a sub-optimal dose for any co-existing N. gonorrhoeae present and thus driven the development of resistance. Currently, in most countries, the only options for first-line treatment of gonorrhoea are the extended spectrum cephalosporins, such as cefixime (oral) and particularly the more potent ceftriaxone (injectable). Early in 2012, our group found the first scary genetic signatures of resistance to these now precious cephalosporins in N. gonorrhoeae circulating in New Zealanders. So we are

Priority 1: CRITICAL*
Acinetobacter baumannii, carbapenem-resistant
Pseudomonas aeruginosa, carbapenem-resistant
Enterobacteriaceae*, carbapenem-resistant
Enterococcus faecium, vancomycin-resistant
Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant
Helicobacter pylori, clarithromycin-resistant
Campylobacter, fluoroquinolone-resistant
Salmonella spp., fluoroquinolone-resistant
Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 2: HIGH
Enterococcus faecium, vancomycin-resistant
Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant
Helicobacter pylori, clarithromycin-resistant
Campylobacter, fluoroquinolone-resistant
Salmonella spp., fluoroquinolone-resistant
Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM
Streptococcus pneumoniae, penicillin-non-susceptible
Haemophilus influenzae, ampicillin-resistant
Shigella spp., fluoroquinolone-resistant


Figure 1: The WHO published its first ever list of antibiotic-resistant ‘priority pathogens’ in February 2017 in a bid to guide and promote research into new antibiotics. Neisseria gonorrhoeae is considered a Priority 2 organism with a high urgency of need for new antibiotics.
only a hair’s breadth away from being unable to treat gonorrhoea with antibiotics at all.

**What makes Neisseria gonorrhoeae such a cunning adversary?**

Gonorrhoea can be easily passed between people through unprotected vaginal, oral or anal sex, as well as sharing vibrators or other sex toys that have not been washed or covered with a new condom each time they are used. About one in 10 infected men and almost half of infected women do not experience any symptoms.

The *N. gonorrhoeae* bacteria comes with a suite of features which combine to make it a special case in its ability to evolve quickly.

**A diversity drive – horizontal gene transfer**

When considering the evolution of many organisms over long periods of time it is common to imagine a simple, branching tree-like structure in which the relationships between species are straightforward. In bacteria, and particularly in *Neisseria*, this model does not adequately capture the relatedness between species. Rather, bacteria frequently exchange genetic material, even between distant relations in a phenomenon called horizontal gene transfer (HGT) (Figure 2). This leads to a pattern of relatedness between bacteria that is more web-like than tree-like, and this process is particularly amplified in *N. gonorrhoeae*.

HGT occurs in bacteria via three primary mechanisms. Transduction is the movement of genetic material between bacterial strains by bacteriophages, the viruses that infect those bacteria. Bacteriophages do this by mistakenly packaging bacterial DNA whilst they are going through their infection cycle. An average bacteriophage might make 40 copies of itself during infection of a single cell but occasional mistakes during this process can have profound effects on bacterial evolution by serving to transport bacterial DNA between cells, rather than viral DNA.

The second route of HGT is conjugation, the transfer of circular DNA elements called plasmids between individuals. Plasmids can contrive to promote these events in order to make more copies of themselves and some build conjugation pili, docking ports, which allow them to send copies of themselves over to new hosts whilst maintaining a copy in their current hosts.

The third mechanism of HGT is one of the most confounding features of *N. gonorrhoeae*: transformation. Transformation is the inheritance of new DNA that is taken up from outside of the cell. With the enthusiasm of a collie dog behind an Italian restaurant, *Neisseria* slurps DNA up from the environment during transformation. Indeed, *N.*
strategy: surely if the cell that formerly had this DNA is lysed (broken open) then something about this DNA was not advantageous in this environment. Why take the risk? It appears that Neisseria has turned that disadvantage on its head by adopting a combination of random autolysis and DNA export into the environment. Consequently, within a population of Neisseria during an active infection, much of the DNA lying around is from successful siblings who have cheerfully contributed it, rather than the genetic remnants of deceased or otherwise less-fit friends.

During an active infection, the clonality of the population will decide the degree to which transformation is simply shuffling slightly different versions of similar genes or bringing in entirely novel genes. Novel DNA can come in tiny fragments or pieces of up to 13 kb in length. Transformation in N. gonorrhoeae can therefore result in large amounts of mosaicism in genes and genomes so that novel combinations of advantageous mutations can be struck upon and lead to new adaptations. Constant transformation of this type has been recognized in other pathogens as well, and it is thought that this property might help bacteria adjust to their host's immune system. This ability, however, really comes into its own in the case of antibiotic resistance.

Evolution towards higher frequencies of antibiotic resistance in pathogens that are of highest concern is not a process that we can stop. Each use of these precious drugs increases the benefit of having resistance in those bacteria that have resistance today and those that will acquire resistance through mutation or HGT tomorrow. To make things worse, many pharmaceutical companies have lost interest in pursuing the expensive R&D required to develop novel antibiotics because rapid resistance leads to a failure to recuperate their investments. Without new therapies, we face a return to the pre-antibiotic era and the days of devastating childhood mortality, amputation and infections that kill millions.

Antibiotics are extremely ancient weapons that have been deployed in the microbial world since before human history began. That is not just hyperbole; swabs were recently taken of the bacteria in New Mexico's Lechuguilla Cave in the Carlsbad Caverns, a 4-million-year-old site that had no exposure to modern antibiotics. Alarming, a single strain of bacteria from the site was resistant to most of our current antibiotics. This means that for any antibiotic we care to invent in the future, we can assume that bacteria exist in the environment that are resistant, and that through HGT, that resistance can spread.

**Bacteriophage therapy**

It has been suggested that we may need to return to older therapeutic approaches that were abandoned when antibiotics were discovered by modern medicine. One such therapy that is still practiced in some parts of the world involves the use of bacteriophages. Bacteriophages (phages for short) are used today in Russia, Georgia and Poland in order to fight bacterial infections. They are simply protein-based entities with a small amount of either DNA or RNA in their head or capsid and a base plate at the end of their tail that allows them to attach to and infect bacterial cells (Figure 3).

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The therapeutic use of bacteriophages comes with its own problems and promises. For example, bacteriophages are highly specific to their hosts. On the one hand, a high degree of specificity means that the heavy-handedness of broad-spectrum antibiotics can be avoided. Phages will only kill the bacteria that they are meant to kill, eliminating any disruption of the greater microbiome that can occur with some antibiotics. This avoids one set of complications while introducing another: one must have an ample supply of potential phages in order to select the right combination in administering a phage-based therapy. The good news is that there are an estimated 10 bacteriophages for every single bacterial cell on the planet. Earth is thought to be home to approximately 1031 phages, a massive and undiscovered source of possible therapeutics. Companies like Amplifli and Intralytix Inc. are currently investigating the efficacy of pure and combinatorial phage therapeutics for topical uses.
Indeed, the use of bacteriophages to destroy pathogens like *N. gonorrhoeae* is not a new idea. Historically, a number of bacteriophages have been detected in sequenced strains of *N. gonorrhoeae*, including NCCP11945, a strain that shows resistance to penicillin, tetracycline and ciprofloxacin (Figure 4). Bacteriophages that have integrated into the bacterial chromosome are called prophages and these generally confer resistance to subsequent infection by the same or similar bacteriophages. The observation of these prophages in sequenced *N. gonorrhoeae* tells us two things: first, that we can reasonably expect that there are phages in nature that can infect this pathogen and second, in order to be therapeutically useful, these phages must be shown to be strictly lytic phages (those that do not integrate into the chromosome and form prophages). Bacteriophages that are too close to those that are already integrated into the chromosome are unlikely to be good candidates for therapy because any strain with a matching prophage will have immunity to that bacteriophage.

To date, a small number of *N. gonorrhoeae* bacteriophages have been sequenced and reported. Some of these have been prophages that have been collected from bacterial cultures of their hosts but these have not been shown to be useful for therapy to date. Phage-mediated immunity is likely to be part of the reason that these prophages are observed in this pathogen.

**What can we practically do to protect ourselves right now?**

Our top priority is to preserve the antibiotics we have left through embracing the principles of antibiotic stewardship: in other words, we must cease abusing antibiotics for things like viral infections.

At a personal level, the next priority is to get yourself and your children immunized with every single vaccine that your healthcare provider recommends, even if you have to pay for it. And watch for the release of new vaccines.

Unfortunately, there is not yet a vaccine available for *N. gonorrhoeae*, primarily because it has proven to be a complicated target. However, a solution may have serendipitously been found in New Zealand.

**Could a vaccine for meningococcal disease prevent gonorrhoea?**

In the late 1990s, the novel MeNZB™ vaccine was developed in New Zealand to protect young adults against an epidemic B strain of *Neisseria meningitidis* bacteria that was causing a local epidemic of devastating meningococcal disease. Between 2004 and 2011, New Zealand health agencies offered free MeNZB vaccination to anyone under the age of 20. In all, more than 1.1 million young New Zealanders received the MeNZB vaccine during this immunization programme.

Recently, a case control study was conducted by Dr Helen Petousis-Harris of Auckland University using anonymized data from sexual health clinics and the National Immunization Registry to look at any effect of the MeNZB vaccine on gonorrhoea infections. Her team found that individuals who received the MeNZB vaccine about 10 years ago were 30% less likely to be diagnosed with gonorrhoea compared with those who were unvaccinated. This may seem surprising as the vaccine was very specific for meningococcal disease, but *N. gonorrhoeae* and *N. meningitidis* share 80–90% of their DNA. Further work is underway to understand how the MeNZB vaccine worked against gonorrhoea and this may help us determine how to

**Figure 4:** *Neisseria gonorrhoeae* NCCP11945 and several known, partly and presumed intact prophages. Colour key: blue regions are scored as questionable for an intact prophage, green are scored as intact (> 90) and red regions are incomplete prophages that are presumed to have lost their ability to replicate independently. From Phaster (http://phaster.ca/) accession number CP001050.1.
make it more effective. So watch this space: we may yet have a prevention strategy for gonorrhoea other than condoms and abstinence.

But how many parents will object to vaccinating their children against a sexually transmitted infection? The highly effective Gardasil® vaccine (Merck) that protects against human papillomavirus-related cancers continues to be controversial in many countries for supposedly ‘promoting promiscuity’. The public genuinely needs to figure out what it is more scared of when it comes to protecting the young and vulnerable: sex or untreatable infections?

**Welcome to the end of the world as we know it**

Antibiotic resistance is a problem for anyone with a pulse on this planet, not just doctors, scientists and pharmaceutical companies. The threat is both public and personal. At the public level, health protection agencies must move from being reactive to proactive. At a personal level, perhaps we should all get real or start thinking about what we will wear to the apocalypse. Let’s face it, if we don’t win this fight, the bugs will carry on here long after we have disappeared.

The authors would like to gratefully acknowledge the artistic skill and comedic genius of Dr Nick D. Kim for his contribution to the ‘James and Sarah’ cartoon created especially for this article.

**Further reading**


**Cartoon:** For further science cartoons see Nick D. Kim’s website: www.lab-initio.com/. Permissions: use of cartoons from this site is currently free for personal, non-profit, research and educational purposes - websites, lab-manuals, newsletters or any conventional publication. See more at: http://www.lab-initio.com/#sthash.jmb7ht6C.dpuf
Good germs, bad germs: citizen science and microbiology

Have you ever wondered about the bacteria that live on your chopping boards? How about those in your sink, or the murky depths of the plughole? And if so, were you thinking only about pathogenic ‘germs’, or also about the wider microbial communities that might persist in your homes? And how does such thinking sit with contemporary understandings of ‘good bacteria’, and the popular discourse that we might be ‘too clean’ for our own good? Taking advantage of recent developments in DNA sequencing, a citizen science project called Good Germs Bad Germs is exploring the ambiguously understood microbial ecologies found in peoples’ kitchens. Working with a small community of public participants, the project is concerned with the questions people ask about bacteria in their homes, and what happens when they work with scientists to find out the answers.

In recent years, scientists from many disciplines have begun working more closely with the public when conducting research. These ‘citizen science’ projects have multiple benefits, including their ability to collate vast datasets and to enthuse the public about the conduct of science. For some practitioners, involving the public in the conduct of scientific research is also an ethical imperative. But ‘citizen science’ is something of a catch-all term. It is used to describe a range of experimental practices that may differ significantly in the forms and depth of public engagement they permit. The riverine metaphors of ‘upstream’ and ‘downstream’ are often used to distinguish these
different types of citizen science. Downstream citizen science aims to educate and enthuse the general public about scientific inquiry whilst also collecting big datasets, and it does this through asking people to collect data according to preset protocols. Common examples of downstream engagement include wildlife surveys, like the RSPB’s Big Garden Birdwatch. By contrast, upstream citizen science aims to involve publics in shaping the goals, directions, and practices of scientific research. It is labelled ‘upstream’ because the public are involved at an earlier stage in the process. Rather than being educated by scientists (acting as the gatekeepers to knowledge), publics work with scientists to decide what questions to ask and how to ask them. While downstream citizen science is increasingly prevalent, especially given the communicative possibilities in a networked age, upstream citizen science remains somewhat rare in comparison.

The Good Germs, Bad Germs project is attempting to facilitate ‘upstream’ citizen science in the field of microbial ecology. It was inspired by recent ‘downstream’ citizen science experiments that have investigated bacterial communities living in the built environment. Led by a cast of high profile microbiologists including Rob Knight, Rob Dunn, Jack Gilbert, Holly Ganz and Jonathan Eisen (amongst others), such work has been enabled by the revolution in DNA sequencing that has made identifying the manifold bacteria in an environmental sample increasingly affordable. Those projects and others like them invited people to swab inside their houses (their kitchens, toilets, beds, clothes, phones and even their pets), their workplaces, and on transport vehicles. They then utilised DNA sequencing (especially 16S rRNA sequencing) to identify the types of bacteria present in each site. These various experiments have produced important and robust scientific findings, and using public participants as ‘data collectors’ has enabled cost-effective science whilst simultaneously educating and enthusing people. But they remain resolutely ‘downstream’.

The Good Germs, Bad Germs project takes citizen microbiology further upstream by asking the participants not simply to swab pre-defined sites, but to help design the experiments as well. The project group consists of the inhabitants of 14 households (all located within walking distance of a community centre in Oxford) working alongside a small team of social and natural scientists. It began by repeating an existing ‘downstream’ citizen science experiment, in which each household was asked to swab five common areas in their kitchens – a microbial ‘kitchen safari’. The aim for the first experiment was to introduce the participants to the technology, so that they might then shape the future experiments themselves. They were also given a sixth swab to sample somewhere they thought might be interesting, in a prelude of things to come. The swabs were processed using 16SrRNA sequencing, and the bacterial communities present in each site were characterized. The results were presented and discussed at a group meeting in the community centre, and the group then decided what they would like to explore in the next experiment.

There have been five rounds of these microbial experiments so far. In addition to their initial ‘kitchen safari’, the households have chosen to explore the bacterial communities on chopping boards, the effects of different cleaning products on microbial communities, and the changing microbial ecologies in fridges. In each round of experiments,
the participant group has taken more ownership of the experimental design, with the academic team shifting into a consulting role about what might or might not work given the vagaries of the microbiological technologies being used. In the most recent round, this devolution of experimental choice and design has proceeded the furthest, with each household selecting their own inquiry – from tracing the microbial signatures of their pets, to the microbi-ecological changes in kitchens concurrent with the introduction of Christmas trees.

Given the small sample sizes in these various ‘experiments’, especially the recent round, the aim is not to produce particularly robust scientific findings. Rather, the aim is to use upstream citizen science as a policy-relevant tool to investigate peoples’ understandings, practices and concerns. As a result, the crucial site in this work is not the kitchen or even the lab, but the group meeting where results are discussed and new experiments shaped. Through allowing participants to choose what to investigate, and through in-depth discussion of the findings (and their limitations), the project can identify putative public concerns that would remain obscure in traditional ‘downstream’ citizen science models. The project is thus using upstream citizen science not simply to ‘educate people’, or even to ‘educate scientists about people’, but to provide important insights into peoples’ hygiene practices and understandings in a world characterized by both ‘good’ and ‘bad’ microbes. After all, the public policy message has, for generations, been to vilify all germs; but increasingly, such messages are becoming less tenable.

Dr Jamie Lorimer is an Associate Professor in the School of Geography and the Environment at the University of Oxford. His research examines popular understandings of Nature and the politics of managing biological life. Past projects have crossed scales from elephants to microbes. He is the author of Wildlife in the Anthropocene: Conservation after Nature. He hopes to develop the research undertaken in the Good Germs project to enable citizens to participate in microbiology and to learn to think with microbes in other spaces, including inside the body. Email: jamie.lorimer@ouce.ox.ac.uk.

Dr Timothy Hodgetts is a postdoctoral researcher at the University of Oxford, working on the Good Germs, Bad Germs project. Timothy is interested in participatory forms of research that explore how people live with nonhuman organisms - from microbes to mammals - in their everyday lives. Email: timothy.hodgetts@worc.ox.ac.uk.

Further reading

- Bloomfield, S.F. 2016 In future we are going to have to view our microbial world very differently. Perspectives in Public Health. 136:4, 183-185
Interview

Flu under the spotlight

Influenza, or ‘flu’, is a common infectious disease that causes huge problems worldwide due largely to its constantly evolving nature. While most of the health burden of flu is caused by yearly seasonal epidemics, occasionally, new, more pathogenic strains can emerge, often from a non-human source such as birds or pigs. These new strains can cause pandemic spread of the disease, such as in the swine flu outbreak of 2009. To find out more about this complex virus, Helen Albert speaks to epidemiologist and flu expert Dr James Rudge from the London School of Hygiene & Tropical Medicine.

**James Rudge** is Assistant Professor Infectious Disease Epidemiology at the Bangkok branch of the London School of Hygiene & Tropical Medicine, where he has been working since 2009. He started his academic career at Imperial College London, where he completed a BSc in Microbiology and an MSc and PhD in Epidemiology. His research to date has focused largely on zoonotic diseases, with a particular interest in influenza. In particular, trying to understand the dynamics of transmission across different host species and how these may be influenced by different factors using a combination of field, mathematical and molecular epidemiology.

**What is your current research focus?**

The main reason we have a group based here in Thailand is that South East Asia is thought to be a hot spot for disease emergence and spread. For example, with lots of avian influenza (H5N1) circulating here, there is quite a lot of speculation that the next flu pandemic might emerge in this region. I've been involved in research on how prepared health systems are to cope with pandemic disease threats in the area and more recently I've been focusing particularly on influenza epidemiology in pigs, specifically in Cambodia.

**Why are bird and swine flu important and how do they influence the spread of flu in humans?**

These viruses are important from a human health perspective because flu viruses in birds and pigs are generally the precursors of new strains emerging in humans and this can then lead to pandemics. Birds in particular have lots of different sub-types of flu, many more than you actually find in humans, and sometimes these will cross the species barrier. For example, a bird flu virus will occasionally infect a pig or a human and might cause quite severe symptoms, but generally bird flu viruses are not well adapted for human to human transmission. What we've been seeing with Avian flu (H5N1) is that it sporadically spills over into humans, but it doesn't spread effectively between humans. However, an important feature of flu is that genes of different viruses of flu can combine together and mix together to create a new virus, which is known as genetic reassortment. Let's say you have a human who is infected with a typical human flu virus and then they also become infected with a bird flu virus at the same time. There is a risk that these two viruses might mix and reassort to generate a new flu virus that can then be more efficiently transmitted between humans. When that happens you might get what is known as an antigenic shift. In other words, it's a novel strain in humans that can transmit effectively between humans, but it's also a new strain so there is very little or no immunity in the human population for that strain. It can therefore spread very quickly and that's when you get a flu pandemic.

Pigs are interesting because they are quite susceptible to both bird and human flu strains and they also have their own flu viruses, so you might vaccinate birds within a certain area, or where you have the outbreak, but that can be more resource intensive than...
culling and culling is probably the most effective if you are going to try and stop the disease in its tracks.

It's difficult, particularly in countries like Cambodia. There are lots of back-yard farms and people may not want to report symptoms of bird flu to the authorities, because they know the government might come and cull all of their birds and maybe they won't be compensated for it. So that presents another challenge for surveillance of bird flu viruses.

**Are viruses from pigs more likely to spread to humans than those from birds?**

It's probably fair to say that, yes. At least, a few serological studies suggest quite high rates of exposure to swine flu viruses among pig workers. I don't think there is any really good empirical evidence of how often these jumps of viruses occur, from pigs to humans or from birds to humans. I think we probably identify them more often from birds to humans because they can be particularly pathogenic in humans. If a human gets a bird flu virus they might get quite different symptoms from normal flu and be at a high risk of death, whereas if they are infected with swine flu the symptoms can be quite similar to human flu symptoms. So it's possible to have the flu and not be sure if you have contracted a human flu virus or a swine flu virus. You have probably caught a human flu virus from another human, but if you work with pigs or you are in close contact with pigs you may have contracted a swine flu virus. Pigs are also quite susceptible to human flu viruses. With the last pandemic, it emerged from pigs and then it was spreading effectively through humans, but there were then quite a few events of that virus going back into pig farms as well.

**How do different farming systems influence the prevalence and diversity of different forms of the flu?**

I think it's a really important question and is something we are trying to understand. Farming systems are undergoing really rapid changes at the moment. If you look at Asia, where rapid economic development and population growth has led to a big increase in demand for meat products and meat consumption, that's causing a livestock revolution, with a shift from traditional back-yard systems to more intensive livestock production systems. We really want to understand how this shift in farming practices could influence disease risk. Is it going to create a bigger risk of pandemics occurring? On the one hand you might expect more smallholder, rural farms to provide good conditions for lots of different flu viruses mingling together, because you might have lower bio-security and lots of different species sharing the same spaces on that farm. You'd also expect these farms, looking at parts of South East Asia, to have paddy fields and be doing rice cultivation. This attracts ducks and they are also an important reservoir for flu viruses. So these kind of traditional or extensive back yard systems could create conditions where lots of flu viruses could mix together. On the other hand, with more intensive or industrial farms you have much more densely packed, more genetically homogeneous livestock so this also creates quite good conditions for flu viruses to spread. Probably the riskiest situation is one where you have a combination of these different farming systems in the same area that are connected through trading of livestock between the different farming systems. To date, there have been not many empirical studies specifically aiming to test these hypotheses. What we are currently doing in Cambodia is looking across the different types of pig farming system, and looking at different stages of the process, for example, at slaughter houses, and trying to see how these different practices may affect flu ecology and diversity.

**In what sense is flu an emerging disease?**

It's emerging in the sense that there are lots of different types of flu virus circulating in animals as well as in humans and these are constantly mutating and changing due to genetic reassortment. This can lead to new flu viruses emerging that might have a different range of hosts to those from their parent viruses. These viruses might also have quite different features in terms of how pathogenic or how severe they are when they infect a human. So in that sense they are emerging because their host range and their pathogenicity keeps changing.

The flu virus changes in two main ways, you've got antigenic drift, which is just gradual mutation. With flu, different strains mutate quite quickly and this causes the seasonal flu epidemics we see each year. That is, you have a slightly different strain that's mutated from the ones
that were circulating last year. However, antigenic shift is when you have two different viruses mixing, such as those from pigs and birds, and that creates a new and (potentially) very different virus to those humans have previously been exposed to.

Generally, with seasonal flu it's fairly predictable how pathogenic it's going to be, as its roughly the same every season. But with pandemics there is the potential for it to be more pathogenic, partly because we won't have any, or very little, cross immunity from previous flu strains, but also because that virus itself might have certain genetic traits that make it more pathogenic in humans. But, it's unpredictable. With the last pandemic the pathogenicity wasn't particularly different from what we typically see in seasonal flu strains.

**What is the difference between the different types of flu?**

Type A is the one which is probably the most important in that you find it in animals such as pigs and birds, as well as in humans, so this is the one that is important in terms of flu being an emerging disease. It's the type that can cause flu pandemics and well as seasonal flu epidemics.

Type B is only really found in humans. It also causes seasonal flu, but it doesn't lead to pandemics, because it doesn't have these animal reservoirs that act as a source of new genetic variation for the virus.

Influenza type C is generally less common and usually has milder symptoms than A or B, but it can still cause outbreaks in humans. I think it's also found in pigs, but there is less known about it than the other two types. Generally, we know it usually causes milder symptoms and that the animal reservoirs are less important.

**How much is individual response to flu linked to a person's immune system and how much to the type of flu?**

That's a good question. I think it's fair to say that with seasonal flu epidemics, the response tends to be related to the host characteristics. In other words, those at risk of having severe flu symptoms tend to be the elderly or the very young or those with underlying medical conditions. So generally it depends on age and your overall health and immune system. That's the case with typical seasonal flu, but it can also depend on the virus. As I mentioned, type C tends to have less severe symptoms than A or B. Also, with a new pandemic virus it can be difficult to predict which age groups might be most at risk of severe disease. With the last pandemic it was a case of the elderly or very young being most affected, as with seasonal flu. But when we had the big Spanish flu pandemic in 1918, which killed something like 3-5% of the world’s population, young adults were particularly hard hit. So it's unpredictable.

**How do different countries prepare for future influenza (or other disease) pandemics?**

It's very difficult to predict what the next pandemic will be, how severe it will be, or when it will occur. To of course it's important to have plans and strategies in place. For example, in terms of how your resources will be allocated and mobilised at different stages of a pandemic and for different types of scenario to cope with the influx of patients that your health system is going to see. But you also need to make sure that these plans take into account health system resources in the country or region, such as the number of beds that can feasibly be made available, while still maintaining core functioning capacity. You can run simulations, through mathematical models, or also using workshops that are designed to stress test your health system and your pandemic preparedness plan.
Another key thing I would say is that countries need to ensure that they have the necessary measures and ethical frameworks in place to make sure that as soon as they have detected the first signs of a pandemic, they can set up clinical trials for treatments or vaccine preparation. It's important to have ethics approvals ready to go in order to quickly get an idea of what kind of virus and what kind of scenario they are dealing with. Then plans for dealing with the outbreak can be adjusted accordingly.

Effective strategies for communicating with the media and the public are also obviously important. Stockpiling antiviral drugs, when we are talking about flu, can also be important. This is something that countries do, although this is a bit of a controversial area because there is some uncertainty as to how effective the current antivirals we have are for flu treatment and prevention. Also, antiviral stockpiles need renewing because drugs expire, so if you don't have a pandemic for several years or even decades, then maybe the public won't necessarily be very keen on continuing to stockpile in that way.

Is there any way of predicting pandemics?
I don't think at this stage we can predict when or where the next pandemic will come. Flu pandemics occur on average every 30 years, but the period between pandemics can be much shorter than that or much longer, so it's very variable. In terms of predicting what kind of scenario we may be looking at, we can look at past flu pandemics to see what the ranges or parameters were in terms of what the fatality rate could be or what the geographical range could be. In that sense we can make slightly educated estimates, but in an interpandemic period there are limits to what you can accurately predict about the next event. You can just do your best to make sure you detect an emerging threat as soon as possible.

What do you think are the top emerging diseases around the world at the moment and why?
A key threat we know will present a huge challenge in the future is influenza. Obviously I'm slightly biased, but we do know that it will cause another pandemic, we just don't know when. And we do know that it will be a global threat and it will potentially have huge economic and public health consequences.

Antimicrobial resistance is another threat, obviously I'm not picking a specific disease there, but antimicrobial resistance is an emerging problem. It's a huge threat that we are already facing and that's only going to get worse. We are quickly running out of antibiotics that can effectively treat a number of serious infections. This means that even what we see as low-risk medical procedures now could become more dangerous.

To a certain extent, this depends on what you class as an emerging disease. Ebola virus is emerging in that it re-emerges every now and again and then you won't see an outbreak for a while, but we know it can come back. A disease like that can pose a much more serious threat to countries with much more fragile health systems, or much poorer populations, where you don't have the health system resources to effectively and quickly contain an emerging outbreak. Those kind of emerging diseases may not present a particular threat to developed countries but are still a huge threat for developing countries.

Things like climate change could potentially affect vector borne diseases quite substantially. For example, it could increase the geographical range of the mosquito vector of the disease and then the disease could be classified as an emerging threat in the new area.

Then of course there are the unknown threats. There isn't much surveillance in wildlife populations so it's hard to know what's lurking in bats in remote jungles of Asia, for example, that could potentially cross into humans and then go onto cause a severe outbreak or pandemic.

I think we need to have more surveillance and understand better the ecology of infectious diseases in animal reservoir populations in both livestock and wild animals and try and understand what factors can lead to these diseases becoming an emerging infectious disease threat in humans.

Further reading

- NHS website – swine flu (H1N1) webpage - http://www.nhs.uk/conditions/pandemic-flu/Pages/Introduction.aspx
- James Rudge – Current Projects
  - LSHTM South East Asia Research Network - Determination of the association between livestock systems and influenza prevalence and diversity in swine, Cambodia (PigFluCam) http://www.searn.org/cdprg/projects/pigflucam-2/
  - LSHTM Molecular Epidemiology of Influenza in Bali, Indonesia (BaliMEI) http://www.cdprg.org/balimei.php
Young scientists quiz key political figures on science policy topics

How will legislation on genetic engineering, cloning and animal experimentation change once the UK leaves the EU? What roles do scientific advice and public opinion play when considering policies where these viewpoints might oppose one another – for example the banning of GM crops? How will the merger of the nine current UK Research Councils into the new UK Research and Innovation affect the funding and delivery of novel research? These are just a few questions that were asked at this year’s Voice of the Future event in Parliament.

Voice of the Future is an annual event organised by the Royal Society of Biology on behalf of the science and engineering community, where young scientists from all over the country take the seats in a Committee room at the Parliament and question MPs and other Government officials on science policy topics.

This year the event involved Jo Johnson MP (Minister of State for Universities, Science, Research and Innovation), Chi Onwurah MP (Shadow Minister for Industrial Strategy, Science and Innovation), Professor Sir Mark Walport (Government Chief Scientific Advisor), Stephen Metcalfe MP (Chair of the House of Commons Science and Technology Select Committee), and his fellow Committee members, Dr Tania Mathias MP, Carol Monaghan MP and Matt Warman MP, acting as witnesses.

The Biochemical Society was represented by six bright young scientists: Alexander Cowley, PhD student at Exeter Medical School, Sarah Palmer, a PostDoc at the University of Glasgow, Nicola Payton, PhD student at Manchester Metropolitan University, Andrew Quigley, a PostDoc at the University of Oxford, Robin Rumney, a PostDoc at the University of Southampton and Hannah Sutcliffe, a PhD student at the University of Edinburgh.

Diversity in science was a topic touched upon during all four panel discussions. Chi Onwurah MP said it was crucial that all scientists dedicated a part of their time to inspire the younger generation, particularly girls. The value of STEM ambassadors and role models was highlighted in this respect. When it came to discussing the diversity further down STEM pipeline, Carol Monaghan MP added that there was an expectation that working in science meant unsociable hours - options like job sharing, which are common in other areas, needed to be considered.

Our member Andrew Quigley had the opportunity to ask what the Government could do to further encourage commercialisation of university research. Jo Johnson MP responded that expansion of knowledge is a valuable exercise in itself, and added that the new Industrial Strategy and formation of UK Research and Innovation (UKRI) will make research commercialization easier.
Mark Walport, who had newly been appointed as the Chief Executive of UKRI, said having the overarching body will make the whole greater than the sum of its parts and ensure ‘interdisciplinary research doesn’t fall through gaps’.

Hannah Sutcliffe asked Sir Mark how the Government should prepare for the ethical challenges associated with emerging genetic technologies, such as genetic discrimination by potential employers or health insurers. Sir Mark said that it was important to understand that genetic modification wasn’t a good or a bad thing in itself, as it was all about the context in which it was applied. Two sides of the argument were discussed: research that may challenge people's personal values, such as embryo research or research involving animals, and research that could alter the insurance market, by disclosing a person’s susceptibility to a particular disease. A good example of politicians addressing emerging technologies was mitochondrial DNA donation in 2015, which was debated and voted on at both Houses of Parliament before it could be implemented. Following this, in March this year researchers in Newcastle were given the first UK licence to carry out mitochondrial donation treatment. Sir Mark added that public engagement and effective regulation were key to preparation for the ethical challenges associated with emerging genetic technologies.

No science policy event can go without a mention of Brexit these days. The impact of Brexit on UK science was picked up by several young researchers: from potential changes in EU legislation to the Government’s plans to ensure that vital collaboration and communication will continue with European colleagues. To the latter, Jo Johnson MP replied by saying that the Government had been clear that European partners are valued and he hoped that collaborations would continue in years to come.

The Science & Technology Committee was also asked for their views on the fact that at the time of the event, the Department of Exiting the EU was one of the only Government Departments which didn’t have a Chief Scientific Adviser appointed. The Committee said that this was of concern and they had already raised it with the Department of Exiting the EU. However, they added that the Department was open to the Committee bringing scientists to them instead to ensure the science community has a way to feed into the discussions.

Carol Monaghan MP added that the brain-drain due to Brexit had already started and it was concerning that, in her view, there didn’t seem to be any measures that the Government was taking to stop it.

After the event, Alexander Cowley said: “The views of the Chief Scientific Advisor, Sir Mark Walport, in relation to ethics around genetic research were particularly interesting. I also found it useful to have the opportunity to network with other attendees from different Societies. Even though our specific disciplines may have been different, our common love of STEM subjects was enough to stimulate discussion.” Sarah Palmer added: “It was a great opportunity to hear MPs and the Chief Scientific Advisor answer questions about science policy and advising the Government. With uncertainties surrounding Brexit it was encouraging to hear such support for STEM research directly from MPs. This unique experience has encouraged me to get more involved in science policy in the future.”

We are pleased to be able to provide our young members with such a great opportunity to experience science policy first hand and look forward to next year’s event.

If you're interested in getting more involved with the Society's policy activities, why not join our new Policy Network! Contact science policy officer Gabriele Butkute gabriele.butkute@biochemistry.org for more information and to join.
Get creative – a look at public engagement activities

James Brown
(Education and Public Engagement Officer, Biochemical Society)

One of the most enjoyable parts of my job is the opportunity to visit numerous science fairs, museums, and festivals across the country and look for inspiration from the varied exhibitors who populate these events. There’s no shortage of places to look for ideas and in just the last three months I’ve been able to fist-bump a robot, put my beating heart in a jar, play scientific “Guess Who”, make a fluorescent kaleidoscope, look at zebra fish embryos using a homemade microscope, edit my own genome bracelet, make an origami virus, identify malarial red blood cells using a magnet and model fluorescing cells using only glitter and glue.

I’m always amazed at the ingenuity and creativity of other peoples’ activities; in contrast I often find it really hard work to come up with ideas. I know I’m not alone – one of the most common questions I get asked is how to come up with ideas for public engagement activities. I wish I had a better answer, but the reality is that the best way to become inspired is to spend time looking at what others are doing and see what is adaptable to your purposes. There’s no point re-inventing the wheel when there are so many tried and tested activities out there in circulation. So, in the spirit of sharing best practice, I thought I’d share a few examples of the best public engagement activities I’ve come across in the last few months.

UV Kaleidoscopes

Led by professional artist Isobel Manning with the support of Crick researchers, this is a hands-on activity which uses ultraviolet light and fluorescent materials, find out how scientists use light to reveal structures and patterns that are normally impossible to see with the naked eye. By the end of the workshop you get to take home your very own fluorescent kaleidoscope inspired by microscopic images of the human body. The combination of arts & crafts and science makes for an activity that will engage the young and old, as you can see from the kaleidoscope I spent far too long making.

Homemade smartphone microscope

I first saw this activity being run by a team from CRUK, but there are plenty of different versions out there; the Royal Society have one entirely made from cardboard that they call the zoom box. These are pretty easy to make and require a small lens, the one from the front...
of a cheap laser pointer tends to work well, and a simple stand to hold your phone steady. This picture shows a zebrafish embryo on display at the Crick Lates event. This is a great activity to show people that you don’t need a lot of expensive equipment to do science at home.

**Heart of maker faire**

At the 2017 Maker Faire UK, the team at NUSTEM (Northumbria University) created the "Heart of Maker Faire", an interactive art installation piece which brings together biology, electronics, coding, engineering and physics. More than 450 people contributed a little piece of themselves, writing a note about something that was in their heart on the day and sealing it inside a jar. They measured their heart rate, then added their jar to the shelves above a set of lights which beat at their heart rate.

The Heart of Maker Faire - each jar beating at a different heart rate. Photo by Jonathan Sanderson. See it in action at https://NUSTEM.uk.

**DNA Dave: the Transcription-Translation Machine**

The SAW education trust and OpenPlant synthetic biology research centre have together used a Biochemical Society Scientific Outreach Grant and the OpenPlant to create ‘DNA Dave: the Transcription-Translation Machine’. This particular activity focuses on the process of taking instructions from DNA to make diverse end products. The details of this are difficult to explain to a general audience and so they developed a Transcription & Translation Machine where people can follow the process by turning over flip cards and then taking puzzle pieces from buckets that represent the different stages from signals to promoters to protein-coding sequences. These are then fed into a machine to transcribe and translate into proteins as final end products. This activity provides the perfect stepping stone to enable visitors to explore the way synthetic biology can make use of parts of this biological system to make biomolecules and high value chemicals in plants in more sustainable and efficient ways.

**Playing with a robot**

The Science Museum’s Robots exhibition includes a cute little robot called Poppy who tells you a story which requires you, at key moments in the narrative, to hold hands, pat her on the head, and even give her a fist-bump. Despite being little more than a fancy iPad, it’s an interesting look at how we interact with technology.


**Soapbox science**

Soapbox science is a public engagement project which promotes women in science and the work they do. This year, the Biochemical Society funded the Yorkshire’s first Soapbox Science event, Soapbox Science Hull 2016. It featured 12 leading female scientists from University of Hull and East Yorkshire Hospitals NHS, ranging from PhD students to professors, engaging passers-by in scientific discussion. Topics included the location of galaxies, lab-on-a-chip, cancer biology, invasive
species, biofuels, and medical engineering. Despite some inclement weather, they managed to engage with nearly 800 visitors over a three-hour period. Soapbox science events are popping up all over the world and are a simple yet effective way to take your research onto the street.

Scientific Scissors

The Biochemical Society’s latest activity is all about genome editing: what is it, how does it work, what can it do, and what are the ethical questions involved? Participants get to explore some of the applications of these technologies and have a go at our ‘Genetic Jenga’ game – how many genes can you knock-out before the genome becomes too unstable?

Sliced Bread Pod

The Best Thing Since Sliced Bread? is a new podcast that investigates the bold claims being made by promising products. Joined by experts and the general public, Greg Foot and his mate Andy go in search of the evidence to find out if these wonder products really are the best thing since sliced bread? Podcasts are a great way to reach a wider audience and there are plenty of science themed podcasts to choose from; the Microbiology Society podcast and the Naked Genetics podcast are particularly worth a listen.

The Society’s Scientific Outreach Grants offer up to £1000 for outreach, public engagement and education based activities. The next round opens on 26 June with a deadline of 22 September; apply on our website: http://biochemistry.org/grants.
Christopher James Caunt (1976–2017)

We are sad to report the untimely death of Dr Christopher James (Jim) Caunt on the 6th of January 2017. Jim obtained his BSc in Cellular and Molecular Pathology at the University of Bristol in 1997. He then completed his PhD in Molecular Immunology at the University of Sheffield before returning to Bristol in 2002 as a postdoctoral research fellow in the laboratory of Professor Craig McArdle. Initially working on signalling downstream of gonadotrophin-releasing hormone receptors, it was during this time that Jim developed a keen interest in the spatiotemporal regulation of mitogen-activated protein kinase (MAPK) signalling. In 2010, Jim accepted a lectureship in the Department of Biology & Biochemistry at the University of Bath, where he continued to work on the regulation of the Ras-MAPK pathway and, in particular, the role of protein phosphatases in shaping the biological outcome of signalling.

Jim was an excellent laboratory scientist with a creative and rigorous approach to problems. He rapidly developed a portfolio of molecular genetic tools and combined these with the use of high content microscopy in order to visualise and quantitate changes in MAPK signalling activity. This allowed Jim to make important predictions as to biological outcome, particularly in cancer cells where MAPK signalling is abnormally activated. Jim published over 40 papers spanning original research and including several highly influential and highly cited reviews. In Bath, Jim threw himself wholeheartedly into building his laboratory. He was a passionate and highly committed undergraduate lecturer and a patient and thoughtful PhD supervisor. Several of us have benefited from Jim’s skill as an undergraduate mentor and research talent spotter, with students passing through Jim’s lab going on to complete successful PhDs. Jim was also an enthusiastic and dedicated chair of Biochemical Society Research Area V (Signalling), where he helped to broaden and diversify its membership whilst actively nurturing the development of a large number of scientific meetings. In particular, Jim organised a very successful conference on “Phosphatases and Signalling in Health and Disease” which was held in Bath in the summer of 2016 and was a scientific contributor to “Pseudoenzymes” in Liverpool later that year. Jim’s work at the society was typically generous, supportive and caring and members will remember the tireless hard work that Jim put into various (often unrewarding) roles. The work of Research Area V will continue in his memory and Jim will be missed by all at the Biochemical Society who were lucky enough to spend time with him.

Those of us who worked and collaborated with Jim will remember a boundless and joyful enthusiasm for science, coupled with an easy charm, sharp wit, good humour and grace that profoundly affected all of those who knew him. Conversations, which started around matters scientific, would invariably digress into other areas of mutual interest such as music, food, the great outdoors, film, politics and the wider world outside the lab, often driven by his slightly mischievous sense of humour. Jim had huge generosity of spirit and consideration for others and these qualities will ensure that Jim’s legacy is wider than the many scientific achievements and publications in his sadly all too short academic career.

Lastly, Jim was married only last year to his long-term partner Lindsay and our thoughts are with her, Jim’s parents, brothers and sister at this most difficult of times.

Stephen M. Keyse (University of Dundee)
Craig A. McArdle (University of Bristol)
David Tosh (University of Bath)
Simon J. Cook (Babraham Institute, Cambridge)
Patrick A. Eyers (University of Liverpool)
Biochemical Society 2018 Award Winners

Anastasia Stefanidou (Communications Officer, Biochemical Society) and Rowena Mitchell (Membership Manager, Biochemical Society)

Eleven eminent scientists and exceptional early career researchers have been honoured in the annual Biochemical Society Awards.

The Biochemical Society Awards recognize excellence and achievement in both specific and general fields of science from established researchers, as well as scientists in the early stages of their career.

Professor Colin Bingle, Acting Chair of the Awards Committee, said: "The Biochemical Society Awards are the perfect way to honour exceptional scientists within the bioscience community. As ever, the entry criteria are tough and the standards high and the awards are a real tribute to the talent within our community. On behalf of the Society, I'd like to congratulate the winners, all of whom have made outstanding contributions in their fields. Well done."

Centenary Award

The 2018 Centenary Award will be presented to Frank McCormick from the University of California San Francisco Helen Diller Family Comprehensive Cancer Center. McCormick has been a leader in the field of RAS oncogene function and regulation for over 30 years, having made a large number of seminal discoveries about the signalling pathway regulated by the RAS protein. His identification of RAS GAP marked the start of the rush to understand the regulation of RAS proteins and their normal role within the cell. With the identification of the NF1 protein as a member of the GAP family this led to fundamental understanding of Neurofibromatosis type I. McCormick has also contributed very important observations about the downstream pathways regulated by RAS, including the RAF/MAPK pathway and PI3K signaling. McCormick has also been hugely influential outside of his own lab, he founded ONYX Pharmaceuticals, a company dedicated to developing new cancer therapies. In addition to all this, he has also been President of the AACR and made many other contributions to the cancer research community at the highest level.

McCormick said: "I am absolutely thrilled to receive this award. It means a great deal to me to be recognized by my peers, especially as I was trained as a biochemist in the UK and attended many outstanding Biochemical Society meetings in which I made connections and gained new insights that have affected my entire career."

Colworth Medal

In 2018 the Colworth Medal will be awarded to Matthew Johnson from the University of Sheffield. A plant biologist with an interest in photosynthesis and respiration, Johnson’s research focuses on the organization and adaptability of thylakoid membranes, which house several major pigment-protein complexes involved photosynthetic electron transport including photosystem II, cytochrome b6f, photosystem I and ATP synthase. A major accomplishment of this work has been the development and application of affinity-mapping atomic force microscopy, which uses a specially functionised probe to ‘recognise’ only a specific type of protein in the membrane. Using this new technique, Johnson discovered novel plastoquinone diffusion nanodomains that facilitate electron transport between photosystem II and cytochrome b6f complexes in spinach thylakoid membranes. This discovery explains how plants avoid a diffusion limitation of electron transport in the severely protein crowded membrane, ensuring the efficiency of photosynthesis.

Johnson commented: "I'd like to thank the Biochemical Society for awarding me this prestigious honour. It is incredibly humbling to be recognised alongside the many great scientists who have previously won the award, including Sir Hans Kornberg, a personal scientific hero of mine. I would also like to acknowledge the inspirational senior scientists who have mentored me and the hardworking students who have supported my work. Without their encouragement and dedication this achievement wouldn't have been possible."
GlaxoSmithKline Award

The 2018 GlaxoSmithKline Award will be awarded to Anne Bertolotti from the Laboratory of Molecular Biology of the Medical Research Council in Cambridge. Bertolotti discovered major components of protein quality control systems in cells. These systems represent the cellular defence against misfolded proteins that accumulate in devastating diseases, such as Alzheimer’s, Parkinson’s or Huntington’s disease.

Bertolotti has made outstanding contributions to our understanding of the molecular mechanisms underpinning neurodegenerative diseases and discovered strategies to enhance protein quality control systems for possible treatment of neurodegenerative diseases. One of the strategies consists of selective inhibition of a phosphatase, an important discovery because phosphatases were thought to be undruggable. The discovery of selective phosphatase inhibitors from Anne’s lab represents a huge advance for basic and medical science with a transformative potential for a group of diseases for which no treatment exists so far.

Bertolotti said: “The award came as a surprise, on an early morning whilst I was visiting a dear friend and colleague in San Francisco. It is a great honour to join the list of distinguished awardees and a wonderful feeling to have our work recognized in this way. The work recognized by the award is the result of a team effort and my heart is with my lab members, past and present who have fearlessly joined me to explore the unexplored.”

Industry and Academic Collaboration Award

The inaugural Industry and Academic Collaboration Award will be awarded in 2018 to Stefan Knapp from the Institute of Pharmaceutical Chemistry, the Buchmann Institute for Molecular Life Sciences at Frankfurt University as well as at the Structural Genomics Consortium at Oxford University. His research team made a major contribution to the understanding of structural mechanisms regulating signalling molecules such as protein kinases, phosphatases, acetylation dependent reader domains of the bromodomain family and the exploitation of this knowledge for the development of highly specific inhibitors. In the framework of a large collaborative network involving many academic research groups and industry he pioneered the development of protein interaction inhibitors targeting bromodomains that function as lysine acetylation dependent reader domains of the epigenetic code as well as highly specific allosteric inhibitors modulating kinase function.

Knapp remarked: “I am extremely honoured and delighted to receive the 2018 Biochemical Society Industry and Academic Collaboration Award. I would like to use this opportunity to thank the outstanding team of scientists in academia and industry that I had the privilege collaborating with.”

International Award

The inaugural International Award will be awarded in 2018 to Job Dekker from the Howard Hughes Medical Institute and the University of Massachusetts Medical School in the US. Dekker introduced the concept that matrices of chromatin contact frequencies can be used to determine the three-dimensional structure of chromosomes. Following this, he invented the chromosome conformation capture (3C) technology to obtain such matrices and solved the first structure of a yeast chromosome in 2002. Since then his group has pioneered development and application of a series of molecular, genomic and computational approaches, such as 5C and Hi-C to map and analyze the three-dimensional folding of genomes at Kb resolution. His work had led to new insights into the internal organization of chromatin fibres, the formation of chromatin looping interactions involved in long-range gene regulation, the organization of the interphase nucleus, the structure of metaphase chromosomes, and the general folding principles of complete genomes. Recently Dekker’s group has started to use 3D genome folding data for de novo genome assembly.

Dekker commented: “I am truly delighted to have been selected for the International Award. This really honours the work of all my team members, collaborators, and colleagues that is starting to reveal how our genomes are folded.”
Keilin Memorial Lecture

The 2018 Keilin Memorial Lecture will be given by Neil Hunter, who holds the Krebs Chair of Biochemistry at the University of Sheffield. Hunter’s research on energy and electron transfers in microbial photosynthesis recently culminated in a complete structural and functional description of an energy-transducing membrane, from collecting sunlight to charge separation, quinone migration, generation of a proton gradient, and finally catalysis by the ATP synthase. Hunter has also made major contributions to understanding the biogenesis of the haem, bacteriochlorophyll, chlorophyll and carotenoid cofactors, and their assembly into energy, electron and proton transfer complexes.

Hunter said: "I am delighted and honoured to be the recipient of the Keilin Medal and Lecture, particularly because I join a list of eminent recipients of this award. I would like to thank past and present members of my research group and my many collaborators for their contributions over the last 33 years."

Morton Lectureship

In 2018, the Morton Lectureship will be awarded to Michael Wakelam from the Babraham Institute, Cambridge. Wakeham’s research focuses upon understanding the role and regulation of lipid signalling pathways in inflammation and cancer and his lab has a major focus upon the use and development of lipidomics methodologies in determining the functions of individual lipid molecular species. His work to develop ways of assessing the acyl-chain composition initially using HPLC and TLC techniques and subsequently with mass spectrometry were amongst the first to allow molecular analysis of lipid sidechains. These studies permitted the understanding of how these critical parts of the lipid molecule contribute to cellular function. Wakelam’s group have produced an extensive body of work describing the regulation, behaviour and cellular functions of phospholipase D. Wakelam also identified how small GTPases such as Ras regulate phospholipase C enzymes, and his lab have continued to produce an important portfolio of work detailing how this family of enzymes is regulated. Wakelam is also expert at lipidomics of phosphoinositides, important signalling molecules that cannot be studied easily by conventional mass spectrometry. Wakelam’s expertise in lipidomics has allowed several high-profile collaborative studies to be achieved, in both basic and translational research that have informed our understanding of lipid metabolism in cancer and PI 3-kinase signalling in health and disease.

Wakelam remarked: “I am delighted and surprised to have been awarded the Morton Lectureship by the Biochemical Society. I am extremely grateful for the efforts of the many excellent scientists who have contributed to the success of my laboratory over the years. Additionally, I am proud to join the list of great lipid scientists who have been previous recipients of this award.”

Novartis Medal and Prize

The 2018 Novartis Medal and Prize will be awarded to Laurence Pearl from the University of Sussex. Pearl has made significant contributions to our understanding of the biochemical and structural basis for assembly, specificity and regulation of the proteins and complexes that carry out DNA repair and DNA damage signalling, signal transduction, and chaperone-dependent protein activation. His work exemplifies an integrated multidisciplinary approach in which biochemical, structural, genetic and cell biology techniques are combined to address questions of biological function, and wherever possible, translated to the discovery of new small molecule therapeutics for the treatment of human diseases.

Pearl said: "I’m delighted and amazed by this award and overawed to be in the company of the previous recipients, which includes so many scientists who have inspired me throughout my career. I’ve been incredibly lucky with the clever and determined people who’ve come to work with me over the years, and our international network of collaborators. We are deeply indebted to Cancer Research UK and the Wellcome Trust for their generous long-term support which has given us the space to ask really interesting and difficult questions.”
Teaching Excellence Award

The inaugural Teaching Excellence Award will be awarded in 2018 to Dee Scadden from the University of Cambridge. Following a successful research career that made a significant contribution to understanding the role of adenosine deaminases acting on RNA (ADARs) and RNA editing in mammalian cells, Scadden has recently focused on developing innovative online teaching tools that aim to support learning within various undergraduate courses in Biochemistry. Use of such resources will increase access, engagement and flexibility for students beyond the conventional classroom, thereby enhancing teaching and learning. They will also provide opportunities for academics to explore new teaching styles to enrich learning.

Scadden commented: “I am absolutely delighted to receive the Teaching Excellence Award, and am grateful to my colleagues for their support. The opportunity to engage closely with students and to develop teaching resources that support and encourage learning is a real privilege.”

Early Career Research Awards

Cells

The 2018 Early Career Research Award for Cells will be awarded to Yasin Dagdas from the Gregor Mendel Institute-Vienna. His work on perturbation of selective autophagy by the Irish potato famine pathogen provided crucial insights on selective autophagy in plants. At the Gregor Mendel Institute, he is combining evolutionary analyses with mechanistic tools to dissect selective autophagy at a cell type specific resolution.

Dagdas said: “I am very pleased, honoured and humbled to receive this award. I owe this award to my amazing mentors Sophien Kamoun and Nick Talbot and to the colleagues in their labs. I also would like to thank the Gatsby Charitable Foundation and the Halpin Trust for supporting my research at The Sainsbury Laboratory and University of Exeter, respectively.”

Molecular Structure and Function

The 2018 Early Career Research Award for Molecular Structure and Function will be awarded to Wojciech Galej from the European Molecular Biology Laboratory, France. Galej has made outstanding contributions to the understanding of the molecular mechanism of pre-mRNA splicing through his structural analysis of the spliceosome and its component using X-ray crystallography and cryo-electron microscopy. He determined the crystal structure of the Prp8 protein, the largest and most conserved protein in the spliceosome. This protein plays crucial roles in organising the RNA catalytic core of the spliceosome and its structure also provided important insight into the evolutionary origin of the spliceosome. Galej played a key role in the structure determination of the fully assembled, 44-subunit catalytic spliceosome using single particle cryo-electron microscopy single particle analysis. This work has contributed enormously to the understanding of the structure and function of the spliceosome.

Galej commented: “I am absolutely thrilled and honoured to receive this award. What makes me particularly happy is that my research was recognized and appreciated by the Awards Committee. I am very grateful to my PhD advisor and a long-time mentor Dr Kiyoshi Nagai and all my colleagues at the MRC Laboratory of Molecular Biology for their continuing support.”
Meeting Reports

Carbohydrate Group 50th Anniversary and Haworth Medal Award Conference

31 October – 1 November 2016, University of Warwick, UK

The Royal Society of Chemistry Carbohydrate Group, supported by the Biochemical Society, held a meeting to both celebrate the 50th Anniversary of the Carbohydrate Group and to celebrate the award of the Haworth Memorial Medal; the most senior prize which the group awards.

The highlight of the conference was a plenary lecture by Professor Sir Fraser Stoddart, who in addition to being the recipient of the Hawworth Memorial Prize, was also the 2016 Nobel Prize Winner for Chemistry. This was the first lecture he gave after the prize was awarded, which was a real privilege for all attendees.

Over 115 people attended and there was a vibrant mix of academics, industrialists, and early career researchers from a diverse range of fields, united by an interest in glycoscience. In addition to Professor Stoddart, the meeting had speakers including 2 x FRS (Ben Davis and Harry Gilbert) and many more world leaders in their fields.

Matthew I. Gibson (University of Warwick)

ROS and mitochondria in nervous system function and disease


Reactive oxygen species (ROS) are both friend and foe, damaging at high levels but also crucial as signalling molecules. Mitochondria, the main source of ROS, are their partners in crime. Neurons, as energy demanding cells, are particularly rich in mitochondria. The aim of this Biochemical Society Focused meeting was to discuss the relationship between ROS, neurons and mitochondria in a single forum. ROS and mitochondria have recently emerged as key regulators of homeostatic signalling pathways. Mis-regulation of these pathways have been implicated in diseases of the brain including Parkinson’s, Alzheimer’s, Huntington’s and Amyotrophic Lateral Sclerosis.

The meeting was very successful in exploring both the physiological response to ROS, as well as the protective responses to the damaging effects of ROS in disease contexts. New roles for mitochondria were also a hot topic. An emerging concept from the meeting was the role of mitochondria as a cellular signalling hub with ROS being the medium of communication. The idea of mitochondrial signalling in neurological diseases was a topic of animated discussion. Overall, one of the very successful features of the meeting was the mix of basic and clinical research. This resulted in a synergy between participants, whose varied perspectives provided new insight. We would like to thank all the participants and the meeting sponsors Abcam, Agilent, Labtech, Bioloegend and the Welcome Trust for making this a timely and scientifically excellent meeting.

Joseph Bateman (King’s College London)

Using e-learning to improve student engagement in the biosciences: a workshop for HE educators


This one-day training event was a valuable opportunity for HE educators to meet and share their experiences of using various e-learning methods.

The morning consisted of talks on applications of e-learning, highlighting some key technologies. Peter Alston (University of Liverpool) shared examples of using e-learning to great effect with large cohorts of students and Pam Scott (University of Glasgow) demonstrated how apps can be a powerful tool for learning in University departments.

In the afternoon hands-on sessions, attendees could try some tools themselves, including virtual labs with Gus Cameron (University of Bristol). Many of the ideas shared were applicable to everyday challenges in HE, including using simple computer programmes to speed up marking (Peter Klappa, University of Kent) and giving students personalised audio feedback on their work (Luciane V. Mello, University of Liverpool).

Attendees were very positive about the day and went back to their students with many new ideas to try.

Helen Watson (Plymouth University, UK)

Meeting Reports

ROS and mitochondria in nervous system function and disease


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Joseph Bateman (King’s College London)
Local Ambassador Focus - Caroline Smith

Caroline Smith is a Course Leader for the Biological Sciences program and Learning and Teaching Coordinator for the Department of Life Sciences at the University of Westminster. She recently became a Senior Fellow of the Higher Education Academy and is a Senior Lecturer in Biochemistry. Her undergraduate degree was in Medical Biochemistry at the University of Surrey and she studied for a collaborative PhD at Cornell University Medical College which was awarded by University of Surrey. She worked as a post-doctoral Research Fellow on a British Heart Foundation program grant at University College London for almost five years before starting at University of Westminster in 2005.

What motivated you to become a scientist? The teachers I had for chemistry and biology at school who were passionate about these subjects and some of the lecturers at University of Surrey who introduced their research into the teaching and brought science out of text books and to life. I probably became hooked on research having joined Professor Steven Gross’s lab at Cornell University Medical College New York.

What inspires you about molecular bioscience? The pace of innovation in the molecular biosciences has been incredibly exciting; for example, I remember as a post-doc in 2001 when Nature published the Human Genome, the culmination of decades of research; now in classes we discuss next generation sequencing, Genome England (100,000 genome project) and the dramatic fall in the costs of sequencing. That so much of the data; generated from sequencing, microarrays and protein crystal structures, remains freely and publicly accessible in carefully curated databases is a real achievement.

What are you reading at the moment? Non-work related bedtime reading? Gerald Durrell’s “Birds, Beasts and Relatives”, the passionate risk-assessment-free pursuit of Corfu wildlife makes me smile.

What’s on your lab bench/desk right now? I’m embarrassed that there are heaps of paper on my desk! University of Westminster has given me a semester for a sabbatical and this is extremely valuable time to think, write up data, catch-up on reading and to attend to some projects which have regrettably been gathering dust on said desk.

What’s been the greatest challenge in your career so far? Becoming a parent of a disabled child; she has taught me about work-life balance.

What is your advice for someone who would like to pursue a career in molecular bioscience? In the age of “fake news” it is incredibly important that you record methods and data accurately so that your experiments can be repeated; back everything up. Take every opportunity that comes along to attend seminars, conferences, apply for funding and present your data. Think of the bigger picture, the majority of people in the UK don’t have a science degree, so you need to be able to translate molecular bioscience to a wide audience.

What do you do in your spare time? I enjoy being with my family, walking, theatre, gardening and sewing. I’m a governor for Perseid School, Morden, London.

Ambassadors are a key group of members that help us to raise awareness of the Biochemical Society, promote its activities, recruit new members and act as the Society’s point of contact at their institution. If you would like to get involved as an Ambassador please contact: membership@biochemistry.org.

Emeritus Lunch

On 7 April, the annual Emeritus Members’ lunch was hosted by the Society at Charles Darwin House. 45 Emeritus members attended the lunch and agreed that it was enjoyable to both meet with old colleagues and friends and also an opportunity to make new acquaintances. Following arrival drinks, Honorary Membership Secretary, Professor Nicola Gray, gave an overview of the past year of Society activities. Emeritus members were able to relax and enjoy lunch and a glass of wine with their peers as well as Society staff. Invitations for the next Emeritus Members’ Lunch will go out in January 2018.

Full members who have been members for more than 10 years and are approaching retirement are eligible for Emeritus Membership, please contact the membership team for more information on +44 (0)20 7685 2444 or email: membership@biochemistry.org.

Members enjoy a pre-lunch drink
Looking to the future for innovation and research

The triggering of Article 50 means we now have a very tangible and definitive timeline for the UK’s exit of the EU. In this time, the Royal Society of Biology will be working to represent the priorities of our members in the forthcoming negotiations, not only to ensure the best possible deals are achieved for scientists based in the UK, but also for those wishing to join in the future.

Looking towards the future has been a theme running through some of the RSB events this year. In March we saw Voice of the Future, a unique event that allows school children through to early career researchers to pitch their questions to the government’s top science policymakers and politicians, right in the heart of Westminster.

Young researchers, representing a wide cross section of membership organisations including the Biochemical Society, we able to discuss science policy with Jo Johnson MP, Sir Mark Walport, Chi Onwurah MP and a selection of members of the House of Commons Science and Technology Committee. It was encouraging to see young representatives asking meaningful and thought provoking questions; questions that were indicative of their enthusiasm for science and research.

Earlier in the same week we were at Portcullis House, this time for STEM for Britain. This year saw the largest number of submissions ever from researchers wishing to take part, with over 250 STEM scientists presenting their research to MPs, policymakers and other academics. It was especially exciting to see a biologist receive the highest accolade of the event – the Westminster medal – for her research on developing a cost-effective device for the rapid detection of the drug mephedrone.

These events remind us that the decisions made in the next two years will resonate not only through the scientific community as it stands, but will also extend and affect the lives of those that are sitting in classrooms, lecture theatres and libraries across the country and are still perhaps unsure about pursuing a career in science.

For those who are still undecided, the RSB have developed a number of resources for pupils considering a career in biosciences. We are also supporting the STEM Insight programme, to allow for teachers to complete placements in universities or industry to expand on their STEM skillsets and experience. Undoubtedly the resources and support from RSB and across the sector will be more important than ever for those at the beginning of their science career or wishing to expand their acumen further.

With this in mind, in February we also responded to the Science and Technology Select Committee enquiry into closing the STEM gap. The UK requires an additional 104,000 STEM graduates and 56,000 STEM technicians each year to plug this deficit and so far is struggling to do so.

The RSB, along with its Member Organisations including the Biochemical Society, have developed resources for pupils considering a career in biosciences. The Biochemical society is also supporting the STEM Insight programme, to allow for teachers to complete placements in universities or industry to expand on their STEM skillsets and experience.

Along with our degree accreditation programme, our wider registration programmes for technicians and researchers and our new Plant Health Professionals Register, we are working hard to raise the standards of education, offer more opportunities for researchers to develop their STEM skillsets, and recognise the excellence of those already working in biosciences.

Closing the STEM skills gap is an endeavour that is vital for ensuring the longevity of our science and technology sector, and one that RSB and all its Member Organisations will continue to address; it is imperative we ensure our current and future researchers are best placed to sustain and develop our UK science base in the months and years to come.

It was particularly encouraging to be present for the launch of the report by Stephen Metcalfe MP, Chair of the Parliamentary and Scientific Committee, on his recommendations for science priorities for Brexit; a report that succinctly and clearly outlined a number of priorities that should be considered and addressed in the coming months for science and research.

The recommendations, focusing on people, investment, collaborative efforts and trade, mirrored our priorities for ensuring that the members of our UK science base are not confined to what they can do and achieve; we want the UK to remain a global leader in science and we need to remain as open and accessible as possible to retain this standard.

We hope that these recommendations, produced after lengthy discussion and drawn from evidence submitted by members of the science community, will be taken forward and form a foundation for the coming negotiations following the triggering of Article 50.

The Royal Society of Biology News

Looking to the future for innovation and research

The House of Commons Science and Technology Committee answer questions from early career researchers at this year’s Voice of the Future
Society News

Introducing the Chair of the Education, Training and Public Engagement Committee

An important role of the Biochemical Society is to support the subject of biochemistry and the members through the activities of the Education, Training and Policy Department. The team, led by Hannah Russell and superbly assisted by Lorenza Gianella, James Brown and Gabriele Butkute, is guided by the Education, Training and Public Engagement Committee and Policy Advisory Panel. I have the privilege to chair the Education Committee.

I was appointed to this role in 2014, at a time when the Society had indicated its desire to shift the focus of educational activities from supporting bioscience education at all ages to focusing more clearly on molecular bioscience-specific support for secondary schools (15 years +), further and higher education. This has meant disengaging from our previous primary-school focused activities and making sure that these projects (for example the Gopher Science Labs) were in safe hands and would continue to develop – in this, our relationship with the Royal Society of Biology has been critical. Our current programme of activities is broad and includes not only informative and engaging content-related support for students and teachers, but also training for higher education educators, careers support and the Society’s popular public engagement programme for families and adults, including training and opportunities for members. We also contribute to the Society’s work on education policy and have been delighted to support the Society’s Awards Committee this year with the new Teaching Excellence Award.

Our objective in training is to provide ‘high quality, hands-on continuing professional development for the molecular bioscience community’. The re-shaping of the Conferences Committee has provided an opportunity this year to expand our provision. Training was previously divided between Education and the (then) Meetings Board; the creation of the Training Theme Panel now offers a single entry point for course proposals, providing a strategic overview of the training programme as a whole and ensuring that we address issues of need, diversity, relevance to the Society’s ambitions and the tricky issue of sustainability.

Other activities delivered by Education are very well recognized as part of the Society ‘brand’. These include our Summer Vacation Studentship programme, Science Communication Competition and the Scientific Outreach Grants Scheme. We work hard to promote awareness of career opportunities in the molecular life sciences, and our publications, including our Careers Guide and our ‘Biochemists in Industry’ booklet are in high demand.

One of the Society’s strengths in Education is acting as a trailblazer for new opportunities. We have worked in partnership with the University of East Anglia and FutureLearn to develop a MOOC (Massive Open Online Course) for 15–19 year olds providing an introduction to biochemistry and the range of

Recent Education, Training and Public Engagement highlights

Supporting Teachers and Educators
We are the first bioscience Society to have engaged in STEM Insight, placing secondary and further education teachers into the University or Industrial Sectors to gain first-hand experience so that they can better inform school leavers about futures (www.stem.org.uk/stem-insight)

Advanced Training
Recent courses have included topics as diverse as the use of technology to engage students, quantitative proteomics and protein modelling. Upcoming events will include ‘Understanding Translational Research’, ‘Shaping your Career in Molecular Bioscience’ and Capture HiC (www.biochemistry.org/training)

Careers and Future
We are currently piloting a new Jobs Board on the Society website, listing molecular bioscience vacancies from across academia and industry, including PhD studentships and research positions as well as other opportunities within and outside the Society (www.biochemistry.org/JobBoard)

Public Engagement
This year we have delivered (in partnership with the Royal Society of Biology) ten public engagement training events around the UK. Our ‘Medicine Makers’ and ‘21st Century Biochallenges’ kits are available to members to download and we aim to have the ‘Hungry Games’ online later this year (www.biochemistry.org/education)
opportunities available in molecular bioscience (www.futurelearn.com/courses/biochemistry). Over 10,000 people signed up to the first two runs and feedback confirms that these new modes of delivery of content and thinking work, and work well. With the same enthusiasm, we are now developing an online Training Portal to widen access to training across our community. We are the first bioscience learned society to work on the STEM Insight scheme, providing opportunities for teachers in secondary schools and further education colleges to go on short work placements with local employers and universities. We funded 16 placements last year and aim to increase this in 2017, allowing teachers to transform their understanding of STEM careers and enrich their teaching with real life context.

Why not consider becoming a member of Education Committee? We meet three times a year and are also very active between meetings. Committee members represent the Society, develop new ideas for training and other activities, support our Studentship and Outreach grants schemes and in many cases host STEM Insight placements within their own organisation or institution. This year we are developing a new ‘Core Curriculum for Biochemistry’ that will be available to all our members for use in course development, in encouraging potential students to study the subject and in preparation for accreditation through the Royal Society of Biology. We aim to be broadly representative of our community (including teachers in schools and colleges) and always welcome new ideas and input. ■

For more information on the Education, Training and Public Engagement Committee or any of our other activities, please visit the Society website or contact Hannah and her team at education@biochemistry.org.

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biomedicalresearch@contacts.bham.ac.uk
Almost a full year has passed since the Society’s 105th Annual General Meeting, and while it seems this time has flown past, I’m looking forward to updating members on another busy year for the Biochemical Society and Portland Press at this year’s meeting which takes place on Wednesday 5th July.

You may remember that at last year’s meeting, the membership approved a new Governance structure, following recommendations of the Governance Review – which is now in the final stages of implementation. A key change arising from the review was the formation of an Executive Management Committee (EMC), which has been meeting monthly since the start of 2017. The EMC focuses on operational matters and this has enabled the Society’s Trustees to focus on the development of the Society’s strategy to greater effect, with the new Council of Trustees reviewing key strategic themes in the run up to our third Strategy Retreat in November of this year, at which we will be looking at progress with the current strategy and ways to enable the Society and Portland Press to face the considerable challenges facing the life sciences sector.

Another important change in the new structure is the expansion of roles available for members, and it has been pleasing that we have received a very positive response to the call for nominations earlier this year through the Society’s electoral platform, MiVoice. This new system has improved member engagement fourfold since its implementation and we have been able to use it to find several enthusiastic new representatives who will be ratified at the AGM.

In April, the Society honoured eleven scientists in the annual Biochemical Society Awards, which recognise excellence amongst distinguished researchers, as well as highlighting achievements of outstanding early career scientists. The 2018 Award Winners include eminent scientists from the UK, Austria, France, Germany and the USA. All the winners have made an outstanding contribution to their field, and we look forward to hearing more about their award-winning work in our programme of Award lectures next year.

At the time of writing, the Society has just launched the first issue of our new journal, Emerging Topics in Life Sciences, at the Experimental Biology conference in Chicago. Each issue of the journal – which is jointly owned by the Royal Society of Biology – focuses on an emergent topic which reflects the interdisciplinary nature of life science research. The first issue (guest edited by Daniel Walker from the University of Glasgow) addresses the timely subject, ‘Antibiotics of the future’ – is available online. Articles from this issue – and from the recent Essays in Biochemistry issue exploring mechanisms of antimicrobial resistance – can also be found in Portland Press’s recent themed collection: Antibiotics – resistance and new directions.

This month, our popular MOOC (or ‘massive open online course’) developed in conjunction with the University of East Anglia and FutureLearn will run for the third time. Previous iterations of the course, entitled ‘Biochemistry: the Molecules of Life’ have attracted thousands of registrants. The course – aimed particularly at 15–19 year olds studying biology and chemistry with an interest in pursuing further studies in biochemistry – is free, and starts 26 June. Anyone interested can register via FutureLearn (www.futurelearn.com/courses/biochemistry). To date over 10,000 people have accessed the MOOC and we hope that this latest run will encourage more to take an interest in molecular biosciences.

The annual Parliamentary Links Day will take place this year at the Houses of Parliament on 27 June. The event – organised by the Royal Society of Biology – is the largest science event on the annual Parliamentary calendar and aims to strengthen the dialogue between scientists and politicians. The theme for this year will be UK Science: Global Opportunities.

Finally, I am pleased to give advance information about our forthcoming collaborative event with the other co-owner societies at Charles Darwin House. International Coffee Day will present opportunities for every life sciences society to offer their perspective, from the ecology to physiology to biochemistry of coffee. On 28–29 September 2017, Charles Darwin House plans to host a celebration of the event. This will take the form of a scientific meeting, as well as a public engagement activity – visitors will be taken on a ‘journey’ following the production of coffee, from bean to cup.

Kate Baillie
(Chief Executive, Biochemical Society and Managing Director, Portland Press)
The Man in the Monkeynut Coat by Kirsten T. Hall

This is a marvellous book and was impossible to put down. William Astbury, a talented X-ray crystallographer, was one of the first to generate an image of DNA in May 1951. Unfortunately for him, he was not to exploit this remarkable data, thereby allowing Watson and Crick to publish the solved DNA structure in *Nature* in 1953.

The book takes the reader on a roller coaster ride of discovery, heartache and dejection. This bitter sweet context is emotive and all the more remarkable bearing in mind the calibre of Asbury’s contemporaries at the time, such as Avery, Crick, Franklin and Watson. Asbury’s rightful presence in this illustrious group cannot be doubted, but the book gives the impression that he became disillusioned and felt marginalized by overly critical colleagues and reluctant funding bodies; issues that will resonate with many researchers today.

This book will appeal to scientists with historical interests in protein structure. Whether others consider Asbury’s contribution to the discovery of DNA as valid and worthy, I don't know. People may say he was too slow to act, or did not have all the pieces of the jigsaw at the time. Regardless, he was a master technician, scientist and thinker and this book does him proud, for it displays his brilliance, his fallibility and most importantly his humanity. Go buy it.

John Phelan (University College Cork, Ireland)

**Innovative Uses of Assessments for Teaching and Research edited by Kendhammer and Murphy**

As a biochemistry lecturer in the UK, I was looking forward to reading this book, as it aimed to provide a collection of innovative ways that assessments have been used for classroom or programmatic assessment, or for research investigations.

The first section focuses on strategic (national) aspects of assessment, for instance, optimizing exam questions for large numbers of students across many institutions. Although I could appreciate the issues involved, the context meant I found nothing to 'take home' from these chapters. A practice exam which didn't improve attainment and a section on (US) government-defined assessment guidelines, left me without anything tangible to benefit my own assessments.

Thankfully there were several nuggets of gold in the second half of the book. For example, feedback regimes that promote assessment-for-learning; the disconnect between students’ own assessments of their performance and their actual attainment and the balancing of skills vs knowledge in taught courses.

Hand on heart, I can't recommend UK lecturers to purchase this book. However, if your university library has a copy, a browse through the final chapters would be time well spent.

David Whitworth (Aberystwyth University, UK)

A Brief History of Everyone Who Ever Lived by Adam Rutherford

Despite being relatively new concepts, the ideas behind DNA, genes and genetics have all entered the public consciousness to a significant degree. The preponderance of newspaper stories about discoveries of the “gene for X” and the popularity of genome sequencing services such as 23andMe, demonstrate the cultural impacts this young science has had on the public imagination. But are we at risk of over-simplification and a lapse into genetic determinism?

Adam Rutherford’s second book aims to set the record straight by carefully outlining exactly what we can, and perhaps more importantly, what we cannot determine from studying our genomes. The book is carefully balanced; for every debunking of a piece of sensationalist journalism, there is an inspiring demonstration of the power of genetic analysis. A particular high point is the comparison of the post-mortem identifications of Richard III and Jack the ripper – a great example of the difference between science well done and misleading pseudoscience.

Determinedly aimed at the non-specialist, the book eschews almost all technical detail other than that necessary to understand the outcomes and ramifications of the various research projects discussed. Whilst the more knowledgeable reader may occasionally be frustrated by the lack of specifics, what Rutherford is really focussed on is telling stories. He is able to relate the importance of the current research landscape to topics of specifics, what Rutherford is really focussed on is telling stories. He is able to relate the importance of the current research landscape to topics a diverse range of examples including history, immigration, evolution, health and disease, and race. The complexity and counter-intuitive nature of biology becomes a recurrent theme through which he is able to challenge us to raise our game when talking about genetics.

If all the above makes the book sound a bit polemical and serious, it is anything but. Rutherford has a wicked sense of humour and is able to pull out a pop-culture reference for almost any occasion, ranging from Philip Larkin to Eric Cartman. There is much fun to be had trying to spot the various cultural touchstones and the book entertains as much as it informs. As a way of restructuring our cultural engagement with genetics, it suggests we follow a less direct, yet smarter path.

James Brown (Biochemical Society, UK)

**Glycobiology in Infectious Disease**

4-5 September 2017, Keele University

Abstract and Earlybird registration deadline: 7 July 2017
Instrumental methods for the analysis and identification of bioactive molecules, edited by G. K. Jayprakasha, B. S.Patil, and F. Pellati

Having a particular interest in analytical science, I was somewhat disappointed to find that little technical and methodological details are described in this book.

The content is a mix of case studies, focussed on a particular set of analytes, e.g. Flavonoid C-glycosides in citrus juices, or generic discussion with an emphasis on a given method, e.g. reverse phase liquid chromatography.

The selection of molecules examined is quite diverse and unusual, ranging from those found in honey to nitro-oxidative agents that affect the organoleptic properties of raw meats.

It was interesting to find out about Fourier transform infrared photoacoustic spectroscopy and its implementation. Otherwise, the techniques reviewed are well-known.

The effects on experimental results of sample harvesting, storage and preparation strategies are mentioned, but not stressed enough. The same applies to the challenges of sample extraction and clean-up.

Overall, the edition might be useful to those interested in studying any of the compounds mentioned. However, for more extensive technical details on analytical techniques and methodologies, more specialized resources are needed.

Evita Hartmane (University of Reading, UK)

People in white coats
By Benoît Leblanc
(http://peopleinwhitecoats.blogspot.co.uk)

Conservative Ken and Tinfoilhat Bob find common cause: their hatred of facts.
Prize Crossword

Across
2. RNA virus spread by 15 across (6)
3. Spanish, swine or bird (3)
4. Affected by brown spot disease (4)
6. Virus that put at risk the 2016 Olympics (4)
8. Meaning ‘to bleed’; severe symptoms of viral disease (12)
11. Victims of ash die back (5)
12. Single celled organisms, can cause infection (8)
13. Anything that can cause disease (8)
15. Female flying ectoparasites (8)
16. A kingdom (5)
17. Also known as pyrexia (7)
18. Tissue damage caused by disease or trauma (7)

Down
1. Invasion of the body by a disease causing agent (9)
2. Transmissible or communicable perhaps (7)
3. Preceded by 2 or 8 across (5)
5. Jenner’s preventative (7)
7. That which transmits from reservoir to host (6)
9. Life savers now tempered by resistance (11)
10. STD caused by Neisseria bacteria (9)
14. Neglected ______ Diseases (8)


Crossword Competition

Win

This month’s crossword prize is a Biohazards themed gift box from Giant Microbes. Simply email the missing word, made up from letters in the highlighted boxes to biochemist@biochemistry.org, by Tuesday 4 July. Please include the words ‘June crossword competition’ in the email subject line.

Congratulations to April’s winner:

Caroline Barwood from the University of Nottingham
The missing word from last issue’s competition was MICROORGANISM. Caroline received a Lakeland Electric Yoghurt Maker as the prize.

Terms and conditions: only one entry per person, entrant must be a current Biochemical Society member; closing date Tuesday 4 July 2017. The winner will be drawn independently at random from the correct entries received. The winner will receive a Biohazards themed giftbox. No cash alternative available. No employee, agent, affiliate, officer or director of Portland Press Limited or the Biochemical Society is eligible to enter. The winner will be notified by email within 7 days of the draw. The name of the winner will be announced in the next issue of The Biochemist. The promoter accepts no responsibility for lost or delayed entries. Promoter: Biochemical Society, Charles Darwin House, 12 Roger Street, London WC1N 2JU; do not send entries to this address.