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microbiologist

The magazine of the
Society for Applied Microbiology

> **INSIDE**

Neglected!

Making diagnostic tests for tropical diseases

Cracks in the antibiotic pipeline

Drug development for visceral leishmaniasis

The cover image is a painting of the Swine Flu Virus by Nancy Dart, the winner of the 2017 SfAM Image Competition



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Paul Sainsbury reviews the content of this issue

microbiologist

A vicious circle kept under the radar

Researching what to include, who to reach out to and then reading the contributions for this issue on Neglected Tropical Diseases (NTDs) has been a bit of an eye-opener for me. Without doubt, the hardest thing for me to comprehend is that if over 1.5 billion people suffer from them, why are they still 'neglected'?

If it is because they attract little public attention and research money since they largely only affect poor populations living in tropical and subtropical climates, then perhaps we should relabel them 'diseases suffered by neglected communities'.

The resulting disabilities from NTDs, such as blindness, immobility, disfigurement and often great pain, keep these people mired in the very poverty that allows these diseases to thrive. What a terrible state of being, especially considering many NTDs can be prevented, eliminated or even eradicated with improved access to existing, safe and cost-effective tools. Diseases of poverty that also contribute to that poverty should be way up there on the public health agenda. Certainly not 'neglected'.

However, as you will read in the features within this issue of *Microbiologist*, there is reason to be optimistic. A remarkable assault on NTDs has been gathering pace, led by organizations such as the World Bank and World Health Organization (WHO), which has cut transmission and pushed the number of new infections to previously unimaginable lows. Humanity is now capable of driving many NTDs out of existence.

The question is whether it will...

In the first of our special features on NTDs, Martin Zoltner introduces us to *Trypanosoma brucei gambiense* – the parasite that causes Human African Trypanosomiasis (sleeping sickness). We then asked Barrie Rooney, who also works with *T. b. gambiense*, to tell us about the difficulties of making diagnostic tests for Human African Trypanosomiasis and NTDs in general.

Susan Wyllie gives us a fascinating insight into drug developments for visceral leishmaniasis, John Spencer looks at strategies to reduce leprosy in hyperendemic regions and Nick Beeching leads on an incredible article on Crimean-Congo haemorrhagic fever, the pathogenesis of which is still not entirely understood.

I was lucky enough to be invited out by James and Tamsin from the SfAM ECS Committee to help them pick a venue for next year's massively popular **Early Career Scientists Research Symposium** – so this issue will announce the location and dates of that on **page 9**. We also have more details on the **2018 Annual Conference** which will be held in Brighton. Both events are always well attended and have limited spaces, so we do encourage our Members to book as early as possible.

...and as this is December, HAPPY CHRISTMAS!!!

NEWS IN BRIEF

Bacteria living in the murky depths of the digestive system seem to influence whether tumours shrink during cancer therapy, say French and US researchers.

www.bbc.co.uk/news/health-41848461

UK Chief Medical Officer, Prof. Dame Sally Davies says action is needed around the world to tackle the 'hidden' problem of antimicrobial resistance that is already claiming lives.

www.theguardian.com/society/2017/oct/13/antibiotic-resistance-could-spell-end-of-modern-medicine-says-chief-med



Paul Sainsbury

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Tamsin Redgwell

ECS Events Officer

10

A massive epidemic followed around the turn of the 19th century, prompting the colonial administrations to solicit for medical research and recruit scientific missions

NEWS

- 03** Editorial
- 06** President's column
- 07** Harper's Postulates:
Notes from the Chief Executive



38



- 08** Early Career Scientists
PhD prospects
- 09** 7th Annual ECS Research Symposium
Epidemiology & Infection Control
- 32** BIOFocus
Making the most of new opportunities
- 59** POLICY Corner
It's life science, Jim, but not as we know it

FEATURES

- 10** African sleeping sickness
An old enemy, but is the end in sight?
- 12** Making diagnostic tests for tropical diseases
- 14** Drug development for visceral leishmaniasis
Light at the end of the tunnel?
- 16** Cracks in the antibiotic pipeline
- 20** A very unpleasant 'kiss'
- 22** Strategies to reduce leprosy transmission in hyperendemic regions in Brazil and elsewhere in the world
- 26** Coming soon... Crimean-Congo haemorrhagic fever
- 30** London's MICROBIOTA
Lunch on a plague pit



22

PUBLICATIONS

- 46** An interview with Jon Turney
Unlocking the secrets of the superorganism
- 48** JournalWATCH: Highlights from the SfAM journals

Super Organism 46

MEMBERS' WALL

- 02** CONTACT POINT
- 29** W H PIERCE Prize
- 34** Applications of plant pathology: from field to clinic
- 36** 2018 SfAM Annual Conference
Passport to Infection: Infections of Travel and Leisure
- 38** Infectious Diseases Hub
The home of medical microbiology
- 42** Career Street
- 44** Membership changes
- 45** What you get for your membership

COMMERCIAL

- 52** Corporate NEWS

16

President's column

During the first term of the new academic year, it is always a pleasure to get to know the new crop of young people entering our world of science. What is most heartening is the increasing number of these folks that choose to stay in microbiology. This is of course nothing we can rely upon, it takes work and the continued modernization, promotion and updating of our subject to keep it fresh and relevant.

It is an exciting time to be a microbiologist in this age of bacteria, and subject areas such as antimicrobial resistance and food safety are regularly in the media. However, we cannot rest on our laurels and preparing students for a future that we can't predict is becoming harder and harder in this post-genomic era.

One resource that students can be directed to is, of course, learned societies. We mustn't forget that, when used correctly, these organizations can provide young scientists with the required support, means to establish solid networks, access to funding and many other tools to help them on their microbiological journeys.

I think we can all recognize and be proud of the role that SfAM has played and continues to play in this arena. We have an excellent Early Career Scientists (ECS) Committee who continue to impress us with their drive, verve and professionalism in all they do for scientists at the start of their career paths. I am really looking forward to the 7th Annual ECS Research Symposium being held on 28 March 2018 at the University of Birmingham. The symposium is always a well put together and hugely popular event that showcases our young scientists brilliantly.

However, SfAM's inclusive nature does not end there, not by any stretch of the imagination.



The recent EMI lecture held in London on 13 October as part of the Royal Society of Biology's Biology Week was another excellent example. In this audience, we had a good representation of undergraduate and postgraduate students as well as some young people from two local schools, all there to listen to Professor Rino Rappuoli talk about his work on vaccines. The lecture was excellent, a real inspiration and an insight as to what can be done to combat and prevent infection using new, exciting methodologies. This was especially welcome following Professor Dame Sally Davies' press release regarding antibiotic resistance earlier in the day. The lecture gave rise to a lot of interest and questions and it was fantastic to hear the insightful points raised and the following debate from the young members in the audience.

Judging by what I have witnessed recently, microbiology will certainly be safe in the next generation's hands, and I am especially proud of all the Members that make up the Society for Applied Microbiology and the Committee Members and staff that support them. Thank you.

The lecture was excellent, a real inspiration and an insight as to what can be done to combat and prevent infection using new, exciting methodologies



Mark Fielder
SfAM President

Harper's Postulates

Notes from the Chief Executive

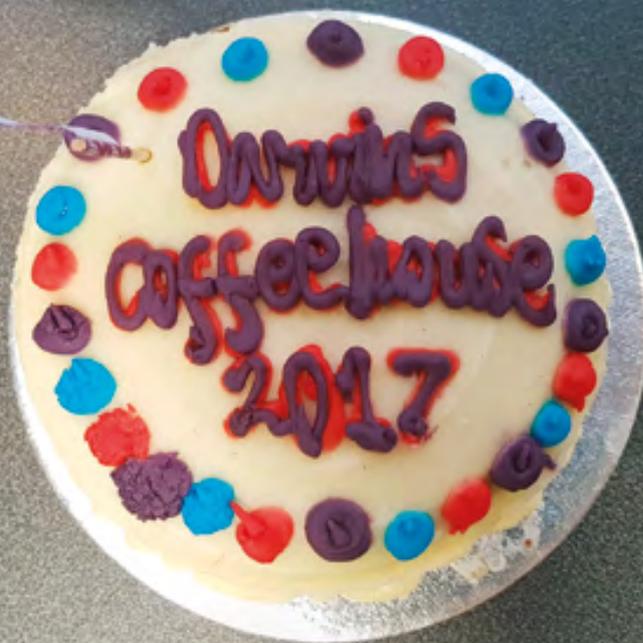
I am excited to report that this year has been another hugely eventful year for the Society, which has seen continued growth and evolution. The team are now settled into the offices here at Charles Darwin House and forging ahead to deliver the work of the Society.

In April we saw record delegate numbers at the Early Career Scientists (ECS) Research Symposium and workshop on Bioinformatics. This hands-on workshop was the first of its kind run entirely by the ECS and feedback from delegates was testament to the hard work and dedication of this excellent team of early career researchers. As Mark described in his piece for this issue of *Microbiologist*, we are extremely proud to have been supporting ECS Members for over a decade now.

Another change for 2017 was the implementation of new Membership categories. The driver behind this change was to ensure that our membership benefits remain relevant to all our Members and to encourage an engaged membership who want to get involved in the work of the Society. Of course we understand that the life of scientists in academia, industry and Government laboratories doesn't stand still and we are continually looking out for ways in which we can provide new membership benefits. So if you have any ideas or comments on our current membership benefits please do get in touch with one of the team.

We took part in the first 'Society Day' run by the American Society of Microbiology this year. The event we held was on the topic of the Microbiome and had presentations from ECS Members, as well as established researchers. My thanks go to all involved in making it a great event and an opportunity for SfAM Members attending the ASM Microbe Congress to meet up, share experiences and potentially begin collaborative relationships.

Another new event for 2017 was a public engagement event which was run jointly by all six co-owners of Charles Darwin House (SfAM, British Ecological Society, Biochemical Society, Society of Experimental Biology, Microbiology Society and Royal Society of Biology). This was a great opportunity to see first-hand the results of collaboration between the six co-owning organizations. 'Darwin's Coffee House' was a two-part event held around International Coffee Day. The first event was a public symposium comprising elements of coffee production, the health effects of coffee and potential



use of coffee waste in energy production. Afterwards, attendees were invited to sample a coffee martini (or two). The second day was set up as a coffee morning with stands from each Society looking at various aspects of coffee. My personal favourite was the effect of music on the taste of coffee.

Finally, we were pleased to announce in July the appointment of a new President of the Society, building on the excellent work of Prof. Christine Dodd. For those who don't know Professor Mark Fielder, he is Professor of Medical Microbiology at Kingston University and comes into his role after many years' involvement with the Society. As is always the case, with a new President comes a new strategy, and we have been working together as a team with the Trustees to develop a new strategic direction for the Society for the next three years from 2018 to 2021.



Lucy Harper
SfAM Chief Executive

PhD prospects

I know that many of our ECS Members are undertaking a PhD and I have also had the pleasure of meeting many at previous conferences. For me though, a lab-based PhD is not a route I currently want to go down and instead I have just begun a Master's in science communication. This is never what I imagined I'd be doing when I graduated. Certainly when I was a fresh-faced student in my first year, I had the idea that at some point in my life I was going to have Dr at the beginning of my name. A lot has changed in the three years of my degree though, namely the fact that I have more enthusiasm for talking about current research than carrying it out myself! I also realized that although a lab-based PhD is 'hands-on', it's not the right type of 'hands-on' for me.

As I follow a lot of PhD students on Twitter, I read a lot of their blogs as well as having befriended quite a few over the years, and I have been able to observe a few key things about these super humans:

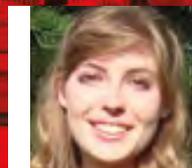
1. *PhD students seem vastly more inquisitive than I am; they will analyse everything and always ask the question 'why?'.*
2. *They are vastly more intelligent than I am and that's not me being humble, it's just a fact.*
3. *The problems that they solve would knock me out of the game before I'd even started and has obviously given rise to their 'out of this world' problem-solving abilities!*

4. *Perseverance is also a key skill that I've seen; when something doesn't work they try to fix it and make it perfect instead of moving on to something else.*
5. *They are genuinely proud and excited about what they're doing. This one goes without saying really but I've witnessed it so many times and it's a great sight to see!*

Despite all of this, people say that a PhD is most often just a delaying tactic so that you don't have to start real life. I think it's so much more than that. A PhD is a badge of honour, a medal that says you've slaved away to discover everything you can about a subject, sacrificing your sanity along the way and still managing to give a coherent oral presentation at the end of the ordeal. It means that you're one dedicated individual and you're prepared to put yourself through hell just to change your title. Who wouldn't want all that? Even though I want it too, there is no way that I could subject myself to the sort of stress that so many of my friends have tried to make light of.

I'm not writing a PhD off altogether though! If the right opportunity comes along I won't hesitate to say yes; I would love the chance to spend three or four years immersed in a project that I'm truly passionate about.

sfam
ECS
EarlyCareer**Scientists**

Jennie French
ECS Publications Officer
University of Nottingham

7th ANNUAL



Society for Applied Microbiology

ECS RESEARCH SYMPOSIUM

Epidemiology & Infection Control

28 March 2018

09:30 – 17:30

University of Birmingham

Birmingham

B15 2TT



Professor Nigel Gibbens CBE*
UK Chief Veterinary Officer

The Early Career Scientists 7th Annual Research Symposium will be held at the University of Birmingham with a focus on Epidemiology and Infection Control. The symposium aims to bring together microbiologists, epidemiologists, public health researchers, academics, practitioners and most importantly early career scientists and undergraduate students. The symposium is a forum for those who wish to exchange and share their experiences, ideas and research on all aspects of epidemiology and infection control.

It will also provide the chance to hear from premier keynote speakers who will discuss the most recent innovations, trends, challenges and adopted solutions in the fields of epidemiology and infection control.

All Early Career Scientists (including undergraduates) are encouraged to contribute to and help shape the conference through submissions of their research abstracts, papers and e-posters. The symposium welcomes contributions from any area of applied microbiology as well as work that addresses the themes and topics of the symposium.

The symposium will offer a light lunch and refreshments for all delegates. Please help us ensure the symposium's success by registering as soon as possible.

DEADLINE FOR ABSTRACT SUBMISSIONS IS 7 FEBRUARY 2018.

member.sfam.org.uk/sfam/events

*Nigel Gibbens is retiring at the end of February/beginning of March so has agreed in principle and will aim to confirm by the end of this year.

Travel expenses within the UK and EU of up to £100 will be paid to oral and poster presenters.

(subject to prior approval)

£50 ECS Members
£25 ECS Undergraduate Members
£75 Members
£100 Non-Members

(one year free membership for non-Members included in this price)



AFRICAN

An old enemy, but is

SLEEPING

the end in sight?

SICKNESS

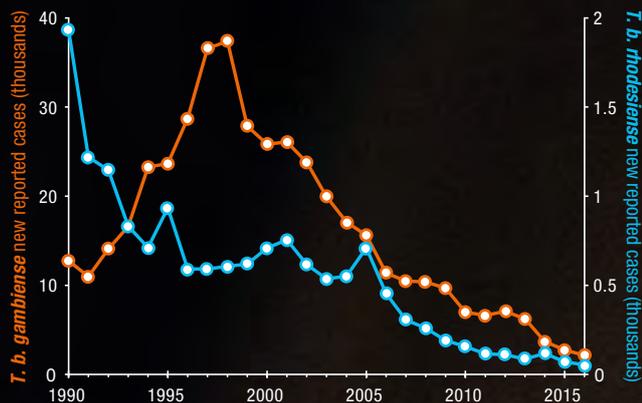


Human African trypanosomiasis (HAT) was first recorded in the 14th century, when the Arab historian Ibn Khaldun wrote about the death of King Diata II of Mali, by what he described as "...the sleeping sickness, a disease that frequently afflicts the inhabitants of that climate". About 500 years later, chaos and instability brought by the colonial adventures of the Europeans, likely contributed to a great expansion of the HAT endemic regions. A massive epidemic followed around the turn of the 19th century, prompting the colonial administrations to solicit for medical research and recruit scientific missions.

As part of this effort, the Scottish microbiologist David Bruce discovered that African trypanosomiasis is a parasitic disease transmitted by *Glossina* spp., the tsetse fly, which is endemic in large parts of sub-Saharan Africa. The causative agent *Trypanosoma brucei*, a unicellular flagellated protozoon, was later named after him. While Bruce anticipated mechanical transmission by the tsetse fly, it was later established that the parasite persistently infects the insect vector and undergoes a complex life cycle: the parasites are taken up into the insect vector midgut during a bloodmeal from an infected host, and differentiate into procyclic trypomastigotes. These forms migrate to the salivary gland generating metacyclic trypomastigotes ready for delivery to the mammalian bloodstream with the next bite. The metacyclics transform into the proliferating long slender form capable of establishing and

maintaining a bloodstream infection rapidly after entering a new mammalian host. Eventually some parasites cross the blood-brain barrier, infecting the central nervous system (CNS) evoking the symptoms described by the common names 'sleeping sickness' for HAT or 'Nagana' for the animal disease, which translates to 'loss of spirit' in Zulu: the host falls into a lethargic state and later becomes comatose which, finally leads to death.

Unlike the related kinetoplastid parasites *Trypanosoma cruzi* and *Leishmania* spp., which are intracellular pathogens, African trypanosomes have adapted to survive in the mammalian host bloodstream. While nutrients are readily available in this environment, a direct and full exposure to the innate and acquired immune systems poses an extreme challenge. Key strategies *T. brucei* has developed for successful immune evasion are the ability to change its surface 'coat' to achieve antigenic variation, in combination with a highly efficient endocytotic apparatus. In the bloodstream stage, the parasite surface is dominated by a single variant surface glycoprotein (VSG) covering approximately 90% of the cell surface. This VSG can be switched to one of hundreds of different isoforms when overwhelmed by high antibody titres, thereby evading the host acquired immune response and establishing recurrent infection. In the patient this manifests as waves of parasitaemia but after 5 to 7 days VSG antibodies are raised that eliminate most



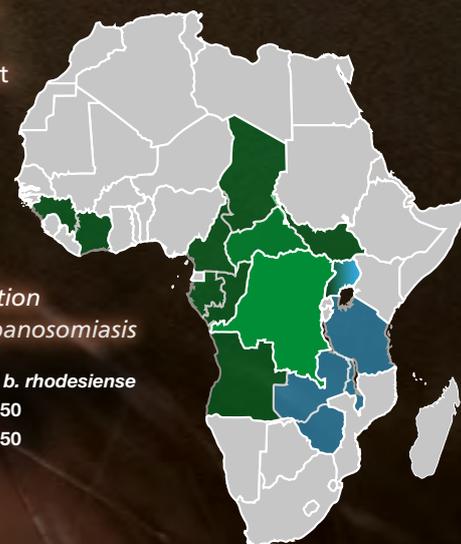
Number of reported cases of *T. b. rhodesiense* and *T. b. gambiense* HAT by year

of the trypanosomes. However, a new wave of trypanosomes then appears, which is unaffected by the antibodies of the previous wave. Extremely rapid clathrin-dependent endocytosis facilitates clearance of antibodies and complement, which would otherwise lead to cell lysis and are likely important in extending the period that a VSG variant can survive, as well as protecting against productive antibody recognition of invariant surface molecules.

Trypanosomiasis is an ancient companion of hominids and primates, and one example of the selective pressure exerted by the parasite is manifested by the omnipresent trypanolytic activity in human blood. Arising during late primate evolution, trypanolytic factor (TLF) confers innate immunity to one subspecies of African trypanosome, *T. brucei brucei*, in humans. TLF is a subclass of serum high-density lipoprotein that contains Apolipoprotein L1 (ApoL1) and a protein that is essential for haem uptake, which is bound by a surface receptor of the parasite. This TLF/receptor

complex is taken up by endocytosis, and trafficked to the lysosome where ApoL1 forms pores in the lysosomal membrane, which ultimately kills the parasite. However, some subspecies have developed strategies to circumvent TLF toxicity, in what seems like an evolutionary arms race between host and parasite. Specifically, West African *T. brucei gambiense* has a modified receptor to avoid uptake of TLF and the East African *T. brucei rhodesiense* expresses serum resistance-associated antigen, which interacts with ApoL1, preventing its lytic effect. There is mounting evidence that the potency of two trypanocidal drugs, suramin and pentamidine, rely on endocytic uptake and hence entry into the parasite. Indeed, this is reminiscent of TLF uptake and it has been recognized that the specialized endocytotic apparatus can be exploited for drug delivery, bypassing conventional delivery routes altogether.

Despite progress, new therapies are urgently needed as the current rely on very old drugs with severe side effects and the emergence of drug resistance is a major threat. The state-of-the-art treatment for CNS stage HAT is a combination therapy of nifurtimox and eflornithine developed by a consortium led by the Drugs for Neglected Diseases Initiative in 2009, which was a step forward but requires a long and costly course of intravenous administration. The World Health Organization is on track to achieve elimination of HAT as a public health problem. Strengthened control and surveillance have significantly reduced the transmission of the disease in a steady decrease from over 25,000 reported cases in 2000 to a historic low of 2,184 cases in 2016. Regrettably, a similar success was celebrated in the 1960s when reported cases stabilized under 5,000; however, this was soon followed by the onset of a new epidemic. Hopefully sustained commitment and, perhaps most importantly, political stability will prevent such a relapse in future.



Geographical distribution of human African trypanosomiasis



FURTHER READING

http://www.who.int/trypanosomiasis_african/

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Martin Zoltner
College of Life Sciences,
University of Dundee

Along the upper reaches of the Congo River a 30-strong Médecins Sans Frontières (MSF) team move from village to village towing a floating laboratory. Our team is searching for *Trypanosoma brucei gambiense*, the parasite that causes sleeping sickness (SS). This fatal disease affects people living in remote areas of central Africa's rainforest where the insect vector thrives.

Transmitted by the bite of the bloodsucking tsetse fly, SS can be a slow killer; taking up to two years to produce the full neurological symptoms, coma and inevitable death. Everyone in the village must be screened, because non-symptomatic carriers act as reservoirs. These carriers must be found and treated in order to break the cycle of transmission for this Neglected Tropical Disease (NTD). Among the designated NTDs, SS is one of three caused by members of the protozoan group *Kinetidoplastidia*. Chagas and leishmaniasis are the other two and together they threaten the lives of over 90 million people.

Following an infective insect bite, the SS patient will suffer peaks of parasitaemia as the host mounts a humoral immune response to the changing surface antigens on the SS parasite. Diagnosis is complex and requires a combination of serological and microscopic

examination of tissue and blood samples. A positive result requires an immediate lumbar puncture to assess the disease stage and therefore the type of treatment required. To make screening more accessible to remote populations, recent efforts have focused on simplifying and reducing the cost of point-of-care (POC) diagnostic tests.

A widely accepted format for these POC serodiagnostic lateral flow tests (RDTs) is the dipstick design of the common pregnancy test (Figure 1). The key to high sensitivity and specificity is the choice of parasitic antigen (or monoclonal antibody) printed on the test line (T). First generation SS-RDTs use purified extracts from laboratory-derived native parasites which are recognized by serum from infected individuals. More recently, recombinant bioengineered antigenic proteins have been favoured as they are cheaper to make and

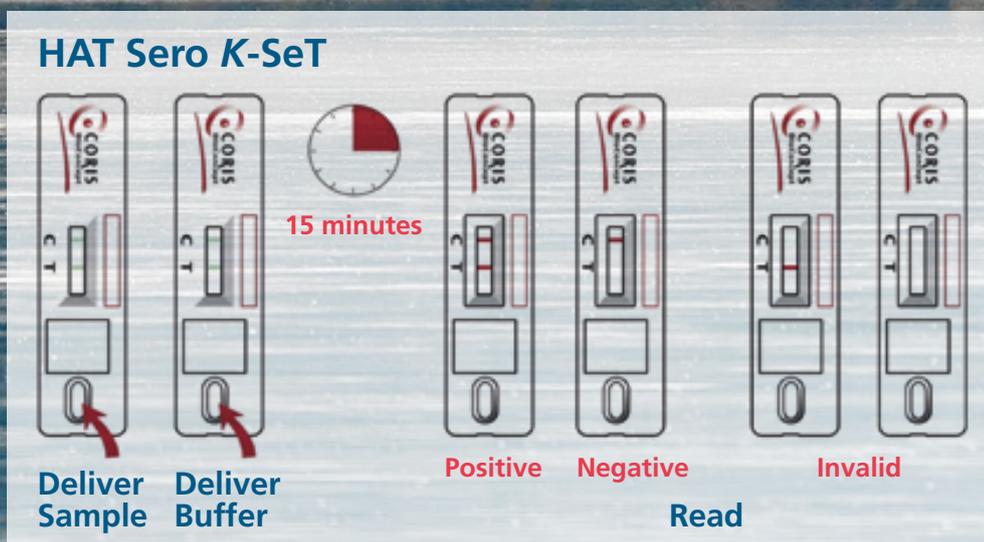


Figure 1
Rapid Diagnostic Test (RDT) for human African trypanosomiasis (HAT)

Making diagnostic tests for tropical diseases



Tsetse fly

more reproducible. However, making biosimilar antigens for parasitic surface proteins can be difficult as they may require complex post-translational modifications. Success has been found by engineering the related species, *Leishmania tarentolae*, and by modifying the glycosylation pathway of the yeast *Pichia*.

The recently awarded BBSRC Innovator of the Year award to the author displays the success of multinational collaborations in translating basic research results into POC tests that stand up to the demands of tropical usage. Access to a WHO SS biobank of characterized serum samples allowed rigorous testing of prototypes before the chosen test was scaled up for manufacture. Commercial companies were persuaded to waive intellectual property rights and made the tests at cost. It is currently undergoing an EU-funded, multicentred field trial in Guinea, DR Congo, Burkina Faso and Cote d'Ivoire.

The detection of human and animal reservoirs for these SS and other Kinetidoplast parasites is crucial to the control of these debilitating diseases in neglected populations. Following WHO guidelines on POC tests, we continue to search for new biomarkers and build international consortia to transform them into user-friendly RDTs.

Acknowledgements

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FURTHER READING



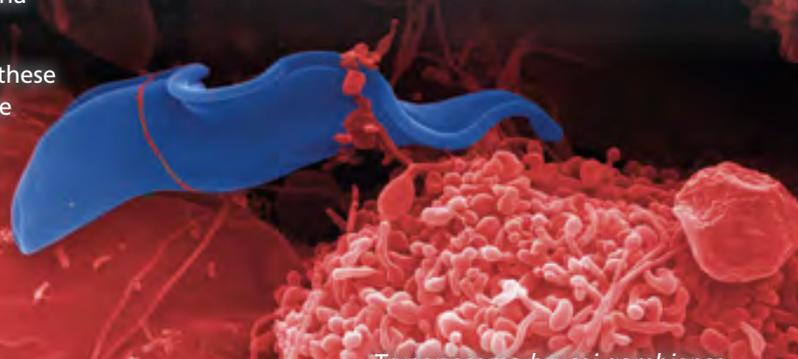
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Trypanosoma brucei gambiense



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DRUG DEVELOPMENT FOR VISCERAL LEISHMANIASIS

LIGHT AT THE END OF THE TUNNEL?

Visceral leishmaniasis (VL) is a tropical disease caused by the protozoan parasites *Leishmania infantum* and *Leishmania donovani*. Current estimates suggest that 500,000 new cases a year result in an annual death toll of approximately 40,000, making VL the second largest parasitic killer after malaria. Additionally, it is the leading cause of morbidity and mortality amongst the World Health Organization's Neglected Tropical Diseases (NTDs) group. The vast majority of VL infections occur in a handful of countries including: India, Bangladesh, Sudan, South Sudan, Somalia, Brazil and Ethiopia. In these endemic countries there is clear evidence that VL disproportionately affects the poorest of the poor with strong links between poor housing, malnutrition, deprivation and this vector-borne disease. Indeed, the severely debilitating nature of this disease can lead directly to the destitution of patients and their families. Outbreaks of VL are also often associated with periods of conflict. In South Sudan, years of forced migration, as a consequence of civil war, have resulted in on-going and lethal epidemics. In short, VL is an insidious disease that preys upon the most vulnerable, often targeting people at their very lowest ebb.

Leishmania spp. are obligate intracellular parasites of the cellular immune system, where they multiply in the hostile environment of macrophage phagolysosomes; transmission is by bloodsucking sandflies. The clinical

manifestations of VL tend to occur months after exposure and include fevers, weight loss, enlargement of the spleen and liver, and anaemia. In 95% of cases, death can be prevented by timely and appropriate drug therapy. However, all current therapies have serious limitations – they are expensive, toxic and have to be applied over long periods of time (mainly by injection) and may become ineffective as the parasites develop drug resistance. Thus, there is an urgent need for better, safer efficacious drugs that are fit-for-purpose in resource-poor settings. It should be noted that the vast majority of VL patients earn below the poverty threshold of US \$1.0 a day and there is little socialized healthcare in endemic countries. With the cost of bringing a new drug to market estimated at over \$1 billion, developing treatments for diseases of poverty, such as VL, has not been a high priority for the pharmaceutical industry. This lack of investment has contributed to the failure to license any new drugs for the treatment of VL for more than 15 years. The combined failure of Governments, pharmaceutical companies and the public at large to recognize the devastating impact of this disease means that VL can rightly claim to be the most neglected of the NTDs.

At the turn of the century two important events led to a sea change in attitudes towards NTD drug discovery. A thought-provoking article by Trouillier and Olliaro in

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1999 revealed that of the more than 1,000 new drugs sold worldwide during the period 1975–1996, less than 1% were destined for tropical diseases, despite the fact that these diseases represented 11.4% of the global health burden. The authors also drew attention to the rather piecemeal approach to NTD drug discovery at this time. The stark facts revealed in this article galvanized the scientific community into action. In 2003, the Drugs for Neglected Diseases Initiative (DNDi) was established, a non-profit organization dedicated to delivering new treatments for NTDs. Seed funding for this initiative was provided by the Nobel Peace Prize awarded to Médecins Sans Frontières in 1999. Over the past decade, DNDi has now been joined in this endeavour by a number of public-private partnerships, charities and Government-funding agencies. In addition, academic centres dedicated to NTD drug discovery have now been established, prompting pharmaceutical companies to become more engaged. Now, more than any other time in history there seems to be the collective will and financial backing to make real progress towards eliminating the scourge of VL and other NTDs. It will take time for these organizations to populate drug pipelines for VL and perhaps even longer before effective drugs reach the clinic. At least we can now dare to dream of a future without this devastating disease. Watch this space...

All current therapies have serious limitations – they are expensive, toxic and have to be applied over long periods of time

Patient receiving intralesional injection for the treatment of cutaneous leishmaniasis, Afghanistan



Dr Susan Wyllie

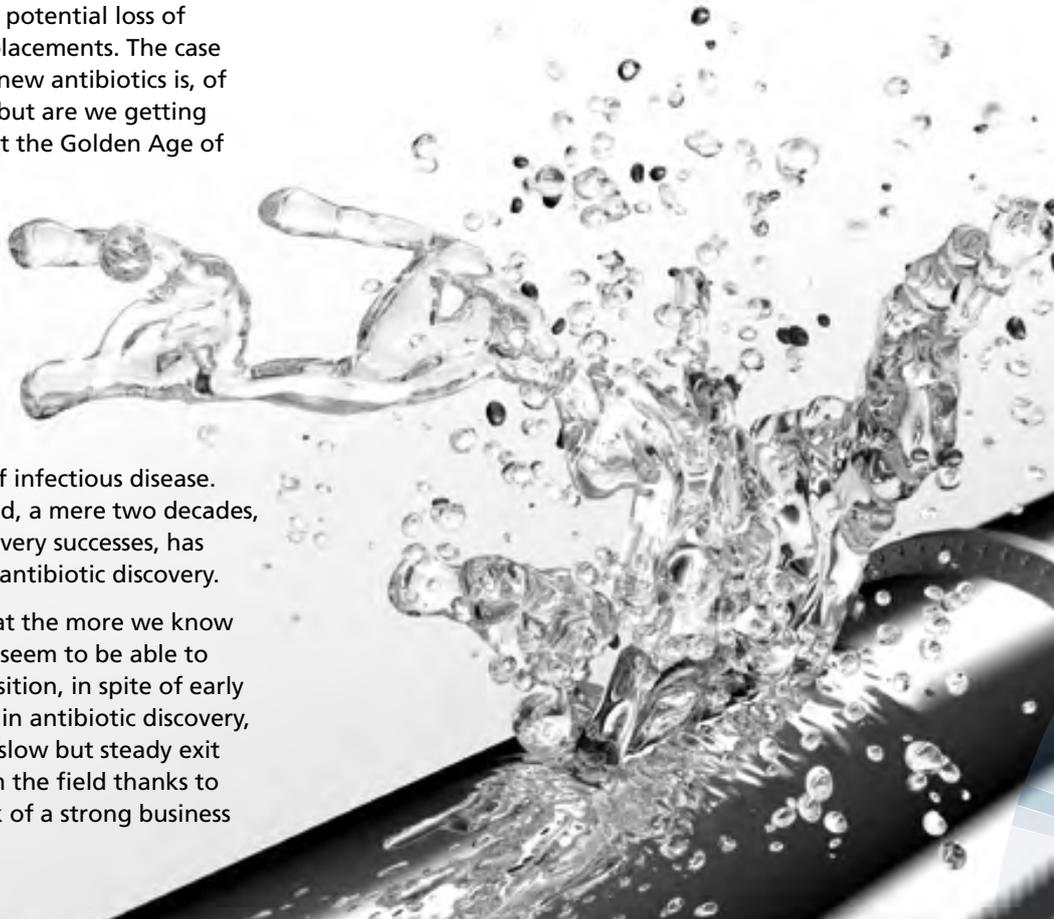
Wellcome Centre for Anti-Infectives Research, University of Dundee

The race to discover new antibiotics, to restock our depleted anti-infective drug arsenal in the face of the relentless emergence and spread of antibiotic resistance, and the necessity to regain lost momentum in antibacterial drug research in the private sector, collectively represent one of the great global challenges in human health for this generation. In a sector whose hand badly needs an ace, perhaps the greatest success of the past few years has been the scientific communities' ability to articulate clearly and persistently the scale of the twin threat from antimicrobial resistance and the potential loss of effective antibiotics without replacements. The case for discovering and developing new antibiotics is, of course, compelling and urgent, but are we getting anywhere? Is it possible to revisit the Golden Age of antibiotic discovery?

The 'Golden Age' of antibiotic discovery, which lasted from the early 1940s to the late 1960s, witnessed the discovery of numerous antibiotic compounds and yielded almost all the main classes of antibiotics we currently employ clinically for the management of infectious disease. However, a relatively brief period, a mere two decades, of extraordinary antibiotic discovery successes, has been followed by stagnation in antibiotic discovery.

Why is it the case, therefore, that the more we know about antibiotics, the fewer we seem to be able to discover? This apparent juxtaposition, in spite of early successes and intensive industry in antibiotic discovery, has ultimately brought about a slow but steady exit of the 'big pharma' players from the field thanks to diminishing returns and the lack of a strong business

case for new antibiotics. In February 2016, the O'Neill Review, in defining the facets of the AMR crisis noted that "*divestment has hollowed out the antibiotic industry over the years as prospective financial rewards diminished*". This combination of unfavourable conditions has created the perfect storm. However, despite the dire headlines and doom-laden warnings, concerted efforts appear to be showing some signs of success. Although encouraging, the field is febrile and setbacks have the potential to send chills through the entire antibiotic sector.



Although encouraging, the field is febrile and setbacks have the potential to send chills through the entire antibiotic sector

Finding new antibiotics is hard. The early pioneers of antibiotic discovery, including Alexander Fleming and, particularly, Selman Waksman, used a culture-based, activity-guided approach to successfully identify environmental microorganisms which produced antimicrobial activities in culture. The 'Waksman platform' widely adopted by the pharmaceutical industry mined soil bacteria for antimicrobial activities. Initially hugely successful, over-mining the limited culturable microbiome of the soil (*circa*. 1% of the microbes present) led to issues with dereplication and rediscovery of the same compounds. Identifying antimicrobial activities from cultured organisms is relatively straightforward, finding good lead compounds with a suitable spectrum of activity and pharmacological profiles (pharmacokinetic and pharmacodynamic parameters) is another matter entirely. As with other drugs, which (in general) must obey a set of rules known as 'Lipinsky's Rules' which predict the ability of a molecule to pass through biological membranes and become bioavailable, candidate antibiotic drugs must be able to rapidly achieve appropriate peak plasma concentrations *in vivo* to

CRACKS in the

ANTIBIOTIC PIPELINE



Previously uncultured Eleftheria terrae are able to make teixobactin, a new antibiotic class

(Image credit: William Fowle, Northeastern University)

FEATURES

ensure lethal or inhibitory concentrations of the drug reach the site of action. Antibiotics typically have to be administered in higher doses than other drugs, meaning the side effect profile is a particular concern. Furthermore, to be active, antibiotic drugs must traverse the lipid membranes of Gram-positive and (in particular) Gram-negative pathogens and evade efflux mechanisms which eject the antibiotic from the cytoplasm, maintaining intracellular concentrations of antibiotic beneath threshold inhibitory/cidal levels. In order to optimize natural products or design better synthetic antibiotics, numerous researchers have called for a similar set of rules to be developed, to facilitate prediction of compounds capable of traversing the protective cell envelope.

In 2015, a novel culture-based approach invented by Professors Kim Lewis and Slava Epstein of Northeastern University, Boston, the iChip, yielded the first new class of antibiotic in over 30 years. The iChip addresses a major bottleneck in antibiotic discovery, accessing a far higher proportion of the microbiome of for example, the soil, which is able to be cultured *in vitro* and can therefore be screened for antibiotic production. Typically, the number of microorganisms which are amenable to culture *in vitro* amounts to *circa* 1% of the total microorganisms present in most environments (the so-called 'great plate count anomaly'). It is this 1% which has, over the years, been interrogated for antibiotic production. This approach represents one effective mechanism by which the Waksman platform may be revisited to discover new antibiotics from soil microbes. Using this approach, Lewis' team isolated and screened over 50,000 soil bacteria, discovering a new class of antibiotic, teixobactin, from the previously unculturable *Eleftheria terrae*, which binds to a highly conserved region of lipid II and lipid III and inhibits cell wall synthesis. Teixobactin is active against *Staphylococcus aureus* and *Mycobacterium tuberculosis* and, to date, no reports of resistance have emerged. Teixobactin is hailed as a game changer in the sector, and its orally available derivatives are being developed by Novabiotic Pharmaceuticals, LLC with support from The Bill & Melinda Gates Foundation. Could innovations like the iChip change the way we discover antibiotics from nature and bring us back to the Golden Age of antibiotic discovery? Apparently the National Institute of Allergy and Infectious Diseases (NIAID) think so, since Lewis's team have just received a \$9M, five-year grant from them to develop the discovery platform and deliver new antibiotics.

Whilst this discovery brings much needed hope to a battle-weary sector, discovery is the first step on a long and sometimes arduous road towards translation to a clinically useful drug. The success rate for clinical development of drugs is notoriously low, and especially so with antibiotics. According to The Pew Charitable Trusts analysis, historical data suggests only one in five infectious disease products entering phase I clinical trials

end up gaining approval for use in patients. So what is the current state of the antibiotic pipeline?

According to the Center for Disease Dynamics, Economics and Public Policy (CDDEP) as of March 2016, there were six new FDA approvals for new antibiotic drug products (none of which represent a new class of antibiotic). These include three new glycopeptides; Dalbavancin (Dalvance[®], Xydalba[®]) (Durata Therapeutics, Actavis), a chemical modification of the teicoplanin scaffold and, Oritavancin (Orbactive[®]) (Eli Lilly, Targanta), a vancomycin derivative, and Tedizolid (Sivextro[®]) (Dong-A, Trius Therapeutics, Cubist Pharmaceuticals), an oxazolidinone derivative, all active against Gram-positives. A new broad-spectrum cephalosporin Ceftobiprole (Zevtera[®], Mabelio[®]) (Basilea) and two new cephalosporin-beta lactamase inhibitor combinations; Ceftazidime-avibactam (Avycaz[®]), (Actavis, AstraZeneca) (old cephalosporin, new ESBL inhibitor) and Ceftolozane-tazobactam (Zerbaxa[®]) (Cubist Pharmaceuticals), a new cephalosporin.

These agents were approved after designation as a Qualified Infectious Disease Product (QIDP) under the *Generating Antibiotic Incentives Now* (GAIN) act. This framework forms part of the US National Strategy for *Combating Antibiotic Resistant Bacteria* (CARB) launched in September 2014 by executive order from US President Barack Obama. QIDP designated drugs are eligible for several incentives, including fast track designation, expedited FDA review and qualification for five years additional marketing exclusivity on top of any exclusivity already provided by the Food, Drug, and Cosmetic Act.

The GAIN incentives, including QIDP designation, which aim to stimulate the sector by providing economic incentives for antibiotic drug discovery, have not escaped criticism from the industry. A 2017 report by the Government Accountability Office (GAO) included complaints from 10 interviewed pharma representatives, that the US FDA have yet to clarify its expectations for developing new antibiotics or to have detailed how to access new incentives, despite having issued 14 updated or new guidances on antibiotics since the GAIN act was passed in 2012. However, the report concedes that despite the lack of clarity, the FDA has approved more than 100 requests for QIDP designation between 2012 and 2015, and has approved six of the drugs (see above). An overall assessment of GAIN is premature however, as stated in the report: "*The GAIN provisions were passed five years ago, but it generally takes 10 to 15 years to develop a new drug and obtain approval from FDA. Therefore, GAIN has not been in place long enough yet to have been a factor in motivating any drug sponsors to develop and submit an application to FDA to market a new antibiotic*".

According to The Pew Charitable Trusts, in March 2016 37 'new' antibiotics (no new classes) are in clinical



The early pioneers of antibiotic discovery including Alexander Fleming (left) and, particularly, Selman Waksman (above) used a culture-based, activity guided approach to successfully identify environmental microorganisms which produced antimicrobial activities in culture

development, with 11 in phase I, 13 in phase II and 13 in phase 3. At least 11 of the antibiotics in development have the potential to treat infections caused by the ESKAPE pathogens. A total of 34 companies are involved, with only five ranking among the top pharmaceutical companies by sales, and 80% of the products in development are being pursued by small companies, half of which are 'pre-revenue' with no current products on the market. As of March 2017, the number of antibiotics in clinical development for the US market which have the potential to treat serious bacterial infections had risen to 41, with 16 having the potential to treat Gram-negative ESKAPE pathogens.

Yet, as followers of the recent story of solithromycin will attest, high profile setbacks remind the scientific community and investors alike of the scale of the challenge of antibiotic development. Solithromycin is a semi-synthetic 4th generation macrolide (fluorketolide subclass), which binds to 23S ribosomal RNA and disrupts bacterial protein synthesis, developed by Cempra Inc. for Gram-positive community acquired pneumonia (CAP) infections. In November 2016 promising results from two phase 3 trials led to a narrow vote (seven votes to six) by the FDA Antimicrobial Drugs Advisory Committee, recommending the drug for CAP. The ADAC also voted (12 votes to one) that "the risk of hepatotoxicity had not been adequately characterized". By late December 2016, the FDA had issued Cempra a 'complete response letter' (CRL) restating the committee's concerns over hepatotoxicity and requesting a 9,000 patient safety trial, amounting to a rejection of the drug. The FDA's CRL to Cempra led to a run of investor sell-off and sent Cempra's share prices into free fall, losing 56% overnight. In February 2017, Cempra hit another setback with solithromycin, which failed to demonstrate non-inferiority to older antibiotics in uncomplicated genitourinary gonorrhoea trials. Again, Cempra shares fell 18% in response. Given that a mere 18 months ago solithromycin was being tipped to be a major success story in a sector desperate for a win, it remains to be

seen how this shock will reverberate through the relatively small antibiotic R&D sector. The majority of the start-up/pre-revenue companies developing new antibiotics are unlikely to be able to absorb a similar financial shock.

The picture is encouraging, if precarious, given attrition rates for antibiotic lead compounds and the profile of companies involved. This indicates there is positive development in the antibiotic pipeline, but still no new classes of drugs becoming available. Any truly new class of antibiotic therefore must be at least 10–15 years away from the clinic given the current approval pathways. However, the mood music is right for antibiotic development generally. A combination of incentives for development activities, funding for early stage discovery research and expedited, streamlined regulation will speed the flow of drugs from a pipeline that has been dry for too long.

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Triatomine bugs (also called reduviid bugs, "kissing" bugs, cone-nosed bugs and bloodsuckers) can live indoors, in cracks and holes of substandard housing, or in a variety of outdoor settings

A very unpleasant 'kiss'

Most people, and all microbiologists, are fully aware of the threat of the rising tide of antimicrobial resistance (AMR) and the potential dawn of a 'post-antibiotic' age when currently routine surgery could lead to life-threatening infections. AMR and the need for new therapies and other measures to mitigate imminently untreatable bacterial infections has become a cause célèbre, attracting the attention of Westminster politicians, Government health officials, the media and, of course, the general public.

However, and in contrast, the so-called Neglected Tropical Diseases (NTDs) remain outside the UK public conscience and garner limited interest from Government, the media, most healthcare professionals and many medical microbiologists. NTDs represent a spectrum of 18 diseases of the developing world, which together affect more than 1 billion of the world's most deprived people and exert a greater burden than malaria, tuberculosis and HIV (more recognized global infectious diseases) combined. This burden is manifested not just in mortality, but also in the social and economic impact that long-term NTD morbidity can have by delaying educational development and reducing employment capacity.

NTDs are caused by a range of bacterial, viral, helminth (worm) and protozoan pathogens which are prevalent in the developing world. As the term NTD suggests, research into these pathogens and the diseases they cause has been historically limited and therefore the tools for control (drugs, vaccines and epidemiological monitoring) have been lacking. However, in 2012 the London Declaration for NTDs pledged many Governments, NGOs and pharmaceutical partners to control or even eliminate many of these diseases by 2020. Five years on and the progress has been excellent for several NTDs, for example, we have seen the number of cases of the protozoan disease Human African trypanosomiasis (HAT or African sleeping sickness) reduced to less than 3,000. This has been achieved through a combination of improved diagnosis and treatment, combined with control of the tsetse fly vector which carries the disease. The NTDs leishmaniasis and Chagas disease are caused by related protozoan parasites however, in contrast to HAT, progress towards elimination, or even control, has been described as a losing battle. The reasons for this are complex and to illustrate I will now focus on Chagas disease.

Chagas disease received its name from Carlos Ribeiro Justiniano Chagas (right), a Brazilian physician and researcher who discovered the disease in 1909. To this day, Brazil bears the greatest burden of this disease, which is endemic in 21 Latin American nations. Eight million people are estimated to



be infected by the parasite that causes Chagas disease, *Trypanosoma cruzi*. As a result of increased migration, these cases are spread worldwide, however the bulk are in Latin America – the only region where transmission of the parasite occurs. This is due to the geographic restriction of the insect vector, the curiously named kissing bug. These bloodsucking triatome bugs live in the walls and roofs of poorly constructed and maintained homes of both urban and rural areas, coming out at night to feed on the inhabitants. Usually, when they take a bloodmeal the kissing bug defaecates, and when the faeces enter the body through the created wound it can carry with it the *Trypanosoma cruzi* parasite – a very unpleasant 'kiss'. However, in addition to this 'natural' route, organ transplantation and blood transfusion from an infected individual can also lead to transmission.

Following infection, Chagas disease has two distinctive phases, first an acute stage during which symptoms are usually mild or even absent. It is during the second, chronic phase that the major health problems occur. In this stage, the parasite is sequestered into cardiac and digestive muscle, and around 30% of patients suffer cardiac problems, with up to 10% succumbing to digestive and/or neurological complications. As the disease progresses, infection can cause death due to heart arrhythmias or progressive cardiac disease. Approximately 10,000 people die each year in this manner, and millions more suffer the consequences of long-term ill health. Despite this burden, and behind the intractability of Chagas disease, only two drugs are available for treatment, benznidazole and nifurtimox, neither of which is very effective in the chronic, and fatal, phase. This means that early treatment is essential, even if an individual is asymptomatic. However, diagnosis can be problematic, and both drugs require prolonged administration and have toxicity issues – for example, nifurtimox is contraindicated in individuals with a history of psychiatric disorders. In the absence of a vaccine new, less toxic drugs are urgently required – therapies which would allow the effective treatment of chronic Chagas disease.

It is in this environment that we, as academic researchers, are labouring. To facilitate drug discovery in all disease areas, it is recognized that well-validated

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Geographical distribution of Chagas disease in Central and South America.



targets must be put forward to allow the high-throughput screening (HTS) of pharmaceutical company compound libraries to proceed with the maximum chance of a successful outcome, i.e., a compound entering clinical trials. However, drug target validation is often fraught with difficulty and expensive failure, leading to widespread concerns regarding the reproducibility of drug target validation studies, with a call to "embrace chemistry at the interface with biology". With the knowledge that NTDs, including Chagas disease, deserve and demand the best validated drug targets, funded by the Medical Research Council, Durham University is leading an international network of endemic countries to develop multidisciplinary skills to address this issue and meet the challenges of *Trypanosoma cruzi* drug target validation head on.



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Durham University

Strategies to reduce leprosy transmission in hyperendemic regions in Brazil and elsewhere in the world



Leprosy is a chronic disease of the skin and nerves caused by infection with the uncultivable intracellular pathogen, *Mycobacterium leprae*. It is an ancient disease, the oldest known to be associated with humans, with osteological evidence of characteristic bone pitting and deformities found in burial sites in India as far back as 2000 BC. Although leprosy is completely curable today with chemotherapy, delays in diagnosis and receiving treatment frequently result in advanced cases of nerve damage, muscle loss, blindness, and bone deformity and resorption, with resulting disfigurement, disability and stigmatization.

Treatment with multidrug therapy (MDT) has been available since the mid-1980s, and by 2001 effective global leprosy elimination campaigns sponsored by the World Health Organization (WHO) had reduced the prevalence by 89%. Gaps exist in the knowledge of how *Myco. leprae* is transmitted, what genetic factors and innate and adaptive immune responses of the host lead to resistance or susceptibility to disease, the long

incubation time prior to the slow development of diverse symptoms, and the very low rate of disease progression in infected individuals, that all create challenges to the development of ways to interrupt transmission. In 2015, 210,758 new cases were diagnosed worldwide, with 8.9% being detected in children less than 15 years old and 6.7% of those having grade 2 disability (G2D). Higher rates of G2D indicate a delay in the detection and diagnosis of leprosy and ranged from 1.8% in Micronesia to 42.1% in Somalia. Leprosy in children is an important epidemiologic indicator and is correlated with multiple active foci of disease transmission in the community. Three countries, India, Brazil and Indonesia, accounted for 81% of all new cases detected in 2015.

Brazil detected 26,395 new cases that year and remains the only country in the world that has not met the WHO goal of less than 1 new case per 10,000 population, and is currently at around 1.2/10,000. There is tremendous regional variation in the new case detection rates (NCDR) in Brazil, with low rates in the southern states like Rio Grande do Sul (0.1/10,000) while high or hyperendemic rates (defined as between 2 and more than 4 new cases per 10,000, respectively) are found in the central-western, northeast and northern

regions of the country. States in the Amazon region have only around 17% of the total population of Brazil, but report over 50% of all of the new cases of leprosy. Recent data from Brazil's national disease notification database (SINAN) show that around 50% of the population living in 19 out of the 27 states of Brazil are exposed to either high or hyperendemic rates of infection. Mathematical modelling studies projecting trends to reach the goal of less than 1/10,000 in the state of Pará, based on NCDR available from SINAN, suggest that this will not be realized until at least 2030 or 2061. Although taking into account the present actual NCDR based on our active case-finding studies in multiple cities, achieving this goal may not realistically be attained until much later. Recent surveys in even supposedly low endemic regions in São Paulo state (0.23/10,000) and the Federal District in Brasília (0.52/10,000) revealed unexpectedly high rates of hidden leprosy cases (24 new cases in 1,398 individuals in Jardimópolis, São Paulo [1.7%], and 44 new cases in 390 individuals in Brasília, [11.3%]), which were only



Brazil detected 26,395 new cases that year and remains the only country in the world that has not met the WHO goal of <1 new case per 10,000 population

revealed with targeted surveillance in these areas. These findings illustrate the importance of active surveillance by experienced leprosy dermatologists and additional case-finding among the household contacts of newly diagnosed cases, since it is estimated that the number of hidden cases of leprosy is likely to be up to 8-fold higher than the prevalence in the area at any given time.

Recent studies in low- or medium-endemic regions of Brazil indicate that there has been a shift in those groups experiencing the highest risk of succumbing to leprosy, primarily with a much higher increase in older individuals (peaking at 60–69 years old), almost a 2-fold higher risk of multibacillary MB disease in men compared with women in all states regardless of economic class, and progressively higher rates of MB disease, indicating a higher bacillary load. These trends are similar to the reduction in the prevalence of leprosy in Norway in the 1920s prior to the availability of drug therapy, where improvements in economic growth, sanitary conditions, clean water, reduction in the housing density and improved hospital infrastructure gradually reduced the bacillary load in the general population and resulted in the eventual elimination of leprosy in that country by the mid-20th century. Although these trends appear to represent that leprosy is on the wane in some parts of Brazil, the integration of leprosy control into the family health strategy means that there are fewer trained professionals capable of recognizing classic symptoms of skin lesions and nerve damage resulting in higher yearly reports of MB disease and G2D, indicating delays in diagnosis that can only increase the rates of disability and transmission. Evidence has accumulated that there are large numbers of asymptomatic, undiagnosed or misdiagnosed cases, and that up to 4 million of these hidden cases may exist by 2020 worldwide, representing a major threat to efforts by endemic countries to interrupt transmission and reach the global elimination target set recently by the London Declaration.

The Human Development Index (HDI) is a composite numeric measurement established by the United Nations Development Programme in 1990 to assess three basic dimensions of human development, namely life expectancy at birth, mean years of schooling and standard of living based on Gross National Income per capita. The HDI in Brazil has improved 23.4% over the last 25 years (currently at 0.755, considered a high HDI). However, due to inequalities in the distribution of human development in different regions of the country, the northern states in the Amazon region, including Pará state, consistently rank near the bottom for the HDI index, which likely reflects issues of health and healthcare availability for people living in the area. Currently, the family health strategy provides basic health coverage for only about 50% of the population in Pará. As a result of integrating leprosy diagnosis into

the family health strategy and reduced numbers of trained physicians capable of correctly diagnosing disease symptoms, new case detection relies mainly on passive detection of cases in most areas of the country, resulting in the relatively low numbers of new cases reported into the SINAN database for this region.

Over the last few years, the principal stakeholders, including the WHO, involved in promulgating strategies aimed at reducing the global burden of leprosy, particularly in hot spots or high to hyperendemic regions, agree that early diagnosis, contact tracing and treatment of all patients should be part of the overall strategy. Since 2009, our group has focused attention on over a dozen cities in the northern state of Pará, Brazil, which historically has had one of the highest NCDR in the country ($>4.0/10,000$), and based on current rates there will be 40,000 new cases in children diagnosed in the next decade in this state alone. Our strategy utilizes active surveillance of schoolchildren and the household contacts of newly diagnosed cases, averaging 4% in children and 8% in household contacts. Each team consists of an experienced leprologist, a physiotherapist to look for muscle weakness and nerve pain, a nurse, a phlebotomist to draw a blood sample to assess anti-PGL-I antibodies (a known biomarker of *Myc. leprae* infection) and laboratory and field personnel to collect demographic data. In addition, we strongly rely on assistance from the local community health agents and health authorities from the basic family health units who live in the area and can direct us to known or suspected cases living there. During our week-long visits, we bleed and examine between 500–1,000 children and household contacts. During the period 2013–2014, we visited seven different cities in the state of Pará, examining 4,617 individuals and diagnosing 387 new cases of leprosy (8.4%). In the laboratory, we used Geographic Information Systems (GIS) to map hot spots within cities so follow-up studies can be performed on families living in the most affected areas. We are also developing and evaluating new rapid diagnostic lateral flow tests and using PCR to screen individuals for *Myc. leprae* earlobe colonization that we hope will eventually be able to identify those individuals that are most at risk of progressing to disease, particularly in families living in these identified hot zones. In addition, there are large-scale clinical trials underway coordinated by national programmes that are examining the efficacy of the use of post-exposure prophylaxis (PEP), either single dose rifampicin (SDR) or other multidrug short-course therapy regimens in multi-country locations to evaluate the potential of accelerating the reduction of transmission in high and hyperendemic areas. There are strong hopes that the use of these kinds of aggressive strategies and rapid diagnostic tests will ultimately break the lines of transmission and successfully remove leprosy as a major health concern.



Support

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John S. Spencer Colorado State University, left
Marco Andrey Cipriani Frade Universidade de São Paulo, centre
Claudio G. Salgado Universidade Federal do Pará, right

Coming soon...

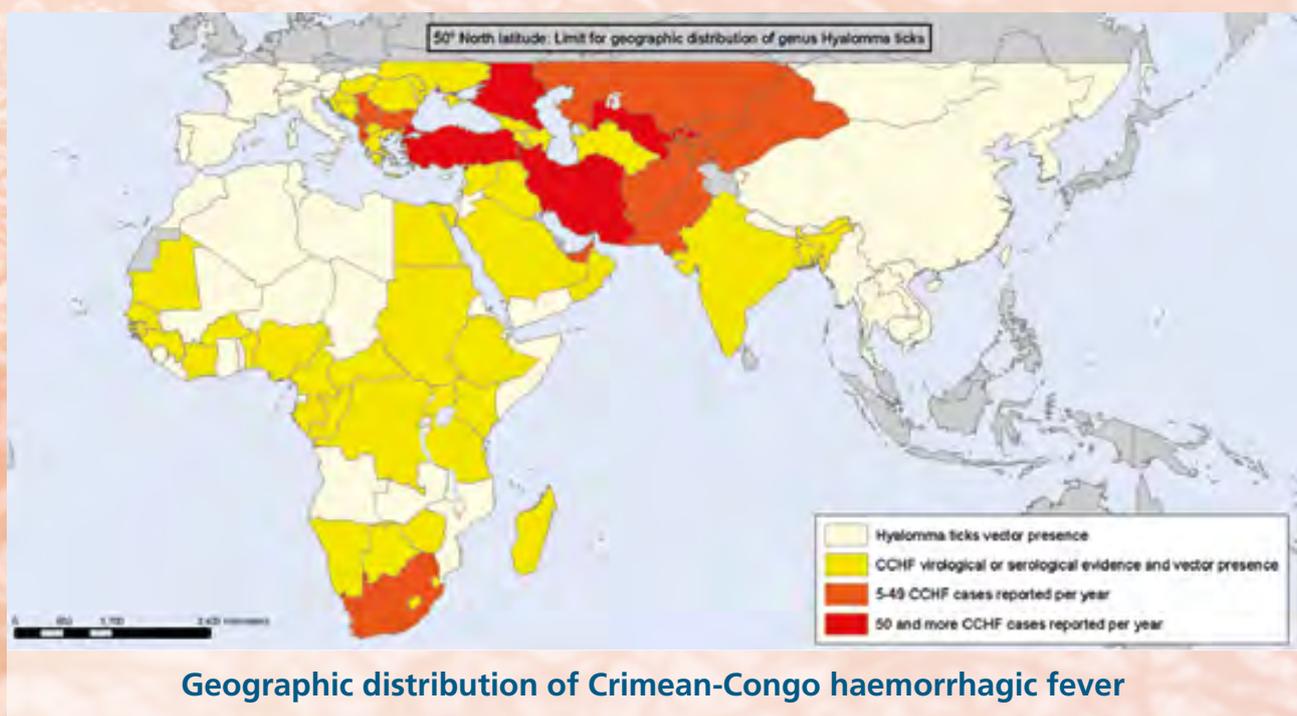
CRIMEAN-CONGO haemorrhagic fever

Crimean-Congo haemorrhagic fever (CCHF) is a severe tick-borne zoonosis with a case fatality rate of up to 30%. CCHF is caused by a negative sense RNA arbovirus (CCHFV), genus *Nairovirus* of the family *Bunyaviridae*. It has been designated as a priority pathogen for research and development by the World Health Organization, with the first reported outbreak occurring in Soviet military personnel in 1944 in the Crimea. In 1956, the same virus was isolated in the Congo and the current distribution pattern of the virus is extensive – from western China to Southern Europe and most of Africa.

The *Hyalomma* spp. (in particular *H. marginatum*) act as both reservoirs and competent vectors; the crushing of attached ticks enhances CCHFV transmission and should

be avoided. Due to the high level of *Hyalomma* spp. tick carriage on livestock, occupations with animal contact are high risk for CCHF – slaughterhouse workers, farmers and livestock handlers. Other well-described routes of transmission include exposure to the blood, body fluids or tissue of asymptomatic viraemic animals. The ritual slaughter of animals during religious festivals is a high-risk scenario for CCHFV transmission – the first confirmed case of CCHF in the UK was in a returning traveller who attended a feast in Afghanistan; a further two cases of CCHF have been described. Following hospital admission there is significant potential for nosocomial transmission – numerous reports have been described following either direct or aerosolized exposure to blood or body fluids.

CCHF distribution map modified and reproduced with permission from the World Health Organization.



Turkey is now at the centre of the Eurasian epidemic with over 10,000 cases reported since its emergence in 2002



The case fatality rate varies from 5% to 30% by location; with the lowest rates consistently reported in Turkey

CCHF outbreaks occur when anthropological events – travel, mass congregations and agricultural practices (such as reclaiming of scrubland for grazing livestock) – coincide with a supportive ecological factor – tick populations and activity peak in summer months or bird migration routes on a background of an overall trend towards a warming climate. The recent case reports from Spain demonstrate the widening geographical area affected by CCHF, the likely low-level persistent circulation of CCHFV within livestock and the role of migrating birds transporting CCHFV-infected ticks to Southern Europe from North Africa.

Turkey is now at the centre of the Eurasian epidemic with over 10,000 cases reported since its emergence in 2002. Significant numbers of cases occur annually in

Pakistan, Iran, Russia and Kazakhstan, but yet are rarely reported. Travel between the UK and this region of Asia is commonplace – particularly around the time of religious festivals such as Eid al-Fitr or Eid al-Adha. Seroprevalence studies have suggested that rates of sub-clinical infection reach up to 12–17% of the population in hyperendemic regions. The case fatality rate varies from 5% to 30% by location; with the lowest rates consistently reported in Turkey. Although Turkey provides high levels of supportive care, including access to critical care interventions, case fatality rates are also influenced by coordinated surveillance programmes including public engagement, which result in the diagnosis of a high proportion of mild cases in Turkey, frequently missed in other countries. There may also be different genetic host immune response factors and differing virulence amongst the circulating CCHFV strains.

The pathogenesis of CCHF is poorly understood, due to a lack of CCHF animal models until recently, and its occurrence in remote locations without biosecurity level 4 laboratories. Sepsis pathophysiology occurs in severe diseases with treatment options for CCHF focused on supportive measures, including access to blood product support. Ribavirin has demonstrated antiviral activity *in vitro* and *in vivo* against CCHFV, but its benefit in clinical disease is controversial. The majority of studies of ribavirin use in CCHF are retrospective observational reports, with significant baseline confounding and potential selective outcome reporting. Systematic reviews have failed to demonstrate clear benefit, but following a recent WHO expert guideline development group meeting, utilizing GRADE methodology and supported by Cochrane reviews, ribavirin was given a conditional recommendation for use, with most efficacy expected in early-stage disease. Although limited by low-quality evidence, there is however, broad consensus of its utility in post-exposure prophylaxis for high-risk CCHFV exposures. Newer therapeutics such as favipiravir and monoclonal antibody combinations are planned for



FEATURES

evaluation in clinical trials in endemic settings, as part of a CCHF R&D roadmap coordinated by the WHO.

In the interim there needs to be concerted effort to improve infection, prevention and control practices in both endemic settings and for exported cases. A recent survey of 23 hospitals in Eurasia that routinely manage CCHF cases demonstrated ongoing nosocomial risk, even in CCHF experienced centres. Unpublished data from hospitals in the North West of England showed that clinicians performed poorly in eliciting a travel history in the initial assessment. Hopefully as a direct result of the West African Ebola epidemic, this has improved in combination with a familiarity of isolation procedures and the safe use of PPE. CCHFV has a much lower risk of person to person or nosocomial transmission than other viral haemorrhagic fevers such as Ebola, and in the healthcare setting can mainly be mitigated by simple measures including: prompt isolation of suspect cases, universal precautions focused on sharps safety and PPE to prevent splash of bodily fluids onto mucous membranes.

Recognizing the emerging threat of CCHF, including the recent confirmation of autochthonous transmission in Spain, clinicians must consider CCHF in febrile returning travellers, particularly in those with a history of tick bite or contact with animal tissue or blood. Although the initial clinical syndrome is non-specific, thrombocytopenia and elevated liver enzymes are almost universal in CCHF. Patients with a travel history and negative malarial screen require further risk assessment and discussion with infection specialists, including with the national fever service as required.

FURTHER READING



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Nick J. Beeching left
Tom E. Fletcher centre
Natalie E. R. Beveridge right

Liverpool School of Tropical Medicine, Liverpool

W H PIERCE PRIZE



Brendan Gilmore 2017



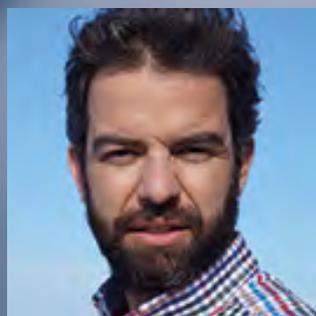
Jack Gilbert 2016



2018



Nicola Stanley-Wall 2015



Vasilis Valdramidis 2014



Lori Snyder 2013



Brian Jones 2011



Mark Webber 2010

Nominations Open

This prestigious prize is awarded each year at the Annual Applied Microbiology Conference to a young microbiologist (under 40!) who has made a substantial contribution to the science of applied microbiology. It is worth £3000! The award was instituted in 1984 by the directors of Oxoid to commemorate the life and works of the late W H (Bill) Pierce, former Chief Bacteriologist of Oxoid Ltd and a long-time Member of the Society. Application is through nomination by Full Members of the Society only. To nominate a candidate please contact the SfAM office, including a full CV of the nominee and a letter of support. The closing date for applications is 12 May 2018.



London's MICROBIOTA

A series on applied microbiology themes in the capital

Lunch on a plague pit

Bunhill Fields cemetery in the City Road is a quiet haven on the edge of the City of London mainly attracting office workers seeking lunchtime tranquillity or possibly a shortcut to the Artillery Arms pub in Bunhill Row. Its history as a burial ground goes back to Saxon times and it was used in 1549 for the disposal of more than a thousand cartloads of bones from the charnel house at St Paul's. As unconsecrated land, it later became widely used as a cemetery for non-conformists and is the final resting place of some literary notables such as William Blake, John Bunyan and Daniel Defoe.

Defoe had a colourful career but is mostly remembered as the author of *Robinson Crusoe*, published in 1719 and credited by some as being the first English novel. In a later work, *A Journal of the Plague Year*, he also founded the literary genre sometimes known as 'faction' where true events are subject to fictional reconstruction. Written 50 years after the events it describes, it gives a London merchant's vivid account of the plague's progress through London in 1665. This was one of the last great outbreaks of the second plague pandemic, and the worst in England since the Black Death of the 14th century had cut a swathe through Europe, killing an estimated 30–40% of the population. It is therefore perhaps fitting that Defoe's final resting place was once designated as a burial pit for plague victims, although it was probably never used as such and Defoe died in 1731, in hiding from his creditors and probably from a stroke.

The book is often taken as an authentic account, but Defoe was only 5 years old at the time of the plague. He did, however, carry out extensive research on his subject and probably also had the recollections of his elders to draw on.

Among other things, he records that the parish of St James, Clerkenwell, close by the SfAM office of today, was one of the areas where an early increase in mortality rates heralded the outbreak. It was apparent that the illness was contagious but centuries before the germ theory of disease the authorities were virtually powerless to control it. An atmosphere of doom and foreboding descended on the city as an estimated 100,000 of the population died. The poor, as ever, were most affected; the rich mainly did what has always served them well in such circumstances and fled the scene – the King, the Court and Parliament decamping to Oxford. Their behaviour was in stark contrast to the inhabitants of the Derbyshire village of Eyam who, when the plague arrived in a batch of cloth sent from London, voluntarily isolated themselves to avoid spreading the infection more widely, incurring increased mortality rates as a result.

Identification of the plague bacillus had to wait until the heyday of the 'microbe hunters' at the end of the 19th





Mass burial uncovered at Crossrail Liverpool Street site

century and the start of the third plague pandemic which emerged in Eastern China. In a famous tale of scientific rivalry, Yersin, a former pupil of Pasteur, arrived in Hong Kong during an outbreak of bubonic plague shortly after the arrival of a larger, better-equipped Japanese team under the leadership of Kitasato, a former pupil of Koch. Kitasato's team was favoured by the Hong Kong authorities and given every facility. They soon claimed to have isolated what they thought was the plague bacillus – a Gram-positive organism – from the finger of a dead sailor. Yersin had only two unskilled assistants, one of whom promptly absconded with his money, and received much less local support, having to work in a straw hut in the grounds of the main hospital. Initially excluded from access to plague victims, he was obliged to bribe mortuary guards enabling him to obtain fluid from a bubo on a victim from which he isolated the Gram-negative *Pasteurella* (now *Yersinia*) *pestis* and demonstrated its transmissibility to animals.

In his paper, Yersin noted the large numbers of dead rats in infected areas and their susceptibility to the infection, leading him to conclude that they were probably the major vector of the disease. In bubonic plague, the organism is injected under the skin through the bite of a rodent flea. It spreads through the tissues and lymphatic system, collecting at the lymph nodes where the haemorrhagic inflammation it causes gives rise to the characteristic buboes. Other forms of the disease, more rapidly fatal if left untreated, are caused when the organism is injected directly into the bloodstream (septicaemic plague) or inhaled in droplets into the lungs (pneumonic plague). These forms of transmission can also occur in a large outbreak initiated as bubonic plague.

Although there is doubt whether Bunhill Fields was ever actually used as a plague pit, archaeologists have recently been given unprecedented access to several other plague sites in London as a result of Crossrail; a project which has entailed digging 42 km of tunnels under London. This has revealed a massive burial pit at Charterhouse Square where victims of the 14th century Black Death were interred, confirmed by detection of *Y. pestis* DNA in tooth pulp from 4 of 12 skeletons tested. Further east, next to Liverpool Street Station, a mass grave containing 45 individuals was discovered in the Bedlam Burial Ground – named after the nearby Bethlehem Hospital for the mentally ill. The presence of *Y. pestis* DNA was again confirmed in 5 of 20 individuals tested. A few years ago, samples from yet another plague burial at East Smithfield, near the Tower of London, enabled the sequencing of the whole genome of *Y. pestis* when it was found to differ little from present-day strains.

Though plague is still with us and 1,000–2,000 cases are reported to the WHO each year, its effect has been mitigated over time and effective antibiotic treatment has been a major factor in this. Ominously though, antibiotic-resistant strains have been reported giving further urgency to campaigns highlighting the problem of antimicrobial resistance. In a recent quiz show a contestant was asked the name of the person, initials A.F., associated with the discovery of penicillin – they answered Aretha Franklin. Clearly we still have some way to go...



Martin Adams

SfAM President 2011–2014

FOCUS
FOR
M

MAKING THE MOST OF NEW OPPORTUNITIES

It's been a busy second half of the year here at the Royal Society of Biology – and activity continues apace as we move into 2018.

With a jam-packed calendar has come a whole host of opportunities too, not just for the RSB, but also for our partners, our individual membership and our Member Organizations, including the Society for Applied Microbiology.

Back in July we saw another successful Parliamentary Links Day take place at Portcullis House in Westminster. The day brought scientists and Government policymakers together at a key point just after the formation of the new Government, for keynote talks and two panel discussions that were well received by the densely packed audience of researchers, sector leaders and those from other organizations, including SfAM. It was a key moment to listen and to make our voice heard.

The theme of *UK Science and Global Opportunities* presented not only an opportunity for researchers to pitch their questions and queries directly to senior leaders, but also for open discussion, and a chance for communities to share their views and work together to ensure the best for their members.

Science Minister Jo Johnson and Chair-designate of UKRI, John Kingman have both continued to highlight the opportunity to improve capacity for interdisciplinary research through the new research council structure and continued commitment to the Haldane Principle. As structural development continues we will need to see how this delivery will emerge.

The theme of global opportunities was also evident at this year's International Biology Olympiad (IBO), which took place at the end of July at the University of Warwick. This year, the IBO saw over 250 students travel from 67 countries to compete in what is arguably the biggest competition in the world for pre-university biologists.

The competition was an opportunity to showcase the UK's strength and achievement in the biological sciences with the UK team of four winning one gold, one silver and two bronze medals – a great achievement.

International movement and collaboration of researchers and investment in projects continue to be topics of importance as we head towards Brexit. The beginning of formal negotiations for the exit is concentrating minds and beginning to bring some clarity about negotiating positions and offers, but there are a huge number of issues to be considered, and many of them will need to draw upon science knowledge or will impact the science community.

The Ministers at BEIS and DExEU with relevant responsibilities, Jo Johnson and Robin Walker, co-chair a high level stakeholder working group on EU exit, universities, research and innovation to which RSB contributes and we continue to seek input from across the biosciences to inform our interactions with this and other forums. It is only by working together that we can truly ensure the right messages are communicated.

Academic communication is also a complex activity and recent changes to the ways and means by which it is supported have implications for the research community. Publishing by learned societies is an important way in which they achieve their charitable objectives to communicate and guard their specialisms, and also derive a surplus to invest in meetings, grants and outreach.

We recently held a meeting for learned societies to discuss proposals by some UK universities for a Scholarly

Communications Licence, and I look forward to engaging as these proposals develop to ensure that they move in a direction that benefits our membership and our Membership Organizations. At the time of writing concerns still exist.

October saw the sixth annual Biology Week, with more than 100 events taking place across the UK and indeed the world, with teachers, students, professors, academics, whole organizations and members of the public alike coming together to celebrate the biosciences.

One of the highlights of the week was our Parliamentary reception; as a Society we aim to provide a unifying voice for the biosciences to Government, and this event very much solidified this sentiment in bringing together politicians, policymakers and our own members in recognizing the vital importance of the biosciences to the UK.

Before the year comes to a close we'll be back at the Houses of Parliament, for the annual Christmas reception organized by the Royal Society of Biology on behalf of the science and engineering community.

Representatives from across a range of STEM disciplines, including those from SfAM, will come together with parliamentarians and reflect on how we have progressed as a community throughout 2017, what we see as the priorities and challenges for 2018, and build community and networks to meet them.

2018 looks to be another busy year, and the RSB and SfAM will continue to work hard to represent the views and interests of our Members and strengthen the biosciences community as a whole.

International movement and collaboration of researchers and investment in projects continue to be topics of importance as we head towards Brexit



Dr Mark Downs CSci FRSB
*Chief Executive of the
Royal Society of Biology*

Applications of plant pathology: from field to clinic

10:00am to 5:30pm | 18 April 2018 | Charles Darwin House | London

REGISTRATION FEES

before 18 March 2018

SfAM & BSPP
Members **£100**

ECS/Life Member **£80**

Non-Member **£200**



Dr Fran Lopez Ruiz
Curtin University, Australia



Dr Saskia van Wees
Utrecht University, Netherlands



Dr Carrie Brady
University of West England, UK



Dr Petra Louis
University of Aberdeen, UK

For further details visit www.sfam.org.uk or contact laura@sfam.org.uk

This meeting will cover rapid responses to emerging pathogens, detection methods, plant-microbe interactions, and the plant microbiome and its importance for plant and human health.

Key speakers include:



Dr Sandra Denman
Forestry Commission, UK



Prof. Gail Preston
University of Oxford, UK



Dr Leighton Pritchard
The James Hutton Institute, UK



Prof. John Draper
Aberystwyth University, UK



Dr Eric Boa
University of Aberdeen, UK



Dr Adrian Fox
Fera Science, UK



ANNUAL CONFERENCE

Passport to Infection Infections of Travel and Leisure

9 – 11 July 2018 | The Grand, Brighton, UK

Highlights

ECS WORKSHOP: PUBLIC SPEAKING

11:00 | 9 JULY 2018

JOURNAL of APPLIED MICROBIOLOGY LECTURE

18:00 | 9 JULY 2018

PRE-CONFERENCE ICEBREAKER and QUIZ NIGHT

19:30 | 9 JULY 2018

WELCOME SPEECH and KEYNOTE LECTURE

09:00 | 10 JULY 2018

SfAM NEW LECTURER RESEARCH GRANT LECTURES

14:30 | 11 JULY 2018

W H PIERCE PRIZE LECTURE

16:00 | 11 JULY 2018

CONFERENCE DINNER and DRINKS RECEPTION

19:00 | 11 JULY 2018

TUESDAY 10 JULY 2018

Fever in the returning traveller
Don't go into the water! Dangers of swimming
Infections from fresh water – lakes to hot tubs
Holiday romance – is it worth it?
Unusual holiday tales (selected case reports)
Migration and health – managing health of mobile populations

WEDNESDAY 11 JULY 2018

Lessons learned from EuroTravNet
Exotic foods and unusual infections
Cruise ships and health
Sun, sea and surgery – infection risks of medical tourism
Veterinary cross-border infection controls

KEY LECTURES

FEES BEFORE 2 JUNE

(INCLUDES ACCOMMODATION):

Member	£450
ECS / Life Member	£390
Non-Member	£780

INDIVIDUAL DAY RATE BEFORE 2 JUNE

(WITHOUT ACCOMMODATION):

Member	£90
ECS / Life Member	£70
Non-Member	£140

Deadline for abstract submissions and Studentship Grant applications:
10 March 2018

To book and for further details see www.member.sfam.org.uk
or contact laura@sfam.org.uk



INFECTIOUS DISEASES HUB

The home of medical microbiology

Without any context, the name 'Infectious Diseases Hub' might not sound an appealing prospect, but for those in the know, Infectious Diseases Hub (ID Hub) is a free-to-access website open to all researchers, students and anyone else who might have an interest in the many aspects of medical microbiology.



'Infectious diseases' is a broad net and we do aim to cover all aspects of microbiology, virology, mycology and parasitology

The site is provided by the Future Science Group – a progressive publisher focused on breakthrough medical, biotechnological and scientific research. The company has previously launched other successful websites in different areas of the life sciences; however, last year it became clear that infectious disease is a huge and exciting research area and with the idea of comprehensively covering this, ID Hub was conceived.

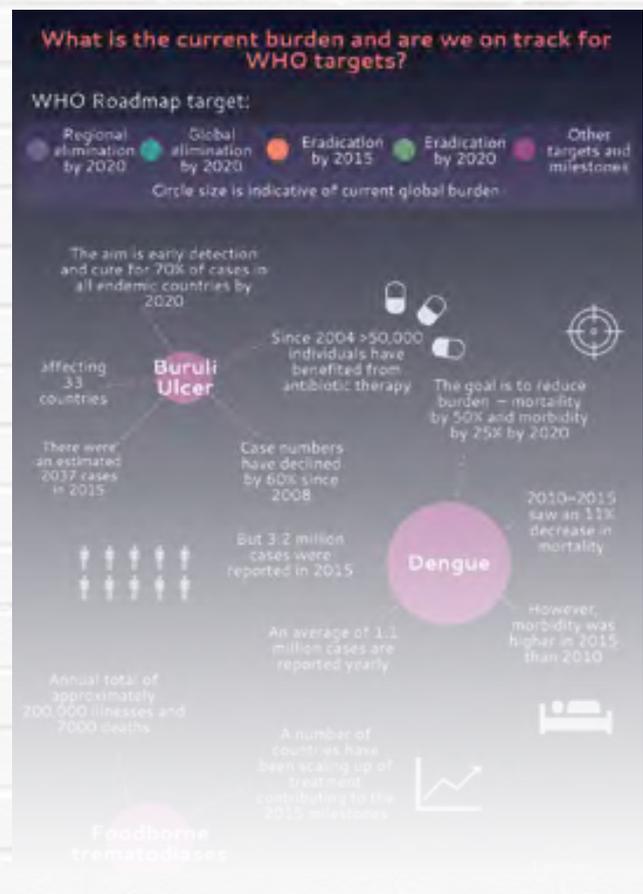
'Infectious diseases' is a broad net and we do aim to cover all aspects of microbiology, virology, mycology and parasitology – from bench to bedside. When I came aboard as Editor in November 2016, this was certainly a slightly daunting prospect! However, what I find compelling is the idea that the subject matter we focus on is not only of use to professionals working in the field. Infectious diseases affect so many individuals globally and are estimated to be among the leading causes of mortality worldwide, giving the site a broad appeal. When commissioning and reading articles for the site, it's this wide impact and applicability that has convinced me ID Hub has something important to say.

The site officially launched in March this year (2017), and has since gone from strength to strength, offering interested parties easy access to breaking news, exclusive features, interviews and peer-reviewed articles from our associated journals. Registration is completely free and allows access to a whole range of content – including multimedia pieces such as infographics and videos! We're keen to have content from a wide range of professionals in the field, both established opinion leaders and early career researchers, for example, our fantastic monthly column 'About AMR' from postdoc, Julie Kaiser, which focuses on the hot topic of antimicrobial resistance.

We've tried to cover the vast scope of the site by looking in-depth at specific topics in a variety of one-month focuses. This kicked off with tuberculosis in March and moved to immunization in April; a month that also saw us attend our first conference, the European Congress of Clinical Microbiology and Infectious Diseases (Vienna, Austria), which was a fantastic experience.

Recently we have carried out a focus on Neglected Tropical Diseases (NTD), which had a fantastic response.

We interviewed Professor Sir Roy Anderson (below) about his work with the London Centre for Neglected Tropical Disease research (you can watch the video interview on ID Hub) as well as featuring pieces on the DeWorm3 project and an infographic on the World Health Organization's NTD Roadmap.



MEMBERS' WALL

Although the focus of the site is primarily on microbes of medical or clinical relevance, the scope is broad and we've recently featured some interesting pieces on microbial evolution, specifically the impact of climate change on pathogens, and gut health, in an interview on the importance of the mycobiome in health and disease.

Microbiology is such a diverse and exciting area, and with the emergence of new technologies giving us the ability to study complex communities and rapidly sequence whole genomes, there has been something of a 'revolution'. Keeping on top of such technological advances and the latest emerging diseases is definitely at the heart of ID Hub, and personally I feel the digital platform really allows us to do so. One aspect of this is our 'Disease Tracker', which not only allows you to see the impact of a given disease in different countries, but also highlights some of the institutions researching the disease in question – a resource that is unique in the field.

Looking forwards, we hope to be able to identify and follow future trends via our exciting platform and as part of this engage the next generation of microbiologists, epidemiologists and public health officials; perhaps with an eye in the future to growing specialized resources and catering more specifically for audiences such as students. In addition to this, we're hoping to build charity partnerships and feature the work of organizations such as the Schistosomiasis Control Initiative, who we're already affiliated with. I hope that working with charities will ensure we can highlight disease not only from a research angle but also a human angle, and I look forward to seeing how this evolves.

As ID Hub becomes more established, and our back catalogue of interesting and informative content grows, I believe the site will increasingly become a valuable, free resource for people working in, interested in or

studying in the field. Personally, as Editor, I have already worked with so many knowledgeable individuals and learnt copious amounts about infectious disease research and its challenges, and I can only hope this continues as we tackle new topics.

In a field that faces a certain amount of uncertainty with regard to what the next major outbreaks might be, or how political will might influence public health and research, it would be challenging to say exactly what 2018 will hold for ID Hub. However, I can say with certainty that whatever comes our way, we will be covering it!

You can find (and sign up to!) Infectious Diseases Hub at www.id-hub.com



Martha Powell

Editor, Infectious Diseases Hub

Diseases: Zika

Displaying Disease: Zika

Disease description: Zika is a mosquito-borne flavivirus transmitted primarily by Aedes mosquitoes. Infection with Zika can lead to symptoms including mild fever, skin rash, conjunctivitis, muscle and joint pain, malaise or headache. In 2015 it was reported that infection with Zika virus was associated with microcephaly and Guillain-Barré syndrome. Links to other neurological complications are currently being investigated.

Markers on the map display Research Centres for Zika



Prevalence may vary within countries by subpopulation and locality. Impact signifies recent cases or active transmission, in some cases low impact signifies an endemic infection or imported cases.

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My life in science

I have spent half of my life working in science; I'll just pause there for a moment. That's a long time in one field, so why have I stayed here? The simple answer is because I love science; it's fascinating and there are always new answers to find. As a lifelong learner, I enjoy researching and discovering new things, which might explain why my career has been so diverse and I now have a string of letters after my name. I couldn't stop at completing just one course. I didn't know that at the time but opportunities arose along the way and I am a great believer in making the most of such opportunities.

Although I am female, my amble through science has not been the simple straight line shown on scissor graphs by scientists highlighting inequality of females in science. My formula has been to embrace opportunities, work hard and remain dedicated. Sometimes I have simply been in the right place at the right time.

I am currently the Head of Operations for the Epidemic diseases Research Group Oxford (ERGO), but how did I

get here? When I applied to university I was interested in food science. With no such degrees existing, I chose biological sciences. I spent a year working as a Medical Laboratory Scientific Officer (MLSO; now Biomedical Scientist, BMS) in an NHS Microbiology Laboratory in Oxford as work experience.

In my final year, I chose the biomedical route to become an MLSO. However, my favourite part of the degree was my project; this started me on the path that I subsequently followed. After finishing my degree I returned to my placement laboratory, finished the training and became a State Registered MLSO. I began a part-time Master's course in medical microbiology which meant travelling to London one day a week for two years (early mornings, late nights). It was during the final research project that I found my vocation. The months of late nights, enthusiastically running experiments after a full day at work, was thoroughly enjoyable.

While completing my MSc project, the next opportunity arose; to move to full-time research. I applied for a research assistant post and began research on the bacterial population and human host susceptibility genes involved in severe *Staphylococcus aureus* disease. I loved the work, excelled and applied for a DPhil (PhD, University of Oxford). As a researcher in the Department of Tropical Medicine, I became part of the wider tropical research community. I travelled abroad to work in



CAREER STREET

Vietnam, Bangkok and on the Thai-Burmese border for six-week stints.

I loved Southeast Asia. I knew if I got the chance I wanted to work there. This didn't happen immediately; however, while working as a postdoc in Oxford, the chance arose to run a microbiology laboratory in Southeast Asia. It was a difficult decision for my husband (not me), a carpenter by trade, but we moved with a young family out to Vientiane, Laos PDR to follow my dream. We lived in Vientiane for four years. In my first year we built a Containment Level 3 laboratory and a molecular laboratory (the first in the country). I ran the laboratories, logistics and built the microbiology capacity in Mahosot Hospital. It was hectic. I adored my co-workers and learned to read, write and speak Laos. While on maternity leave with my third child (born in Bangkok) I was on the board of Directors at the Vientiane International School, leading a team to recruit a new school director.

Within six months of returning, a further opportunity arose; I moved my family to Siem Reap, Cambodia, and ran a small microbiology laboratory at the Angkor Hospital for Children. A research study diagnosing the aetiology of disease in children admitted with fever was underway; the laboratory needed guidance and training. Although I was busy, I wanted to learn about management so I began an online, global Master's in Business Administration (MBA) in my spare time (!). I loved the course, finding it exciting and interesting. I was thinking out of my 'science box'.

I really loved Siem Reap: the culture, the wonderful people and the huge variety of work. However, for me and my family, after two years, it was time to return to the UK. Partway through my MBA, I applied for jobs in the UK (that wasn't stressful at all!). Knowing that I had been out of the UK scientific field for six years, I

wanted to learn new molecular techniques. The timing was right. A postdoc position was available in the Modernising Medical Microbiology laboratory in Oxford and I became a postdoc sequencing *Streptococcus pneumoniae*. My children started school and we settled back into UK life.

At the end of my MBA I completed a qualitative research project. The inequalities facing researchers in the UK interested me, particularly postdoctoral female scientists. I learned about the Athena SWAN initiative and mentoring. As a researcher, most of us are on short-term contracts and after two years I was looking for a new position; 2014 was a new era – I was suddenly thrown into Ebola. I became the project manager for ERGO, in charge of logistics, contracts etc.; I sent nearly 40 medical staff to Sierra Leone to run a clinical trial on an experimental drug given to patients with Ebola. It was extremely challenging!

Our clinical trial finished and my job changed. I became Head of Operations, overseeing the project portfolio; HR, launching a website and in charge of the group budget to name but a few things. I still make time to learn; my current focus is teaching including mentoring of MSc students. I also run numerous outreach projects including science fairs in Cheltenham and Oxford, the New Scientist Live and an activity at the Curiosity Carnival. I love to hear our visitors' stories and to inspire children to become the leading scientists of the future.

What does the future hold for me? Who knows? I am writing this article while in Cape Town running a workshop at the Global Evidence Summit; I will probably visit Africa frequently with the many projects based here.



Dr Catrin Moore
University of Oxford

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Super Organism

How would you define a 'superorganism'?

In this case, it means that a whole person is a coalition of a collective of human cells with other, equally numerous, collectives, gathered in several differently located ecosystems with shifting populations. All interacting with the human cellular community.

You've written books on *Frankenstein*, heart health and the future – why tackle the microbiome?

Mainly because I was fascinated by the outpouring of findings about microbial complexity affecting other multicellular organisms that emerged when the tools of post-genomic biology spread more widely through the labs. I wanted to educate myself about what was being found, and assess its significance and think about what sense others might make of it, and what the social impact might be as the biology became clearer.

What surprised you when researching the book?

The main thing is the big picture and how it lay obscured for so long – almost hidden in plain sight. We've known these microbes were there for hundreds of years, but the variety, complexity and importance of microbiomes seems to have passed largely unnoticed. My copy of Theodore Rosebury's excellent *Life on Man* has been with me since 1976. When I look at it again,

I find that it is almost all history and anthropology, and some psychiatry. The actual microbiology occupies a couple of chapters that barely exceed 20 pages (and Rosebury owned the subject). We've come a long way since then. Other specific things that make me think hard are the ideas developed recently, especially by Professor Margaret McFall-Ngai, about the way our highly adaptive immune system may have evolved to allow co-existence with a complex microbiome, and the way that the composition of breast milk is regulated to feed the infant microbiome as well as the infant.

You raise a healthy, hefty eyebrow at much of the (commercial) claims made about the microbiome, what area do you suspect will deliver results?

My guess is there'll be fortunes made at some point from cosmetic applications – anti-acne, anti-dandruff, perhaps breath freshening and tooth-preservation by encouraging the right biofilm.

You contemplate the possibility of 'a legal prebiotic and a microbe that metabolizes it into something more pharmacologically interesting' – is this a future we're likely to see in this lifetime?

That depends on how enterprising bio-hackers and people planning to stay one step ahead of drug-



Jon Turney

An interview with **Jon Turney**

*Science Writer,
Editor and Reviewer*



Stewart Cumiskey
Society for Applied Microbiology

regulators prove to be. If they pick up the idea, I'm sure they'll be able to research ways it might work. As we in the UK have a Government that, rather ludicrously, has now banned everything psychoactive, perhaps they'll have a new incentive to offer substances that are a step away from that and need microbial finishing!

Recently, the BMJ had a shift in policy re: finishing a course of antibiotics. Do you agree with this stance and are we (the public) able to juggle the subtleties of such decisions?

Sure, eventually. But this does seem a major shift from what one previously understood (that failing to finish a course might promote the spread of resistance, though now I think of it I'm not sure I ever understood why beyond some vague connection with "whatever does not kill me makes me stronger" applied to microbes). So, it'll take a while and plenty of repeats of the message for it to filter through and affect habits of prescribing and compliance.

I, *Superorganism* feels contemporary, yet a work in progress as we're still learning so much. Is there any research you've come across since publication that's either changed or progressed your stance on the microbiome?

I thought it would get out of date quite fast! That's the hazard of publishing a book on a hot topic. Thankfully that hasn't happened as quickly as I feared. Lots of results contradict previous studies, so large claims remain compromised and we see how much we don't yet understand. I'm not following the work in so much detail now, but the paper that seemed most startling to me came out early last year and showed that microRNAs from mouse and human gut epithelial cells are normal components of faeces, and that they enter bacteria – where they can regulate bacterial gene expression. That is, co-evolution has allowed us to reach into microbial cells and alter how they operate when they are inside us. It's one example of the important idea that the microbiome doesn't just show up, but the population that gets established is actively shaped by the host. And, for me, it was a glimpse of a whole new layer of hitherto unsuspected interaction, unsuspected partly because microRNAs are a pretty evanescent species and were themselves only discovered relatively

recently. I don't know what impact this work has had on the field, but it seemed important to me.

You spoke about communicating the microbiome at the FEMS Microbiology Congress 2017 – what tips would you give to those starting out or anticipating a career in science communication?

It's fun and (sometimes) useful, so go for it. Be prepared to listen (receive as well as transmit), especially listen to the people you want to get the benefit. Their questions will be more important to them than yours. Imagine how things may look to them, or what mental models they may be using to understand what's going on (consciously or not). My favourite slogan is due to the cognitive psychologist Jerome Bruner, and holds that you can explain anything to anyone, at some level, if you take the trouble to formulate what he calls "*a courteous explanation*". That's the kind of courtesy he had in mind.

As both a scientist and a writer, do you have confidence that our Government and media do enough to promote science, reason and evidence?

That's a hard one these days. I'm one of those now trying to break the lifetime habit of having easy opinions about such things because the Brexit vote and Trump's ascendancy have taught me that, really, I understand hardly anything. Government is in a difficult position promoting reason (though will always tend to claim it is doing so) as so few people credit what Government representatives say. The media are a mosaic, with good and frighteningly bad examples on either side of this question. And social media? We're all trying to figure that out. The losses and gains are complex and still unfolding.

Have you been persuaded by evidence, circumstantial or otherwise to take a probiotic?

Not yet. And the enthusiasm for fermented foods is interesting, but leaves me cold – and scientifically unconvinced. But then I have always felt healthy so far, so I lack incentive to experiment. I do think prebiotics are worth thinking about, but that mainly leads to adherence to the guidelines for a healthy diet that we all knew well before the current explosion of microbiome science happened.

JournalWATCH

Highlights and featured articles from the SfAM journals

Environmental Microbiology

www.env-micro.com

Cooperation in microbial communities and their biotechnological applications

M. Cavaliere, S. Feng, O. S. Soyer, J. I. Jiménez

This review illustrates the relevance of cooperative interactions in microbial biotechnological processes, discusses their mechanistic origins and analyses their evolutionary resilience.



Microbial communities are increasingly utilized in biotechnology. Efficiency and productivity in many of these applications depends on the presence of cooperative interactions between members of the community. Two key processes underlying these interactions are the production of public goods and metabolic cross-feeding, which can be understood in the general

framework of ecological and evolutionary (eco-evo) dynamics. Cooperative behaviours can be damaged by the emergence of 'cheating' cells that benefit from the cooperative interactions but do not contribute to them. Despite this, cooperative interactions can be stabilized by spatial segregation, by the presence of feedbacks between the evolutionary dynamics and the ecology of the community, by the role of regulatory systems coupled to the environmental conditions and by the action of horizontal gene transfer. Cooperative interactions enrich microbial communities with a higher degree of robustness against environmental stress and can facilitate the evolution of more complex traits. Therefore, the evolutionary resilience of microbial communities and their ability to constrain detrimental mutants should be considered to design robust biotechnological applications.

<http://onlinelibrary.wiley.com/doi/10.1111/1462-2920.13767/full>

Comparative genomics of *Mortierella elongata* and its bacterial endosymbiont *Mycoavidus cysteinexigens*

J. Uehling, A. Gryganskyi, K. Hameed, T. Tschaplinski, P.K. Misztal, S. Wu, A. Desirò, N. Vande Pol, Z. Du, A. Zienkiewicz, K. Zienkiewicz, E. Morin, E. Tisserant, R. Splivallo, M. Hainaut, B. Henrissat, R. Ohm, A. Kuo, J. Yan, A. Lipzen, M. Nolan, K. LaButti, K. Barry, A.H. Goldstein, J. Labbé, C. Schadt, G. Tuskan, I. Grigoriev, F. Martin, R. Vilgalys, G. Bonito

Endosymbiosis of bacteria by eukaryotes is a defining feature of cellular evolution. In addition to well-known bacterial origins for mitochondria and chloroplasts, multiple origins of bacterial endosymbiosis are known within the cells of diverse animals, plants and fungi.

Early-diverging lineages of terrestrial fungi harbour endosymbiotic bacteria belonging to the Burkholderiaceae. The authors sequenced the metagenome of the soil-inhabiting fungus *Mortierella elongata* and assembled the complete circular chromosome of its endosymbiont, *Mycoavidus cysteinexigens*, which they place within a lineage of endofungal symbionts that are a sister clade to *Burkholderia*. The genome of *M. elongata* strain AG77 features a core set of primary metabolic pathways for the degradation of simple carbohydrates and lipid biosynthesis, while the *M. cysteinexigens* (AG77) genome is reduced in size and function. Experiments using antibiotics to cure the endobacterium from the host demonstrate that the fungal host metabolism is highly modulated by the presence/absence of *M. cysteinexigens*. Independent comparative phylogenomic analyses of fungal and bacterial genomes are consistent with an ancient origin for *M. elongata* – *M. cysteinexigens* symbiosis, most likely over 350 million years ago and concomitant with the terrestrialization of Earth and diversification of land fungi and plants.

<http://onlinelibrary.wiley.com/doi/10.1111/1462-2920.13669/full>

Environmental Microbiology Reports

www.env-micro-reports.com

The life sulfuric: microbial ecology of sulfur cycling in marine sediments

Kenneth Wasmund, Marc Mußmann, Alexander Loy

Extraordinary discoveries have increased our knowledge of microbial sulfur cycling, mainly in sulfate-rich surface sediments, yet many questions remain regarding how sulfur redox processes may sustain the deep-subsurface biosphere and the impact of organic sulfur compounds on the marine sulfur cycle.



Almost the entire seafloor is covered with sediments that can be more than 10,000 m thick and represent a vast microbial ecosystem that is a major component of Earth's element and energy cycles. Notably, a significant proportion of microbial life in marine sediments can exploit energy conserved during transformations of sulfur compounds among different redox states.

Sulfur cycling, which is primarily driven by sulfate reduction, is tightly interwoven with other important element cycles (carbon, nitrogen, iron, manganese) and therefore has profound implications for both cellular- and ecosystem-level processes. Sulfur-transforming microorganisms have evolved diverse genetic, metabolic, and in some cases, peculiar phenotypic features to fill an array of ecological niches in marine sediments. The authors review recent and selected findings on the microbial guilds that are involved in the transformation of different sulfur compounds in marine sediments and emphasize how these are interlinked and have a major influence on ecology and biogeochemistry in the seafloor.

<http://onlinelibrary.wiley.com/doi/10.1111/1758-2229.12538/full>

The skin microbiome of the common thresher shark (*Alopias vulpinus*) has low taxonomic and gene function β -diversity

Michael P. Doane, John Matthew Haggerty, Dovi Kacey, Bhavya Papudeshi, Elizabeth A. Dinsdale

The health of sharks, like all organisms, is linked to their microbiome. At the skin interface, sharks have dermal denticles that protrude above the mucus, which may affect the types of microbes that occur here. The authors characterized the microbiome from the skin of the common thresher shark (*Alopias vulpinus*) to investigate the structure and composition of the skin microbiome.

On average 618,812 (80.9% \pm S.D. 0.44%) reads per metagenomic library contained open reading frames; of those, between 7.6% and 12.8% matched known protein sequences. Genera distinguishing the *A. vulpinus* microbiome from the water column included *Pseudoalteromonas* (12.8% \pm 4.7 of sequences), *Erythrobacter* (5.3% \pm 0.5) and *Idiomarina* (4.2% \pm 1.2), and distinguishing gene pathways included cobalt, zinc and cadmium resistance (2.2% \pm 0.1), iron acquisition (1.2% \pm 0.1) and ton/tol transport (1.3% \pm 0.08). Taxonomic community overlap (100 – dissimilarity index) was greater in the skin microbiome (77.6) relative to the water column microbiome (70.6) and a reference host-associated microbiome (algae: 71.5). The authors conclude the *A. vulpinus* skin microbiome is influenced by filtering processes, including biochemical and biophysical components of the shark skin and result in a structured microbiome.

<http://onlinelibrary.wiley.com/doi/10.1111/1758-2229.12537/full>

Microbial Biotechnology is 10 years old!

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Should the biofilm mode of life be taken into consideration for microbial biocontrol agents?

Caroline Pandin, Dominique Le Coq, Alexis Canette, Stéphane Aymerich, Romain Briandet

The aim of this review is to summarize the evidence of biofilm formation by biocontrol agents on crops and discuss how this surface-associated mode of life may influence their biology and interactions with other microorganisms and the host and, finally, their overall beneficial activity.



Almost one-third of crop yields are lost every year due to microbial alterations and diseases. The main control strategy to limit these losses is the use of an array of chemicals active against spoilage and unwanted pathogenic microorganisms. Their massive use has led to extensive environmental pollution, human poisoning and a variety of diseases.

An emerging alternative to this chemical approach is the use of microbial biocontrol agents. Biopesticides have been used with success in several fields, but a better understanding of their mode of action is necessary to better control their activity and increase their use. Very few studies have considered that biofilms

PUBLICATIONS

are the preferred mode of life of microorganisms in the target agricultural biotopes. Increasing evidence shows that the spatial organization of microbial communities on crop surfaces may drive important bioprotection mechanisms.

<http://onlinelibrary.wiley.com/doi/10.1111/1751-7915.12693/full>

The *XylS/Pm* regulator/promoter system and its use in fundamental studies of bacterial gene expression, recombinant protein production and metabolic engineering

Agnieszka Gawin, Svein Valla, Trygve Brautaset

In this review, the authors summarize constructions, characteristics, refinements and applications of expression tools using the *XylS/Pm* system.

The *XylS/Pm* regulator/promoter system, originating from the *Pseudomonas putida* TOL plasmid pWW0, is widely used for regulated low- and high-level recombinant expression of genes and gene clusters in *E. coli* and other bacteria. Induction of this system can be graded by using different cheap benzoic acid derivatives, which enter cells by passive diffusion, operate in a dose-dependent manner and are typically not metabolized by the host cells. Combinatorial mutagenesis and selection using the *bla* gene encoding β -lactamase as a reporter have demonstrated that the *Pm* promoter, the DNA sequence corresponding to the 5' untranslated end of its cognate mRNA and the *xylS* coding region, can be modified and improved relative to various types of applications. By combining such mutant genetic elements, altered and extended expression profiles were achieved. Due to their unique properties, obtained systems serve as a genetic toolbox valuable for heterologous protein production and metabolic engineering, as well as for basic studies aiming to understand the fundamental parameters affecting bacterial gene expression. The approaches used to modify *XylS/Pm* should also be adaptable for similar improvements of other microbial expression systems.

<http://onlinelibrary.wiley.com/doi/10.1111/1751-7915.12701/full>

Journal of Applied Microbiology

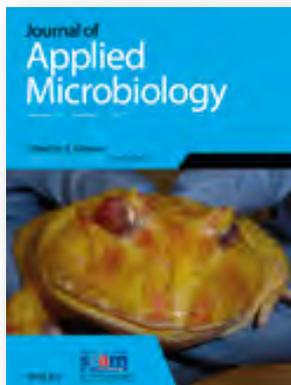
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Fish intestinal microbiome: diversity and symbiosis unravelled by metagenomics

A.M. Tarnecki, F.A. Burgos, C.L. Ray, C.R. Arias

This review aims to summarize the available knowledge on fish gastrointestinal communities obtained from metagenomics, including biases from sample processing, factors influencing assemblage

structure, intestinal microbiology of important aquaculture species and description of the teleostean core microbiome.



The gut microbiome of vertebrates plays an integral role in host health by stimulating development of the immune system, aiding in nutrient acquisition and outcompeting opportunistic pathogens. Development of next-generation sequencing technologies allows researchers to survey complex communities of microorganisms within the microbiome at great depth

with minimal costs, resulting in a surge of studies investigating the bacterial diversity of fishes. Many of these studies have focused on the microbial structure of economically significant aquaculture species with the goal of manipulating the microbes to increase feed efficiency and decrease disease susceptibility. The unravelling of intricate host–microbe symbioses and identification of core microbiome functions is essential to our ability to use the benefits of a healthy microbiome to our advantage in fish culture, as well as gain deeper understanding of bacterial roles in vertebrate health.

<http://onlinelibrary.wiley.com/doi/10.1111/jam.13415/full>

Environmental *E. coli*: ecology and public health implications—a review

J. Jang, H.-G. Hur, M.J. Sadowsky, M.N. Byappanahalli, T. Yan, S. Ishii

This review examines the current knowledge on the ecology of *E. coli* strains in various environments with regard to its role as a faecal indicator bacterium (FIB) and as a naturalized member of indigenous microbial communities.

Special emphasis is given to the growth of pathogenic *E. coli* in the environment, and population genetics of environmental members of the genus *Escherichia*. The impact of environmental *E. coli* on water quality and public health is also discussed. The presence of *E. coli* in environmental waters has long been considered as an indicator of recent faecal pollution. However, numerous recent studies have reported that some specific strains of *E. coli* can survive for long periods of time, and potentially reproduce, in extraintestinal environments. This indicates that *E. coli* can be integrated into indigenous microbial communities in the environment. This naturalization phenomenon calls into question the reliability of *E. coli* as an FIB. Recently, many studies reported that *E. coli* populations in the environment are affected by ambient environmental conditions affecting their long-term survival. Large-scale studies of population genetics revealed

the diversity and complexity of *E. coli* strains in various environments, which are affected by multiple environmental factors.

<http://onlinelibrary.wiley.com/doi/10.1111/jam.13468/full>

Letters in Applied Microbiology

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Bacteriophages as indicators of faecal pollution and enteric virus removal

B.R. McMinn, N.J. Ashbolt, A. Korajkic

Bacteriophages are an attractive alternative to faecal indicator bacteria (FIB), particularly as surrogates of enteric virus fate and transport, due to their closer morphological and biological properties.



Based on a review of published data, the authors summarize densities of coliphages (F+ and somatic), *Bacteroides* spp. and enterococci bacteriophages (phages) in individual human waste, raw wastewater, ambient fresh and marine waters, and removal through wastewater treatment processes utilizing traditional treatments. They also provide comparisons with

FIB and enteric viruses whenever possible. Lastly, they examine fate and transport characteristics in the aquatic environment and provide an overview of the environmental factors affecting their survival. In summary, concentrations of bacteriophages in various sources were consistently lower than FIB, but more reflective of infectious enteric virus levels. Overall, this investigation indicates that bacteriophages may be adequate viral surrogates, especially in built systems, such as wastewater treatment plants.

<http://onlinelibrary.wiley.com/doi/10.1111/lam.12736/full>

Fermented cereal beverages: from probiotic, prebiotic and synbiotic towards Nanoscience designed healthy drinks

I. Salmerón

The consumption of fermented foods by humankind goes a long way back in history and there are as many types of fermented food as civilizations.

Food science and technology has progressed from designing nutritional foods towards food with health improvement characteristics such as functional foods. In this sense, the area of food with properties to improve gastrointestinal health such as probiotics, prebiotics and synbiotics has been the most important segment within functional foods. Most of these products are dairy based so the development of non-dairy gut improvement products has been of great interest for the food industry, resulting in the rise of cereal-based probiotic and synbiotic products. Finally, through Nanoscience and the application of Nanotechnology techniques in the food sector, it has been possible to design fermented beverages with synbiotic properties, and the incorporation of nanoparticles with unique and specific bioactivity, which has opened a new horizon in this segment of food created to improve human health and well-being.

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Journal of Applied Microbiology and Letters in Applied Microbiology have recently revised their Aims & Scopes:

Journal of Applied Microbiology publishes high-quality full-length research and review papers on novel aspects of applied microbiology in relation to agriculture and soils, animals and animal health, biodefence, biotransformation, biodegradation and bioremediation, biotechnology (except where the principal thrust of the work is optimization), environment, food and beverages, medicine and public health, mycology (except where work is concerned with macro-fungi), pharmacy, plants and plant health, probiotics and the intestine and water of all types. Papers reporting work on all microorganisms, including viruses, are welcomed, as are those reporting the use of newer technologies and approaches provided they demonstrate new findings of significance to the field as a whole.

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Claire Fewson
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Prompted by an increasing concern from regulatory inspectors and internal quality assurance professionals, the increased emphasis on risk assessment and consequent risk reduction in aseptic manufacturing has required many small changes to accepted best practice. The latest type of project to make this transition from single customer enquiry to routine industry demand is the Cherwell settle plate stand.

The risk from settle plates on the floor are several and the consequences of stepping on an agar plate include:

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A trial undertaken at Campden BRI showed that *Salmonella enteritidis* and *Salmonella typhimurium* isolates from a range foodstuff sources would give a positive reaction within 24 hours, while there were no false reactions with *Staphylococcus aureus* or *Escherichia coli*.

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NCIMB appoints bioinformatics expert

NCIMB is delighted to welcome Dr. Daniel Swan in a new role as Bioinformatics Delivery Manager. Daniel is responsible the delivery and continued development of NCIMB's bioinformatics services and comes directly from running one of the UK's largest genomics facilities.

His expertise is the analysis of Next-Generation Sequencing (NGS) data which is revolutionising our understanding of microbial communities and environmental microbiology.

Commenting on his appointment Daniel said: "*NGS has an exciting role to play in realising the full potential of NCIMB's culture collection, offering both industry and academic researchers a deep dive into the biology of the strains through fully-sequenced genomes.*"

I will also be developing NCIMB's bacterial and fungal identification services, extending the existing strain identification with high-throughput 'metagenomics' approaches which will provide even greater resolution of microbial communities and their functions in production environments."

NCIMB manages the UK's National Collection of Industrial Food and Marine Bacteria and provides specialist microbiology, chemical analysis and biomaterial storage products and services. We support clients in their quality control procedures, research and development projects, intellectual property protection and compliance with environmental regulations.

For more information about NCIMB's bioinformatics capabilities contact Daniel Swan e: d.swan@ncimb.com t: 01224 711100.

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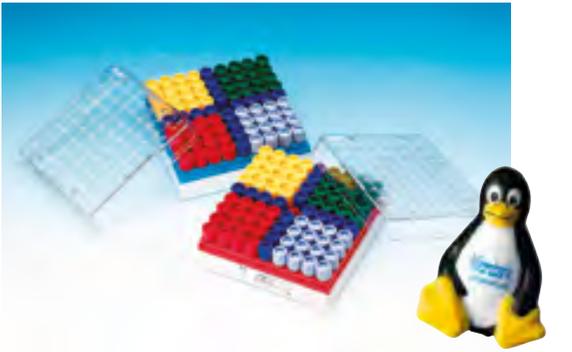
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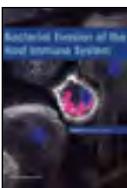
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POLICY Corner

It's life science, Jim, but not as we know it

All health research may be life science, but is all life science health research?

Ask any scientist how they would define life science, and they'll most likely reply with something similar to that given by the World Health Organization:

Life sciences comprise all sciences that deal with living organisms, including human beings, animals and plants. It is a broad field that encompasses biology, biotechnology, genomics, proteomics, bioinformatics, pharmaceutical and biomedical research and techniques.

It stands to reason that life science would be the reserve of all things living – the philosophical debate on how we define life can wait until another day. The above definition also fits in nicely with the 'One Health' agenda, where environmental, animal and human health is seen as a multidisciplinary research endeavour. Nevertheless, in the eyes of the policymaker, life sciences is often viewed through the rather narrow lens of human healthcare alone. Indeed, the UK Government's Office for Life Sciences is split exclusively across the Department for Business, Energy & Industrial Strategy and the Department of Health. Other areas of Government, which cover environmental and animal sciences, cannot boast such direct oversight.

This case of mistaken identity extends beyond Government, too. For instance, the internet is littered with reports from the private sector on how successful and lucrative the life sciences industry is. There's just one problem: these documents almost invariably focus only on healthcare-related R&D and manufacturing. The impact of other sectors, for example, industrial biotechnology, is often overlooked.

The healthcare-oriented view of life science was more recently demonstrated by the long-awaited Life Sciences Industrial Strategy, spearheaded by Professor Sir John Bell. Set out as a response to the UK Government Industrial Strategy green paper, the report includes recommendations to incentivize research, support STEM skills, make better use of data and support the international movement of skilled people.



Is this truncated viewpoint really a cause for concern? After all, the report was well received across the science community, reflecting the fact that many of its recommendations would be generally beneficial for scientists. The danger, however, is that policymakers only see this one side of the coin, viewing support for healthcare R&D as sufficient for a thriving life sciences industry. This in turn could restrict the ability of scientists (who work in fields beyond human health) to inform and influence future policy decisions.

How can the life sciences agenda be expanded, so that policymakers and scientists are on the same page? There are positive examples to be followed. Earlier this year, Scotland published its own Life Sciences Strategy, which emphasizes the importance of research across areas including human healthcare, animal and plant sciences, aquaculture, agritech and industrial biotechnology. To quote the foreword directly:

Life sciences in Scotland is broader than many people perceive. It includes all life and health sciences; human, animal and plant.

Recognizing a wider definition of life science is important to avoid confusion beyond policy circles. This key point was raised by the Royal Society of Biology in its response, to which SfAM contributed, to a recent parliamentary inquiry into Life Sciences and the Industrial Strategy. It lies with the scientific community to convince policymakers that the science of life extends beyond the doctor's surgery.



Chris Brown
SfAM Policy Officer

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