Microbiologist

The magazine of the Society for Applied Microbiology ■ December 2012 ■ Vol 13 No 4 ISSN 1479-2699

Virology and vaccines

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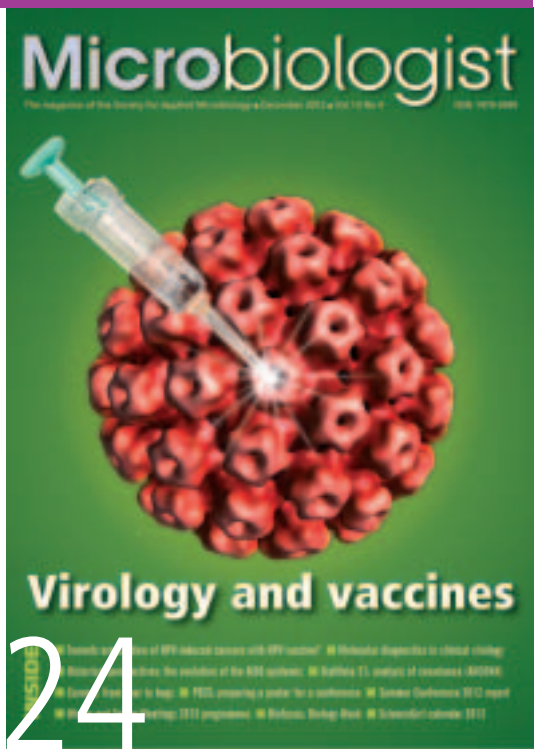

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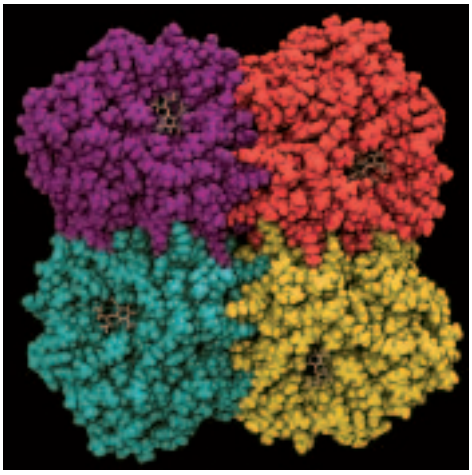
editorial

Lucy Harper discusses virology and vaccines



We live in a world where the level of threat from the spread of infectious disease is now so much lower than in past generations. Long gone are the days of hospital wards lined with polio patients thrust inside an iron lung, or the onset of a wound infection becoming a threat to one's life.

One development which has had an enormous impact in making these such distant memories has been vaccination. The first example of the phenomenon of inoculation isn't clear, but certainly since the 'father of immunology' Edward Jenner pioneered inoculation against smallpox in the 17-1800s, vaccination has been protecting us against infectious disease to the extent that complete global eradication of a disease has succeeded (smallpox) or is close (polio).

This fact alone, it could be argued, may contribute to people questioning the safety of vaccination vs not immunizing children. Memories are short and the current generation of parents may not have first-hand experience of such diseases. I think we can all agree that the overall benefits of vaccination outweigh any potential risks associated with immunization.

In this issue of *Microbiologist*, we're looking at viruses, a vaccine against one of which can protect women against cervical cancer. In her article on the human papilloma virus (HPV) vaccination, Heather Cubie writes: "*An exciting opportunity exists to reduce and even eliminate the problem of serious disease and cancers associated with the common virus, HPV. In the UK, the sustained high vaccine uptake in schoolgirls and the availability of a national call and recall cervical screening programme give high hopes for significant reduction in cervical cancers and precancers*." Turn to page 24 to read more.

We also take a look at techniques which are used to diagnose viral infection in an article by our Meetings Secretary, Andy Sails. He writes "*Diagnostic tests can be grouped into three categories; direct detection (within the patient sample), indirect examination (e.g., virus isolation), and serology (looking for an antibody response in the host).*" He continues: "*The introduction of molecular diagnostic methods into clinical virology has improved the detection of infectious disease agents and led to improvements in patient treatment and management. Newly emerging technologies such as next generation sequencing (NGS) will supplement and may even completely replace PCR and other current molecular methodologies in the future*." You can read the full article on page 30.

We take an historical look at the evolution of the AIDS epidemic, with an article from Brian Gazzard who says: "*The timing of the first HIV infections in man has recently been determined with surprising precision. Many people dying unexpectedly in Lusaka in the Congo in the 1950s had histological material stored. These have recently been examined for HIV DNA and, in a proportion of cases, proviral DNA (from the incorporated virus) was found*." Read more on page 33.

And finally, I wish you all a happy and fun festive season.

Lucy Harper

contribute

We are always looking for enthusiastic writers who wish to contribute articles to the magazine on their chosen microbiological subject.

For further information please email the editor, Lucy Harper at: **lucy@sfam.org.uk**

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Advertising: Information about advertising in *Microbiologist* and how to submit advertisements can be found on the Society website.

Website: our website **(www.sfam.org.uk)** is a timely source of up-to-date information on all Society matters and maintains a comprehensive archive of articles and reports on a variety of microbiological topics.

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benefits

The Society for Applied Microbiology is the voice of applied microbiology within the UK and was founded in 1931. Society members play a leading role in shaping the future of applied microbiology, and enjoy many benefits, including:

- The opportunity to apply for one of our many grants or funds.
- Eligibility to win any of our awards or nominate a candidate for the SfAM Communications Award.
- Access to our five peer–reviewed Journals: *Journal of Applied Microbiology, Letters in Applied Microbiology*, *Environmental Microbiology, Environmental Microbiology Reports* and *Microbial Biotechnology.*
- Free access to the entire collection of digitized back files for *JAM* and *LAM* dating back to 1938.
- A topical quarterly magazine, *Microbiologist.*
- Substantially reduced rates for attendance at SfAM meetings and conferences.
- Networking with worldwide professionals in over 80 countries.
- Access to private members' area of the SfAM website.
- Monthly email bulletins with the latest news from SfAM.
- Invitation to the annual *Environmental Microbiology* lecture.
- Fostering cross disciplinary research.
- A 25% discount on the extensive Wiley–Blackwell collection of titles.

Detailed information about all these benefits and more can be found on the Society website at: www.sfam.org.uk.

GRANTS & AWARDS: Many grants, awards and prizes are available to members including the W H Pierce Memorial Prize and prizes for student oral presentations and posters at the Summer Conference. In addition to these substantial awards, the Society has funds to assist members in their careers as microbiologists. These include the President's Fund, Conference Studentships, Sponsored Lecture Grants and the popular Students into Work Scheme.

Full details of all the Society's grants and awards can be found on the website together with application forms.

JOURNALS: The Society publishes two monthly journals: *Journal of Applied Microbiology* and *Letters in Applied Microbiology*. We also produce this quarterly colour magazine, *Microbiologist*, which contains features, topical news stories and full details of our meetings. The Society is also a partner with Wiley–Blackwell in the monthly journals: *Environmental Microbiology, Environmental Microbiology Reports* and *Microbial Biotechnology.*

All Full and Student Members receive free access to the online versions of the Society's journals, and can also submit papers to our journals via an online submission service.

MEETINGS: We hold three annual meetings; the Winter Meeting is a one-day meeting with parallel sessions on topical subjects. The Spring Meeting is a one–day meeting tailored for personnel in clinical microbiology. The Summer Conference is held every July and comprises a main symposium, a poster session, the AGM and a lively social programme. All members are invited to our prestigious annual lecture held to commemorate the success of our *Environmental Microbiology* journal. We also hold joint ventures with other organizations on topics of mutual interest.

WEBSITE: The website is the best source of detailed information on the Society and its many activities. It has fully interactive membership areas where you can find archive issues of *Microbiologist*, exclusive SfAM documentation and much more.

membership options

■ **Full Ordinary Membership** gives access to our many grants and awards, online access to the *Journal of Applied Microbiology*, *Letters in Applied Microbiology*, *Environmental Microbiology, Environmental Microbiology Reports* and *Microbial Biotechnology*, copies of *Microbiologist*, preferential registration rates at Society meetings and access to the members' areas of the website.

■ **Full Student Membership** confers the same benefits as Full Membership at a specially reduced rate for full time students not in receipt of a taxable salary.

■ **Associate Membership** is only open to those with an interest in applied microbiology without it being a prime aspect of their job. For example, school teachers and those taking a career break; on maternity leave, or working temporarily in other areas. It does not provide access to any journals or Society grants and awards.

■ **Honorary Membership** of the Society is by election only and this honour is conferred on persons of distinction in the field of applied microbiology. Honorary Members have access to our online journals.

■ **Retired Membership** is available to Full Members once they have retired from their employment. Retired Members are entitled to all the benefits of Full Membership except grants and access to the Society's journals.

■ **eAffiliate Membership:** This category of membership is open to microbiologists residing in Band I developing countries and is free of charge. It is an online only membership and provides access to the eAffiliate bursary only.

■ **eStudent Membership:** This category of membership is open to undergraduate students only. It is an online only membership and is free of charge. This category of membership does not provide access to the Society's grants or journals.

■ **Corporate Membership** is open to all companies with an interest in microbiology. Corporate Members benefits include:

- Quarter page advertisement in each issue of *Microbiologist* (which can be upgraded to a larger size at discounted rates).
- The opportunity to publish press releases, company news, etc., in each issue of *Microbiologist.*
- FREE banner advert on the Society website with a direct link to your company site.
- Up to three members of company staff attending Society meetings at members' rate (this means a 50% discount on non member registration rate).

JOIN US!

You can apply for membership on, or offline. To apply offline, please contact the Membership & Finance Co-ordinator, Julie Wright on **+44 (0)1234 326846**, or email **julie@sfam.org.uk.**

ceo's and **president's** column

SfAM CEO **Philip Wheat** and President, **Professor Martin Adams** talk about open access publishing

In both the President's and CEO's columns, we frequently extol the generous benefits available to members in the form of grants, subsidized meetings, free publications and website facilities such as the Virtual Microbiology Laboratory. It is unarguably a fantastic return on what is a relatively modest contribution in terms of the membership fee. In fact a brief examination of our Annual Report will show that the membership subscription does not even cover the production costs of our quarterly magazine, *Microbiologist*, and that the real source of the Society's munificence is the income we receive from our academic journals.

The last year has seen widespread questioning of the currently predominant subscription-based model of academic publishing. There has been extensive media coverage of moves in the UK and elsewhere towards some form of open access publication, providing the results of published research freely to all. In June 2012 a report was produced which had been commissioned on behalf of the United Kingdom Government entitled *Accessibility, sustainability, excellence: how to expand access to research publications* (the full report can be accessed at http://www.researchinfonet.org/wp-content/uploads/2012/06/Finch-Group-report-FINAL-VERSION.pdf). The 15-strong group which produced the report was chaired by Dame Janet Finch, a distinguished sociologist and academic. It was made up of representatives of universities, research funders, publishers, libraries and included representatives of three learned societies like ourselves: the Institute of Physics, the Society of Biology and the Royal Geographical Society. In their work they tackled the important question: how to achieve better, faster access to research publications for anyone who wants to read or use them?

The report reminds us that communicating research findings through journals and other publications has been at the heart of the scientific and broader research enterprise for over 350 years. While it recognizes the profound changes that the Internet has brought across all sectors of society; transforming interactions and relationships, reducing costs, sparking innovation, and overturning established modes of business, it acknowledges that the full benefits of advances in technology have not been fully realized when it comes to accessing journals. The

report points out that currently many professionals and the public at large can only access journals either through their institution paying for access through a subscription contract with the publisher, or paying a pay-per-view fee of up to £20 in order to read a single journal article. Researchers in the higher education and related sectors and in large research intensive companies want online access free at the point of use, at any time of day and wherever they can connect to the Internet. Also, it is clear that barriers to access, in particular when the published research has been publicly funded, are increasingly unacceptable in an online world, and restrict the innovation, growth and other benefits which can flow from research. The problem is how to expand and improve access to research publications for the greatest benefit of all who have a stake or an interest in research and its results.

The current environment for publishing, disseminating and gaining access to research findings is a mixture of:

- *Subscription-based journals* which predominate currently and where institutions, or sometimes individuals, subscribe to access publications.

- *Open access journals* where instead of relying on subscription income from institutions, most charge a fee to authors known as article processing or publishing charge (APC).

In its conclusions, the report made 10 recommendations, the leading and defining one being that a clear policy direction should be set towards support for publication in open access or hybrid journals, funded by APCs, as the main vehicle for the publication of research, especially when it is publicly funded. With the exception of one point on the levying of value added tax for e-books, the report's recommendations have been accepted by the Government. The Government recognizes and will support the movement towards so-called gold open access which accepts that there are costs associated with publication and that these should be met by the author rather than the reader. Indeed this development was anticipated by the Society and our publishers, Wiley-Blackwell, some time ago and authors have had the option to take the APC/open access route in our journals for a considerable amount of time.

After the report was published it was felt appropriate that the Society should respond and we, as Hon. President and Chief Executive wrote on behalf of the Society to David Willetts, the Minister of State for Universities and Science. In our letter we welcomed what we felt was the Finch group's comprehensive and balanced report, and its recognition that the needs of all stakeholders (associated with research publishing) must be considered in what the report described as a 'complex ecosystem'. We commented that it was vital that in any transition from the current subscription-based model to a predominantly APC model, the world leading status and performance of the UK research community is maintained or indeed enhanced and we welcomed the report's recognition that this status is partly underpinned by the support researchers receive from learned societies.

One point we raised in our letter was that the journals that S*f*AM is associated with service a truly international market, publishing papers from researchers in many countries. For many, their research is not publicly funded and funds are not available for the APC. Therefore, these authors would be penalized if the APC model became the only system available to publish peer-reviewed work. In particular, we also highlighted that supervisors of overseas postgraduate students who receive funding from their home country are often in the same situation. It is an issue that we felt should be taken into account when developing future policy concerning the transition to open access publishing.

In his reply the Minister acknowledged the important role of the learned societies in the UK research landscape and that he did not want to lose this inadvertently in the course of these changes. He also recognized the importance of revenue from publications in supporting this role.

In accepting the Finch report, the Government has also agreed to the suggestion that the Group reconvene in a year to assess the progress that has been made. Clearly this transition must be carefully managed and S*f*AM has expressed its willingness to be involved in this, both as an individual learned society and as a member organization of the Society of Biology.

Finally, may we wish all our Members the very best for the coming season and a very successful and happy New Year.

Philip Wheat
Chief Executive Officer

Martin Adams
President of the Society

Scientific Meeting Attendance Grant or President's Fund? You decide!

Are you going to a scientific meeting? Do you need funding? Do you know which of our grants to apply for?

The **Scientific Meeting Attendance Grant** will fund your travel, accommodation and registration fees at any relevant scientific meeting, including S*f*AM meetings, up to a value of £300. This is ideal if you wish to attend a conference or one-day meeting/symposium but you're not presenting a poster or giving an oral presentation or contributing to the meeting in any other way.

The **President's Fund** is designed for you if you're presenting a poster or giving an oral presentation at a relevant scientific conference, meeting or workshop, including S*f*AM meetings. It will fund travel, subsistence and conference fees up to a value of £1200.

For more information about all our grants and awards, please visit:
www.sfam.org.uk/en/grants--awards/index.cfm

Membership changes

NEW MEMBERS

We would like to warmly welcome the following new members and hope that you will participate fully in the activities of the Society.

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Belgium

H. Mith

Brazil

E. Catao

Burkina Faso

C. S. Compaore; D. Kabore

Canada

E. Deziel; N. Gashi

Estonia

N. Netseporuk

France

F. Fuche

Greece

I. Giavasis

India

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F. Nejati

Ireland

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Italy

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T. Ishibashi

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Zimbabwe

L. K. Nyanga

book review

Invisible Things

By Sara Andersson
Illustrated by Susan Litsios
CreateSpace Independent Publishing Platform (29 May 2012).
ISBN 978-1-4699-8571-8.
Large Print paperback £10.40 (RRP)
54 pages
Reviewed by Clare Taylor
S*f*AM Executive Committee Member

Available from Amazon UK
www.amazon.co.uk/Invisible-Things-Sara-Andersson/dp/1469985713

If you have ever tried to explain the complexities of microbes and infection to young children, you'll know what a challenge it can be with constant "Why?" and "How?" questions coming from intrigued youngsters.

In '*Invisible Things*,' author Sara Andersson weaves together a charming tale of mystery and microbial infection in an easy-to-read and engaging manner suitable for even the youngest of enquiring minds. With delightful accompanying illustrations, the story of a class trip that ends in illness is told by the central character, Sara, who unfortunately misses the trip as a result of flu. With her feline companion Rostam at her side, Sara begins to investigate what has made her classmates ill and discovers the 'microscopic creatures' that cause food poisoning. Through conversations with her health inspector father, she begins to piece together the clues to a better understanding of what microbes are and how they cause infection.

The author, through her experience as a senior scientist at the World Health Organization, brings the story together in an engaging fashion which will appeal to children of all ages. Rather than being a preachy tale of food safety rules, the story imaginatively informs and is both educational and fun to read. For those fluent in French, the original French version, '*Les Invisibles*' is also available!

ScienceGrrl Calendar 2013: celebrating the female face of science

Scientists and science communicators have joined forces to showcase the diversity and range of career opportunities available to women in science. Earlier this year, ScienceGrrl Calendar 2013 was launched to raise money for projects that break down gender stereotypes and encourage young women and girls to see science as an enriching, exciting and productive career choice.

The calendar is supported by S*f*AM amongst others and showcases the real face of female scientists, with photographs that demonstrate the impact of their work: three engineers on a London rooftop overlook a striking cityscape, showing the structural impact of science, technology, engineering and mathematics (STEM); a medical physicist explains her work to a busy group of colleagues and a patient in the University of Manchester's PETCT scanner; and in Bristol an epidemiologist is surrounded by a blur of pedestrians as she examines data for a link between cannabis smoking and mental health.

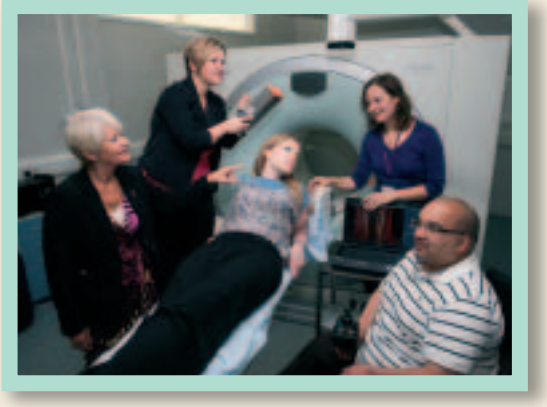


image credits

calendar cover designer: Cosima Dinkel; page 11 bottom: Naomi Coggin/ScienceGrrl; page 11 top: Greg Funnell/ScienceGrrl; page 11 bottom: Ben Gilbert/ScienceGrrl

Several of the images also feature men, to show that, as we all know, men and women work alongside each other. Dr James Logan, entomologist and presenter of Channel 4's *Embarrassing Bodies* is shown working alongside female colleagues; and BBC *Horizon* presenters Dallas Campbell, Dr Kevin Fong and Dr Adam Rutherford display portraits of female scientists who have inspired their careers.

The diversity of careers on show is evident: from solar cell chemist to Curator of Modern Physics to performers Helen Keen and Helen Arney, whose stage shows are based around scientific topics and themes.

The calendar will be sold to raise funds for projects that encourage careers in science by providing opportunities for those who may not otherwise consider science as a realistic career choice. These include the development of Breakthrough: the gender stereotypes project, which aims to challenge gender stereotypes through tailored school lessons; funding places at the Mission Discovery summer school for young people — the majority girls — who would otherwise be unable to attend; and enabling teams of university science students to take part in the iGEM synthetic biology competition.

It stemmed from a conversation about women in science that took place on Twitter. The number of people involved in the conversation quickly grew: a constitution was written, ScienceGrrl was formed and three months later the calendar was complete. Founder and Director of ScienceGrrl, Heather Williams of Central Manchester University Hospitals, said: "*ScienceGrrl celebrates what female scientists are already doing and encourages girls and young women to follow in our footsteps — and achieve even greater things. The 13 images in the ScienceGrrl Calendar 2013 can only showcase a small part of the fascinating and valuable work undertaken by the diverse range of women in STEM, but it is a beautiful introduction to the female face of science.*"

Professor Dame Nancy Rothwell, President and Vice Chancellor of the University of Manchester and President of the Society of Biology took part: "*I am delighted to take part in an innovative project such as this which aims to support women in science,*" she said. "*There are far too few women in some disciplines in science and particularly in senior positions — I want to tell younger women that it's great to be in a leading position, fun as well as very rewarding.*"

The calendar is available from the Science Museum, London, and the Museum of Science and Industry, Manchester, and you can also buy it online:
http://www.sciencegrrl.co.uk/#/shop/4566816455

Lucy Harper
Communications Manager
Society for Applied Microbiology

journalWatch

News about the Society's journals

Microbial Biotechnology

Microbial Biotechnology moves to Open Access.

In January 2013, *Microbial Biotechnology* will become part of the Wiley Open Access program, bringing you research articles that are immediately free to read, download and share.

With a first time Impact Factor (IF©) of 2.534, *Microbial Biotechnology* publishes papers of original research reporting significant advances in any aspect of microbial applications to biotechnologies, including: Biotechnologies related to chemicals; pharmaceuticals; energy; mining; materials; agriculture; food; and environmental.

Microbial Biotechnology will transition to an author-pays open access model from 2013. We believe open access will offer the journal a number of advantages, including a substantial increase in exposure, with all articles being made freely available. *Microbial Biotechnology's* transition to open access will significantly benefit both authors and readers, and hence the field of biotechnology as a whole. For more information about *Microbial Biotechnology's* transition to Open Access, visit **www.microbialbiotech.com** today.

Want to know more?

Are you interested in submitting to *Microbial Biotechnology*, but would like to know more about what the journal has to offer? Chief Editor Ken Timmis has put together an Editor's Choice Virtual Issue highlighting key papers from 2011 and 2012 that he believes showcase key research from *Microbial Biotechnology*. The issue is online now, so why not read it today.

Journal of Applied Microbiology

Two Virtual Issues are now available from the *Journal of Applied Microbiology* at **www.journalappliedmicro.com**:

Priobiotics Virtual Issue. Edited by Koen Venema and Trudy Wassenaar.

In the last decade, papers in the area of probiotics have been prominent in the *Journal of Applied Microbiology*. This Virtual Special Issue focuses on papers featuring in recent years in the area of bacterial probiotics and applications in humans.

This includes papers featuring the production of vitamins by potential probiotics, potential mechanisms of action of probiotics, detection of a specific probiotic in faecal material, and a practical study on the combined use of probiotics and antibiotics.

Plant Resistance Virtual Issue. Edited by Max Dow and Rob Zdor.

Plants live in complex environments filled with potential microbial friends and foes. In light of optimizing plant health, it is prudent to understand the potential that microbes brings to the field of agriculture and to determine the underlying mechanisms of action, which are undoubtedly diverse.

The papers highlighted in this Virtual Issue help highlight the importance of these interactions and efforts to increase our understanding of the mechanisms involved. Using data from both the laboratory- and field-based experiments, the potential of harnessing bacteria and fungi for promoting plant health in the broadest context is showcased and serves as a platform for extending knowledge in the particular field of biological control of plant diseases.

Letters in Applied Microbiology

We highlighted in the September issue of *Microbiologist*, that the format of *Letters in Applied Microbiology* was changing to highlight the significance and impact of the published article. These changes were designed to provide authors with an opportunity to focus on communicating the significance and impact of their research.

This change has now taken place, with the first articles in the new format now online. Why not go online and read the following featured articles and more: **www.lettersappliedmicro.com**

A Streptococcus iniae DNA vaccine delivered by a live attenuated Edwardsiella tarda via natural infection induces cross-genus protection.

As oral feeding and immersion treatments are of low cost and easily conducted, vaccination via these approaches is more feasible, particularly in areas where economy has to be considered as one of the top priorities. This study investigates an alternative means for the construction and delivery of DNA vaccines, which are commonly administered via the costly method of injection.

Characterization and antagonistic properties of Streptomyces strains isolated from Saharan soils, and evaluation of their ability to control seedling blight of barley caused by Fusarium culmorum.

This study highlights the effectiveness of some antagonistic *Streptomyces* isolated from Algerian Saharan soils to control *Fusarium culmorum* by the reduction in disease occurrence and disease severity, suggesting their potential use in microbial biocontrol formulation against soilborne diseases.

A novel Fe(II)/α-ketoglutarate-dependent dioxygenase from Burkholderia ambifaria has β-hydroxylating activity of N-succinyl l-leucine.

The authors found that SadA of *Burkholderia ambifaria* AMMD stereoselectively catalyzed β-hydroxylation of aliphatic amino acid derivatives. By using SadA as a biocatalyst, optically pure β-hydroxy amino acids like *N*-succinyl L-threo-β-hydroxyleucine could be provided in large amounts and at low cost for various industrial applications.

To view these and other articles from *Letters in Applied Microbiology*, or if you would like to read Jean-Yves Maillard's Editorial about the changes in full, please visit **www.lettersappliedmicro.com**

Environmental Microbiology

Volume 14 of the *Environmental Microbiology* Editor's Choice Virtual Issue is available to read online now on the Wiley Online Library. Why not visit **www.env-micro.com** today to read these and other articles from the Editor's Choice Virtual Issue.

The logicome of environmental bacteria: merging catabolic and regulatory events with Boolean formalisms.

The regulatory and metabolic networks that rule the biodegradation of pollutants by environmental bacteria are wired to the rest of the cellular physiology through both transcriptional factors and intermediary signal molecules. In this review, we examine some formalisms for describing catalytic/regulatory circuits of this sort and advocate the adoption of Boolean logic for combining transcriptional and enzymatic occurrences in the same biological system.

Microbial metatranscriptomics in a permanent marine oxygen minimum zone.

Simultaneous characterization of taxonomic composition, metabolic gene content and gene expression in marine oxygen minimum zones (OMZs) has potential to broaden perspectives on the microbial and biogeochemical dynamics in these environments. Here, we present a metatranscriptomic survey of microbial community metabolism in the Eastern Tropical South Pacific OMZ off northern Chile.

Environmental Microbiology Reports

Environmental Microbiology Reports Editor's Choice Virtual Issue Volume 5 is available to read online now on the Wiley Online Library. Read these and other online articles today at **www.env-micro-reports.com.**

Microbial respiration in ice at subzero temperatures (–4°C to –33°C).

The habitability of icy environments may be limited by low temperature, low nutrient concentrations, high solute concentrations and the physical ice matrix. The basal ice of ice sheets and glaciers contains sediments that may be a source of nutrients for microbial activity. Here we quantify microbial respiration and active cell populations of Antarctic glacial isolates *Paenisporosarcina* sp. B5 and *Chryseobacterium* sp. V3519-10 in laboratory ices with abundant nutrients at temperatures from –4°C to –33°C. Our results suggest that the debris-rich basal ice that exists at temperatures just below the freezing point and underlies portions of both the Greenland and Antarctic ice sheets represents a significant potential habitat for metabolically active microbial communities.

Vancomycin tolerance in Gram-positive cocci.

Vancomycin, a glycopeptide antimicrobial agent, represents the last line of defence against a wide range of multi-resistant Gram-positive pathogens such as enterococci, staphylococci and streptococci. However, vancomycin-resistant enterococci and staphylococci, along with vancomycin-tolerant clinical isolates, are compromising the therapeutic efficacy of vancomycin. It is conceivable that tolerance may emerge during prolonged vancomycin use. It has not been until recently, however, that the molecular basis of this tolerance began to be understood.

Melissa McCulloch
Wiley-Blackwell

bio**Focus**

Mark Downs talks about the UK's first ever 'Biology Week'

The Society of Biology is a single unified voice for biology:

- advising Government and influencing policy.
- advancing education and professional development.
- supporting our members.
- engaging and encouraging public interest in the life sciences.

For further information visit:

www.societyofbiology.org

Biology is exciting. Who could think otherwise? It holds potential solutions to many global challenges from climate change or food security to disease prevention and provides the evidence and understanding for many decisions we take individually and at a societal level. When integrated with the other sciences, maths, engineering and technology the impact is even greater. As *Sf*AM members know better than most, at the smallest level of life, organisms can help make drugs, neutralize waste, create energy sources and "manufacture" raw materials. With such accolades biology must surely have a bright future?

I am sure individual members and member organisations of the Society of Biology can all sign up to that. We all work in the sector and can see the extraordinary contribution of biology through history and its even greater untapped potential for the future. The only problem is that most people are not biologists and, as our MORI poll three years ago showed, many just think of biology as a subject they vaguely remember from school involving the dissection of frogs. To overcome these misconceptions we need to engage with the public and work alongside schools and career advisors. Most member organisations of the Society of Biology are other specialist biology-based charities with a sub-discipline focus and already have public outreach and education objections, undertaking some really excellent projects either individually or in partnership with sister Societies. But historically there has not been a single focus for all of biology to try to raise public awareness. We have been trying to help that by facilitating multi-society events bringing disparate resources together under one "biology banner" but it is clear there is much more that could be achieved. The UK's first ever '*Biology Week*' (13–19 October 2012) was intended to provide a national focus for all of the bioscience sector. We hope it will become an annual event and grow in reputation and impact.

Over 40 events took place across the country and the media were keen to get behind us covering events on BBC 1 Breakfast, BBC Radio 1, local radio, BBC online and the broadsheets.

Biology Week was quite literally given a flying start with the launch of the flying ant survey in July to promote the week ahead of time. We wanted to engage with new people, asking them to report sightings of flying ants which traditionally have been thought to fly on a single day. We were aiming for 1000 respondents to provide rich data to interpret in collaboration with Professor Adam Hart from the University of Gloucestershire alongside a plan to announce the result during *Biology Week*. We were overwhelmed with the response from nearly 6500 people helped, again, by major media coverage. The data has shown that there were two "flying ant days" rather than one and is set to lead to academic publications as a great example of "citizen science" linking into the research needs of academia. We will certainly be repeating the survey in 2013!

There was similar enthusiasm for our debate on biodiversity, "should we save the panda?" It was co-hosted with the Linnean Society in a full auditorium and overflow room with video link. The panda won the day but a wider ballot carried out over several days, and announced at the week's formal launch in the House of Commons, saw a tie between the giant panda and the spoon-billed sandpiper! Andrew Miller MP, chair of the House of Commons Select Committee on Science and Technology, together with Dr Julian Huppert MP and Stephen Metcalfe MP hosted this lively BBSRC-sponsored event with wide attendance from the science community and both Houses. I was delighted to be able to promote the value of biology to this important audience and to be able to present four of our first Registered Science Technicians and Registered Scientists with their certificates, part of a new Science Council led professional recognition system available to our individual members and individuals within our member organisations.

In another first the Royal Veterinary College opened its doors to the public for a *Biology Week* event including the opportunity to attend a dissection, learn about epilepsy and other research, and view the impressive anatomical library / museum. Importantly for the Society, this was not just about centrally organized events however, we were delighted to see so many member organisations and individual members organizing their own events around the country including our regional branch network where more than one Nobel laureate gave their time to help us promote biology.

A fitting conclusion to *Biology Week* was a successful attempt to break the world record for the most number of people carrying out an experiment at the same time, ably supported by Professor Bruce Hood and his work on memory. Over 50 locations took part involving more than 1,500 participants with an independent witness at each site to comply with *Guinness Book of Records* requirements and support material available on the wonders of the brain readily available. Radio 1 joined in and many thousands more people around the UK were able to take part helping to move us forward towards the aim of promoting biology in all its forms to the public.

We are already starting to plan Biology Week 2013 and hope to make it bigger and better. Please do get involved. To read more visit http://www.societyofbiology.org/biologyweek.

Dr Mark Downs, PhD, FSB
Chief Executive, Society of Biology

Summer Conference 2012 report

- **Microbial resistance to antibiotics and biocides**
- **Natural and experimental adaptation in bacteria**
- **Bioremediation**

■ Including the Lewis B Perry Memorial Lecture:
Globalization of antimicrobial resistance. *David Livermore, University of East Anglia, UK*

Monday 2 July–Thursday 5 July 2012 The George Hotel, Edinburgh, UK

This year's topics covered ***Microbial resistance to antibiotics and biocides***, ***Natural and experimental adaptation in bacteria*** and ***Bioremediation***. This was all accompanied by the Annual General Meeting of the Society and a lively social programme including a general knowledge quiz, the conference dinner and Science showoff.

To begin there was a pre-conference workshop on ***Intellectual Property*** co-ordinated by Mike Dempsey, featuring many fascinating speakers and talks. In traditional fashion the conference formally began with the final Lewis B Perry Memorial Lecture. David Livermore, Professor of Medical Microbiology at the University of East Anglia and Lead of Antibiotic Resistance at the Health Protection Agency, described the impact of medical tourism on the spread of antimicrobial resistance around the globe. Professor Livermore opened with a historical perspective describing, for example, how the opening of trade routes between Europe and the Far East led to the spread of plague from China to Europe as far back as the 14th century AD. The consequences of this spread were devastating: approximately one third of the European population was wiped out in the ensuing epidemic. In the modern age, where literally anywhere in the world can be reached in 48 hours, the risks of global transmission of infection are greater than ever. As well as spreading diseases, travellers also disperse antimicrobial resistance traits, carried on mobilizable plasmids. Professor Livermore gave several examples where the migration of antibiotic resistance in organisms such as *Neisseria gonorrhoeae* or *Streptococcus pneumoniae* has been traced, albeit on the basis of circumstantial evidence. Prospective studies are now beginning to provide much stronger evidence that travellers themselves act as vehicles for the import of non-native microorganisms from foreign locations. The admission of patients to hospitals in developing countries shortly before international travel is a major risk factor for the transfer of new dangerous antibiotic resistance traits, such as New Delhi Metallo-β-lactamase (NDM-1). Many of the 29 patients in UK hospitals that were found to be carrying NDM-1 bacteria had recently been hospitalized in the Indian subcontinent. Although reliable statistics are difficult to obtain, it is clear that the numbers of people travelling across borders to obtain medical care are growing at an alarming rate. In countries with a weak public health infrastructure, even first-rate hospitals cannot provide an effective barrier against the transmission of microbes and examples are already emerging of patients returning to the UK from liver transplant surgery in Pakistan infected by NDM-1 bacteria. The growth of the medical tourism market is unlikely to be halted in the near future and monitoring and controlling the global spread of antibiotic-resistant microorganisms will present a major challenge for public health microbiologists over the coming years.

Nick Jakubovics *Sf*AM Executive Committee Member

The first full day of the S*f*AM Summer Conference 2012 commenced with William Rutala of the University of North Carolina, USA, providing delegates with an overview of the '***Impact of bacterial resistance to biocides in the healthcare setting***'. He began by drawing distinctions between antiseptics/antibiotics used for treating humans and

disinfectants used for cleaning hospital equipment and environments. He informed the audience that disinfectant resistance has never been observed in the healthcare setting, unlike antibiotic resistance, despite the huge difference between working concentrations of disinfectants and MICs of targeted bacteria. He also advised that there was no evidence that antibiotic-resistant microorganisms are also resistant to disinfectants, although they do exhibit decreased susceptibility (evidenced by higher MIC) on occasion. The implication of this is that antibiotic-resistant pathogens can still be killed by clinically used concentrations of appropriate disinfectants.

The second speaker, Jean-Yves Maillard of Cardiff University, addressed the question of whether '***Bacterial resistance and cross-resistance is an overrated story or a real concern***?' He started by advising us that microbicide was becoming the more generally accepted terminology, rather than biocide, and went on to define several resistance types (innate resistance/resistance in practice/reduced susceptibility/tolerance), which was helpful. He then gave examples of resistance mechanisms, e.g., *Salmonella* Typhimurium efflux pumps and resistance at population level within biofilms. An important take home message was that MBC was more important and more informative than MIC, because if bacteria were not killed outright then development of antibiotic resistance was a possibility.

The third talk by Keith Poole of Queen's University, Kingston, Ontario, focused on his recent research on '***Stress responses as determinants of antimicrobial resistance in Pseudomonas aeruginosa***', the cystic fibrosis (CF)-associated bacterium. He informed us that antibiotic resistance was a hallmark of *Ps. aeruginosa* infections, which was thought to be facilitated by multidrug efflux systems, inducible by environmental stresses (oxidative and nitrosative stresses), existing in CF affected lungs as a consequence of gross inflammation.

Patrice Courvalin of Institut Pasteur, France, considered the question of why vancomycin-resistant Enterococci have spread and become established as a problem when VanA-type meticillin-resistant *Staphylococcus aureus* (MRSA) have not? He explained that glycopeptide resistance in Gram-positive enterococci was inducible meaning that cells expend a lot of effort to become vancomycin resistant, so there is a biological cost on the cell (a change in biological fitness). In contrast, vancomycin resistance in MRSA is carried on multiplasmids giving the host a fitness disadvantage, which in the absence of selective pressure, may account for the lack of dissemination of VanA-type vancomycin-resistant MRSA.

The fifth speaker, Neil Woodford of the Health Protection Agency, reviewed the history of the development of β-lactam (penicillin, penicillin/inhibitor combination, cephalosporin and carbapenem) resistance in Enterobacteriaceae over the past 70 years. He particularly focused on CTX-M-15 a uro-pathogenic clone (ST131) that is widely encountered and has extended spectrum β-lactamases (ESBL). The jury is still out on the risk to humans of ESBL *E. coli*. The current risk from ESBL *E. coli* in poultry in the UK appears small, so presently the human reservoir of these strains is considered to be more important. However, there has been a notable rise in incidence of carbapenem resistance in *E. coli* and Dr Woodford suggested that this was likely to be an issue for the next 5–10 years.

The final talk in the session, given by Rob Townsend, a Consultant Microbiologist from Sheffield Teaching Hospitals,

was on antibiotic stewardship in the health service. It is a fact that every hour, delay in initiating the correct antibiotic treatment for septic shock and other ITU conditions leads to increased mortality. Antibiotic audits by Dr Townsend in Sheffield Hospital have revealed that 30–45% of antibiotic prescriptions for chest infections are inappropriate, despite the prominent display of guidelines on which antibiotics to use as posters and badges within hospital departments. In particular, overuse of broad spectrum antibiotics has been noted, rather than antibiotics targeted against the actual infectious agent involved. This highlights the continued need for education regarding appropriate antibiotic use for Health Trust staff. On a more positive note, Dr Townsend reported that the recent adoption of MALDI-TOF analysis to quickly identify the microorganism in blood cultures within 20 minutes was enabling physicians to prescribe more effective antibiotic regimes earlier.

Irene Grant SfAM Executive Committee Member

Natural and experimental adaptation in bacteria was the theme of the Second Session of the Summer Conference, which began on Tuesday afternoon. The session opened with a talk by Eric Déziel from the INRS-Institut Armand-Frappier, Canada, on '***The various lifestyles of Burkholderia cepacia complex species: a tribute to adaptation***'. *B. cepacia* are often thought of as human pathogens because they cause severe lung disease in cystic fibrosis (CF) patients. However the *B. cepacia* complex, which is defined as a group of 17 related species with >98%S in their 16S rDNA, are mostly rhizosphere components which promote plant growth, through nodulation, N_2 fixation and phytohormone biosynthesis. Some species are also antifungal and could be useful as biocontrol agents. However, all 17 species can be opportunistic human pathogens. The talk concentrated on the importance of phase variation in moving between the two phenotypic types: the CF virulent form and the environmental form. Clinical isolates have been found which will lose a

defined set of virulence factors making them less virulent and at the same time better adapted to the rhizosphere. Thus, there is a clear environmental niche adaptation which could potentially be exploited by making permanently switched variant strains for fungal biocontrol on plants, without the risk of these strains causing human disease.

The second talk was on '***Adaptive evolution in Geobacter***' by Pier-Luc Trembley from the University of Massachusetts. *Geobacter* is an anaerobe which carries out the dissimilatory reduction of metals such as iron and manganese, and is used in the bioremediation of aromatic hydrocarbons and uranium. A key ability is that they oxidize compounds by direct electron transfer. The talk centred on laboratory experiments to adaptively evolve strains, through exposure to repeated stress, which then have an improved ability for bioremediation. The identification of the role of a c-type cytochrome in Fe(III) oxide reduction was discussed, as was the role of pili in acting as 'wires' for electron transfer to other species and the alternative routes pilus mutants found under pressure. Such studies allow a better understanding of the physiology of the organism and potentially could produce better bioremediation strains.

The third talk was by Tom McGenity, University of Essex, on halophiles and hypersaline environments such as salt glaciers and salt lakes. Halophily has evolved many times with saline tolerant bacterial species such as *Salinibacteria*, but the Archaea such as the Haloarchaea and some methanogens are the most tolerant at 80–90% NaCl. These organisms can show particular adaptations such as *Haloquadratum walsbyi* which have very thin square cells with gas vesicles allowing them to float to the surface for O_2. Species such as *Halobacterium* can become entombed with other species such as *Salinibacter* and the algae *Dunaliella* in brine inclusions in halide crystals for several years and still be recoverable. Cellular adaptations to high salt conditions include proteins with high surface negative charge through the inclusion of aspartate and glutamate. The final part of the talk compared the communities in two very specialist deep-sea brine environments in the Mediterranean: Discovery Basin which is $MgCl_2$ rich and Bannock Basin which is NaCl rich (8x seawater). The chaotropic activity of $MgCl_2$, which destabilizes biological macromolecules, resulted in no mRNA activity at an $MgCl_2$ concentration giving an a_w of 0.8 and so at a higher a_w than the limit for NaCl controlling life. This suggests it is chaotropy and not a_w which is the limit for viability. However, the possibility of novel chaophiles may exist.

Christine Dodd *Sf*AM Executive Committee Member

Professor Mark Fielder introduced the speaker Jan Polley who started the session addressing a crucial question to the audience: "how can networking be 'done' properly when it is a skill?" Jan herself admitted, that she never thought how important networking was until she got to a certain stage in her own career. Her point was to make the audience aware of the importance of networking — the skill of building relationships between people. Jan then conducted an activity with the audience; we were asked to find a pair that we had not had a chance to speak to until that point and swap ideas about the five most important characteristics of the prospective collaborator. The most important characteristics students chose were: how interesting the person was, common interests, overlapping fields of interest, how that person helps you and how can you help them in return. Most of the students agreed that personal values are very important. The potential collaborator needs to be open-minded, trustworthy and respectful to each other's ideas, and able to maintain a certain level of professionalism. Jan asked everyone present at the session to think about their strengths and weaknesses. This self-awareness helps you to control your weaknesses and show off your strengths which will help you to approach others.

Next we were asked to conduct two activities. First, one person in our pair was asked to talk to the other person avoiding eye contact. This activity exposed how eye contact is crucial in showing respect and maintaining the good relationship between two people. For the second activity one of our pair had to tell a story using a monotonous voice. This highlighted another very important factor when networking — you need to sound interesting, passionate and enthusiastic, otherwise you may lose the interest of the other party.

Finally Jan asked "why do we need to network?" Simply because the people you are networking with may be your sponsors, your advocates and your supporters, and you will never know who you are going to come across in your journey. That way the right network is always valid.

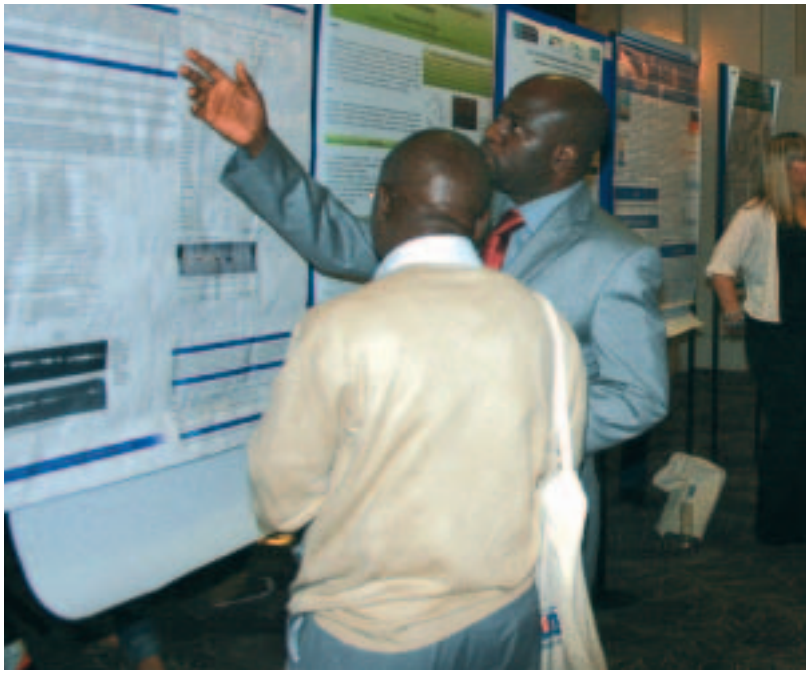
At the end Jan gave some examples of ways of maintaining networks. Luckily, there are tools that make our lives a lot easier. We have Facebook, Twitter, LinkedIn and other resources. Networking is all about building trust, understanding the other party and maintaining the relationship over time whilst also building our own confidence at the same time.

Agnieszka Piotrowska PECS Committee Member

The Natural and experimental adaptation in bacteria Session continued on Wednesday morning with a lecture by Sven Panke from ETH-Zurich, Switzerland, who enlightened the audience about the trials and tribulations of designing

orthogonal biochemical reaction networks. He described the use of microbes in biochemical reactions such as for the synthesis of pharmaceuticals, polymers, cosmetics, food processing and within agriculture. He went on to discuss how restrictions of these cell-based systems can be overcome by the use of cell-free systems, by escaping the confines of cells, greater design control can be exerted with reduced cost and potentially enhanced yields. These systems often utilize multi-enzyme reaction networks in order to artificially metabolize the process required. Some of the major advantages of this approach are that accumulation of toxic substrates or products are no longer an issue. However, the challenges are embedded within the design and assembly of such systems together with regeneration of essential co-factors. Once functioning, the network topology can be further refined by increasing the production of desired products and removing unwanted products. Through understanding the system dynamics, the network complexity can be reduced by removal of superfluous pathways. He described ingenious methods by which the dynamics of such systems can be manipulated through inserting recognition sites of selective proteases into permissive sites of essential proteins, and how the system dynamics can be assessed in real-time, for example, through electrospray mass spectroscopy, disclosing the amino acid composition of various proteins over time. Application of such analytical approaches facilitated further fine tuning of the system by assessing the effects of pulsing the system with a combination of different enzymes to further optimize the system towards its ultimate goal of reliable and reproducible synthesis of its desired product.

Keeping with our theme of Swiss speakers, we then shifted focus towards the potential to engineer bacteria to serve as bioreporters for various pollutants. This intriguing lecture by Jan Roelof van der Meer, from the University of Lausanne, covered some of the principles of engineering bioreporter strains, as well as different types of reporter assays and quantitative interpretation of bioassay results. The use of microbes as bioreporters is based upon the simple concept of living cells having the capability to produce a specific protein in response to sensing a particular environmental stimulus. Bioassays can then be used to quantify resulting changes. Utilization of bioreporter systems alleviates the use of live animals for toxicology studies and is now often the first-line analytical approach. Its application can be to measure a target producing sensitive and specific detection; or to investigate environmental bioavailability or toxicity. Following orthogonal design, it requires calibration prior to assessment in field settings. Even when target substrates are of extreme toxicity, biosensors can be used to sample gas phases thus in close proximity to the target, but not subjected to its toxic effects. Jan went on to describe how natural filter-feeders can provide biological methods of concentrating a target that can then be assessed by bioreporter systems. Indeed, crab urine provides an accessible sample for such analysis. Practical improvements can make these systems more portable, thus enhancing their applicability. He described two differing approaches, firstly whereby the bioreporter organism is embedded in beads within a microfluidic platform. These can be frozen and used as required giving reporter activity for some three days. An alternative approach that has shown excellent applicability to water testing in developing countries has been to freeze-dry the reporter culture into the bottom of



glass vials to which the test sample can then be added. By using parallel series, this approach can enable water supplies to be assayed from whole villages in just one afternoon!

Willy Verstraete from the University of Gent, Belgium, launched the bioremediation session with a thought-provoking lecture brimming with promise for harnessing microbial resources to overcome some of the major challenges to modern society. He described the major 21st century challenges facing mankind, such as climate change; pandemics; environmental quality; obesity and the need for sources of renewable energy, and how biotechnology might hold the key to providing pragmatic solutions to these. The diverse resource furnished by our microbial world provides us with the essential tools that through targeted application, supplemented with our growing biotechnological knowledge, could provide solutions to current global challenges. Our recognition and understanding of microbial diversity is rapidly expanding, with organisms such as those found at highly polluted sites providing potential tools for dealing with reclaiming polluted sites. Invariably, microbial populations work in harmony with many diverse composite species. Willy explained it is probably best to assess these holistically rather than at the level of the individual. Key questions should include what species are present? What are their roles? And are they working within a community structure? Within these complex mixtures it is common that the top 20 components are likely to deliver 80% of the work, a principle that works well in microbial ecology. It is also prudent to recognize that these populations are never static, but instead should be considered as dynamic continually evolving microbiomes. Given these insights, 'omic' analyses can usually disclose the principle players in given situations that can be managed to deliver 'eco-system' services such as energy supply, food production or are able to clear up environmental contamination.

This was then followed by a lecture delivered by Tino Krell from EEZ, based in Spain. He described how we could utilize the motility phenotype towards various pollutants such as

monocyclic and polycyclic aromatic hydrocarbons, nitroaromatics, aminoaromatics, chloroaromatics and aliphatic hydrocarbons, an indication of microbial potential for biodegradation. His experimental model was *Pseudomonas putida*, an organism able to degrade various toxic aromatic compounds through possession of its toluene dioxygenase pathway. Assessment of different phenotypes revealed the various plasmid-mediated mechanisms by which resistance was achieved, such as the possession of efflux pumps combined with the ability to degrade toxic substrates. Tino then described the way that this knowledge could be applied to enhance biodegradation around a plant root through manipulation of the rhizosphere, thus enhancing growth in an environment polluted with toxic aromatic compounds.

Sally Cutler *Sf*AM Executive Committee Member

The next session of the day was the student presentations which were chaired by Emmanuel Adukwu, Chair, Postgraduate and Early Career Scientists (PECS) Committee of S*f*AM. This session provided the opportunity for four PhD students to present their work on different aspects of applied microbiology.

The first speaker was Abigail Edwards. Abigail gave an introduction to the serious problems to animal and human health posed by extended spectrum β-lactamases (ESBL) including the CTX-M family, as these antimicrobial resistance gene products substantially reduce the number of effective therapeutic antibiotics. Next, she explained the various investigations she had undertaken on two ESBL *E. coli* strains isolated from a cattle farm outbreak. These included sequencing and annotating both plasmids, establishing RNA silencing of large plasmid encoded genes and determining the fitness contribution of the plasmid in relation to the host. Her results indicated that silencing of plasmid genes provided a viable option for studying gene function and in addition to conferring drug resistance, ESBL plasmids contributed to the fitness advantages of their hosts.

Following on from Abigail, Nina Holling discussed an investigation to elucidate the genes and pathways involved in *Proteus mirabilis* biofilm formation as well as crystalline biofilm formation leading to catheter encrustation. She highlighted the point that catheter associated urinary tract infections (CAUTIs) are one of the most frequent healthcare acquired infections, with *Pr. mirabilis* being responsible for over 40% of these infections. Nina had created a *Pr. mirabilis* mini Tn5 mutant library and screened 3,000 mutants for phenotypic alterations including swarming, biofilm formation and ability to encrust silicone urethral catheters. Interestingly, her results showed that there was no correlation between the ability of mutants to form biofilms in 96-well microtitre plates, swarming ability and catheter blockage. Also, two novel genes were identified to be important in catheter blockage. Further work will involve scanning electron microscopy and environmental scanning electron microscopy of catheters.

The penultimate presentation was given by Dorota Jamrozy, who presented her work on characterizing plasmid-associated antimicrobial resistance amongst meticillin-resistant *Staphylococcus aureus* (MRSA) ST398 strains. Dorota explained that MRSA ST398 is a novel MRSA lineage that displays a high prevalence of antimicrobial resistance genes and is highly prevalent in some European countries. Plasmid DNA from 18 MRSA ST398 strains was transformed into *Staph. aureus*; transformants were then subjected to plasmid isolation, screening for antimicrobial resistance genes by PCR and confirmation with MIC testing. Sequence analysis revealed the presence of novel plasmid elements including antimicrobial resistance genes. Her work concluded that MRSA ST398 strains carry small single-resistance and larger multiple-resistance marker plasmids.

To finish, Benjamin Folwell introduced the audience to the interesting world of high molecular-weight polycyclic aromatic hydrocarbons (HMW-PAHs), an important pollutant in aquatic environments. Ben's work focused on enriching a consortia of microorganisms able to degrade HMW-PAHs and describe changes in both planktonic and biofilm communities during degradation. Results showed that mixed microbial communities isolated from hydrocarbon-contaminated environments are required to metabolize recalcitrant HMW-PAHs. Ben concluded that optimization of interactions between members of microbial consortia could enhance biodegradation of these pollutants and results could then be applied to develop more efficient bioremediation strategies to remove HMW-PAHs in aquatic ecosystems.

The session was brought to an end by Emmanuel thanking the students for their excellent presentations.

Amara Anyogu PECS Secretary

The first presentation of the award lectures was given by Nick Jakubovics (Newcastle University, UK) who had received the New Lecturer Research Grant from S*f*AM. He gave a fascinating talk on the '***Extracellular DNA in oral biofilms and beyond***'. In the UK over 30% of adults have active caries (tooth decay) due to plaque caused by oral biofilm formation. A key component of biofilms is the extracellular matrix, consisting of carbohydrates, proteins and nucleic acids which protect the microbial cells within it. It has been shown that *Pseudomonas aeruginosa* biofilms are rich in carbohydrates but extracellular DNA (eDNA) is found to be more abundant in

the matrix. Treatment with the enzyme DNase I disrupts *Ps. aeruginosa* biofilms and removes them from the surface they had attached to; therefore, eDNA is critical in maintaining the structural integrity of biofilms. Nick's work has involved investigating if oral bacteria produce mixed-species biofilms containing eDNA and if this is required to maintain biofilm structure. They have found that a variety of common dental plaque bacteria produce eDNA in the biofilm matrix, and when biofilms have been treated with DNase there is a reduction in biofilm biomass. It was found, during an agar plate assay, that *Streptococcus gordonii* produced an enzyme capable of digesting eDNA. The gene encoding this extracellular DNase activity was cloned into *E. coli* to assess the function of this enzyme and if it could be used to control multi-species biofilms. Nick went on to tell us that they have also shown that DNase from the bacterium isolated from the surface of seaweed, *Bacillus licheniformis*, has the potential to disrupt mixed-species biofilms including dental plaque, biofilms associated with chronic rhinosinusitis and microbial communities on speech valves. To conclude, Nick told us how his studies indicate that eDNA is a natural substrate for biofilm remodelling processes and that eDNA may be a novel approach to biofilm control. This could potentially be used in oral healthcare, so in the future you could be saying to your dentist "no fillings today, I've brushed my teeth with seaweed enzyme"!

The next speaker in this interesting session was the winner of the W H Pierce Prize, Robert Ryan of University College Cork, Ireland, who discussed '***Bacterial interspecies signalling during cystic fibrosis lung infection***'. Robert described how bacterial infections of the lung are the foremost cause of morbidity and mortality in cystic fibrosis (CF) patients. The CF lung is often co-infected with *Pseudomonas aeruginosa* and other pathogens including *Burkholderia cenocepacia* and *Stenotrophomonas maltophilia*. Understanding the interaction between these pathogens during infection is becoming crucial for improving the therapy of polymicrobial diseases like the CF lung. Many pathogenic bacteria have evolved cell-cell signalling systems to co-ordinate gene expression and the signalling molecules produced have been found to be structurally diverse. Signal molecules of the diffusible signal family (DSF) are *cis*-unsaturated fatty acids and it has been found that *B. cenocepacia* and *S. maltophilia* can produce these. Previous *in vitro* studies have shown that DSF from *B. cenocepacia* and *S. maltophilia* leads to altered biofilm formation and increased tolerance to antibiotics by *Ps. aeruginosa*. Robert went on to tell us that DSF signals are present in the sputum of CF patients, however, the role of DSF signalling during infection of the CF lung is poorly understood. Clinical isolates of *Ps. aeruginosa* were analysed and it was found that each of them responded to the presence of synthetic DSF by increased antibiotic resistance. He concluded that interspecies DSF-mediated bacterial infections do occur in the CF lung and may influence the severity of the disease, and the outcome of antibiotic treatment.

Samantha Law *Sf*AM Executive Committee Member

The bioremediation theme continued in the Thursday morning session which was chaired by the President of the Society, Martin Adams. The first presentation, '***Biodegradation of petroleum hydrocarbon contaminants in oxic and anoxic marine environments***', was given by Ian Head, University of Newcastle, UK.

Ian started by explaining that crude oil is a highly complex chemical mixture; ultra-high resolution mass spectrometry has identified tens of thousands of constituent compounds. Although the biggest source (47%) of oil in the sea comes from natural seeps, oil spills (only 8%) are significant as they represent an acute high-level input. A range of hydrocarbon-degrading bacteria are ubiquitous in the marine environment. It was demonstrated that the process of oil spill bioremediation can be managed by the provision of inorganic nutrients to stimulate selected organisms. Studies have shown that the degradation of crude oil occurs at a much more rapid rate in oxic conditions than in anoxic conditions. Ian concluded by considering some future developments and described the Volta experiment in which the addition of nutrients and other stimulants to an oil reservoir, through an injection well, increases the yield of oil with methane via the production well.

'***Exploiting fungi in bioremediation of hazardous chemicals***' was the title of the second talk, given by Hauke Harms, UFZ, Germany. Biodegradation of soil pollutants is limited by their bioavailability to degrading bacteria and manual mixing of polluted soil is not a practical approach.

Investigations have been carried out to determine whether fungal hyphae can act as highways for bacteria and as pipelines for pollutants, whether they improve pollutant bioavailability and whether they increase the rate of biodegradation. Hauke showed that the answer to all of these questions is yes. Motility of bacteria through the soil is especially enhanced for flagellated bacteria navigating along the hyphae of hydrophilic fungi. This is particularly important when there are otherwise unfavourable dispersal conditions. An analogy was drawn between subsurface mycelia and sushi trains whereby pollutants are transported along pipelines (hyphae) and consequently degraded by the bacteria lining the pipelines. Although this mechanism has been shown to work in principle, it is now necessary to test library strains to select appropriate fungi for this application.

The final talk of the conference to complete the session on bioremediation was presented by Geoffrey Gadd, University of Dundee, UK. He spoke on '***Metals and minerals: geomicrobiology and bioremediation***'. Geoffrey concentrated on geomycology as a subset of geomicrobiology. With their filamentous growth and production of extracellular enzymes and metabolites for metal/nutrient release, fungi can exploit heterogeneous environments. The Kirkcudbright depleted uranium gardens were used as an example of migration through a mycelial system. Fungi which have been exposed to depleted uranium from armour-piercing munitions at this site have demonstrated the ability to accumulate mobilized uranium in their biomass.

The formation of secondary mycogenic minerals was described, as seen in the biodeterioration of concrete where oxalate crystals can be found encrusting the penetrating fungal hyphae. The final aspect of the talk concerned bioreactor applications using sulfate-reducing bacteria to precipitate metal sulfides.

Louise Hill-King
Microbiologist Editorial Group Member

Environmental Microbiology Lecture
2012 report

Professor Sang Yup Lee (left) receiving a commemorative plaque from the Chief Editor of Environmental Microbiology Ken Timmis (right)

The 2012 *Environmental Microbiology* lecture, '***Metabolic Engineering for a Green Chemical Industry***' was delivered by Professor Sang Yup Lee from the Korea Advanced Institute of Science and Technology (KAIST). This was the fifth in the series of lectures designed to highlight and celebrate the success of the journal, *Environmental Microbiology* and present the latest developments in The field.

Professor Lee began by demonstrating the many different products and challenges that could potentially be addressed using system metabolic engineering. From creating spandex through to making computer components, Sang Yup asked whether these could be moved from traditional fossil fuel processes to bioprocesses using systems metabolic engineering. Professor Lee explained that microorganisms isolated from nature use their own metabolism to produce certain chemicals, but these processes are often inefficient, so metabolic engineering is used to improve microbial performance.

He went on to clarify that metabolic engineering involves the modification of microbial cells to enhance the production of what's known as a bioproduct. This bioproduct can be something that the cell produces naturally, like ethanol or butanol or something that the cells mechanisms can produce if their natural metabolic pathways are altered in some way. The range of uses of this bioproduct can be broadened through metabolic engineering, which may also optimize the overall process of bioproduct synthesis.

Next, Sang Yup described some of his work utilizing systems metabolic engineering including its potential for producing chemicals and fuels. Sang Yup highlighted one particular project they had been working on, producing spider silk.

Spider silk is incredibly tough and as strong as Kevlar, importantly it is also incredibly light. Sang Yup provided us with an example of a cape made of golden orb spider silk which had recently been in an exhibition. The cape had taken four and a half years to make, and involved 82 people going out every day to collect golden orb spiders. Whilst the cape was beautiful, Sang Yup joked that it was very difficult to get 82 grad students to go out every day to collect spider silk and that it was not a very efficient process. So, he and his team had begun looking at ways to create spider silk quickly and efficiently using *E. coli*.

Finally Professor Lee provided a few further examples of the work he and his team had been doing which included using bioprocesses to create plastics and industrial solvents. In conclusion Sang Yup took us back to the very first part of his talk and explained how it should one day be possible to create many everyday products through systems metabolic processes. The lecture ended the presentation of a plaque to Profesor Lee by *Environmental Microbiology* Chief Editor, Ken Timmis before delegates were given the opportunity to ask Sang Yup any questions over a drink and canapé reception.

If you were unable to attend the lecture it is now available online at:

http://www.yada-yada.co.uk/Blackwell/SFAM2012/SfAM2012_v1.html

Clare Doggett
Communications Officer
Society for Applied Microbiology

Wednesday 9 January 2013

Winter Meeting

- **Food mycology**
- **Emerging technologies in applied microbiology**

■ Including the Denver Russell Memorial Lecture

■ In conjunction with the British Mycological Society

The Royal Society, London, UK

IBMS CPD ACCREDITATION 6 POINTS

Programme

10.00 – 10.30 **Tea, coffee and registration**

Chair: **Martin Adams**

10.30 – 11.15 **The Denver Russell Memorial Lecture**
Geoff Hanlon, University of Brighton, UK

11.15 – 11.50 **Molecular and ecophysiology aspects and impacts on mycotoxin contamination**
Naresh Magan, Cranfield University, UK

11.50 – 12.25 **Plex-ID in the microbiology laboratory**
Mark Wilcox, Leeds General Hospital, UK

12.25 – 13.30 **Lunch**

Session A Food mycology

Chair: **Naresh Magan**

13.30 – 14.05 **Metabolomics and taxonomy aspects of food spoilage moulds**
Ulf Thrane, Technical University of Denmark

14.05 – 14.40 **Modelling spoilage fungal growth**
Sonia Marin, University of Lleida, Spain

14.40 – 15.00 **Tea and coffee**

15.00 – 15.35 **Spoilage fungi in the factory environment**
Phil Voysey, Campden BRI, UK

15.35 – 16.10 **Spoilage fungi and sex in the food environment**
Paul Dyer, Nottingham University, UK

Session B Emerging technologies in applied microbiology

Chair: **Andrew Sails**

13.30 – 14.05 **Applications of next generation sequencing in microbiology**
Nick Loman, University of Birmingham, UK

14.05 – 14.40 **Molecular methods in food and water microbiology**
Andrew Fox, HPA, Royal Preston Hospital, UK

14.40 – 15.00 **Tea and coffee**

15.00 – 15.35 **MALDI-TOF in microbiology**
Markus Kostrzewa, Bruker Daltonik GmbH, Germany

15.35 – 16.10 **Automating the bacteriology laboratory**
Neil Bentley, HPA Cambridge, UK

16.10 **Close**

To register online for this meeting please visit www.sfam.org.uk/en/events/index.cfm/Winter_meeting or contact Sally Hawkes ■ Email: sally@sfam.org.uk ■ Telephone +44 (0)1933 382191

Tuesday 23 April 2013

Spring Meeting

STIs in the 21st Century

■ Including the Procter and Gamble Applied Healthcare Microbiology Award Lecture

The Stratford Q Hotel, Stratford-upon-Avon, UK

IBMS CPD ACCREDITATION 6 POINTS

Programme

09.15 – 10.15	**Tea, coffee, trade exhibition and registration**
10.15 – 10.20	**Chairman's welcome**
Chair:	**Sally Cutler**
10.20 – 11.00	**Procter and Gamble Applied Healthcare Microbiology Award Lecture** Speaker to be confirmed
11.05 – 11.35	**Changing trends in chlamydia infection** Gwenda Hughes, HPA, London, UK
11.35 – 12.05	**Gonorrhoea — may be untreatable by 2015!** Cathy Ison, HPA, UK
12.05 – 12.35	**Epidemiology of STIs in the UK** Ian Simms, Health Protection Agency Communicable Disease Surveillance Centre, London, UK
12.35 – 14.00	**Lunch and trade exhibition**
Chair:	**Steve Davies**
14.00 – 14.30	**The overlooked problem — *Trichomonas vaginalis*** John White, Guy's and St Thomas NHS Foundation Trust, London, UK
14.30 – 15.00	**HPV vaccines, are they doing the job?** Margaret Stanley, University of Cambridge, UK
15.00 – 15.30	**Resurgence of syphilis the "great pretender" in the UK** Andrew Turner, HPA, Manchester, UK
15.30 – 16.00	**BV or Overview & closing remarks** Philip Hay, St Georges, UK
16.00	**Close, tea and coffee**

To register online for this meeting please visit www.sfam.org.uk/en/events/index.cfm/springmeeting or contact Sally Hawkes ■ Email: sally@sfam.org.uk ■ Telephone +44 (0)1933 382191

Towards eradication of HPV-induced cancers with HPV vaccine?

One of the most exciting developments in cancer prevention has been the development, commercial production, and large-scale administration of two vaccines effective against infection with human papillomavirus (HPV). HPV is a stable, ubiquitous and evolutionarily well-adapted virus, initially associated with cutaneous and genital warts, but which is also associated with cervical cancer. Virtually all cervical cancers and associated precancerous lesions are due to persistent infection with oncogenic or high-risk HPV oncotypes (HR-HPV). These oncotypes can transform infected cells to a malignant state through the interaction of viral genes, particularly

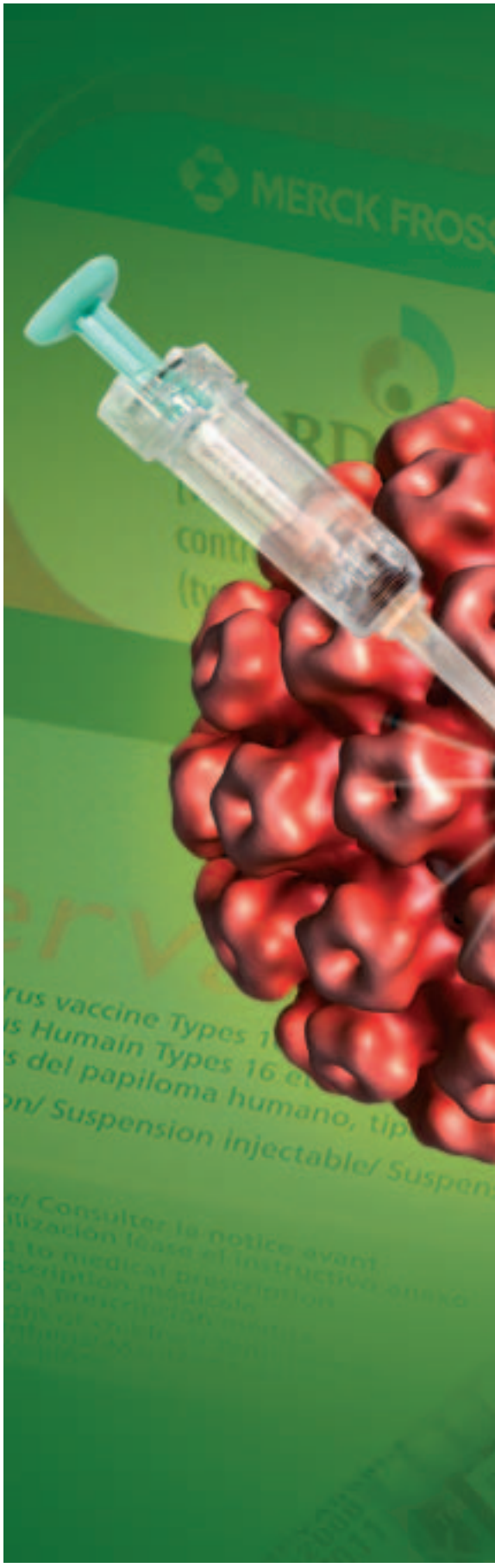
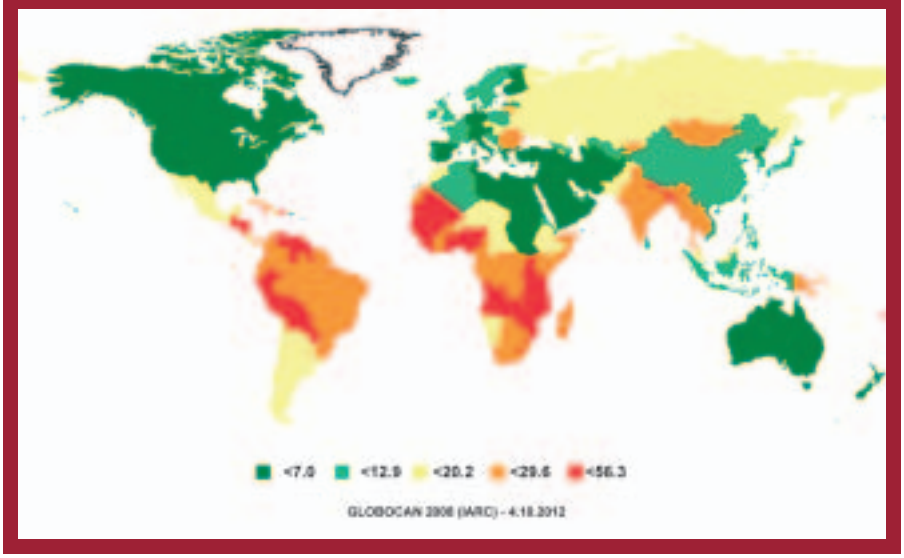
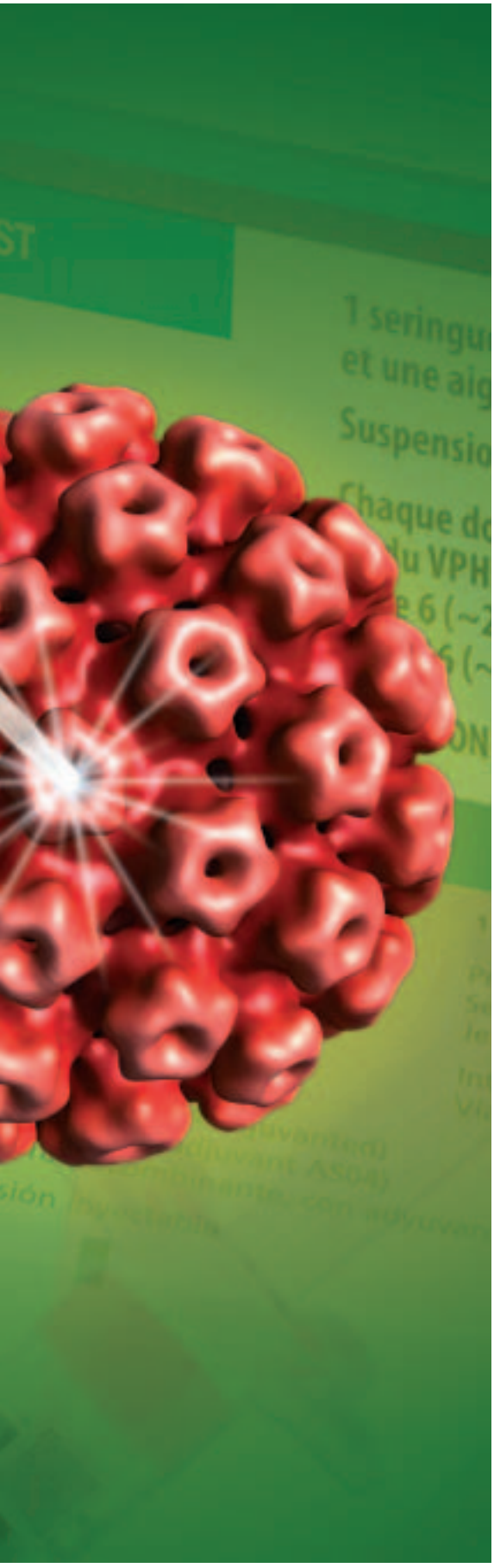


Figure 1. *World map of cervical cancer incidence; GLOBOCAN 2008; (http://globocan.iarc.fr/) Estimated age-standardized incidence rate per 100,000 Cervix uteri, all ages*





E6 and E7, with cellular tumour suppressor genes, p53 and pRb respectively.

Cervical cancer is the most common cancer in women in sub-Saharan Africa, South Asia and parts of Latin America, and is the third most common cancer in the world, affecting around 500,000 women globally, particularly during childbearing years. Cervical cancer kills almost 300,000 annually and disproportionately affects the poorest and most vulnerable in society (Figure 1). As the global population and life expectancy increases, the International Agency for Cancer on Research (IARC) has predicted a 40% increase in cervical cancer by 2020 (IARC, 2005). There are two interventions which can significantly reduce the incidence of cervical cancer: cervical screening and vaccination against HPV.

Cervical screening

The more established intervention is the screening of exfoliated cervical cells under a microscope to search for abnormalities in cell and nuclear structure, the so-called 'Pap test' or 'cervical smear', which was introduced for cervical screening in the 1950s/60s. However an impact on cervical cancer incidence wasn't noted until countries introduced quality-assured national screening programmes (Figure 2) and in the UK, it is estimated that 1 in 80 women have been prevented from developing cervical cancer by accessing the screening programme since its introduction (Peto *et al.*, 2004). Continued investment in services and the recent introduction of new technologies such as liquid-based cytology, has greatly reduced the number of inadequate smears and consequent return visits. Further investment in HPV testing is also beginning to improve the sensitivity of cytology, but that's another story. Many countries are envious of the UK's screening programmes; cervical cytology is not an option for low-resource countries with few trained staff and inadequate facilities. But screening is also an ineffective intervention if used opportunistically where it tends to lead to over-screening of women at little risk, while missing those at highest risk. Until recently, high-quality programmes have only existed in Scandinavia, UK and the Netherlands, but most other developed countries have, or are in the process of introducing national screening. A recent study of over 30,000 cervical cancers revealed the 12 most common HR-HPV oncotypes to be 16, 18, 58, 33, 45, 31, 52, 35, 59, 39, 51, 56, with HPV 16 by far the most common, and HPV 16 and 18 accounting for over 70% of invasive cervical cancer worldwide (Li *et al.*, 2011). No other major human cancer has a single necessary cause, thus making it amenable to significant prevention and potential eradication, through immunization. This knowledge led to the second preventative intervention: HPV vaccine.

HPV vaccine development

The first major breakthrough in developing HPV vaccines came about 20 years ago, when it was recognized that the major coat protein could self-assemble into virus-like particles (VLPs) (Zhou *et al.*, 1991; Kirnbauer *et al.*, 1992). Shortly after, a monovalent vaccine for HPV 16 was trialled in human volunteers and showed promising protection (Koutsky *et al.*, 2002). Since then, prophylactic VLP vaccines have provided a unique opportunity to limit the spread of HPV infection and the global burden of HPV-related disease. Currently there are two licensed HPV vaccines: a quadrivalent vaccine (qHPV) containing HPV 6, 11, 16 and 18 VLPs directed against both genital warts and cervical cancer prevention (Gardasil®; Merck), and a bivalent vaccine (bHPV) containing HPV 16 and 18 VLPs directed solely at cancer prevention (Cervarix®; GlaxoSmithKline). Characteristics of the two vaccines, both of which contain non-infectious recombinant HPV VLPs are shown in Figure 3. The results of Phase III trials with both vaccines have so far been impressive. In a Gardasil® trial there were no cases of HPV 6/11/16/18-related precancerous cervical dysplasia or genital warts in vaccine recipients in contrast to six cases in placebo recipients after five years of follow-up (Villa *et al.*, 2006; Romanowski, 2011), while sustained efficacy of Cervarix® over >8 years was recently reported, with all women remaining seropositive to both HPV types (Roteli-Martins *et al.*, 2012). Such outcomes have encouraged researchers and policymakers alike to advocate the introduction of national HPV vaccination, although vaccine efficacy in the community is expected to be lower

Figure 2a. *Impact of screening on cervical cancer. Since 1988 when the national screening programme was introduced, the incidence of cervical cancer in England has halved and in 2008 stood at an age-standardized incidence rate (ASIR) of 8.3 per 100,000 female population. (http://www.ncin.org.uk/publications/data_briefings/cervical_incidence_and_screening.aspx)*

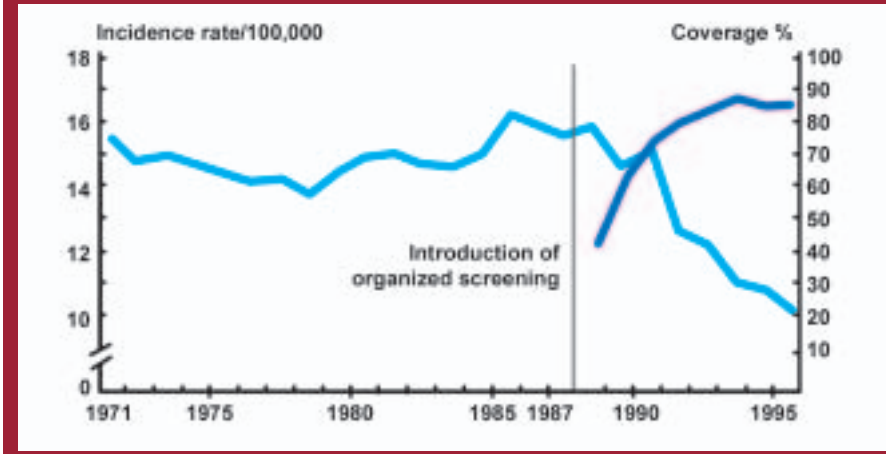
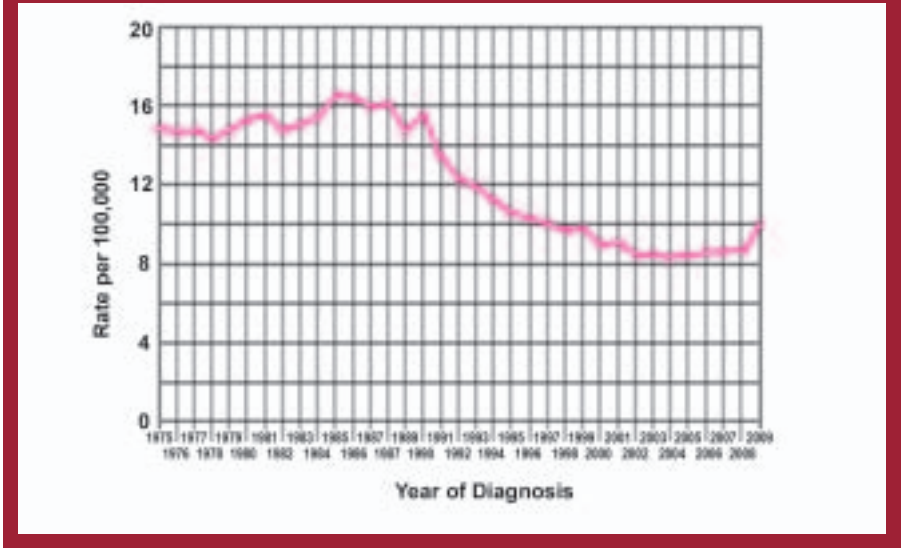


Figure 2b. *c/f updated CxCa incidence but not with screening superimposed*



than in the highly controlled environment of clinical trials, but hopes remain for an impressive reduction in HPV prevalence, precancerous cervical disease and eventually in cervical cancer. In 2007, Australia launched a publicly funded programme with a quadrivalent vaccine (Australian Government, 2012) while the UK introduced a national schoolgirl immunization programme for 12–13 year olds in 2008, with catch-up to age 18 for the first two years in England and three years in Scotland. With good information for girls, parents and teachers, largely constructive media coverage and efficient organization in schools, immunization coverage exceeded the Department of Health's expected 80% for cost-effectiveness across the whole of the UK, and in Scotland coverage has been maintained at around 90% (Figure 4). School-based programmes have been shown to have a much higher success rate than community-based programmes (ISD Scotland, 2012) and the recommendation now across many countries is to implement HPV vaccine for adolescent girls at whatever stage of education is most appropriate. Vaccine is available in most countries, but is still expensive, however since the GAVI Alliance began financing HPV vaccination in partnership with Merck, Rwanda has demonstrated over 90% coverage among girls aged 12–14 through a school-based programme (Binagwaho *et al.*, 2012). Such an example should motivate other countries to explore universal HPV vaccine delivery, perhaps to boys as well as girls so that the implementation of cervical screening programmes becomes unnecessary. While protection from infection is now possible, it will be many years before the impact of vaccine on cervical cancer statistics is evident; even then, this will only be achieved through robust programmes of surveillance. It is hoped that improving access to HPV vaccines will promote more equitable and efficient cervical cancer prevention at the global level.

Major issues associated with HPV vaccine introduction

Neither vaccine is effective in the presence of a pre-existing infection, and because HPV is largely sexually transmitted, vaccine has most efficacy if given before sexual debut. This has led to much debate and opposition to national immunization programmes and the major issues are detailed below.

Societal, cultural and ethnic barriers to HPV vaccine

Many, well-established vaccines remain controversial and HPV vaccine is no exception. Indeed, there has been significant media coverage — both positive and negative — since 2006 when licensing began. For example, in the US, an early mandate that all girls entering the 6th grade receive HPV vaccine resulted in public concern that the vaccine programme was an intrusion on parental rights and would encourage teenage promiscuity (Charo, 2007). Ensuing political pressure and the fact that vaccination is a state-level policy, now means that only Virginia and Washington DC, mandate HPV vaccination in 6th graders, although opportunities to opt out are available. In some European countries, debate fuelled by negative publications from public health professionals, has resulted in low promotion and low uptake of the vaccine (ECDC, 2012), and the Catholic Church in Canada continues to disrupt Provincial programmes despite Government recommendations (Rooke, 2012). Such attitudes undermine the potential of the HPV vaccine.

It is important to recognize that while HPV is a sexually transmitted infection, cervical and other cancers associated

with HPV are NOT sexually transmitted diseases. Indeed it is thought that about 80% of sexually active adults will have contracted an HPV infection at some point in their lives (often soon after sexual debut), but will clear the infection without any clinical consequences (Cubie, 2003). Despite this, women in many cultures are ostracized when they develop cervical cancer, receive little or no support and are left to suffer a painful and unpleasant death. However, the debate should not be about sexual practices, but about eradicating the harmful effects of a common virus. There is therefore a real need to get clear and compelling educational messages to girls, their parents, and to healthcare professionals across religious and ethnic divisions to encourage HPV immunization in pre-sexually active youngsters.

Safety

One of the biggest problems associated with delivery of any vaccine is the public propensity to relate temporal vaccine administration to coincidental events. This is a particular concern for a vaccine delivered during teenage years and adolescence — a stage at which a number of common conditions, including autoimmune diseases such as Guillain–Barré syndrome, become manifest. Rigorous European and American monitoring agencies, covering tens of millions of doses, have shown few serious adverse events, none with greater frequency than in non-vaccinated girls of the same age, or showing a pattern suggesting an association with vaccine. Review of the first 23 million doses of qHPV in the US (CDC, 2011), and of the first six million doses in Australia (TGA, 2011), did not reveal any unusual patterns. In the UK analysis of the first 4.5 million doses of bHPV showed no serious side effects (MHRA, 2010) and overall, the vaccine has been shown to have an excellent safety profile, revealing only minor side effects such as those listed in the product information. Despite this, stories in the press can show a remarkable lack of understanding. For example, news on the Internet of the death of a young girl who had just received bHPV had millions of hits within days, while news of the unrelated, underlying cause of death received only tens of thousands of hits a few days later. Elsewhere, cases of epilepsy and other deaths have led to the temporary suspension of programmes although linkage to vaccine has not been sustained. Perhaps the most sinister demonstration of lack of knowledge was in 2011 when Michele Bachmann, a potential Republican Presidential candidate, claimed that HPV vaccine was responsible for mental retardation, prompting a political row and professional outcry. A simple Google search of 'HPV vaccine adverse events' reveals how extensive the controversies have been.

Figure 3. *Comparison of current bivalent (Cervarix®) and quadrivalent (Gardasil®) HPV VLP vaccines*

	Cervarix®	Gardasil®
Manufacturer	GSK	SP-MSD
VLP Types	Bivalent HPV 16,18	Quadrivalent: HP 6,11, 16, 18
Production	L1 expressing baculovirus from Hi5 insect cell line	Saccaromyces cerevisiae expressing L1
Dose of L1 protein	20, 20mg	20, 40, 40, 20mg
Adjuvant	500mg aluminium hydroxide, 50mg 3-O-deacylated-4O monophosphoryl lipid A	225mg aluminium hydroxyphosphate sulphate
Immunization schedule	0, 1, 6 months	0, 2, 6 months

Extended coverage

Evidence from both vaccines shows strikingly high efficacy against the HPV oncotypes included in the vaccines. HPV 16 and 18 are responsible for around 70% of cervical cancers worldwide, but how do we protect against the remaining 30%? For those countries where quality assured, national cytology-based cervical screening programmes exist, lesions associated with other HPV types should still be detected by regular screening at the precancerous and therefore treatable stage, so the need to have the correct educational messages to ensure vaccinated women come for screening when invited, still remains.

There is great interest in the potential for cross-protection against additional HPV types from existing vaccines. The PATRICIA trial of bHPV recently reported high efficacy against the two vaccine oncotypes, but protection against HPV 31, 33, 45 and 51 was also evident (Lehtinen *et al.*, 2012; Wheeler *et al.*, 2012), and a commentary in Nature Medicine summarizes the implications (Kim *et al.*, 2012). While it is not so clear cut, a degree of cross-protection arising from qHPV has also recently been reported (Malagon *et al.*, 2012; McCormack and Joura, 2010). Protection against HPV infection has also been demonstrated in unvaccinated cohorts; so called 'herd immunity' was observed in a study which showed a 50% drop in vaccine type HPV in unvaccinated women within four years of introducing qHPV into the community (Kahn *et al.*, 2012). The newest debate surrounds whether it is cost-effective to immunize boys as well as girls to ensure maximum herd immunity.

Concern has been expressed about HPV type replacement when HPV 16/18 is largely eliminated through vaccination. Evidence already suggests an increase in prevalence of infection with non-vaccine types (Kahn *et al.*, 2012), but HPVs are genetically stable DNA viruses which have co-evolved with humans over millennia and there is no evidence as yet to suggest that this will impact adversely on the numbers of HPV-associated cancers. Nevertheless, this area of surveillance warrants careful long-term studies on a global scale.

Other HPV cancers preventable by vaccine

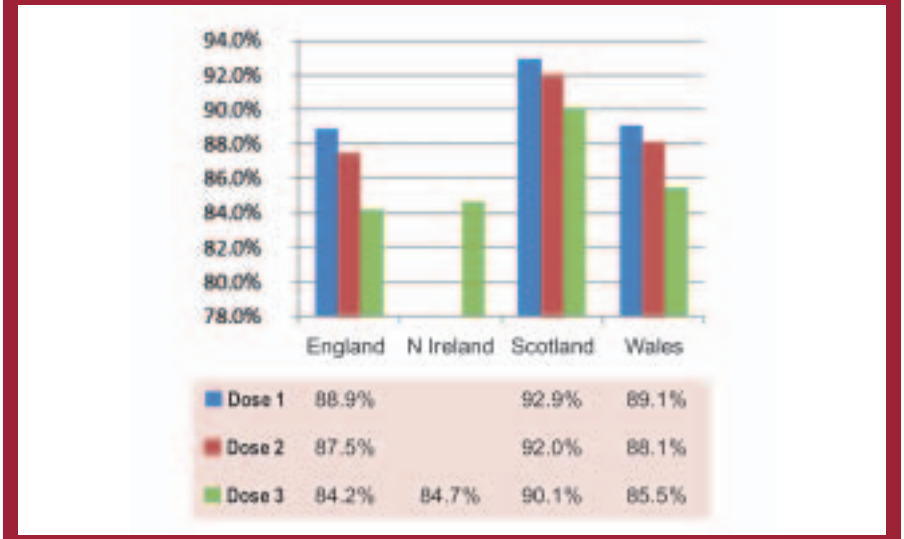
An even higher percentage of HPV induced non-cervical cancers are associated with HPV 16/18 and therefore amenable to prevention by

vaccination. Consequently, protection against vaginal and vulval cancers in women but also against anal and oropharyngeal cancers in both men and women is possible. The incidence of oropharyngeal cancers is growing faster than for almost any other cancer and is thought to reflect increase in sexual practices such as oral sex or earlier onset of sexual experience (D'Souza *et al.*, 2009). In relation to the financial burden of treating genital warts, universal immunization of pre-teens looks increasingly attractive, and in October 2011, the CDC recommended HPV vaccine for boys and girls (ACIP, 2011). More recently Australia has provided federal funds for a programme which includes boys and in September 2012, the UK changed from bHPV to qHPV, thus opening the door for introduction of HPV vaccine to boys.

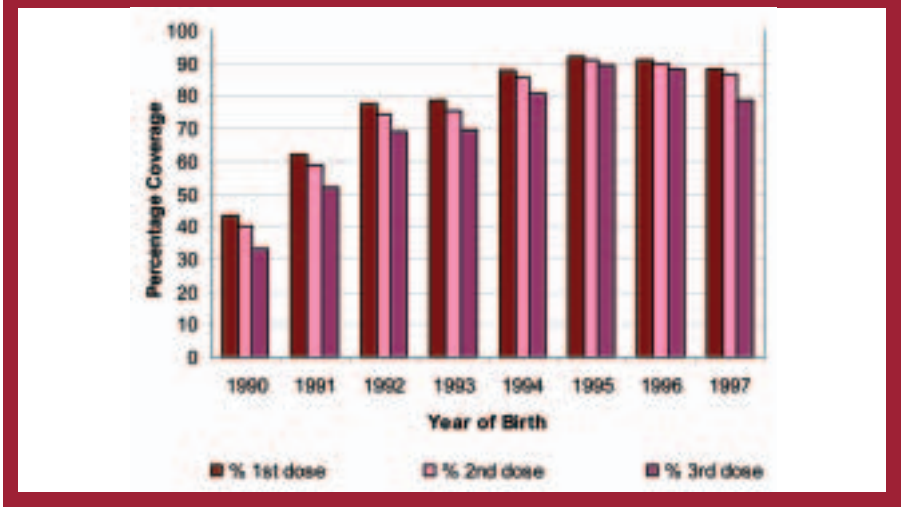
Cost

HPV vaccines are the most expensive vaccines ever produced, with cost per dose ranging from $5 to $130 (Kim *et al.*, 2012). Three doses are required over six months also making administration costs expensive, hence there is a need for programmes to be sustainable and to show impact. Until recently, HPV vaccine programmes were confined to high-income countries, however in 2011, the GAVI Alliance agreed to support implementation of HPV vaccine programmes in schools in low-income countries provided they could meet significant criteria relating to delivery (Markowitz *et al.*, 2012). Cost-effectiveness may be hard to demonstrate however, the health charity PATH conducted demonstration projects of HPV vaccination in several countries and showed that high coverage was achieved (LaMontagne *et al.*, 2011); but controversy has arisen over the project in India where it is argued that the incompleteness of cancer registration and monitoring would make it impossible to judge the impact (Mattheij *et al.*, 2012).

Figure 4. *UK vaccine uptake*
a) *2010/11 Uptake of national programme across all administrations, as of 25th September 2012 (adapted from http://www.isdscotland.org/Health-Topics/Child-Health/Publications/2012-09-25/2012-09-25-HPV-Uptake-Report.pdf)*



b) *HPV immunization coverage for girls resident in Scotland as of 30th June 2011, by year of birth (http://www.isdscotland.org/Health-Topics/Child-Health/Publications/2011-09-22/2011-09-22-ImmunisationHPV-Report.pdf)*



Concluding remarks

An exciting opportunity exists to reduce and even eliminate the problem of serious disease and cancers associated with the common virus, HPV. In the UK, the sustained high vaccine uptake in schoolgirls and the availability of a national call and recall cervical screening programme give high hopes for significant reduction in cervical cancers and precancers. We have in place good infrastructure to assure delivery, data collection and funded surveillance programmes to inform future health service needs but we still need to consider the position of boys, the prevention of non-cervical HPV-associated cancers and the duration of vaccine protection against HPV 16, 18 and other non-vaccine types. Is the world up to the challenge? I believe it needs constructive partnerships, Government buy-in, ring-fenced resources and appreciation that a programme that suits one country is not only impractical for another, but could be wasteful and even harmful. The research community also needs to better understand the natural history of HPV in different settings; how transmission can be mitigated and persistent infection averted in order to develop the next generation of prophylactic and therapeutic vaccines and provide the epidemiological and qualitative evidence to ensure better control of HPV in the future.

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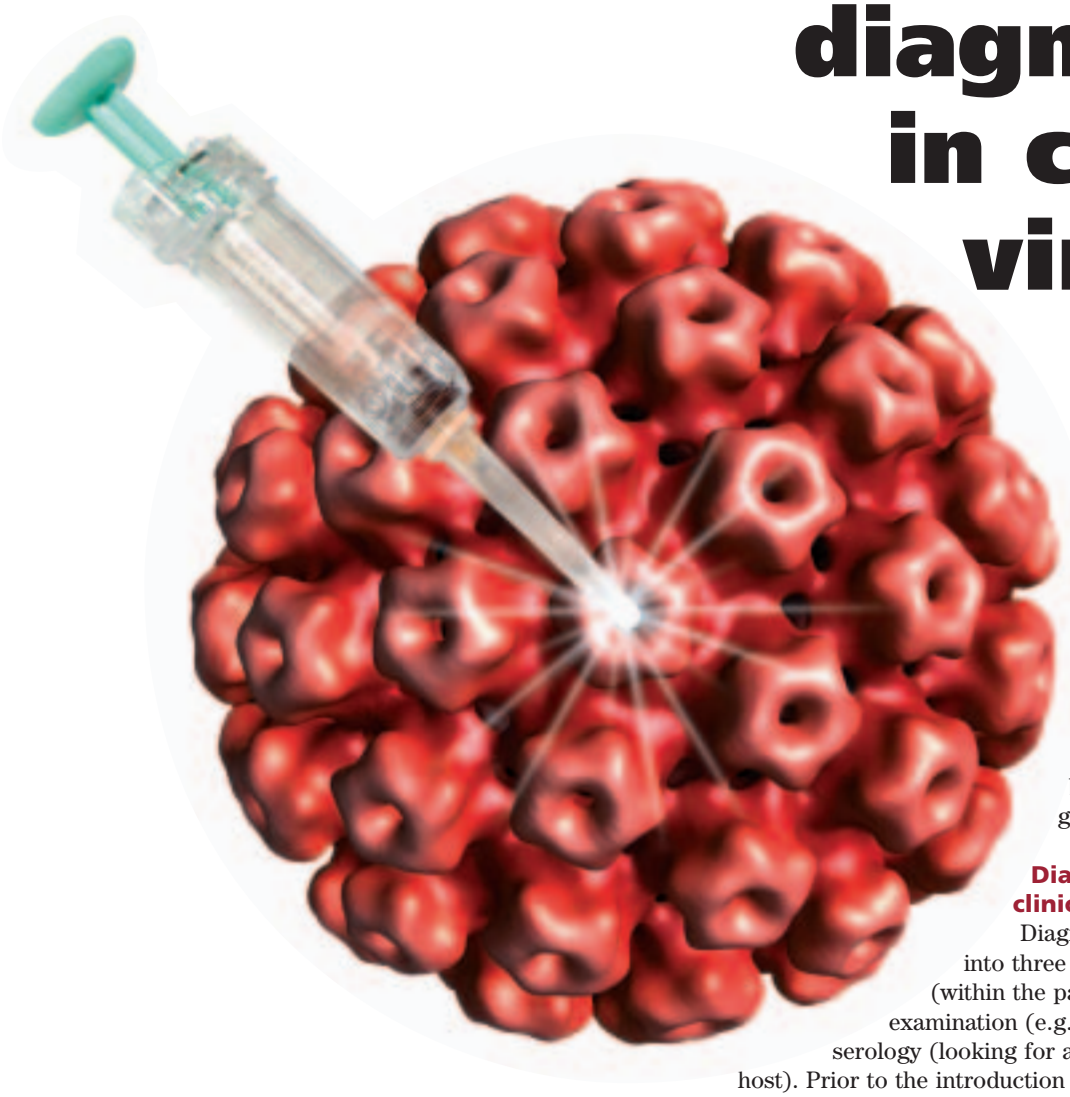
Molecular diagnostics in clinical virology



There are a myriad of viral pathogens which cause disease in humans ranging from the common cold to meningitis and encephalitis. The diagnosis of the causative agent of viral disease has always been more problematic when compared with bacterial disease because many viruses cannot be grown in culture or only grow very slowly.

Diagnostic methods in clinical virology

Diagnostic tests can be grouped into three categories; direct detection (within the patient sample), indirect examination (e.g., virus isolation), and serology (looking for an antibody response in the host). Prior to the introduction of molecular diagnostic methods, direct detection was reliant on electron microscopy, which has a low sensitivity of detection. Alternatively, antigen detection using immunofluoresence (IFAT) or ELISA-based methods can be used but this also lacks sensitivity and specificity. Virus isolation (indirect detection) in cell culture is laborious with some viruses growing slowly or not at all, and the presence of the growing virus is usually detected by the cytopathic effect (CPE), which may be specific or non-specific e.g., Herpes simplex virus (HSV) and Cytomegalovirus (CMV) produces a specific CPE, whereas enteroviruses do not. Alternatively, hemadsorption can be used with the cells acquiring the ability to stick to mammalian red blood cells which is mainly used for the detection of influenza and parainfluenza viruses.

Because of the limitations of these direct and indirect methods, serology remains the mainstay of viral diagnosis for many infections. Following exposure to a viral pathogen, the first antibody class to appear is IgM, which is followed by a much higher titre of IgG. In cases of reinfection, the level of specific IgM either remains the same or rises slightly however, IgG rises more rapidly and earlier than in a primary infection.

Interpretation of serology testing is far from easy and clinical symptoms such as gastroenteritis or respiratory disease occur before antibody responses can take place. However, with some viruses such as rubella and hepatitis A, the onset of clinical symptoms does coincide with the antibody response and so the detection of IgM or rising titres of IgG in the serum of the patient is indicative of active disease.

The advantages of molecular diagnostics in clinical virology

PCR was first described by Saiki *et al*. in 1985 and the first description of its application in virology was for the detection of HIV in established infected cell lines and in cells cultured from infected individuals (Kwok *et al*., 1987). Shirley Kwok's paper led to an increasing interest in utilizing PCR in clinical virology, however initial methods were mainly limited to reference laboratories and academic research. This was because early PCR methods were laborious and detection of amplification relied on agarose gel electrophoresis which also lacked specificity. The introduction of probe-based amplification methods such as real-time PCR facilitated the transition of these research-based methods to the routine clinical virology lab. Real-time PCR instruments are closed-tube systems which reduce the risk of false positive results due to amplicon carryover, because the samples are not opened following thermal cycling. In addition, many instruments process samples more rapidly than conventional PCR instruments, making pathogen testing much more rapid. The progression of the PCR reaction is monitored in real-time using probes labelled with fluorescent dyes. There are a multitude of fluorescent dyes available which fluoresce over a range of wavelengths measured by real-time PCR instruments and this allows the use of multiple dyes within assays. This means that assays can be multiplexed to detect a range of pathogens within the same tube. This has proven to be particularly useful for diagnosing conditions where the same symptoms can be caused by a range of pathogens. In addition, the ability to monitor the reaction in real-time allows quantitation of the number of copies of the original target sequence over many orders of magnitude. This has facilitated the development of assays for viral genome quantitation which have become increasingly useful in the diagnosis and management of viral disease.

Multiplex detection of viral respiratory pathogens

A wide range of viruses can cause respiratory disease in humans including influenza virus, parainfluenza virus, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, coronavirus and rhinovirus. These can cause symptoms which range from a mild cold-like illness all the way through to severe acute respiratory distress and pneumonia. Diagnosis based on symptoms alone isn't possible because a wide range of viruses can be associated with similar symptoms. The world has also witnessed the recent emergence of corona virus-associated severe acute respiratory syndrome (SARS), influenza A H5N1 (avian influenza) and pandemic influenza H1N1 (swine variant). The emergence of these new viruses has placed new emphasis on the need for rapid and specific diagnostic tests to differentiate between patients suffering from more common respiratory pathogens i.e., the common cold and those infected with these highly pathogenic viruses. Although there are no effective licensed antiviral treatments for many viral respiratory pathogens, the rapid identification of influenza infection facilitates timely initiation of antiviral therapy using antiviral compounds such as neuraminidase inhibitors.

Prior to the introduction of molecular methods, detection of respiratory viruses was based on virus culture, ELISA or immunofluorescence (IFAT) which have limited sensitivity and specificity. It is now usual for labs to screen samples from patients with infectious respiratory disease with multiplex assays which can detect a wide range of viral respiratory pathogens. Such assays can rapidly identify the causative organism and improve both patient management and infection control. Prior to introducing multiplex PCR testing in our laboratory we compared the detection of 16 individual viruses by multiplex PCR with IFAT and viral culture tests. The viruses targeted included: influenza, parainfluenza, respiratory syncytial virus, metapnuemovirus coronavirus rhinovirus and adenovirus. A total of 183 respiratory specimens were tested and 73 samples (40%) were negative by both PCR and IFAT/culture testing and 72 (39%) were positive for the same organisms by both methods. The multiplex PCR assay also detected target viruses in an additional 38 samples (21%), however no samples were positive by IFAT/culture and negative by PCR. The multiplex PCR assay also detected significantly more dual infections, 18 compared with two detected by IFAT/culture. The results of the study demonstrated that the multiplex PCR method was more sensitive when compared with conventional testing and validated the approach prior to the introduction of the method in our laboratory.

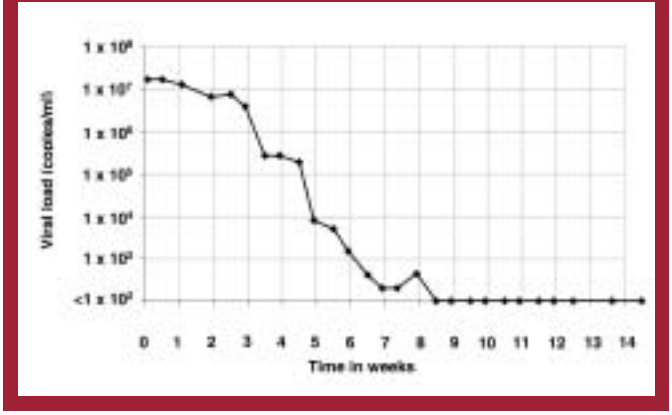
Detection of CNS infections

Human herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), enteroviruses (EV) and human parechovirus (HPeV) are the most common viral causes of infection of the CNS (Davis & Tyler, 2005). Before the introduction of molecular methods, diagnosis of viral meningitis and encephalitis was reliant on cell culture of cerebrospinal fluid (CSF) samples, however, such methods were very slow with turnaround times far too long to influence patient management. Thankfully, molecular diagnostic methods have become the new gold standard for the detection of these viruses in CSF. Enteroviruses are the most common cause of CNS infections and it has been estimated that they are responsible for 70–80% of the cases of viral meningitis. Most clinical virology laboratories now screen all CSF samples from suspected cases of viral meningitis with molecular assays for EV, HSV-1 and 2, and VZV. Rapid identification of EV as the cause of CNS infection facilitates more informed patient management with reduced use of unnecessary procedures and irrelevant treatment; whereas, rapid diagnosis of CNS infection by HSV, which can be fatal, enables timely administration of antiviral therapy resulting in reduced morbidity and mortality.

Diagnosis of genital ulcer disease

The most common causes of genital ulcer disease (GUD) are *Treponema pallidum* (syphilis), HSV-1 and -2 (genital herpes), and more rarely in the UK, *Haemophilus ducreyi* (chancroid). Unfortunately, a diagnosis of GUD based on clinical presentation can be problematic because atypical presentations can occur, mixed infections are common and

Figure 1. *Monitoring human cytomegalovirus (CMV) viral load in a patient with disseminated CMV disease demonstrating the usefulness of viral load testing to monitor response to antiviral therapy. The patient was treated with multiple antivirals at onset of disease*



treatment of the individual causative agents differs, therefore the accurate identification of the etiological cause is important. Unfortunately, these pathogens are difficult to grow in culture so this has led to the development of multiplex PCR assays for herpes and syphilis (some also include *H. ducreyi*) which help to streamline the diagnosis of GUD. These PCR assays have been demonstrated to be more sensitive than either dark ground microscopy or serological testing for the diagnosis of primary syphilis and facilitate the rapid identification of herpes infection. Overall, the adoption of multiplex PCR testing for HSV and syphilis on ulcer swabs has improved detection rates and reduced both turnaround time and cost, ultimately lowering the onwards transmission risk of primary syphilis and the development of sequelae.

Viral genome quantitation by real-time PCR

Molecular methods also allow us not only to detect the presence or absence of a pathogen, but also allow us to determine the precise amount of virus present in a sample. This process of viral genome quantitation or viral load (VL) testing has become very useful in the diagnosis and management of viral disease (Mackay *et al.*, 2002). CMV, Epstein–Barr virus (EBV) and adenovirus are a significant cause of morbidity and mortality in immunosuppressed patients following solid organ or bone marrow transplantation (BMT), in individuals with HIV infection and in other patients on immunosuppressive therapy. Quantitation of these three viruses by real-time PCR has become a very useful diagnostic test for the management of such patients. CMV can cause a severe disease in such individuals and the presence of a CMV viraemia greatly increases the risk of CMV disease. There are currently four antiviral drugs licensed for the treatment of CMV infections: ganciclovir, valganciclovir, foscarnet and cidofovir. VL testing is very useful for monitoring the efficacy of antiviral therapy once CMV disease is diagnosed and can show if the infection is responding positively to the treatment (Figure 1).

Human adenovirus (HAdV) can cause serious life-threatening infections in immunocompromised hosts such as BMT patients, and HAdV infections are frequently associated with viraemia. Similarly to CMV, quantitation of HAdV DNA in blood samples by PCR provides more informative data for predicting the risk of disseminated infection in immunocompromised patients. Although there is no specific antiviral therapy for disseminated HAdV infection, cidofovir and ribavirin have been used to treat severe infections in patients. Again, VL testing can monitor the efficacy of these treatments and may prove useful for monitoring HAdV VL in patients during clinical trials of new antiviral treatments for disseminated infection.

EBV infects more than 90% of the population worldwide and in immunocompetent individuals the virus establishes a life-long asymptomatic infection. In immunocompromised patients, active EBV infection is a strong risk factor for the development of post-transplant lymphoproliferative disease (PTLD), AIDS-related lymphoma, and X-linked proliferative syndrome. The monitoring of EBV load in transplant patients has been shown to be a useful tool in the diagnosis and management of PTLD however, the association between detection of circulating virus and disease is not as clear. In addition, the detection of latent EBV in immunosuppressed patients without symptoms of EBV disease suggests that the presence of EBV DNA alone does not always indicate active EBV disease.

Conclusion

The introduction of molecular diagnostic methods into clinical virology has improved the detection of infectious disease agents and led to improvements in patient treatment and management. Newly emerging technologies such as next generation sequencing (NGS) will supplement and may even completely replace PCR and other current molecular methodologies in the future.

As the price of NGS instrumentation falls and the cost of applying these tools to diagnostic clinical virology becomes more affordable, we may replace our amplification assays targeting limited numbers of genes with whole genome based methodologies.

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historical**Perspectives**

The evolution of the AIDS epidemic

Illustration: Pan troglodytes troglodytes

Approximately a million years ago an epidemic of Simian immunodeficiency virus (SIV) infection occurred in chimpanzees. It is clear from sequence analysis that this infection occurred as a recombination event between the virus infecting a red-capped mangabey and that infecting a spot-nosed monkey. It is unlikely that this was sexual transmission, but more likely that a chimpanzee was bitten successively by these two monkeys, the relevant virus entered the same cell and a recombination event occurred which allowed viral replication. The chances of such a sequence of events occurring is extremely rare and it has only happened once in evolutionary time, which gives credence to the observation of Richard Darwich, that over the time period of evolution all possible events will occur; it is just a question of when.

This recombination event produced a virulent infection which is likely to have been responsible for the very severe reduction in the numbers of chimpanzees over the next 100,000 years. It is striking that one of the major genetic differences between chimpanzees and humans is the diversity of the MHC class antigens which are very restricted in chimpanzees in comparison with humans. One of the restricted epitopes which has survived is in the mu 2 region which is analogous to the B5701 ancestral haplotype in humans which is itself associated with slow progression of human immunodeficiency virus (HIV) disease. The implication is that this particular MHC repertoire provided a survival advantage for chimpanzees with an SIV infection, and so became predominant in this population. Adhesion molecules also map to this area of the chimpanzee genome and an alternative hypothesis would be that there was a survival advantage derived from particular adhesion molecules which would enable better control of SIV infection in a chimpanzee (Gao *et al.*, 1999).

The reason for considerable interest in the evolution of a chimpanzee SIV is its close similarity to HIV. The closest identity is with the SIV affecting the chimpanzee *Pan troglodytes troglodytes*, which lives in a restricted area of West Africa, particularly in the area previously known as the Cameroons. While it is thought unusual for an infectious organism to jump the species barrier, chimpanzee SIV was able

Sooty mangabey (Cercocebus atys)

to infect humans because of a single change in the coding for one amino acid in the core protein. Interestingly, this is the same single amino acid change that allowed SIV from the mangabey to infect humans with HIV 2.

The timing of the first HIV infections in man has recently been determined with surprising precision. Many people dying unexpectedly in Lusaka in the Congo in the 1950s had histological material stored. These have recently been examined for HIV DNA and, in a proportion of cases, proviral DNA (from the incorporated virus) was found. The sequence diversity of these samples can be compared with the present diversity of HIV and back calculation techniques have shown that HIV was transmitted to man from chimpanzees at the beginning of the twentieth century on three separate occasions. It is believed that the likely route of transmission is from chimpanzees biting humans as a result of being hunted for so-called bush meat. These transmissions almost certainly occurred in an isolated region of the area previously known as the Cameroons, where the only transport system was the river Congo and the first major settlement to be reached was Kinshasa.

Human-to-human transmission was established there which maintained the virus in the human community over the next 60–70 years, but the causes of the explosive epidemic are less clear. It is obvious that rapid urbanization of Kinshasa and other cities in Africa will have contributed to anonymous sex and establishing chains of transmission. It is also clear that areas of high HIV prevalence occur particularly along transport routes through Africa and it is thought that lorry drivers transmitted HIV to groups of commercial sex workers congregating at stopping points. More controversially, it is also possible that, like other bloodborne viruses, transmission of HIV was facilitated by the habit of repeated use of the same needles for blood transfusion, drug injection and the administration of vaccines in the late 50s and 60s. The possibility that HIV was transmitted by contaminated polio vaccine has been comprehensively disproved.

While isolated cases of HIV have been recognized retrospectively in Manchester in the 50s and elsewhere around the globe, the first studies of epidemic HIV appeared in 1981. In this year, outbreaks of a previously extremely rare pneumonia caused by *Pneumocystis carinii* (now renamed *Pneumocystis jirovecii*) were reported amongst gay men in San Francisco and outbreaks of Kaposi's sarcoma were reported amongst gay men in New York (CDC, 1981).

P. jirovecii had previously been recognized following the Second World War in orphans across Europe and was associated with the immune deficiency of malnutrition. Kaposi's sarcoma was previously a tumour described primarily in elderly Ashkenazi Jews, but was also known to be an occasional complication of iatrogenic immune suppression.

Following the initial reports of AIDS in 1981 it rapidly became apparent that there was a widespread epidemic in gay men, that the disease was also occurring in individuals who had received blood transfusions, particularly those receiving factor VIII or IX concentrates for the treatment of haemophilia, and that a similar disease was prevalent in Africa which was initially labelled 'slim disease' because of the prominent wasting. Retrospectively, slim disease was almost certainly associated with widespread cryptosporidial diarrhoea and/or oesophageal candidiasis.

From an early stage it was apparent that people receiving blood or blood products who developed AIDS were not in otherwise established risk groups and that the blood donor was usually an individual with symptoms of AIDS. This remains the best refutation to the small minority of scientists who continue to claim that the HIV virus itself is not important in the genesis of AIDS.

Immediately after 1981 the search started for a virus which caused the infection. It was likely that this virus infected and destroyed lymphocytes so a retrovirus was an obvious candidate. Researchers were lucky that there had been considerable interest in retroviruses in the 1970s because of the possibility that they were a major cause of cancer. In 1982, Professor Rosenbaum in France took a lymph node from a patient with AIDS to Professor Mantagnier who asked his research fellow, Barré-Senoussi, to see if she could grow a virus from this tissue. His lab was using immortalized B cells for tissue culture and although HIV would grow in this, it destroyed the cells very quickly and as such only small amounts of virus were detectable. The original paper showing that a retrovirus, then incorrectly named HTLV-III, was a likely cause of AIDS appeared just two years after the first descriptions of the epidemic (Barré-Sinoussi *et al.*, 1983).

These research workers were recently awarded the Nobel Prize and their discovery was followed by confirmation, by Roberto Gallo and his co-workers in 1984, that this retrovirus could be reliably grown in T cell tissue cultures maintained by IL-2 from all individuals suffering from the clinical symptoms of AIDS.

It is difficult for people who did not live through this period to understand the degree of fear that this epidemic created. Doctors saw an ever-expanding group of individuals all of whom died as a result of the infection. They were unaware precisely how it was acquired, how infectious it was and how likely this epidemic was to spread to and decimate the entire population. With the advent of the discovery of HIV, antibody tests were rapidly developed and it became apparent from epidemiological studies that HIV was transmitted by body fluids, particularly semen during sexual intercourse. It was also established that HIV was vertically transmitted from mother to child, that the virus was not destroyed by the standard methods of preparing blood concentrates and that the virus was not transmitted through intact skin.

We now know more about the biology of HIV than any other virus and this is a great tribute to academic researchers and the drug industry, both of whom were anxious to find unique viral targets to develop drugs which would potentially have minimal human toxicity but would be lethal to the virus.

The first and most obvious target was the reverse transcriptase enzyme, which converted the RNA contained in the viral capsid to a DNA copy which was subsequently incorporated in the human genome. Nucleoside analogues were an obvious drug class to use and one of these, azidothymidine (AZT), was already available as it had been developed by Glaxo-Wellcome for use as an anti-cancer agent. A dramatic report by Margaret Fishl and her colleagues demonstrated an amazing short-term improvement in survival when this drug was used in symptomatic patients (Fischl *et al.*, 1987). As there was tremendous public pressure for a treatment that worked, AZT was licensed after a very small number of patients had been exposed to the drug for longer than six months, despite toxicity which required blood transfusion in up to 50% of the patients. Subsequently it was found that lower and less toxic doses of AZT were equally effective. American studies suggested that earlier use of AZT in asymptomatic HIV patients also reduced the risk of the development of opportunistic infections and, although no survival advantage had been shown, AZT began to be widely used in all patients who were HIV infected.

Greater spot-nosed monkey (Cercopithecus nictitans)

However, a long-term study resulting from collaboration between the British MRC and the French ARNS (CONCORDE) showed that when used in the long term, AZT had no effect on the prognosis compared with when AZT was only used for symptomatic patients (Concorde Coordinating Committee, 1994). At the time, this study was widely misinterpreted to suggest that AZT did not work. What the study in fact demonstrated was that it only worked for a short period. Workers at Glaxo-Wellcome, led by Brendan Larder, showed the reason for this: virtually all the viruses isolated from patients prior to treatment showed high degrees of sensitivity to the drug *in vitro* (Larder *et al.*, 1989). Following a few months of treatment, most of the viruses were resistant to the drug.

John Coffin from the United States was amongst the first to recognize the reason for this. HIV is typical of many other retroviruses in that it has an extremely high replication rate and a small but significant error rate every time the RNA is transcribed with no proofreading correction enzymes. Although the genome of HIV is relatively small, as a result of the massive replication rate, every single viable mutation is produced many times a day in the viral swarm, as are double and triple mutations however, they are extremely rare.

Thus, it became apparent that to prevent resistance two things were crucial. Firstly, highly potent drugs were required that would stop replication completely and therefore prevent the development of new resistance. Secondly, that to prevent the selection of resistance either individual drugs or drug combinations with a sufficiently high 'genetic barrier' were required, i.e., those requiring three or four mutations in the genome to reduce drug sensitivity. This was the theory behind highly active antiretroviral therapy (HAART). In practice, studies showing this pragmatically had already started before the theory had been worked through. Thus, the DELTA study, also sponsored by the MRC and the ARNS, showed that a drug combination, particularly of AZT and didanosine (DDI), could reduce

mortality from HIV by up to a third over a three year period. This turned out to be because the use of DDI delayed the development of resistance to AZT (Darbyshire, 1996).

Developments at the very exciting Vancouver conference in 1996 changed the face of HIV infection from the situation of ameliorating the inevitable fatal outcome to it being a treatable disease. These developments were the first to use PCR technology to measure the virus in the plasma and so estimate the continuing replication of HIV. It was shown that dual therapy like AZT and DDI was associated with continuing replication whereas the use of triple therapies was associated with undetectable virus in the plasma. This has fortunately turned out to be associated with complete inhibition of viral replication and so enabled long-term survival to be a possibility. These triple therapies became possible because of the development of two new classes of drugs.

It was known from crystallography studies that the viral reverse transcriptase had a pocket adjacent to the catalytic site and a class of drugs called non-reverse transcriptase inhibitors fitted into this pocket and prevented the enzyme from working. These drugs were initially developed by Dr Paul Janssen at Janssen Pharmaceuticals, who, during his illustrious career, brought more than 80 drugs to market and was shortlisted on two separate occasions for the Nobel Prize (Pauwels *et al.*, 1990). At the conference in 1996 the first results from a study using one of these drugs Nevirapine, made by a competitor, Boehringer Ingelheim, was shown to be highly effective at inhibiting viral replication when used in combination with AZT and DDI (Montaner *et al.*, 1998). The results of the first protease inhibitor Indinavir, were also presented at the 1996 conference.

One of the other viral targets for drug development, examined soon after HIV was discovered, was the viral protease (Hammer *et al.*, 1997). This enzyme was responsible for the cleavage of the polyprotein, produced as a result of viral replication, into active smaller proteins at a unique site not used by mammalian proteases. Much of this work started in the laboratory of Professor Don Jeffries, who died recently.

Most of the drugs that have been developed as protease inhibitors are metabolized by cytochrome P450 and are only effective when a blocker of this system is also co-administered. The blocker used until recently was Ritonavir, which was originally developed as a protease inhibitor in its own right but is now mostly used in low doses to block the cytochrome P450 system.

Initially, patients were expected to take large numbers of tablets (up to 23 a day) in a highly complicated regimen: some required food for absorption while others required an empty stomach for maximum absorption. It rapidly became apparent that a considerable proportion of patients were unable to tolerate the complexity of such regimens and so drug development concentrated on providing less toxic drugs in simplified regimens. The ultimate success of this is now a single tablet once a day which contains three separate drugs.

This is amazing progress: from the first sign of the epidemic in 1981, to the discovery of the virus two years later, to the development of an effective treatment within 15 years. Now instead of telling patients who are HIV positive that they will die but we will try and ensure that the quality of their remaining life is good, we now tell patients that providing that they are prepared to take one tablet regularly at night they will have a virtually normal life span.

Of course, problems remain. At present, the regimens we have are not perfect and the search continues for new targets, to produce better drugs with even less toxicity.

It is now known that HIV gains entry primarily to CD4 positive lymphocytes using the CD4 receptor as the mechanism of entry. It had been known from an early stage of HIV infection that the CD4 receptor was not the only mechanism used by the virus as mouse cells with a human CD4 receptor on their surface were not susceptible to infection. It transpired that the second receptor which was also required for HIV entry was a chemokine receptor predominantly either CCR5 or CXCR4. The CCR5 receptor is preferentially used particularly in early infection and CCR5 receptor antagonists, which have been developed, have proved highly effective in HIV infection, are free of drug interactions and do not require inhibition of the cytochrome P450 system. Unfortunately, early in the development, precise measurements of whether the virus in an individual was using the CCR5 receptor or the CXCR4 receptor were cumbersome and not entirely accurate. As a result of this, initial studies using the prototype drug Maviroc showed it to be slightly less effective than standard care. Were such studies to be repeated with an easier and probably more sensitive assay, the outcome might be different (Cooper *et al.*, 2010).

The process of integration is now much more clearly understood. The DNA produced by reverse transcriptase is made into a circle and transported using a viral chaperone into the nucleus. Integration into the human genome is then catalysed by a unique viral enzyme, integrase, which uses a human small molecule, lens epithelium-derived growth factor (LEDGF), as a co-factor. It has been possible to design highly effective drugs that inhibit this process of integration. One of these, Raltegravir, is already on the market and a number of others will certainly follow. Their optimum role in HIV infection remains to be determined; they work very effectively as first-line treatment but equally they work when standard therapies have failed. Studies are also at an early stage using inhibitors of the LEDGF integrase interaction, either on their own or as an adjunct to other integrase inhibitors.

A second and important revolution in the treatment of HIV has also occurred in the last five or six years. People failing first-line regimens do so either because they do not take their drugs at all, in which case the virus remains sensitive to all antiviral drugs, or they fail because of resistance. Occasionally this resistance is transmitted from the infecting partner in which case failure is usually rapid. However, a small number of patients continue to fail first-line regimens with the development of resistance, and it is likely that this is because of less-than-perfect adherence. Such patients were initially placed upon very complex salvage regimens because of overlapping resistance of available drugs which made it very difficult to prevent viral replication. Now, because of the development of these new classes of drugs, treatment of second-line or even third-line failures has become relatively straightforward, and provided patients now adhere to their therapy, viral replication can be inhibited and it is likely that they will live for prolonged periods (Steigbigel *et al.*, 2008).

What does the future hold?

Many people would like to be cured of their HIV infection. This possibility has arisen because one patient who had acute leukaemia was treated by total body irradiation and then transplanted with a CCR5 deleted donor bone marrow (Hütter *et al.*, 2009). The first bone marrow transplantation failed but the second one was successful and the patient has now eradicated all signs of HIV infection in his body. This is particularly surprising as it was known before the transplantation that the virus was in fact dual tropic, i.e., was able to use both the CCR5 receptor and the CXCR4 receptor. The precise reason for this man having been 'cured' is therefore not clear. However, this finding has led to an enormous amount of research in attempting to provide a cure.

Clearly, the main stumbling block to eradication of the virus from the body in a reasonable time period is the fact that the virus is incorporated within the genome of long-lived cells. If all those genomes could be activated and the patient was on effective antiretroviral therapy, then subsequent rounds of replication could be prevented and the virus could be eradicated. Clearly, the ability to do this depends upon our increased understanding of the normal control mechanisms for DNA. Most of the DNA in the cell is inactive and what makes part of the DNA active in particular cells, allowing replications of essential proteins is incompletely understood. It is clear that the amount of histones around DNA is very important and that histone deacetylase is an important enzyme in activating certain portions of the DNA. Thus, there has been considerable recent interest in using histone deacetylase inhibitors (which have already been developed for the treatment of some forms of leukaemia).

Following these attempts to activate the HIV within latent cells, the virus could then be eliminated as further rounds of replication are inhibited by antiretrovirals. Such studies are in their infancy but do hold out prospects for long-term cure of this infection.

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StatNote 31

In the 31st of a series of articles about statistics for biologists, **Anthony Hilton** & **Richard Armstrong** discuss: **Analysis of Covariance** (ANCOVA)

Introduction

In a previous StatNote (StatNote 30, Hilton & Armstrong, 2012), a one-way analysis of variance (ANOVA) was described in which the objective was to compare the effectiveness of two azoles in the treatment of a superficial fungal eye infection. Fisher's 'protected least significant difference' (PLSD) suggested that the number of colonies of *Aspergillus fumigatus* isolated from the eye was significantly higher in the control group compared with the group treated with econazole but, that the difference between the group treated with itraconazole and the control was not statistically significant. A more conservative *post–hoc* test, *viz.*, Scheffé's test, however, did not indicate any significant differences between the group means, and therefore, that neither azole significantly reduced the abundance of the fungi on the eye surface. Further examination of the data suggested there was considerable variation in the abundance of fungal colonies isolated from individual patients. The effect of this variation is to increase the mean square for error (error variance) in the ANOVA and reduce the 'power' of the analysis (StatNote 10, Hilton and Armstrong, 2007a). Consequently, consideration should be given to methods of reducing this variation. An important method of 'error control' is analysis of covariance (ANCOVA), which has many potential uses. It can be used to increase the precision of experiments, to analyse the nature of treatment effects in randomized experiments, and to adjust for sources of bias in observational studies (Snedecor & Cochran, 1980).

Scenario

We return to the scenario described in StatNote 30 (Hilton & Armstrong, 2012). This scenario involved the effectiveness of econazole and itraconazole in the treatment of a superficial infection of the cornea ('keratomycosis') caused by the fungus *A. fumigatus*. Three groups of patients were allocated at random to three treatments. One group was given econazole, the second itraconazole, while the third was given a placebo as a control. After treatment, a swab of the eye was taken on six subsequent occasions, transferred to agar, and the number of fungal colonies that developed on each plate counted. The final measurement was an average of the colony counts of the six occasions from each patient. In addition, a swab of the eye was taken from each patient before any treatment was applied to obtain an estimate of the initial abundance of fungal colonies present. These data are presented in Table 1.

Table 1. Effectiveness of econazole and itraconazole in the treatment of keratomycosis caused by the fungus *Aspergillus fumigatus*. Data are the number of colonies of the fungus isolated from the surface of the eye from 10 patients per group averaged over six occasions (Y) and an initial estimate of the number of colonies present before treatment was applied (X)

	Treatment					
Patient	*Control (Placebo)*		*Econazole*		*Itraconazole*	
	X	Y	X	Y	X	Y
1	13	10	8	0	8	1
2	16	13	5	2	7	3
3	11	18	11	6	6	2
4	7	1	19	11	6	0
5	12	20	14	8	5	1
6	15	12	6	1	19	14
7	9	5	6	4	8	4
8	12	16	10	13	8	9
9	12	5	3	0	18	18
10	21	23	11	8	15	9

Analysis

Theory

ANCOVA is a method of controlling or reducing the error variation in an experiment and makes use of the methods of regression (StatNote 16, Hilton & Armstrong, 2009). If a measure can be made on each patient before the experiment, which is closely related to the final measurement, then the initial measurement can be used to 'adjust' the final measurement, thus reducing the error variance (Ridgman, 1975; Snedecor & Cochran, 1980). A specific notation is used to describe the basic model of an ANOVA. Hence, the subscript 'i' is used to denote the group or class (i.e., the treatment group), 'i' taking the values '1 to a', whereas the subscript 'j' designates the members of the class, 'j' taking the values '1 to n' (hence, 'a' groups and 'n' replicates per group). Within class 'i', the observations x_{ij} are assumed to be normally distributed about a mean μ with variance s^2. This linear model can be written:

$$x_{ij} = \mu + a_i + e_{ij}$$

Hence, an observed value x_{ij} is the sum of three parts: (1) the overall mean of the observations (μ), (2) a treatment or class deviation 'a', and (3) a random element 'e' which is normally distributed. The random element reflects the combined effects of natural variation between replications and errors of measurement.

The model for ANCOVA is a simple modification of this model and is defined as follows where: y_{ij} = a final measure, x_i = an initial measure, x* = mean of 'x' values, 'b' = regression coefficient of Y on X:

$$y_{ij} = \mu + a_i + b(x_{ij} - x^*) + e_{ij}$$

The major change over the original model is the addition of the term $b(x_{ij} - x^*)$ which is the slope of the regression of the final measure (Y) on the initial measure (X). This term can be added to any experimental design including experiments in randomized blocks (StatNote 10, Hilton & Armstrong, 2007a) and to various factorial designs (StatNote 11, Hilton & Armstrong, 2007b). Hence, the error in the original model (e_{ij}) may be reduced because a proportion of it is accounted for by the term $b(x_{ij} - x^*)$ and as a consequence, the error variance in the ANCOVA should be smaller.

How is the analysis carried out?

First, a one-way ANOVA is carried out separately on the initial and final measures, thus obtaining the sums of squares (SS) for X (SSx) and Y (SSy). As in regression studies (StatNote 16, Hilton & Armstrong, 2009), the sums of products (SxSy) is also calculated. A test of whether there is a linear relationship between X and Y is then carried out. If

Table 2. Analysis of covariance (ANCOVA) of the data in Table 1

Source	DF	SSx	SSy	SxSy	MS	F	P
Treatment (X)	2	72.9	-	-	36.43	1.66	>0.05
Error (X)	27	593.0	-	-	21.96		
Treatment (Y)	2	-	293.6		146.8	3.98	<0.05
Error (Y)	27	-	995.1		**38.86**		
Treatment (XY)	2	-	-	145.8			
Error (XY)	27	-	-	585.4			

Reduction due to regression: $(995.1 - (585.4)^2) / 593 = 417.2$
Deviation from regression mean square: $417.2/26 =$ **16.05**

Abbreviations: DF= Degrees of freedom, *SSx* = Sums of squares of X variable, *SSy* = Sums of squares of Y variable, *SxSy* = Sums of products, *MS* = Mean square, *F* = variance ratio, *P* = probability

Table 3. Adjusted means and *post-hoc* tests

Treatment	Original group means	Adjusted group means
Control	12.3	10.16
Econazole	5.3	6.71
Itraconazole	6.1	6.82

Post-hoc tests comparing treatments: Fishers PLSD: Control/Econazole $P < 0.001$, Control/Itraconazole $P < 0.01$; Scheffé's test: Control/Econazole $P < 0.01$, Control/Itraconazole $P < 0.01$

there is no statistically significant linear relationship between X and Y, then the slope of the regression line 'b' is zero, and it is unlikely that the procedure will reduce the error variance. If, however, 'b' is not zero, then X can serve as a predictor of Y, and the treatment means at the end of the experiment can be 'adjusted' to remove differences in the initial number of colonies of *A. fumigatus* associated with the eyes of the patients.

Assumptions of the analysis

ANCOVA makes certain additional assumptions to those normally required in an ANOVA (StatNote 30, Hilton & Armstrong, 2012). First, it is assumed that the term $b(x_{ij} - x^*)$ is independent of the treatment effect and second, that 'b' is constant throughout the experiment, i.e., the relationship between X and Y is essentially the same for each treatment group.

Interpretation

The results of the analysis are shown in Table 2. The first four lines of the table are the one-way ANOVAS of the X and Y variables taken separately. Hence, when the initial measure (X) is analysed, there are no significant differences between the treatment groups ($F = 1.66$, $P > 0.05$). This result provides some confidence that there were no differences in the number of colonies of *A. fumigatus* between the patients allocated to the three groups before the experiment. When the final measure (Y) is analysed, there is a significant difference between the treatments and this analysis is identical to that presented in StatNote 30 (Hilton & Armstrong, 2012). Note that the error variance used to test the treatment effect is 38.86. The fifth and sixth lines of Table 2 contain the SxSy for treatments and error and enable the reduction in SS due to the regression of Y on X to be calculated. Finally, the deviation from regression can be calculated, giving a value of 16.05, significantly less than the original error variance of 38.86. As a consequence, the error variance has been lowered and this experimental design should have more 'power' in testing the individual treatment effects.

The adjusted treatment means and the result of the *post-hoc* tests are shown in Table 3. The control mean has been adjusted from 12.3 to 10.16, i.e., originally, the control group contained a slightly higher number of patients with greater initial numbers of colonies of *A. fumigatus*. As a result of the adjustment, both econazole and itraconazole significantly reduced colony counts regardless of whether the more liberal Fisher's PLSD or conservative Scheffé's *post–hoc* test is applied to the data. In the original analysis (StatNote 30, Hilton & Armstrong, 2012), by contrast, Fisher's PLSD suggested only econazole significantly reduced colony counts while Scheffé's test did not indicate any significant differences between the group means.

Conclusion

ANCOVA is a useful method of 'error control', i.e., it can reduce the size of the error variance in an experimental or observational study. An initial measure obtained before the experiment, which is closely related to the final measurement, is used to adjust the final measurements, thus, reducing the error variance. When this method is used to reduce the error term, the X variable must not itself be affected by the experimental treatments, because part of the treatment effect would then also be removed. Hence, the method can only be safely used when X is measured *before* an experiment. A further limitation of the analysis is that only the linear effect of Y on X is being removed and it is possible that Y could be a curvilinear function of X (StatNote 20, Hilton & Armstrong, 2010). A question often raised is whether ANCOVA should be used routinely in experiments rather than a randomized blocks or split-plot design, which may also reduce the error variance (StatNote 10, Hilton & Armstrong, 2007a). The answer to this question depends on the relative precision of the different methods with reference to each scenario. Considerable judgment is often required to select the best experimental design and statistical help should be sought at an early stage of an investigation.

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careers

From beer to bugs

Samantha Law charts the varied jobs that led to her present post as Senior Microbiologist with NCIMB

Although I was interested in biology from a young age, it was at Nottingham Trent University that I began my love affair with microbiology in particular. I was amazed at how microorganisms were able to have such an impact on our everyday lives. I just could not get enough of them and at the end of my second year chose to specialize in microbiology and molecular biology.

My degree course gave me a good grounding in microbiology and microbiological techniques and I was also lucky enough to spend my university placement at Guinness Brewing Great Britain, where I worked in the quality analysis department for 10 months. This job involved the use of various chemical tests to monitor the quality of beer produced on-site and from overseas breweries. One of the quality tests at Guinness was beer tasting and this has been a major talking point of my CV ever since! During my time there I also carried out a project to increase the awareness of sensory analysis within the brewery. On a weekly basis I would give a presentation and tasting session for my colleagues on aromas and/or flavours associated with the beer we produced which was always very popular.

After gaining my degree and a brief spell as a bingo caller, I started my PhD at the Robert Gordon University in Aberdeen. I spent four years investigating the microbial biochemistry of slow sand filters. Slow sand filtration is the method used in the North East of Scotland to produce potable water. This involves the water from the River Dee being passed slowly through a bed of sand, allowing physical, chemical and biological processes to remove particulates and microorganisms. Through completing my PhD I gained a better understanding of the biological processes occurring within these filters and the effect of pre-ozonation and temperature upon the growth and development of heterotrophic bacteria, within the biofilm formed in the slow sand filters. I also gained a lot of experience in the production of media, did some demonstrating in student labs and even a spot of teaching.

While I was writing up my PhD I also had a short-term contract at the Robert Gordon University, working on an EU-funded project to improve the microbiological monitoring of sterilized milk. This involved the development of rapid microbiological methods and a wide range of techniques to detect spoilage bacteria in less than eight hours. This role gave me additional experience in microbiological methods, report writing and presenting our results to the other partners involved.

Once I had completed my PhD and my contract with the EU project had finished, I realized I had been so focused on my PhD that I had forgotten I would need to get a job afterwards! To keep a roof over my head and a beer in my hand, I managed to get a temporary job as a laboratory assistant carrying out the microbiological monitoring of bathing water for the Scottish Environment Protection Agency (SEPA). I must admit that routine processing of samples felt like a bit of a comedown, but looking back I did gain some valuable experience. As well as the experience of new microbiological methods, I gained a good introduction to quality assurance (QA) and complying with the UKAS accredited system. Love it or hate it, everybody who works in a laboratory has to work to certain quality standards and in the short time I was at SEPA I learnt so much about quality assurance that I have been able to use this in the job that I do today.

After leaving SEPA, I once again found myself without a job and in a moment of madness applied to be a trainee commercial manager for a major retailer. Unfortunately/fortunately I got the job. However, it didn't take me long to realize that I didn't really care about Easter eggs or what the best-selling pair of trousers were. I missed my beloved bacteria and realized I had to move on — staff discount or not. Looking back, although I did not enjoy the job, I did take away some valuable experience and

training in customer service, managing a team and dealing with human resource issues.

Having made that decision, I was lucky enough to be offered a job at the National Collection of Industrial, Food and Marine Bacteria (NCIMB). The core of NCIMB's business is the public collection of reference strains which now numbers approximately 8,000. This important national resource is comprised of strains that have been isolated from a wide variety of environmental sources both in the UK and overseas, including marine hydrothermal vents, the gills of fish and wallaby droppings. I was taken on as a senior microbiologist and, over the years, it has been the role of me and my team to maintain the current bacterial culture collection and ensure that a number of new bacteria are added to the collection every year to help maintain its relevance to the scientific community. I was also taken on as the production supervisor so I had to ensure the smooth running of the production department. The production department is responsible for the manufacture of media that is used in-house and sold externally, as well as the preservation of cultures through freeze-drying.

What I immediately liked about working at the NCIMB was that no two days were the same; I was continually learning about the bacteria we held within the collection and it allowed me to use experience I had gained from all my previous jobs (even the ones I didn't think were that relevant at the time) — my job not only required skills in microbiology, but also in QA, human resources and customer care. Pursuing a career in science is not always straightforward, but I do believe that there is something to be gained from every job you end up doing, science related or not. Early on in my career, I was very nervous about a conference presentation that I was about to give and my father put me at ease by reminding me of my bingo caller days. He was right: if I could stand up in front of a crowd baying for blood if I called out the incorrect number, I had nothing to fear from the conference attendees.

It is now seven years since I joined the NCIMB and in the past year I have been promoted to deputy curator. I am still involved in the maintenance of the collection and supervision of the production department. However, I now

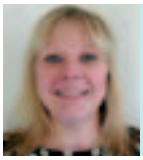
also play a senior role in operating the safe, patent and secure storage facilities that the company offers. These storage facilities are home to key strains derived from academic or industrial research and which require confidential and reliable off-site maintenance to ISO or cGMP standards.

As the company is an International Depository Authority (IDA) under the Budapest Treaty we maintain strains of microorganisms and seeds that are involved in patented processes. Our patent deposit service includes plant seeds, making NCIMB one of only a handful of global collections offering this facility. Being a patent depository we have to be able to preserve the microorganism or seed in a viable state for 30 years. It is interesting to see what gets deposited and my knowledge of Latin plant names has grown considerably. I love to impress my friends by knowing things like lettuce is actually *Lactuca sativa*!

The cultures in our private and public collections are mainly preserved by being freeze-dried or stored in liquid nitrogen. This is a very effective method of preserving a large variety of microorganisms and this enables us to store the majority of them for at least 30 years. As in the early days of the collection, we still rely heavily on phenotypic characteristics when working with cultures, however, the identification of strains within our collection has been made much easier by the use of genetic methods like 16s ribosomal DNA sequencing. Looking forward, I predict that the use of genomics and proteomics will greatly enhance the collection by allowing us to discover the unique properties and commercial potential of the strains we hold. NCIMB meanwhile continues to operate a polyphasic approach to taxonomy and species identification, which we consider a more rounded and inclusive approach to best characterize, and/or identify strains and to circumscribe new taxa.

Some strains in the collection may have potential applications that were not identified at the time they were isolated, and so I am currently looking at working with partners to investigate ways of determining the genetic maps of our strains to look for novel properties and processes which may lead to new therapeutics or industrial applications. With 8,000 strains in the collection there have to be some 'hidden gems' in there with great, but as yet undiscovered, industrial or medical importance. One approach to tackling this could be to establish a screening programme that involves looking for particular functions or properties or, in other words, looking for the DNA sequences that are known to be associated with useful biochemical functions and characteristics such as the production of antibiotics or particular classes of enzymes. This approach may enable a relatively quick and efficient screening of a large number of strains, but would still be a major undertaking, and consequently I have been investigating the availability of funding for such a programme, as well as the possibility of partnering with other companies in order to continue to develop the collection for the next generation of research.

I am very excited about the future for the NCIMB and my role here as we look forward to working with researchers to preserve new strains of bacteria they have discovered, as well as serving our customers across the globe. The interaction with our customers, learning what is important to them and adapting our services and products to suit their changing needs is what I find most satisfying and is essential to ensuring the continued relevance of the culture collection. A fundamental element of our remit at the NCIMB and one that I, and my colleagues, are very passionate about, is preservation of a genetic resource for future generations and it is important that we find the right balance between meeting commercial demands and maintaining a resource that will be of value to researchers in the future.



Samantha Law
Senior Microbiologist
NCIMB

In the loop pecs

News from the SfAM Postgraduate and Early Career Scientist Committee

Andy's 10 tips for poster presenters

1. Plan well in advance and don't be tempted to leave it until the week before the meeting.

2. Keep it simple! Emphasis should be on the simplicity and immediacy of the message.

3. Strictly keep to the poster dimensions described in the "instructions for poster presenters". Don't re-cycle posters from other meetings if the dimensions are not the same as for the current meeting.

4. "A picture is worth a thousand words". Use pictures to illustrate and simplify the message.

5. Pay close attention to text size and make sure the poster is readable at a distance of 1–2 metres.

6. Make the material being presented attractive to draw in the reader.

7. Keep it brief! A poster should not be a scientific paper and worse still not your entire PhD thesis. Less is more!

8. If you have been asked to stand by your poster in an attended poster session make sure you are there at the times stated. This is your opportunity to discuss your findings with your peers.

9. Proofread the content thoroughly and ask a colleague to check it as well before you print the final version for presentation. Mistakes in posters undermine the credibility of the message.

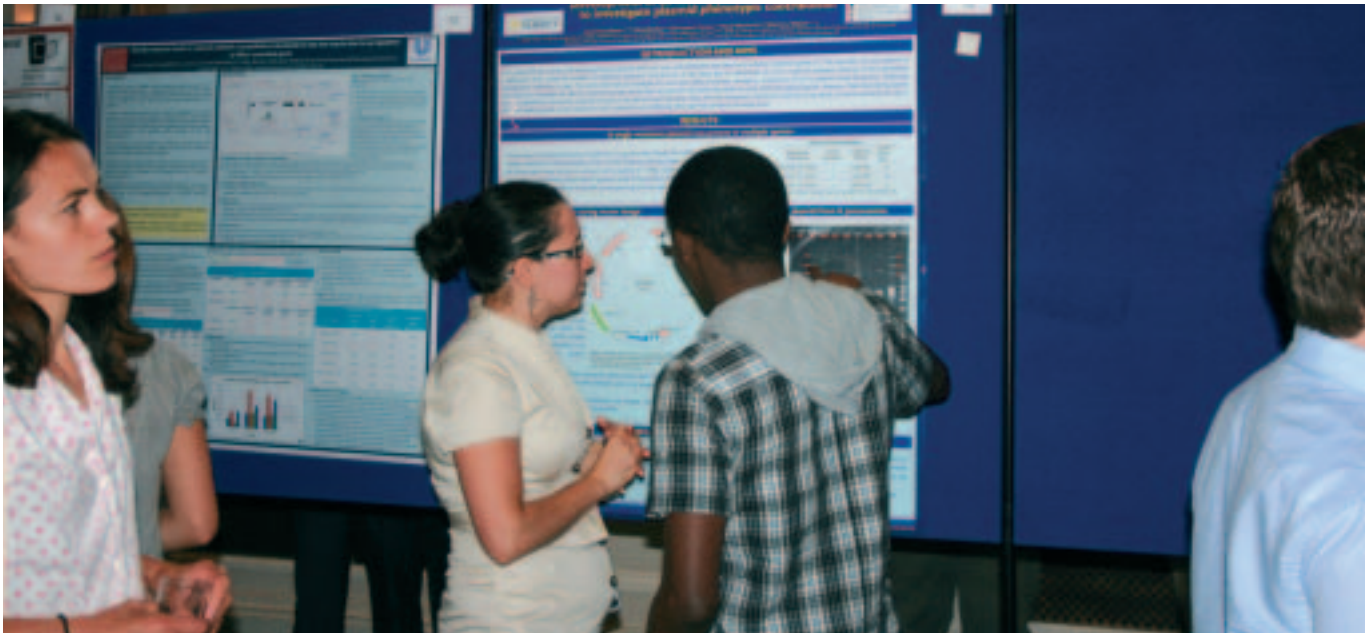
10. Most important is to have respect for your poster audience. Make the job of reading and understanding your poster as easy as possible for a given audience.

Finally, have fun and enjoy the opportunity to present your work to others.

Andy Sails
Honorary Meetings Secretary

PECS NEWS

Congratulations to PECS Committee Member Jo Tarrant on the birth of twins!



Preparing a poster for a conference

As a postgraduate student, attending conferences is an exciting part of academic life. Conferences are a chance to share ideas, discuss your field of research, learn about new methods, and even an opportunity to travel. A crucial aspect of attending a conference is communicating your research to the wider scientific community, and one very effective way to do this is by presenting a poster.

Preparing your research to present at a conference is a balance. You need to include the same details that you would put into a paper or report, but at the same time make it concise enough to fit into a poster format. When writing a poster for a specialist conference, it may help to investigate the style and content of abstracts from previous years. This can help you to adapt your material accordingly, for example, you can tailor your abstract by working out the key issues from your work that would be most relevant to the reader. Before you start, make sure you check the conference guidelines on poster size and orientation. Most conferences allow A0 portrait posters, however, some are different and it is advisable to check this before beginning to write. Generally posters follow a bullet point style divided into four main sections: introduction or background, methods, results, and discussion or conclusions. However, there are some other areas of the poster that will need attention too.

Firstly, a snappy title is essential. The title must cover the basic outline of the study, yet be intriguing, so that the viewer wants to read on. The title must be considered during abstract preparation, as whatever you name your abstract will be reflected in your poster title. Author names and affiliations sit below the title; the order of this can be important but must be agreed upon by your research group before poster publication.

The introduction covers the background details of the research involved, using current literature and references. You will want to set the scene by indicating the relevance of the study to the general scientific community. The aims and objectives of the research should be included in the introduction, preferably at the end just before the method section to give a sense of flow.

Methods should be concise, showing what you did to achieve your results. It's good to be aware of any ethical approval gained for the study, and noting participant numbers, gender and ages, statistical methods used and any chemicals or techniques in their full unabbreviated names initially, with subsequent references made using the standard abbreviations or acronyms. If the method is tricky to explain, a diagram or photo may help, making it unnecessary to explain it in words.

The results section needs to cover all relevant findings. Tables, graphs or figures can really help show data, so be imaginative! You'll need to include statistical p-values to show if there were any significant findings. Throughout the results section explain what each experiment or figure means, what is the outcome? This will help you lead directly into the conclusions and give a clear overview of the benefits of your work to the reader.

Finally, the discussion or conclusion section highlights the key findings from your results, usually these are presented in bullet point form so that they can be read easily. They need to be clear and concise, covering the exact findings of your work, and the relevance they have to the study, but also to scientists in other fields of research.

When presenting a poster at a conference, be confident. Who knows your work better than you? This will help you tackle any questions and comments posed, and give you a chance to meet fellow researchers and possible future collaborators. Be clear and engaging, and above all enjoy yourself!

Caroline Withers
University of Reading

Students into Work Grant reports

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Expression of genes carried by the bacteriophages responsible for Shigatoxin production by *E. coli*

***E. coli* O157 attracts major media** interest several times a year in Great Britain, as the recent outbreak in Surrey demonstrates (BBC, 2009). In 2008, the Health Protection Agency reported 948 cases of *E. coli* O157 in England and Wales (HPA, 2009), indicating that this zoonotic infection is more common than may appear at first sight. The serotype belongs to the group of Shiga-like toxin-producing *E. coli* (STEC) that cause potentially fatal human disease manifested as haemorrhagic colitis (bloody diarrhoea) and haemolytic-uremic syndrome (kidney failure) (Smith *et al.*, 2007). Stx-phages are related to lambda and can integrate into the *E. coli* genome to form a lysogen, which can subsequently release both phage particles and toxin into the intestine.

I spent 10 weeks alongside PhD student Marta Veses-Garcia in the Microbiology Research Lab at the University of Liverpool, attempting to show that other unidentified Stx-phage borne genes are also expressed by *E. coli*. Two of these genes were cloned into a plasmid vector in order to obtain sufficient expression to purify and characterize their protein products. The genes were provisionally named p8 (200 bp), expressed during the phage lytic lifecycle, and p24 (367 bp), which is expressed in the *E. coli* lysogen genome. The two genes were amplified by PCR, purified with commercial purification and gel extraction kits, and cloned into *E. coli*. Clones with potential DNA inserts were screened by PCR amplification (specific p8 and p24 primers were used) directly from picked colonies (Figure 1a). The plasmids containing inserts were double digested

Figure 1.

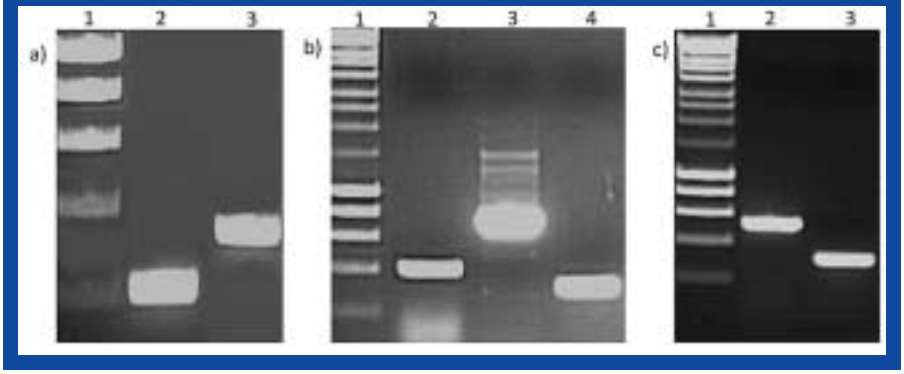
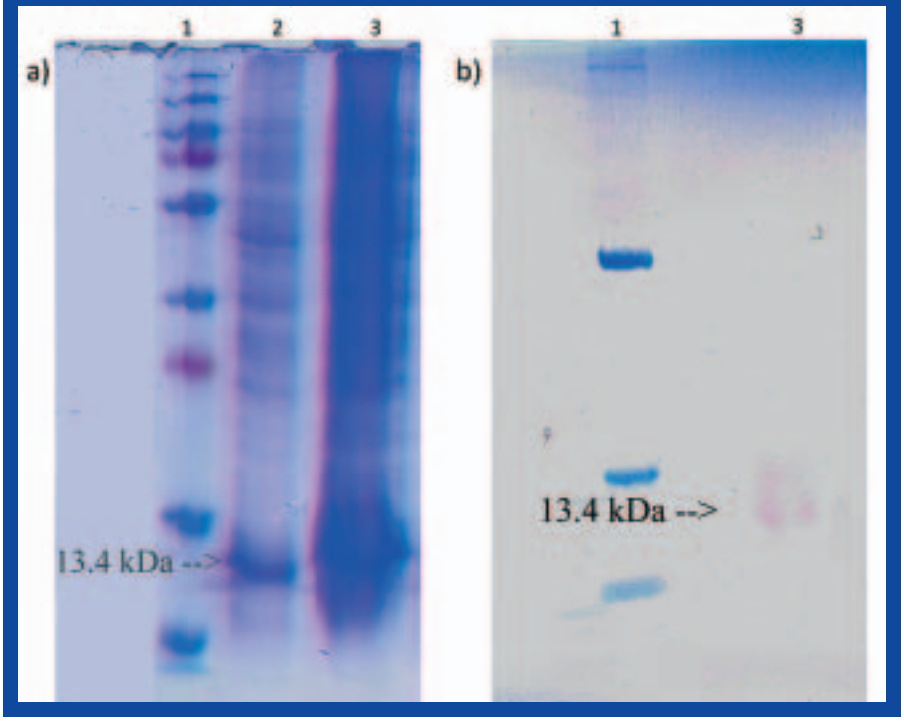


Figure 2.



with NcoI and SalI, prior to ligation into the over-expression vector pBAD/Myc-His. Potential clones with the fusion genes p8-His and p24-His respectively were screened by PCR amplification (Figures 1b, 1c). This creation of fusions to a Histidine tag should enable the gene products to be easily purified by nickel column chromatography (Schmitt *et al.*, 1993).

The selected clones were grown in 10ml L-broth cultures at 37°C, lysed by sonication and the proteins separated on a 12% acrylamide gel (Figure 2a). To control that the actual target protein was over-expressed, a Western Blot was subsequently performed (Figure 2b), in which His-antibodies bound to the His-tag of the p24-His fusion protein. Although the p8-His fusion gene product could not be isolated because the predicted size of 7 kDa is too small to detect on conventional tris-glycine acrylamide gels, the p24-His fusion gene-product (13.4 kDa) could be detected and is now ready to be produced in sufficient quantities to enable its characterization. The bacteriophages that carry the Shiga toxin gene and infect *E. coli* contain a very large number of unknown genes, such as p8 and p24, and it is important that their function is determined in order to produce a much more complete understanding of the biology of pathogens such as *E. coli* 0157. This could ultimately lead to the development of new therapies for the life-threatening infections caused by STEC strains.

Working in a microbiology lab for this extended period was a good experience for me, where postgrad students and postdocs showed me core procedures and techniques for my further career progression as a scientist. I had the opportunity to learn how to design my experiments and used many techniques, which were new to me, including gene cloning, PCR amplification and protein electrophoresis. This will help me during my honours project in the final year as a microbiology undergraduate student, when I will apply these recombinant DNA techniques to study *Herpesvirus saimiri*.

I would like to thank Marta Veses-Garcia particularly for the help and support with the lab work, but also all of the PhD students and staff of the Microbiology Research Lab of the School of Biological Sciences at the University of Liverpool. Finally, of course, the Students into Work Grant by S*f*AM is gratefully acknowledged.

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Bjoern Meyer

Use of PCR for identifying proteolytic strains of *Clostridium botulinum* and for detecting a neurotoxin regulatory gene deletion in type A strains

I spent 10 weeks this summer working in the Foodborne Pathogens Reference Unit (FPRU) at the Health Protection Agency, Centre for Infections in London. The FPRU provides microbiological reference services for a range of foodborne bacterial pathogens including *Listeria monocytogenes*, *Clostridium perfringens*, *Staphylcoccus aureus*, *Bacillus* spp. as well as for *C. botulinum*. The FPRU provides a botulism diagnostic service for the UK and Ireland and for other European countries that do not have facilities for testing.

Cl. botulinum is a Gram-positive, spore forming, anaerobic bacterium that produces a highly potent, characteristic neurotoxin (BoNT) responsible for the rare but potentially fatal paralytic disease, botulism, in humans and animals. In general, there are three clinical forms of botulism: foodborne, which occurs via the consumption of BoNT in contaminated food; infant botulism, which occurs when *Cl. botulinum* multiplies and produces toxin in the infant gut; wound botulism, which is the result of BoNT production in a *Cl. botulinum* infected wound. Confirmation of a clinical case of botulism depends upon detecting BoNT in clinical specimens and/or food specimens and isolating the organism.

There are seven antigenically distinct types of toxin produced by *Cl. botulinum* (types A-G), which exert their effect by blocking the release of the neurotransmitter, acetylcholine, at neuromuscular junctions. This results in flaccid paralysis and may lead to death by respiratory failure. As well as causing serious disease, BoNT is used therapeutically to treat more than 200 medical conditions (e.g., dystonia), as well as for cosmetic purposes. BoNT types A, B, E, and more rarely F, are associated with human disease whereas types C and D cause botulism in animal species and, to date, there is no direct evidence linking type G with disease.

Cl. botulinum is organized into four physiologically and phylogenetically distinct groups (I-IV) of which two (groups I and II) are associated with human botulism. These two groups have different growth characteristics, such as optimal growth temperature and differences in spore heat resistance and, as such, pose different health risks to humans through foods and the environment. It is important for understanding the epidemiology of botulism to be able to distinguish between group I and group II strains.

The classical method of identifying group I and II isolates involves observing proteolytic activity on casein-based agar. However, this test relies on phenotypic expression of enzymes, and takes 48 hours to perform. The first project I worked on in the FPRU involved evaluating a rapid PCR-based assay to distinguish between groups I and II *Cl. botulinum* strains. The assay is based on the detection of a fragment of the *fld*B gene which encodes a protein associated with phenylalanine metabolism in proteolytic group I strains, but which is absent in non-

proteolytic group II strains (Dahlsten *et al.*, 2008).

With this assay, proteolytic *Cl. botulinum* strains amplify a 556 bp PCR product with the *fld*B primers whereas non-proteolytic strains fail to give an amplicon. The assay also employs an internal amplification control targeted to conserved 16s sequences in group I and group II *Cl. botulinum*, which generates a 762 bp amplicon. This PCR assay amplifies a band with all group I and II strains, indicating the presence of amplifiable DNA and thus demonstrating successful DNA extraction. The assay was evaluated under the conditions described by Dahlsten *et al.* (2008) using known proteolytic and non-proteolytic *Cl. botulinum* strains. A previously identified proteolytic type B strain was used as a positive control and a type E strain (non-proteolytic) as a negative control. A range of clostridia, other than *Cl. botulinum*, were used to assess the specificity of the PCR assay and *C. tetani* was found to be proteolytic. This was not unexpected as *C. tetani* is phylogenetically more closely related to group I *Cl. botulinum* than group II. Through the use of this PCR assay, proteolytic and non-proteolytic strains of *Cl. botulinum* could be readily distinguished.

The second part of the project I undertook during my time at FPRU involved establishing a PCR assay to detect a 76 bp deletion in the promoter region of the *Cl. botulinum* regulatory gene (*Bot*R). Strains with this deletion give a 444 bp amplicon as opposed to the 520bp amplicon produced with the full sized *Bot*R gene. This deletion has been described in a novel subset of type A strains (A5) that contain a silent type B toxin gene (Carter *et al.*, in press). The aim of this work was to investigate whether the deletion occurred in other type A strains and the results I obtained indicate that the deletion is in fact quite rare. From this work I gained an understanding of the methodical steps which are required to take a procedure from paper to practice. To optimize the procedure it was necessary to individually adjust the assay variables involved, until the effective balance was found.

My time at the Health Protection Agency has been a highly rewarding one. I have carried out many microbiological procedures, acquired knowledge of a variety of laboratory techniques and have used a range of laboratory equipment. I have had the unique opportunity to experience both research and routine work performed by a reference laboratory. I would like to express my thanks to the Unit Head, Kathie Grant, and all the staff in the Foodborne Pathogen Reference Unit, in particular, Philip Ashton, a PhD student who I worked alongside for the duration of my time at the HPA, Colindale, and to S*f*AM for funding the project.

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David Lawrence

President's Fund reports

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Commensal Neisseria in the nasopharynx: a new 'probiotic'?

'Probiotic' is a term that has, since the 1970s, been given to a culture of ingested bacteria that are reported to have a beneficial effect on the host following colonization of the gastrointestinal (GI) mucosa. In fact, as far back as 1908, the eminent scientist Ellie Metchnikoff postulated that having lactobacilli as a large component of the GI flora was important in human health. Anecdotally, yoghurts that naturally contain cultures of 'healthy' bacteria have been used for years to treat patients with irritable bowel syndrome.

The ability of so-called 'friendly' bacteria to protect healthy mucosa against infection, as claimed in advertisements, had at the time of writing, not been really examined. A feature article in *Microbiologist* suggested that protection against infection may occur through secretion of bacterial effector molecules that regulate gene expression in co-colonizing bacteria (Edward-Jones, 2008). Other studies in the GI tract have demonstrated that a number of commensal gut species, such as *Bacteroides thetaiotamicron*, are able to regulate or attenuate host innate immune responses to related or unrelated pathogens (Kelly, 2004).

For the first time our research has examined the potential 'probiotic effect' of an upper respiratory tract (URT) commensal, *Neisseria lactamica*. We examined its ability to maintain epithelial cell 'health' during colonization by a potential pathogen of public health concern (Tezera, *et al.*, 2008). *Neisseria meningitidis* serogroup B (Men-B) was selected as a

relevant pathogen, as it is the species responsible for almost 80% of the UK's meningococcal disease, including sepsis and meningitis (www.hpa.org.uk).

There is currently no UK programme of vaccination against Men-B, as trials for vaccines to protect against all the major strains circulating in any particular country are still in their infancy. One method of natural protection against Men-B, however, was postulated to result from carriage of the childhood commensal *N. lactamica* (Goldschneider *et al.*, 1969). This was thought to occur through an increase in protective serum bactericidal activity (SBA), or complement fixing antibodies.

Subsequent studies confirmed that mice challenged with pathogenic Men-B are protected by *N. lactamica*, and coincident with increased SBA (Oliver *et al.*, 2002). In contrast, recent human studies demonstrated no conclusive impact of *N. lactamica* colonization on SBA in healthy adults (Evans *et al.*, 2008). In another study examining cellular responses in human tonsils, *N. lactamica* was found to stimulate antibody production but only through the induction of innate immunity (Vaughan *et al.*, 2008).

Previous studies of innate immunity to *N. lactamica* and Men-B in epithelial cells from the brain have shown that the commensal is consistently less able to stimulate cytokine and chemokine responses than the pathogen (Fowler *et al.*, 2006). At the University of West of England we have combined these observations with the known probiotic effects of certain commensals in the GI tract. We hypothesized that colonization by *N. lactamica* may selectively inhibit innate mucosal responses to the pathogen Men-B.

As both the Neisseria species of interest, *N. lactamica* and Men-B, initially colonize the nasopharyngeal region of the URT, we have focused on a nasopharyngeal-derived epithelial cell line, Detroit 562, for all our studies. In order to validate the use of this relatively uncharacterized nasopharyngeal cell line, we have shown that the cells consistently express all the relevant host receptors proposed to be used by Neisseria for binding and entry; and those used by the host for sensing bacterial infection.

Using this cell line we have confirmed, that *N. lactamica* is less able to adhere than the pathogen but able to invade to the same extent, albeit more slowly. We have confirmed that cytokines and chemokines are induced by each organism to differing extents. Most importantly, when both organisms are present at the same time, the commensal is able to suppress the responses to the pathogen. As such, we suggest that commensal *N. lactamica* demonstrates a probiotic effect in the URT.

The implications of these findings are far-reaching. Innate immunity is a key factor in the subsequent programming of acquired immunity or immunological memory. The levels of inflammation at the mucosal epithelium help control the maturation of dendritic cells which survey the peripheral tissues for damage, danger or disease. The latter then migrate back to the underlying lymphoid tissues and inform the T and B cells what sort of immune protection is required.

If innate immunity to a pathogen is suppressed by the presence of a commensal then tolerance of the pathogen may occur, allowing persistent colonization and potentially increasing person-to-person spread. The latter hypothesis is supported by our previous findings that, within the tonsils of healthy adults, regulatory T cells exist which suppress responses to Men-B (Davenport *et al.*, 2007). Taking this further, intranasal vaccination against a URT pathogen in the presence of a commensal could theoretically lead to the induction of long-term tolerance to the organism you are trying to vaccinate against.

On the other hand, over production of inflammatory cytokines and chemokines is a key feature of bacterial sepsis, and excess inflammation is also associated with loss of mucosal barrier function. Under these circumstances, control of such responses is of paramount importance and we propose that harnessing commensal probiotic modes of action may be one such solution for protecting the URT.

I would like thank S*f*AM for their generous award from the President's Fund which enabled participation in and presentation at the International Pathogenic Neisseria Conference, Rotterdam, 2008.

Victoria Davenport
University of the West of England

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Novel applications of low-dose irradiation as a food decontamination technology

Changes in the lifestyle of populations, especially in Western countries, which have less time for food preparation, have resulted in the onset of foodborne outbreaks worldwide. A number of emerging pathogenic microorganisms and parasites in food have been responsible for foodborne diseases. The subsequent economic impact to the society is enormous. Additionally, a preference for fresh or "fresh-like" minimally processed and convenience foods has resulted in a need to develop proper strategies and technologies to protect the health of consumers, especially with regard to food of animal origin.

Food irradiation is one means of food preservation that may not be familiar to many, but it has been in development since the early decades of the twentieth century. If properly applied, irradiation can be an effective way to treat a variety of problems in our food supply, such as insect infestation of grains, sprouting of potatoes, rapid ripening of fruits and bacterial growth. The biggest contribution of man's use of radiation has been in the medical field — medical and dental X-rays, detection and treatment of diseases, sterilization of medical equipment, medical devices, pharmaceutical products, home products, and production of sterilized food for special hospital diets.

Despite the known benefits of irradiation and the technologies to control its use, consumer acceptance and concern for nuclear issues have hindered the potential for widespread commercial success in this country. However, more than 30 countries have approved and are using food irradiation technologies to ensure food safety. Countries utilizing food irradiation for various purposes include Japan, China, Russia, the Netherlands and France. In the US, irradiated foods have been used by astronauts, the military and hospital patients, but the adoption of the technology for other purposes has been slow despite approvals from the FDA. The FDA has approved irradiation of meat and poultry and allows its use for a variety of other foods, including fresh fruits and vegetables, and spices. Irradiation does not make foods radioactive, just as an airport luggage scanner does not make luggage radioactive. Nor does it cause harmful chemical changes. The process may cause a small loss of nutrients but no more so than with other processing methods such as cooking, canning, or heat pasteurization.

Recent results (Savvaidis *et al.*, 2002; Chouliara *et al.*, 2005; Chouliara *et al.*, 2006; Samelis *et al.*, 2005) have shown that low-dose irradiation, as a decontamination technology to ensure the microbiological safety of foods of animal origin, is effective in controlling growth of the natural product's spoilage microflora and pathogens. In one study, irradiation (4kGy) was effective in controlling *Listeria monocytogenes* (inoculated on to trout) and also reduced populations of bacterial species, including *Pseudomonas* spp., lactic acid bacteria, H_2S-producing bacteria and Enterobacteriaceae. Sensory analysis of irradiated (2kGy) samples gave a shelf life of 28 days compared with a shelf life of seven days for the non-irradiated sample. In a related study of the preservation of fresh Mediterranean sea bream, γ-irradiation (3kGy) of vacuum-packaged sea bream stored at 4°C gave a shelf life of 28 days for sea bream, compared with a shelf life of nine to ten days for the non-irradiated sample.

In other studies on Greek dry fermented sausages, results showed that irradiating meat/fat trimmings at two or four kGy, prior to the sausage production, eliminated natural contamination with *Listeria* spp. and reduced *Pseudomonas* spp., Enterococci, pathogenic Staphylococci and Enterobacteriaceae to less than two and one log CFU/g, respectively. Growth of the starter bacteria, inoculated in the sausage batters post-irradiation was unaffected by the two or four kGy pre-treatment of the trimmings. Irradiation had little or no effect at the end of the ripening period (28 days) on pH, moisture content and colour; in a related study, evaluating the survival of *Listeria* spp. and *E. coli* O157:H7 strain ATCC 43888, during the fermentation and ripening of Greek dry sausages formulated from meat and pork fat trimmings, previously inoculated with 6 log CFU/g of the target bacteria and then irradiated in frozen (-25°C) blocks at doses of 2 and 4kGy, irradiation assisted in the faster decline of *Listeria* spp. during fermentation, and showed promise for controlling growth of *E. coli* O157:H7 and, to a lesser extent, *L. monocytogenes* in fermented sausages.

Food irradiation is not a miracle process that can convert spoiled food into high-quality food, but it can provide considerable advantages during food preservation. Irradiation provides more benefits in connection with conventional food processing methods. Recently (see http://www.cfsan.fda.gov/~dms/cfsup185.html), the FDA announced a final rule amending the food additive regulations to provide for the safe use of ionizing radiation in the control of foodborne pathogens and extension of shelf life in fresh iceberg lettuce and fresh spinach.

Finally, I would like to thank S*f*AM for the President's Fund Grant Award to give an oral presentation and attend the 21st International ICFMH Symposium "Evolving Microbial Food Quality and Safety" held in Aberdeen, 1–4 September 2008.

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The use of thermophilic biocatalysts in microreactors

Biocatalysts have recently received much attention with regard to the synthesis of certain target chemicals required for drug and fine chemical production. They are often capable of producing products of higher purity and with fewer side products than chemical synthesis. However, while biocatalysts have found applications in research, their use in industry has been limited to single applications for a specific purpose and most biocatalysts do not undergo further screening. Quite often biocatalysts are only used when chemical synthesis fails to produce a product of the required purity or chirality and the value of required product far exceeds the perceived cost of the enzymes used. Extensive screening of enzymes may yield significantly more industrial biocatalysts, but in order to do so the cost of screening would need to be kept to a minimum. Microreactors offer a possible solution to this problem, due to their reduced scale.

Microreactors, or microfluidic reactors, operate on a μl scale and first came to prominence in the field of chemical analysis, in the form of micro total analysis systems (μTAS). The field of synthetic organic chemistry soon followed and they have received much attention due to their potential to generate products of higher purity and achieve greater yields. Given their success in chemistry, it is not surprising that they have begun to attract attention in the field of biocatalysis.

Use of microreactors as screening vessels allows screening to take place on a very small scale, resulting in a reduction in the amounts of all constituents e.g., buffers, enzymes, substrates, co-factors etc., required for enzyme screening, while also facilitating a reduction in other expenses, e.g., heating, cooling and mixing, thus reducing the overall cost of the screening process. Their use could allow high-throughput screening of a number of substrates over a short period of time and the small scale would allow temperature to be controlled quite easily by methods as simple as placing the microreactor on a thermostatically controlled hotplate.

While the use of microreactors significantly lowers the volume of an enzyme required for screening, this amount is often further lowered by incorporating an immobilized enzyme in the microreactor. A number of gel immobilization methods have been employed in larger scale bioreactors but these are not suited to microreactors, due to the back pressures they would generate. Enzyme immobilization has been achieved in microreactors by adsorption to membranes, as has been the case with trypsin (Gao *et al.*, 2001), polymer formation on the surface of the microreactor, as was the case with aminoacylase (Honda *et al.*, 2006) or covalent cross-linking to a monolith (Peterson *et al.*, 2002).

With regard to their employment in biocatalysis, thermophilic enzymes offer a further advantage in that they are capable of operating at high temperatures, while quite often, exhibiting significant activity at ambient temperatures also. Their potential to act over a very large range of temperatures enables their use with poorly soluble substrates and in combination with chemical synthesis, which often requires higher temperatures than those tolerated by mesophilic enzymes. A thermophilic β-glycosidase from *Pyrococcus furiosus* has been immobilized by cross-linking to the microreactor surface and has been shown to remain stable and active for five days under operational conditions at 80^{o}C, allowing for continuous conversion of substrate over this period (Thomsen & Nidetzky, 2008).

An initial investigation into the use of a thermophilic enzyme, L-aminoacylase, in microreactors indicated the suitability of the system for enzyme investigation (Hickey *et al.*, 2007). Further investigations, involving this enzyme, L-aminoacylase immobilized on monoliths in microreactor channels, a γ-lactamase which was polymerized and immobilized in capillary column reactors and an oxidoreductase have also yielded positive findings. Work involving L-aminoacylase and γ-lactamase is advanced and has been submitted for publication (Hickey *et al.*, 2009), and work with the co-factor-dependent oxidoreductase is ongoing.

It has been demonstrated in the field of chemical synthesis that scale-up may be as simple as increasing the number of microreactors used. This would provide a distinct advantage over conventional scale-up methods since it is often upon scale-up from flask to plant-scale fermentor that problems of reduced yield are observed, due to vast differences in the design of vessels used. Thus, the use of microreactors for biosynthesis could result in a reduction in the time taken to transfer the production of enzyme products from laboratory-scale investigations to plant-scale production.

In conclusion, while the use of microreactors in the field of biocatalysis is in its infancy, it offers a viable alternative for the screening and production of certain chemicals using thermophilic and mesophilic biocatalysts.

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corporate news

The latest news, views and microbiological developments from our Corporate Members

Recent additions to the National Collection of Industrial, Food and Marine Bacteria

Three of the most recent accessions to the National Collection of Industrial, Food and Marine Bacteria are an actinomycete species isolated from sediment collected from a Norwegian Fjord, and two newly described species of bacteria found in the gut of a bee.

The sole strain of *Verrucosispora fiedleri* which has been added to the collection was discovered by Prof. Michael Goodfellow MBE and his team in the School of Biology at Newcastle University. *Verrucosispora* strains are currently the focus of considerable interest as the source of new bioactive compounds and this strain could be commercially significant as a source of new anti-cancer drugs, so it is an exciting addition to the collection.

The two species found in the honey bee gut were deposited by Waldan Kwong, a PhD student in Prof. Nancy Moran's lab at Yale University, and have been named *Gilliamella apicola* and *Snodgrassella alvi*. Some possible roles of these species may be protection against parasites, or helping with digestion of pollen, but further research is needed to find out more about the function of the bacteria and the nature of their relationship with the bee.

For further information on depositing a strain with NCIMB, or to obtain these new strains contact Dr. Samantha Law.

further Information

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In conjunction with their specialist suppliers, Cherwell Laboratories can also offer customers application advice and technical support on the validation of VHP sterilization, which has not been used as extensively as steam, dry heat or ethylene oxide sterilization.

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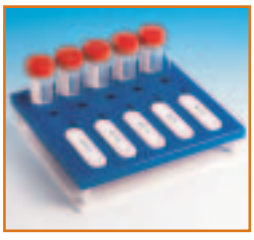
Prolab expanded range

Pro-Lab Diagnostics has recently expanded it's range with the addition of affordable bench equipment. The range includes Dry Baths, Vortex Mixers, Hot plates, Magnetic Stirrers, Mini Centrifuges and the Bactizapper. The Bactizapper has proven to be very successful for laboratories looking at safety issues with the use of naked flames, and the high costs of using disposable loops. Bactizappers sterilise wire loops, a variety of inoculation and manipulation laboratory tools, tubes and bottle necks. Using a unique infrared core, a temperature of 815'C, sterilises within 7 seconds. The "Zapper" can also be used in cabinets and fume hoods.



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Don Whitley Scientific announce the launch of the Whitley **A95 Workstation**, the largest model in the range. It boasts a huge capacity of up to 1400 Petri dishes, a 30 litre airlock and, uniquely, the latest in colour touchscreen technology. With four sleeved gloveports the A95 enables two people to operate within the same controlled atmosphere simultaneously.

The A95 has been designed with cost-savings in mind — the airlock is 25% faster than the MG1000, allowing a considerable saving in gas. Each gloveport also acts as a mini-airlock so you can transfer up to 40 Petri dishes without having to use the airlock at all.

The A95 is fitted with a fully automatic de-humidification system that requires only minor operator intervention.

Several options are available to tailor the workstation to your requirements, ie. single plate entry system; internal power sockets; automatic sleeve gassing system; or the fully integrated Anaerobic Conditions Monitor with data download facility, which provides confirmation that anaerobic conditions exist inside the workstation and an early indication if conditions begin to vary. The data logging option allows the recording of workstation temperature, humidity and chamber pressure for traceability/reference.

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Lab M adds new distribution partners to growing network

In line with product and market expansion plans signalled during the recent move to new headquarters, Lab M has added a further six distribution partners to its global network. These appointments enable delivery of increasingly localised support to users of Lab M culture media and associated products in Western and Eastern Europe and the Middle East.

In Switzerland Lab M has appointed Foodtech AG, who offer microbiology and environmental testing products, and in Poland, Sterbios, a specialist microbiology company providing tools and solutions to food testing laboratories. For Romania, Bivaria Grup brings experienced distribution of high-tech products serving clinical laboratories, and in Russia Simas provides laboratory equipment, with a specialisation in microbiology products. Expansion in the Middle East sees the appointment of Arcomex, specialist distributors of laboratory equipment in Jordan, and MEATO, scientific product distribution specialists in Lebanon.

"*Our new UK headquarters are designed to accommodate Lab M's continued growth and provide the R&D and manufacturing capacity needed to support it*," said Sales and Marketing Manager Phil Large. "*Extending our distribution channels is part of the overall expansion process and I'm delighted to welcome our new colleagues on board.*"

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Inoculating loops began to be used as diagnostic tools in the 1960's with the development of the "standard loopful" method for quantification of bacteria in urine specimens by O'Sullivan in Birmingham, and McGeachie & Kennedy in Glasgow. These methods are now routine. Platinum has largely been replaced by nichrome, and plastic disposable loops are also widely used when Bunsens are not available or desirable.

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