Carl Julius Salomonsen and the Start of Medical Microbiology in Denmark

Streptococcus pyogenes. The Danish clinical microbiologist Carl Julius Salomonsen dealt with this pathogen in his pioneering work. (see page 32)
Dear Colleagues

Since the last edition of ESCMID News, the world has been recovering from and pondering the implications and consequences of the Asian tsunami catastrophe. The infectious complications are now emerging and range from traumatic wound infections, food and water-borne disease and of great concern the potential for epidemic illness. In less than 24 hours the cataclysmic consequences of this natural disaster unfolded and made threats from bioterrorism pale by contrast. It would appear to be only a matter of time before the current outbreak of avian H5N1 influenza in South East Asia ceases to be an epizoonosis and becomes the next influenza pandemic despite the heroic measures being undertaken in Cambodia, Thailand and Vietnam to contain the epidemic. This will add yet another major infectious disease burden to the global statistics in which malaria, tuberculosis and HIV account for many thousands of deaths daily.

Problems such as these require effective alert and response systems and a global strategy for their containment. The partnerships between international health agencies, governments and national services for the diagnosis, treatment and prevention of infection need to be rapidly strengthened. They also require sufficient specialists in the Infection disciplines to deal with these challenges. Academia and industrial partnerships will be crucial to developing new technologies if these threats are to be contained. It is also essential that the bureaucracy of decision making be streamlined so that speedy and effective solutions can be developed.

Professional societies have a role in education and promoting professional and scientific concerns and solutions. ESCMID has established a number of links that are supportive of this international effort. However, a clear framework for action appears to be desirable so that efforts become neither diffused nor duplicated. Better integration of policy makers, healthcare planners and specialists in the Infection disciplines would appear to be central to not only informing policy but translating policy into action.

This is my last editorial for ESCMID News as I step down from the Executive Committee after a eight year period. It has proved not only a challenging but also a highly rewarding experience. I should like to thank all members of the Executive Committee, both past and present, and also colleagues in the Executive Offices in Basel and Munich, as well as the hardworking members of the Editorial Team in Nottingham and Paris, who have faithfully strived to support the aims of the Society by promoting the science, education and professional interests of all those involved in the management of infection. May the Society continue to prosper for the benefit of its members, the professional and scientific community and the populations they serve.

Roger Finch
Past President
Chairman, Publications Committee
Dear Friends

This is my last message to you in this Newsletter as President of the Society. It has been an honour to steer our still young and growing organisation over the past two years. I am very pleased at the progress made and indebted to the members of the Executive Committee who worked hard to lead many exciting projects on your behalf. An excellent team spirit has helped in reaching balanced decisions. Transforming great ideas into reality and delivering it on time could not happen without the support of a competent and dedicated Executive Office. Credits are due here to our Managing Director Peter Schoch and office staff members in Basel, Paris, Munich and Brussels for a job so well done despite the pressure due to mushrooming of activities.

Many of the objectives set two years ago have been largely met. The Society's financial health has been restored with sound budget control by our Treasurer Andreas Voss. New sources of public funding have been secured, such as DG SANCO's support for EUCAST. Contracts with AKM have been revised to provide the Society with efficient support for its office and congress. In the professional area, a second ESCMID workshop was held last year in Leuven to review progress and set the agenda for improved training curricula and service models in Clinical Microbiology, Infectious Disease and Infection Control. The Conference proceedings and ESCMID consensus declaration are now published in Clinical Microbiology and Infection. Elisabeth Nagy and Ragnar Norrby have strongly endorsed the recognition of both specialties of Clinical Microbiology and Infectious Diseases across Europe and supported their cooperation in UEMS. European accreditation of continuing medical education activities is making progress with the support of ESCMID to the UEMS accreditation process. Thanks to the efforts of Giuseppe Cornaglia, the renewed ESCMID European Council is now gathering speed with the affiliation of many national societies of microbiology and infectious diseases, and offers greater interaction with international societies from related medical and scientific fields.

Advanced research in microbiology and infection has also been supported actively by the Society. This is illustrated by the establishment of two new Study Groups under the guidance of Jordi Vila and the growing publication output of Study Groups. ESCMID has supported several scientific conferences and co-organised with DG Research the Rome Conference on The role of research in combating antimicrobial resistance which was influential in setting priorities for EU-funded research. The multi-study group ARPAC project supported by DG Research concluded its activities with a Consensus Conference and Recommendations towards improved antibiotic use and control of antibiotic resistance in European hospitals (see page 19). ESCMID has committed its educational contribution to a FP6 grant application for a Network of Excellence on resistance in respiratory tract infection. Finally, the Society's journal has established itself under its successive Editors as a leading European scientific publication in its field, and continues to improve in quality thanks to authors, reviewers and the enthusiastic editorial team led by Kevin Towner.

Public health is moving up the European Union's political agenda. The former Commissioner for Health, David Byrne, launched a new public health action plan addressing three priorities: improving knowledge about health; responding rapidly to threats; and addressing health determinants. International co-operation is particularly crucial in the field of Infectious Diseases, to protect the public and deliver high quality of care. ESCMID has contributed to the consultation in support of this ambitious EU agenda and has recommended key actions to deal with Infectious Diseases priorities (see www.escmid.org, Position Papers for ESCMID's comments on the new EU New Health Strategy). The start this spring of the European Centre for Disease Prevention and Control is an encouraging step towards greater co-ordination of communicable disease control in the enlarged EU. ESCMID is committed to providing expert support to the Centre as it already gives to DG SANCO and DG Research programmes. We have developed better links with EU policy makers including the Commission and Parliament under the European Public Affairs Programme led by a Task Force with the support of Interel, a well known public affairs office, based in Brussels. Based on progress made, this programme has been renewed for two years.

As professionals, we can contribute to fostering international exchange of expertise in the management and control of infection. To this end, the broadest participation of colleagues from all countries in ESCMID activities is essential. We have a special responsibility for providing state-of-the-art education and professional development opportunities to young scientists and clinicians. Our educational programmes led by Claude Carbon with a special input by Giuseppe Cornaglia have therefore been staged in many parts of the continent, including old and new EU countries, Russia and former Soviet Union countries. In this respect, it is gratifying to note that attendance and travel grants have allowed a record number of young colleagues to attend last year's ESCMID School, post-graduate courses, laboratory training courses, educational workshops and ECCMID.

The annual European Congress of Clinical Microbiology and Infectious Diseases is our major educational output. I hope that this issue of ESCMID News finds you in Copenhagen while you are participating in the 15th ECCMID. Its leading position as Europe's premier international congress in study, diagnosis, therapy and prevention of infection is illustrated by the growing number and quality of submitted abstracts. This year's superb Scientific Programme has been developed by the ECCMID Programme Committee under the experienced leadership of Patrick Francioli, in association with Danish colleagues of the Organising Committee. We are most grateful to them and to Niels Høiby, President of the Congress, as well as to all the scientists who are contributing to this programme. I hope that the 15th ECCMID will offer you the scientific excellence, inter-disciplinary exchanges and social experience that you expect from a world class congress with its...
special touch of pan-European “think-tank” and “culture blender”.

Upon concluding my term as ESCMID President, I am particularly glad that our Society has now successfully developed synergies and concrete collaboration with scientific societies and professional organisations in related disciplines, including the Federation of European Microbiological Societies (FEMS), International Society for Chemotherapy (ISC), European Public Health Association-Infectious Diseases Control Section (EUPHA-IDC), European Respiratory Society (ERS) and European Society for Intensive Care Medicine (ESICM). There is no doubt that strengthening these partnerships will allow us to fulfil our mission more effectively and expand our contribution to research, education and advocacy for health in the infection field. I welcome all representatives of specialist societies to attend the meeting of the renewed European Council on 2 April to discuss ESCMID activities and exchange information about our partnership with national societies of Microbiology and Infectious Diseases and other continental societies.

The ESCMID General Assembly of Members will be held in the late afternoon on 3 April. I encourage all members to attend and comment on the Executive Committee’s report of activities. Your feedback is essential to ensure that ESCMID meets your expectations. The annual ECCMID offers you also the opportunity to participate in business meetings of ESCMID Study Groups and EUCAST, the European Committee on Antimicrobial Susceptibility Testing. I encourage you to attend these meetings if you are interested in becoming a member of these groups and contribute to their projects. The European Network Corner allows you to learn more about ESCMID Study Groups, partner organisations and networks and meet with their representatives.

This year’s elections for the Executive Committee have strongly confirmed Patrick Francioli, Giuseppe Cornaglia and Andreas Voss for a second term in office. Robert Read and Javier Garau have been newly elected in replacement of Roger Finch and Claude Carbon, who have both reached the end of their second term. I welcome our new officers and wish to express my appreciation of Roger’s and Claude’s outstanding contributions to the advancement of ESCMID’s professional, educational and scientific outputs. They deserve our gratitude for their dedicated service to the Society. I trust that the renewed Executive will bring the right mix of experience, fresh enthusiasm and creativity to build upon these successes under the wise leadership of Ragnar Norrby as the next President. Finally, I thank you for your continuing support. With a strong membership committed to work together, I am confident that ESCMID will continue to thrive and deploy its range of activities towards disseminating excellence in the infection disciplines and guiding sound health policy.

Marc Struelens
ESCMID President

The ESCMID Assembly of Members 2005

Dear ESCMID Member

On behalf of the Executive Committee, I cordially invite you to the next regular Assembly of Members of the European Society of Clinical Microbiology and Infectious Diseases, which will be held during the 15th European Congress of Clinical Microbiology and Infectious Diseases in Copenhagen.

Date and Time: Sunday, 3 April 2005, 17:45 h - 19:00 h
Location: Hall 9, Bella Center, Center Boulevard 5, 2300 Copenhagen S, Denmark

The Agenda reflects the wide range of activities in which the Society is involved and also features the inauguration of Ragnar Norrby, Stockholm, as new President. The Executive Committee is counting on your attendance and is looking forward to meeting you in Copenhagen.

Yours sincerely,

Marc Struelens, President

Agenda

1 Welcome and President’s report (M. Struelens)
2 Report of the Secretary General (G. Cornaglia)
3 Presentation of the ESCMID Research Fellowships (R. Finch)
4 Financial report of the Treasurer (A. Voss)
5 Approval of the accounts (vote) (M. Struelens)
6 Report of the Education Officer (C. Carbon)
7 Report of the Professional Affairs Officer, Clinical Microbiology (E. Nagy)
8 Report of the Professional Affairs Officer, Infectious Diseases (R. Norrby)
9 Report of the Scientific Affairs Officer (J. Vila)
10 Report of the Chair of the Publication Committee (R. Finch)
11 Report of the President of the 15th ECCMID (N. Hoiby)
12 Report of the Chair of the 15th ECCMID Programme Committee (P. Francioli)
13 Endorsement of the Executive’s Performance (vote) (M. Struelens)
14 Any other business (M. Struelens)
15 Inauguration of the new President (M. Struelens, R. Norrby)
ESCMID Executive Committee

Results of the Election 2005

Farewell from Claude Carbon and Roger Finch

Election to the Executive Committee

At the Assembly of Members in April 2005 the office terms of five current members of the Executive Committee will end:
- Claude Carbon, Paris, France
- Roger Finch, Nottingham, UK
- Giuseppe Cornaglia, Verona, Italy
- Patrick Francioli, Lausanne, Switzerland
- Andreas Voss, Nijmegen, the Netherlands

The first two have served for eight years and cannot be re-elected, while the latter are eligible for a second term.

Elections were held in accordance with the Statutes and Bylaws. The selection of candidates was the responsibility of the Nomination Committee chaired by the past President. It was based on professional, personal and geographical criteria to ensure a well-balanced and competent Executive Committee. We cordially thank the following people for running for an office in the Executive Committee:

Clinical Microbiologists
- Prof Giuseppe Cornaglia, Verona, Italy (standing for re-election)
- Prof Patrice Nordmann, Le Kremlin-Bicêtre, France
- Prof Luisa Peixe, Porto, Portugal
- Prof Andreas Voss, Nijmegen, the Netherlands (standing for re-election)

Infectious Disease Specialists
- Prof Patrick Francioli, Lausanne, Switzerland (standing for re-election)
- Prof Javier Garau, Barcelona, Spain
- Prof Andy Hoepelman, Utrecht, The Netherlands
- Prof Winfried Kern, Freiburg, Germany
- Prof Vilma Maresova, Prague, Czech Republic
- Prof Robert Read, Sheffield, UK

A total of 2485 ballots were mailed to all members in good standing as of end of September 2004; 960 ballots were returned by 15 January 2005.

Elected were by simple majority:
- Giuseppe Cornaglia (532 votes)
- Patrick Francioli (570 votes)
- Javier Garau (440 votes)
- Robert Read (429 votes)
- Andreas Voss (545 votes)

The Executive congratulated the elected members on their office and also thanked the runner-ups for their candidature which made this democratic election possible.

Farewell from Claude Carbon and Roger Finch

The new Executive Committee will constitute itself at its first meeting during the 15th ECCMID in Copenhagen and discuss the (re-)assignments of the various portfolios. This meeting will also be the last one attended by Claude Carbon and Roger Finch whose terms will definitively end after 8 years of Executive functions.

Claude Carbon was elected to the Executive in 1996 and has been a devoted Education Officer since 1997. Thousands of professionals have benefited from his experience and guidance in creating stimulating educational programmes consisting of numerous postgraduate education courses, laboratory workshops, ECCMID meet-the-expert sessions and since 2002 also of the ESCMID School.

Roger Finch’s ESCMID career started in 1997 as Professional Affairs Officer. From 2001 to 2003 he served as an inspiring President and until 2005 as past President. Under his leadership the Society has expanded its portfolio and grown in stature.

I would like to thank Claude Carbon and Roger Finch on behalf of their colleagues in the Executive and the members of Society for their enthusiasm and spirited contributions to achieving ESCMID’s objectives which are to improve the professional competence of infection specialists and to advocate a solid health policy in Europe.

Peter Schoch
ESCMID Managing Director

ESCMID Awards and Fellowships 2006

ESCMID Award for Excellence in Clinical Microbiology and Infectious Diseases 2006

The European Society of Clinical Microbiology and Infectious Diseases will present the ESCMID Award for Excellence in Clinical Microbiology and Infectious Diseases in the year 2006 to honour a senior scientist for his/her overall achievements in these fields.

Purpose
The purpose of this award is to recognise and reward an outstanding lifetime contribution in the areas of science, education or professional affairs in clinical microbiology and/or infectious diseases.

Award
The award of EUR 10’000 will be presented by the President of ESCMID at the 16th ECCMID 2006 in Nice. The recipient will be honoured at the occasion of a 45-min lecture to be given by the awardee. The name of the recipient will be published in the Final Programme, ESCMID News, Clinical Microbiology and Infection (CMJ) and on ESCMID’s website.
Eligibility criteria

Nominees for the award must be senior scientists who are professionally active and prepared to give a plenary lecture in their field of research of 45 min during the 16th ECCMID. Members of the ESCMID Executive Committee are ineligible.

Nomination procedure

All medical schools and institutions active in the fields of clinical microbiology and infectious diseases in Europe, ESCMID’s European Council, ESCMID members as well as ESCMID committees and study groups are asked to nominate candidates for the award. Each nomination should include:

1. A biographical sketch of the nominee (maximum two pages).
2. A summary and analysis of the nominee’s major contributions to research in the fields of clinical microbiology and/or infectious diseases.
3. A list of the major original publications in refereed journals.
4. The complete postal and e-mail address, phone and fax number, and a colour photograph of the nominee (on paper or electronic).
5. In addition, two letters of support from individuals outside the nominating institution should be mailed directly or together with the nomination to the ESCMID Award Committee.

Seven copies of the nomination package must be received by 1 October 2005. The recipient of the award will be asked for a manuscript on the research field to which she/he mostly contributed for publication in CMI.

Selection procedure

The recipient will be determined by the ESCMID Awards Committee. No correspondence beyond that necessary for the nomination will be accepted. Self-applications will not be considered.

ESCMID Young Investigator Award for Research in Clinical Microbiology and Infectious Diseases 2006

The purpose of these awards is to acknowledge excellence in research, and to stimulate further research of the highest scientific level.

Awards

The awards of EUR 7500 each, which should be used to support further research, will be presented by the ESCMID past President at the 16th ECCMID in Nice on the occasion of a 20-min lecture to be given by the awardees on topics of their main field of research. In addition, the awardees are expected to write a review paper reflecting their field(s) of research for publication in Clinical Microbiology and Infection (CMI). The names of the recipients will be published in the Final Programme, ESCMID News, CMI and on ESCMID’s website.

Eligibility criteria

Nominees for the award should be born on 1 January 1966 or after. Appropriate research may be based on laboratory investigations, clinical studies, experimental animal studies, or a combination thereof. Nominees must have been employed in a European laboratory or hospital or have a future appointment in one. Members of the ESCMID Executive Committee are ineligible.

Nomination procedure

Nominations must be received no later than 1 October 2005. They must be submitted in writing together with proof of the nominee’s age, and include a CV, a complete list of publications as well as up to five original papers published in 2003, 2004 or 2005 or accepted for publication. The nominations should describe the candidate, his/her career, his/her research interests and personal contributions to the various research projects, in which he or she has been participating. At least two additional supporting letters should be presented by individuals outside the nominating institution. Self-applications will not be considered. The complete postal and e-mail address, phone and fax number of the nominee must be included. Six copies of all materials plus one colour photograph (on paper or electronic) must be sent to the ESCMID Award Committee, who will select the recipients. No correspondence beyond that necessary for the nomination will be accepted.

Please send your nomination to:
ESCMID Membership Office
(see left down)

ESCMID Research Fellowship 2006

The purpose of these awards is to encourage young investigators and to promote the development of research in the fields of clinical microbiology and/or infectious diseases.

Fellowships

The fellowships, each consisting of a cash award of EUR 5’000, will be presented by the ESCMID past President at the Assembly of Members taking place during the 16th ECCMID 2006 in Nice. The names of the recipients will be published in the
ESCMID Awardees 2005

Award for Excellence in Clinical Microbiology and Infectious Diseases

Fernando Baquero Mochales

- Born 1941 in Madrid, Spain; MD, Director of the Department of Microbiology at the Ramón y Cajal Hospital, Madrid, in recognition of his outstanding contributions to our understanding of antimicrobial resistance through a combination of state-of-the-art molecular biology techniques, population genetics, large scale epidemiology studies and evolutionary theory. He was also a pioneer in Europe in initiating many studies and projects in the fields of clinical microbiology, antimicrobial chemotherapy, infection control, containment of resistance and public health.

Research Interests

Throughout his career, Fernando Baquero has made countless contributions in the area of research, education and reference work for laboratories. Highlights are the discovery and genetic basis of microcins and their differentiation from colicins, first demonstrations of plasmids in Listeria spp, first documentation of inducible/constitutive MLSB resistance in Bacteroides and Peptostreptococcus and first description of beta-lactamase in anaerobic cocci. He published seminal papers about the origin, evolution and epidemiology of beta-lactamases, particularly ESBLs and IRTs and about the importance of mutators in the development of resistance. His current research focusses on new definitions in the epidemiology of resistance and highlights the role of genes surrounding resistance genes in the evolution, selection and spread of resistant determinants and resistant bacteria.

Application procedure

The deadline for submission is 1 October 2005. Applications must be submitted in writing together with a CV, a list of publications, and two supporting letters, including a specific description of the applicant’s present research and a detailed research plan. Applicants must include their complete postal and e-mail address, telephone and fax number and send six copies of all materials plus one colour photograph (on paper or electronic) to the ESCMID Award Committee, who will select the fellows. No correspondence beyond that necessary for the application will be accepted.

Please send your application to:
ESCMID Membership Office
Hainbuchenstrasse 65
D-82024 Taufkirchen / Germany
Phone +49 89 6126162
Fax +49 89 6128176
Email birgit.menzemer@escmid.org

Research Interests

Fernando Baquero has made countless contributions in the area of research, education and reference work for laboratories. Highlights are the discovery and genetic basis of microcins and their differentiation from colicins, first demonstrations of plasmids in Listeria spp, first documentation of inducible/constitutive MLSB resistance in Bacteroides and Peptostreptococcus and first description of beta-lactamase in anaerobic cocci. He published seminal papers about the origin, evolution and epidemiology of beta-lactamases, particularly ESBLs and IRTs and about the importance of mutators in the development of resistance. His current research focusses on new definitions in the epidemiology of resistance and highlights the role of genes surrounding resistance genes in the evolution, selection and spread of resistant determinants and resistant bacteria.

Young Investigator Awards for Research in Clinical Microbiology and Infectious Diseases

Mihai G. Netea

- Born 1968 in Cluj-Napoca, Romania; MD, Researcher at the Nijmegen University Centre for Infectious Diseases, Nijmegen, the Netherlands, in recognition of his outstanding research accomplishments in the field of pathogenesis of infection, especially host defence mechanisms and cytokine responses.

Mihai Netea is currently working for a one-year sabbatical period at the University of Colorado Health Sciences Center in Denver, CO, USA.

Research Interests

The research interests of Mihai Netea have focused on the pathogenetic mechanisms of septic shock, in particular the mechanisms of regulation of proinflammatory cytokines. Important contributions to the field are represented by his research on the role of proinflammatory cytokines in the host defense against fungal pathogens, as well as his pioneering research on the interplay between the lipoprotein metabolism and innate immunity. During the last years, his research interest was directed at the pathogen recognition by Toll-like receptors (TLRs). His research has contributed to several important discoveries in the field: the role of TLRs for the recognition of fungal pathogens; and the novel concept in which TLR-mediated signals trigger either Th1 or Th2 responses through specific downstream pathways. In addition, he was one of the researchers who identified TLRs as a crucial link between the innate and adaptive immune response through modulation of T-regulatory cell function.

Evelina Tacconelli

- Born 1967 in Chieti, Italy; MD, PhD, Assistant Professor for Infectious Diseases, Assistant Professor for Infectious Diseases, Assistant Professor for Infectious Diseases.
Catholic University, Rome, Italy, and Lecturer on Medicine at the BIDMC, Harvard Medical School, Boston, USA, in recognition of her outstanding contributions to our understanding of the epidemiology of various nosocomial infections and resistant pathogens. She has also contributed extensively to the clinical and epidemiological knowledge base of HIV infections and opportunistic infections occurring in this patient population.

Research Interests
Evelina Tacconelli’s research interest was initially focused on the clinical aspects of HIV disease and bacterial and fungal infections. In this area she contributed in identifying the so-called unexpected non-conventional beneficial effects of highly active antiretroviral therapy (HAART). She then moved into studying the clinical epidemiology of antibiotic resistant bacteria such as vancomycin-resistant enterococci (VRE), methicillin-resistant Staphylococcus aureus (MRSA), and glycopeptide-resistant coagulase negative staphylococci. In particular, she pursued a series of projects on how to prevent the spreading of antibiotic resistant infections in the hospital. She developed a score for identifying VRE-positive and MRSA-positive patients at hospital admission. She also performed a meta-analysis on the efficacy of mupirocin in preventing S. aureus infections in the dialysis population. Her current research interests include the application of intelligence technology to reduce morbidity and mortality associated with antibiotic-resistant infections.

Research Interests
Adrian Whitehouse’s research has been focused on study of virus-host cell interactions which regulate the early events in gamma-2 herpesvirus replication cycles. These are an important sub-family of herpesviruses with oncogenic potential, particularly as a result of the identification of the first human gamma-2 herpesvirus, Kaposis’s sarcoma-associated herpesvirus. This involves establishing the role of the latent genes and elucidating the molecular events which govern disruption of the latent state reactivating the lytic replication cycle, and identification of the mechanisms utilised by gamma-2 herpesviruses to regulate the lytic temporal cascade. These studies could identify specific antiviral targets which may be developed as a novel treatment for KSHV.

A complementary area of Adrian Whitehouse’s interest is in the development of herpesviruses as gene delivery vectors. In particular, he has shown that herpesvirus saimiri has the ability to infect a broad range of human carcinoma cell lines and primary cultures and establish a persistent episomal state within these cells, in both in vitro and in vivo studies. These properties offer characteristics similar to an artificial chromosome, combined with an efficient delivery system and as such may be developed as a vector for the treatment of chronic diseases.

The Young Investigator Awards are sponsored by Pfizer.

ESCMID / FEMS Research Fellowships

ESCMID and FEMS have agreed to offer each year two joint fellowships to foster outstanding research in microbiology by young Europeans. Each organisation will select every year one individual among their recipients of a research fellowship to receive an additional amount of €1000 from the other organisation. We are delighted to announce that the 2005 ESCMID / FEMS fellowship goes to Adilia Warris from Nijmegen, the Netherlands.

Project
- Host-pathogen interactions in the innate immune response against Aspergillus fumigatus

Research Interests
The focus of Adilia Warris’ research is the study of host-pathogen interactions in the innate immune response against Aspergillus fumigatus. An important process in the antifungal host defence is the recognition of the pathogen and the activation of phagocytes after proper message transduction. The information regarding these functions of phagocytes in the innate immune response to A. fumigatus is very scarce. Pathogen-associated molecular pat-terns on the A. fumigatus cell wall and pattern recognition receptors on mononuclear cells need to be identified to get insight into the recognition of this fungus by the immune system and the activation of antifungal defence mechanisms. Elucidating the interaction between A. fumigatus and the host recognition receptors could potentially provide a basis for novel therapeutic strategies in immunomodulation and pharmacological targeting, which might contribute to successfully coping with the threat of invasive aspergillosis.

ESCMID Research Fellowships

Pedro Cravo
- Born 1970 in Lisbon, Portugal; PhD, Centre for Malaria Studies, Institute of Hygiene and Tropical Medicine, Lisbon, Portugal.

Project
- Studies on the dynamics and genetics of resistance to Artemisinin Combination Therapy (ACT) in malaria

Research Interests
Despite huge scientific advances over the past hundred years, the overall burden of malaria is currently increasing, especially in sub-Saharan Africa. Much of this increase is due to drug resistance of the major human malaria parasite, Plasmodium falciparum. In this trend, understanding the mechanisms underlying drug resist-
Research Interests

Ronan McMullan’s research interests have ranged from the evaluation of molecular tools for the diagnosis of infectious disease to the epidemiology of both nosocomial and community-acquired infections. The theme central to much of his research is invasive Candida infection which is the principal subject of his ongoing area of study. The main research question he is currently addressing is whether quantitative PCR technology can overcome the deficiencies of extant molecular techniques currently available for diagnosing invasive candidosis.

Sepsis Award

Ronar Wernich Thomsen
born 1971 in Tønder, Denmark; MD, PhD, Aarhus University Hospital, Department of Clinical Epidemiology, Aalborg, Denmark, in recognition of his excellent abstract submitted for presentation at the 15th ECCMID.

Summary of his abstract
Association of statin therapy with 30-day and 180-day mortality in patients with bacteremia: population-based cohort study

Statins have been suggested to decrease mortality after severe infection, due to anti-inflammatory properties. We conducted a population-based cohort study to examine the association of statin use with mortality in 5,353 adult cases of bacteremia. After adjustment for multiple confounding factors, 30-day mortality in statin users vs. non-users was similar (20.0% vs. 21.6%, adjusted mortality rate ratio (MRR) = 0.9; 95% CI: 0.7–1.3), whereas statin therapy was associated with a substantially decreased mortality 30–180 days after the bacteremia (8.4% vs. 17.5%, adjusted MRR=0.4; 95% CI: 0.2–0.8). The study provides evidence for the hypothesis that statin use is associated with lower mortality after bacteremia, although we observed no effect on survival during the acute phase of infection.

The Sepsis Award is sponsored by the International Sepsis Forum.

1st Training Course in Multilocus Variable Number Tandem Repeat-Genotyping of Mycobacterium tuberculosis

31st ESCMID Postgraduate Education Course
Lille, France, 23 – 28 May 2005

Tuberculosis is the leading cause of death in adults due to a single infectious agent, killing about 3 million people every year. In several regions of the world, there is an alarming rising incidence, linked to the increasing impact of HIV epidemics, deficiencies of current TB control programmes, and emergence of multi-drug resistance. The worldwide development of transport and migration contributes to globalise those threats. In this context powerful approaches in the epidemiological tuberculosis surveillance are needed, which provide quantitative bases to assess or define new control strategies. To achieve this goal, effective methods for accurate identification and monitoring of large numbers of M. tuberculosis strains are required. The course will include the theoretical and practical teaching of a novel and highly efficient technology for M. tuberculosis multilocus genotyping, analogous to human genotyping techniques, placed into a larger perspective of the use of molecular markers for epidemiological control.

We invite scientists, engineers, technicians, medical doctors, and clinicians who want to expand their knowledge on the state-of-the-art technology and advanced methods of molecular genotyping to participate in this course.

For further information please contact: Marie-José Truong, Phone +33 3 20 43 86 72, Email marie-jose.truong@pasteur-lille.fr or consult the website at www.escmid.org, Courses & Workshops
Assessment of the European Market

Laboratory Diagnostics for Infectious Diseases

There is consensus among infection specialists that the microbiological laboratory plays an ever increasing role in the management of infectious diseases, may they be caused by common, emerging or resistant pathogens. It is obvious that these expectations can only be met if diagnostic tests are available that are:
- reliable
- accurate
- sensitive
- easy to handle
- fast
- cheap
- reimbursed by health insurance.

HBS Consulting has conducted a large study on the use of molecular diagnostic tests for 43 infectious pathogens in 11 European countries. Some key findings of tests for 43 infectious pathogens in 11 European countries. Some key findings of diagnostic tests are available that are:

- laboratories performing nucleic acid testing such as PCR, Hybridowell™, TMA, HCA and other; and
- laboratories performing exclusively conventional test methods (serology, culture, strips etc.). The latter were excluded from the study.

**National differences in clinical microbiology**

The following Table provides exemplary data from 5 out of 11 surveyed European countries for Chlamydia trachomatis, one of the most frequently tested pathogens.

<table>
<thead>
<tr>
<th>Chlamydia trachomatis</th>
<th>GERMANY</th>
<th>FRANCE</th>
<th>UK</th>
<th>ITALY</th>
<th>SPAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of microbiology labs in country</td>
<td>413</td>
<td>607*</td>
<td>767</td>
<td>324</td>
<td>350</td>
</tr>
<tr>
<td>% of labs that test for Chlamydia</td>
<td>94%</td>
<td>77%</td>
<td>80%</td>
<td>78%</td>
<td>70%</td>
</tr>
<tr>
<td>Overall number of tests x 1000</td>
<td>700–1100</td>
<td>380–450</td>
<td>2800–5000</td>
<td>290–605</td>
<td>108–154</td>
</tr>
<tr>
<td>% of labs that use PCR</td>
<td>53%</td>
<td>60%</td>
<td>40%</td>
<td>60%</td>
<td>24%</td>
</tr>
<tr>
<td>% of labs that use HCA/TMA/SDA</td>
<td>10%</td>
<td>16%</td>
<td>32%</td>
<td>9.1%</td>
<td>–</td>
</tr>
<tr>
<td>% of labs that use Cultures</td>
<td>13%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>28%</td>
</tr>
<tr>
<td>% of labs that use ELISA</td>
<td>7%</td>
<td>–</td>
<td>25%</td>
<td>–</td>
<td>20%</td>
</tr>
<tr>
<td>Number of tests with MT per year x 1000</td>
<td>250–460</td>
<td>200–250</td>
<td>760–1200</td>
<td>150–300</td>
<td>5.2–13.3</td>
</tr>
<tr>
<td>Main sample used</td>
<td>Swab 60%</td>
<td>Urine 42%</td>
<td>Swab 47%</td>
<td>Urine 41%</td>
<td>Swab 64%</td>
</tr>
<tr>
<td>Market leader (devices)</td>
<td>Roche (53%)</td>
<td>Roche (85%)</td>
<td>Roche (40%)</td>
<td>Roche (30%)</td>
<td>bioMérieux (31%)</td>
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<tr>
<td>Averaged costs PCR tests</td>
<td>11</td>
<td>19</td>
<td>10</td>
<td>32</td>
<td>24**</td>
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</tbody>
</table>

*excluding private laboratories, **large price range from _6 to _1 20 per test

Centralised laboratory infrastructure is associated with fewer suppliers and there is an order of magnitude higher number of Chlamydia tests due to nationwide screening programmes. As a consequence, the UK market is characterised by lower and more homogeneous prices.

The share of NAT among all Chlamydia tests depicted in Figure 1 (projection based on sample population).

**Market growth of molecular diagnostics**

The number of molecular tests (MT) performed by clinical microbiology laboratories differs according to country and, of course, to pathogen. If no commercial MT are available but relatively high tests numbers are run, self made “homebrew” tests make up a considerable share of the total PCR tests. An example is MRSA testing in France: 60% of the PCR tests for the antibiotic susceptibility are “homebrew” tests.

Clinical microbiology laboratories in Europe are still undergoing major technology-driven changes that started some ten years ago. The introduction of new techniques that allowed significant improvements in the ability to rapidly diagnose and characterise infections with high sensitivity include:
- advances in automation, and
- molecular testing methods.

While newer molecular technologies have attracted the most attention, advances in conventional microbiology testing, including culturing and immunoassay methods have produced significant benefits for the laboratory as well – mainly based on automation. The time required to obtain results for a blood culture specimen has dropped to less than a week and susceptibility testing turnaround times went down from 24 hours to about four hours.

The largest growth of the market for products used in microbiological testing is however in the molecular diagnostics segment. Testing for infectious disease was the first major clinical application for molecular diagnostics in the clinical laboratory and continues to dominate the market. As can be seen in Figure 2, more than two...
thirds of the interviewed laboratories expect STD-related pathogen tests to increase in number within the next three to five years.

The demand for NAT of antibiotic resistance genes in organisms like *Streptococcus* or *Enterococcus* is also expected to increase. There is plenty of potential in the NAT segment. Among the laboratories surveyed, only 4 of 11 countries use molecular techniques to test for MRSA or VRE routinely.

The sensitivity of NAT has been identified as the most favourable characteristic that drives the increased use of molecular tests for infectious pathogens. The frequency by which the other drivers of the NAT market were mentioned across the 11 countries surveyed is shown in Figure 3.

There is no doubt that the number of molecular diagnostic tests for infectious diseases and antibiotic susceptibility tests performed by microbiological laboratories across Europe will continue to increase in the years to come. Factors identified by the HBS Consulting study that will limit this increase include:

- the current test prices (mentioned among the top three by 9 of 11 countries surveyed)
- unsatisfactory reimbursement of NAT costs
- lack of standardisation, especially of quantitative PCR
- need for skilled laboratory personnel, special equipment and additional space.

Scientists in both the academic and industrial setting have the tools to react to the demands of new or re-emerging infectious diseases. It is up to the healthcare authorities, insurance companies and governments to take action so that new technologies like NAT are installed in healthcare settings to make full use of their potential to save lives and reduce costs.

*Martin Pfister*
External consultant to HBS Consulting

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Meeting Report

Clinical and Laboratory Standards Institute (CLSI) and EUCAST

The Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) Sub-committee on Antimicrobial Susceptibility Testing (CLSI-AST) held their bi-annual meeting in Tampa, FL, USA from 8th to 11th January 2005.

On the 8th of January the CLSI, EUCAST and the Food and Drug Administration (FDA) had an ad hoc joint 2.5 hour session. Six members of the EUCAST Steering Committee attended as EUCAST representatives and the ESCMID Secretary General, Giuseppe Cornaglia attended on behalf of ESGARS. After initial presentations by EUCAST and CLSI, the two committees agreed that sharing data and co-ordinating the review process for breakpoints would be beneficial to both parties. Decision processes and their formal relationship to regulatory authorities were discussed including a description by Gunnar Kahlmeter (EUCAST) of the planned co-operation between EUCAST and EMEA, which allows EMEA to utilise EUCAST as a breakpoint committee in the formal registration process for new drugs. Much of the ensuing discussion related to the lack of a legal framework, which would allow CLSI a formal role in reviewing existing breakpoints in the USA.

During two sessions on 8th and 9th January the CLSI Working Group on Enterobacteriaceae, headed by Mike Dudley, reviewed the background to and the process for revising cefepime breakpoints for Enterobacteriaceae. It was pointed out that this work had been ongoing for over six meetings (3 years) and so far had neither led to any actual changes in breakpoints nor to the working group having convinced the majority of the voting sub-committee of the need for a change. The STMA (Susceptibility Testing Manufacturers Association), represented by Barbara Zimmer, described the difficulties faced by the manufacturers following a major revision of a large set of breakpoints. Some of them are related to the legal process to obtain necessary approval for new concentration ranges from the FDA. As on other occasions during the meeting, FDA representatives questioned the process by which CLSI could change breakpoints.

Much of the discussions centred on the problems inherent in reviewing breakpoints. CLSI pointed out the limitations of current screening tests for extended spectrum β-lactamases (ESBLs) and the difficulties in identifying resistance mechanisms (ESBLs, AmpC, permeability). Lowering of the breakpoints would obviate the need for screening with lower concentrations than current breakpoints. FDA representatives questioned the public health hazard of some ESBLs and called for more and better clinical data to prove that this problem was of a magnitude requiring any action from either FDA or CLSI.

At the full sub-committee meeting on 10th January (“voting-day”) Gunnar Kahlmeter gave a 30-minute presentation on the structure of EUCAST, its relationship to national breakpoint committees, ESCMID and EMEA and of the process for setting breakpoints. The rationale documents for EUCAST breakpoints were described and also the EUCAST wild type MIC distribution programme was demonstrated.

At the full sub-committee meeting discussion on the need for revising CLSI breakpoints for cephalosporins continued after a summary presentation of the issues by Mike Dudley. Consensus was reached that a scientific process to review the current cephalosporin breakpoints in Enterobacteriaceae is needed, and that this should be done in collaboration with EUCAST. This review could be tied in with review of carbapenem and aztreonam breakpoints. The Enterobacteriaceae Working Group was charged with producing preliminary revised breakpoints and background data sheets including data such as wild type distributions of relevant bacteria, Pk/Pd data and simulations for relevant dosages and target attainment rates. These would be presented at the CLSI meeting in June 2005.

During the Staphylococcal Working Group meeting Fred Tenover presented data to support lowering the vancomycin breakpoints for Staphylococcus aureus. The current CLSI breakpoints are \( \geq 8 \) mg/L and \( \geq 32 \) mg/L (as compared to the recently revised EUCAST breakpoints of \( \geq 4 \) mg/L and \( \geq 8 \) mg/L). It was argued that \( S. aureus \) with MICs of 4 mg/L isolated after long-term vancomycin therapy exhibited clear biological changes (thickened cell walls). After having reviewed a number of case reports with poor therapeutic outcome, the working group members voted to suggest to the full committee that a revision of the vancomycin breakpoint should be considered during 2005. This was subsequently endorsed by the full sub-committee on 11th January. The FDA representative, John Powers, again questioned the need for the change and the process by which CLSI could make the change.

From the EUCAST and ESCMID viewpoint the meeting was successful.

- The work performed by EUCAST was taken seriously by CLSI members. The EUCAST model for co-operating with EMEA, the wild type distribution programme, the EUCAST website including the way the breakpoint tables were presented and the rationale documents were viewed positively.
- The CLSI Working Group on Enterobacteriaceae was encouraged to work together with EUCAST in the quest for new breakpoints for cephalosporins.
- There was positive progress towards the goal set by EUCAST to find a way to work together with CLSI towards greater harmonisation of breakpoints between Europe and the USA.

Gunnar Kahlmeter
EUCAST Chairman

Derek Brown
EUCAST Scientific Secretary
The UEMS (Union Européenne des Médecins Spécialistes) was founded in 1954 by the professional organisations of medical specialists in the European Community member and associated countries. It acts as a lobby organisation to the European Commission and its main interest is to work for a consistent standard of quality of training of medical specialists and in the quality of continuing medical education/continuing professional development (CME/CPD) in all countries in Europe. The aim is that as freedom of movement of professionals between the EU member countries increases, there will be confidence that a specialist recognised in one country will have the competence required from a specialist in a receiving country.

The UEMS has a central office located in Brussels close to the European Commission. Information about UEMS and documents pertaining to its activities can be found on the UEMS home page (www.uems.net). Within the UEMS there are at present 37 monospecialist Sections and 4 multidisciplinary joint committees (Intensive Care, Pediatric Urology, Hand Surgery and Pain Medicine). The National Medical Associations of 28 countries in Europe are full members of the UEMS and 4 are associated members (Tables 1 and 2). After nomination by the National Specialist Organisation and acknowledgment by the UEMS, each National Association is requested to send two delegates to each monospecialist Section. These Sections can appoint observers to the Section if, for instance, the specialty is not officially recognised in a European country. This is the case with Infectious Diseases in some countries where the specialty does have extensive clinical activity. Table 1 shows the official status of the specialty of Infectious Diseases in the European countries and also shows which countries are represented in the Section, either as full members or as observers. In addition, the major scientific society, the European Society for Clinical Microbiology and Infectious Diseases, ESCMID, has been granted observer status.

The Section for Infectious Diseases was constituted in March 1997. Its first President was Barbara Bannister from the UK who was succeeded in 1999 by Daniel Lew from Switzerland. In 2001 the position was passed to Ingrid Nilsson-Ehle from Sweden and she was succeeded in September 2004 by Mike McKendrick from the UK. Section secretaries have been Ingrid Nilsson-Ehle (1997–2000), Håkon Sjursen, Norway (2000–2003) and the present secretary is Winfried Kern, Germany.

The Section has appointed a European Board of Infectious Diseases (EBID). The Board is the executive branch of the Section where most of the actual work regarding the development of specialist training and CME/CPD is performed. Its first President was Mike McKendrick, who has been succeeded by the current EBID President, Mary Horgan from Ireland. EBID has produced several documents delineating the Section’s views on specialist training and CME/CPD which have been approved by the Section during their annual meetings. These documents can be found on the Section’s home page (www.uemsinfect.org):

- a European Charter for Specialist Training in Infectious Diseases
- a model European log book for training
- a model European supervisor report for training in Infectious Diseases
- a Continuing Medical Education (CME) guideline for Infectious Diseases
- minutes from the Section’s annual meeting
- minutes from the meetings of EBID
- list of Section members and observers

<table>
<thead>
<tr>
<th>National Medical Associations which are full UEMS members</th>
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<tbody>
<tr>
<td><strong>Country</strong></td>
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<td>Austria</td>
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<tr>
<td>Switzerland</td>
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<tr>
<td>United Kingdom</td>
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Table 1
The charter for specialist training and the CME guidelines represent the consensus opinion of the members and observers to the Section for Infectious Diseases on the content and quality assurance of specialist training and CME in the specialty. The purpose is to define the minimum education level for European infectious disease professionals and, hopefully, these documents are of value for the member countries when setting up their own training programs. The documents have no legal standing; the responsibility for national systems for training of specialists and for developing systems for CME/CPD lies firmly under the jurisdiction of national authorities. By working within the UEMS, the Section hopes to facilitate and harmonise the training of infectious disease specialists to an adequate and consistent standard with regard to content and quality and thus to ensure the good quality of care of patients with infectious diseases in a Europe where movement of specialists between countries becomes more common.

CME/CPD is an important issue with the increasing awareness that doctors must update their competence as the field of medicine expands. Most countries which do not at present have a system for CME/CPD are now working to implement such a system. The UEMS has developed a central organisation for the accreditation of educational activities by constituting the European Accreditation Council for Continuing Medical Education (EACCME). This institution, however, cannot evaluate the scientific and educational contents of an event, only validate and grant the official number of European credits after professional evaluation has been performed.

To evaluate the scientific and educational value of educational events an organisation consisting of professionals within the specialty is needed. In countries where there is a national body set up for such evaluations, the event organiser can have the event evaluated by this body, especially for national CME activities. However, to facilitate European recognition for CME activities and to obtain European accreditation in countries where there is no national CME authority, there is a need for a European organisation to do the evaluation. The UEMS Section for Infectious Diseases has, by actively collaborating with ESCMID, developed a system for accreditation of educational events at the European level. This work is done by the European Board for Accreditation in Infectious Diseases (EBAID) which consists of members of the Section and representatives from the ESCMID Executive Committee (Peter Schoch, Managing Director and Ragnar Norrby, Professional Affairs Officer for Infectious Diseases and current President-elect of ESCMID). EBAID is chaired by Finn T. Black from Denmark. Information about the accreditation process and forms for application for European credits for educational events can be found on the EBAID website (www.ebaid.org).

The Section for Infectious Diseases and the UEMS Commission for Microbiology (subsection within the UEMS Section for Medical Biopathology) have initiated collaborative work. It is recognised that there are areas of mutual interest with regard to specialist training and CME. Dr Edmund Smyth, convener of the Commission for Microbiology, attended the annual meeting of the Section for Infectious Diseases in September 2004 and it was agreed to investigate areas of common interest. The Section and the Commission will have cross-representation at future meetings.

Some countries are not represented in the UEMS Section for Infectious Diseases despite efforts from officers of the Section to establish contact with national organisations in all countries. The Section would be very pleased to welcome more countries to participate in the work of the Section. For additional information please contact the Section secretary, Winfried Kern (e-mail: kern@med1.uzh.unimi-freiburg.de).

<table>
<thead>
<tr>
<th>Country</th>
<th>Recognition of Infectious Diseases as medical specialty</th>
<th>Status at UEMS ID</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Azerbaijan</td>
<td>?</td>
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</tr>
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</table>

### Table 2: National Medical Associations which are associated UEMS members

The UEMS Section for Infectious Diseases (EBAID) which consists of members of the Section and representatives from the ESCMID Executive Committee (Peter Schoch, Managing Director and Ragnar Norrby, Professional Affairs Officer for Infectious Diseases and current President-elect of ESCMID). EBAID is chaired by Finn T. Black from Denmark. Information about the accreditation process and forms for application for European credits for educational events can be found on the EBAID website (www.ebaid.org).

Ingrid Nilsson-Ehle
Past President, UEMS Section for Infectious Diseases

Mike McKendrick
President, UEMS Section for Infectious Diseases

Winfried Kern
Secretary, UEMS Section for Infectious Diseases

Mary Horgan
President, EBAID

Finn T. Black
President, EBAID

### Join ESCMID Now!

**As an ESCMID member you can...**

- Attend ECCMID, ESCMID School, and educational courses at reduced registration fees
- Read *Clinical Microbiology and Infection*, the official ESCMID journal, and ESCMID News
- Join the Study Groups
- Benefit from research fellowships and travel grants
- Access ESCMID members-only webpages
- Influence decisions through the Assembly of Members, European Council, and lobbying of Executive Members

Please visit the ESCMID website (www.escmid.org) for more information about ESCMID activities, and to register online or to print out the membership form.

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**Table 2:**

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</table>
In his position paper, David Byrne encouraged individuals and organisations to become involved in developing a new EU health strategy. ESCMID submitted the following comments to the paper:

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID), a learned society with a membership of 2800 professionals active in medical microbiology, clinical infectious diseases, infection control and biomedical research, is dedicated to promote excellence in the prevention, diagnosis and treatment of infectious diseases by supporting professional, educational and scientific activities, stimulating debate between stakeholders and advising health policymakers. ESCMID endorses entirely the objectives laid out in Commissioner Byrne’s Position paper “Enabling good health for all”. In particular, we support the view that promoting good health and well being of people in Europe and the world should receive higher political priority. In this perspective, we welcome the greater role of the EU as a catalyst committed to bringing together all partners in this long term effort, including governments, healthcare professionals, non-governmental organisations, health industry and citizens.

In these comments, we identify major infectious diseases threats for consideration by the Commission to be included as targets for the EU health strategy and we suggest possible initiatives to better protect citizens from these threats.

1. Infectious diseases – public health priorities:
   - AIDS & tuberculosis
   - Healthcare associated infections
   - Antimicrobial resistance
   - Epidemic infections and bio-terrorism

2. New EU initiatives for effective prevention and control of infectious diseases:
   - Expansion of the European CDC: research on microbial virulence, drug resistance and ecology
   - Health technology assessment: laboratory diagnosis, therapy, surveillance and control
   - Capacity building: infection surveillance, management, and prevention
   - Partnerships for health
   - EU international leadership for communicable disease control

1. Infectious Diseases are a Public Health Priority for Europe

As recognised by the EU, infectious diseases are increasing threats to public health. Disease outbreaks as well as ever-increasing antimicrobial drug resistance in pathogens causing community and hospital-acquired infections demand close monitoring, vigilant alert systems and continuous revision of diagnosis, management and control strategies.

Faced with these rapidly evolving challenges, public health and patient care delivery systems need to adapt in a flexible and pro-active manner. Progress depends on dialogue and co-operation between health sciences and medical practice, between health care professionals managing infection and national health systems with their diverse organisation, local priorities and assets (1).

Major threats from infectious diseases:

**AIDS and tuberculosis**

The marked regional disparities around the world but also across Europe in the incidence of transmission and drug resistance of AIDS and tuberculosis are clear indications of the need for international co-operation in sharing best practice for prevention and treatment programmes for these diseases. These policies should ensure equal access of all, including persons in low income and underprivileged communities, to health education, prevention and effective therapy. In co-operation with WHO, the EU should support these policies and stimulate systematic collection of process and outcome data from member states to allow benchmarking of the capacity of health care systems and international co-operation programmes to deliver these benefits.

Healthcare-associated infections and antimicrobial resistance

Healthcare-associated, or nosocomial infections, which affect too many patients admitted to acute care, long term and home care facilities, carry a tremendous burden of morbidity and healthcare and disability costs. Effective therapies for these infections are dwindling away due to accumulation of multi-drug resistant bacteria in healthcare settings and their rapid emergence in the general population as well. Studies have shown that infections caused by some of the resistant bacteria add significantly to the health care cost and may increase the risk of treatment failure and death from severe infection. More research is urgently needed to measure the health and economic costs and better understand the determinants of nosocomial infections and antibiotic resistance in Europe.

In all health care institutions, an infection prevention programme should be developed by physicians trained in health care epidemiology and implemented with the support of dedicated infection control practitioners. It is a matter for concern that there is no certified medical speciality training in infection control in most European countries and that many hospitals lack such specialists. The EU should support capacity building in healthcare epidemiology and infection control specialists, operational research and exchange of best practice towards prevention of nosocomial infection. It should stimulate systematic collection of process and outcome data from member states to allow the benchmarking of the capacity of health care systems to deliver effective prevention of healthcare associated infection.

In this era of increasing resistance to available antibiotics, the current trend in
major pharmaceutical companies to discontinue their antibacterial drug research and development programmes is a matter of great concern (2). The decreasing market incentives related to the rising cost and length of clinical development of anti-infective drugs and to pressure on drug price and consumption need to be addressed. Concerted action by the pharmaceutical and biotechnology industry, the EMEA, national drug regulation authorities, and academic bodies should identify ways to achieve a better balance between public health needs for new antimicrobial drugs and the economic constraints of research and development.

Epidemic infections and bio-terrorism

The rapid spread of the Severe Acute Respiratory Syndrome (SARS) has shown the vulnerability of our global society to unpredicted epidemics. Ecological and social changes, international travel and trade of goods facilitate the dispersion of microbial pathogens and infectious diseases around the globe, creating complex challenges for health care systems. The preparation of national pandemic influenza response plans is an illustration of the difficulties to co-ordinate health systems and summon scarce resources to meet potential threats. Bio-terrorism is another emerging threat that was illustrated by the anthrax attacks in the USA in 2001. This event stressed the need to improve the level of preparedness of health care providers and microbiologists to diagnose and manage infectious disease caused by unusual agents and toxins.

Following up on the BICHAT initiative led by the Commission, EU should increase its support of biodefence planning against deliberate release of biological agents. These systems should be upgraded and integrated into generic infection surveillance, alert and response systems. International co-ordination of these national systems need to be improved and put to the test through international exercises.

2. New EU Initiatives for Combating Infectious Disease

Expansion of the European CDC: biological research on virulence, drug resistance and ecology of microbial pathogens

ESCMID has given its full support to the launching of the European CDC to coordinate more effectively surveillance and control of communicable diseases at the European level (3). To enable containment of antimicrobial resistance and develop novel strategies for limiting the dissemination of more virulent viruses and microbial pathogens, the EU should further support research into the ecological determinants and genetic mechanisms that underlie the evolution of microbial pathogens and their interaction with animal and human hosts. This research field would greatly benefit from a closer interaction with epidemiologists investigating infectious diseases epidemiology in Europe and elsewhere. This interaction could be ideally developed at the European CDC. Establishing European reference laboratory facilities at the ECDC to support communicable disease surveillance, and integrating them with centres of excellence in infectious diseases research would boost the European research capacity. It would also help in developing a sense of collective responsibility among biomedical scientists and healthcare professionals who are tackling the global threats of infectious disease and constitute a highly effective and visible EU investment in international solidarity for health protection.

Health technology assessment: laboratory diagnosis, therapy, surveillance and control of infectious diseases

In Europe, academic centres and biotechnology companies are contributing significantly to innovative technologies (including nucleic acid amplification tests, nanotechnologies, and bio-sensors) that lead to high performance microbiological assays for testing in the diagnosis, case-screening or surveillance of infections. The EU should further support the development and validation of technologies that are likely to impact on the quality of care, containment of resistance or disease control. Co-ordinated health technology assessment should be actively promoted through the support of large scale clinical, epidemiological and health economic studies of the cost-effectiveness of novel diagnostic and microbial genotyping tests in the management of infected patients and the control of communicable infections.

Likewise, there are a number of therapeutical modalities for infection with currently marketed drugs as well as infection control measures using currently available technologies that lack a robust scientific basis to establish their effectiveness. It is unlikely that the pharmaceutical or health technology industries will fund studies to validate or improve these strategies where there is no market incentive to do so. It would be of great benefit for the EU and its citizens to help funding clinical trials and epidemiological intervention trials to determine the real benefit of these traditional medical and public health practices.

Capacity building: infection surveillance, management, and prevention

Effective infectious diseases surveillance, alert and response systems rely very much on individual competence of health care providers and microbiologists if warning signs are to be identified early and adequate response to be deployed in a timely manner. Health care as well as laboratory specialists need basic epidemiological skills and perspective that is too often lacking in current speciality training curricula. Conversely, public health agencies need to have staff members with sufficient clinical experience and laboratory expertise to engage in a fruitful dialogue with these care providers to improve the feedback and use of pertinent surveillance data.

Continuing medical education and special professional development schemes have to be devised to address these training needs for effective participation of all health professionals in epidemiological surveillance and outbreak control interventions. In addition, there is a need for continuous exchange of best practice among players in the infectious disease service line.

3. ESCMID Contribution

The ESCMID contribution can contribute to filling these gaps by its educational programme. Its annual congress is attended by 5000 participants in the infection disciplines, biomedical researchers and public health practitioners. ESCMID post-graduate courses, workshops, and summer school offer advanced training by an international faculty to over 500 health professionals each year.

Partnerships for health

ESCMID welcomes the vision offered by Mr Byrne that EU should continue developing mechanisms, such as the EU Health Forum, to work ever closely with all stakeholders involved in health, including academic and professional organisations on health-related Community initiatives.

ESCMID is the leading professional organisation for medical microbiologist and infectious disease specialists in Europe and undertakes regular consultation with various stakeholders in public health to meet the challenges in the field of infectious diseases.
In fall 2004, the European Commission launched a consultation process following the publication of the Communication Science and Technology, the Key to Europe’s Future – Guidelines for Future European Union Policy to Support Research. ESCMID participated in the consultation by completing an online questionnaire. The results of the consultation will be used by the Commission when preparing its proposal for the Seventh Framework Programme. In the following, the results of this consultation are summarised, together with some personal comments.

**Main messages: objectives supported by over 85%**

1. **There was very strong support** (over 97% of responses rating the objectives as either “very important” or “important”) **for the need to strengthen support for the research at the European level.** Furthermore, there was strong agreement that this would have an important impact on Europe’s research capacities and capabilities and that this would contribute significantly to Europe’s competitiveness, social welfare and sustainability (over 92% of responses).

2. **There was strong support** (over 80% of responses) **for the 6 major objectives set out in the Commission Communication.** Support is particularly strong to make Europe more attractive to the best researchers and biological practice in the service of diagnosis, surveillance and treatment of infection. The funding under the Community Health Programme of the European Committee for Antimicrobial Susceptibility Testing (EUCAST, organised by ESCMID) is a recognition of its role in this area.

**EU International leadership for communicable disease control**

ESCMID together with other national and international scientific societies shall put emphasis on the fact that infectious diseases, although recognised as a threat to European citizens, have not received the necessary degree of attention by governments in the European region. By mobilising the creative energy of scientists and clinicians combating infectious diseases, ESCMID will advocate the vision proposed by Commissioner Byrne to invest the necessary resources that will secure a strong EU international leadership in the field of communicable disease control.

Marc Struelens
ESCMID President

**Results of the Commission’s Online Consultation**

**Shaping Europe’s Research**

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<thead>
<tr>
<th>Participants</th>
<th>Number</th>
<th>Percentage</th>
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<td>University/higher education</td>
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<tr>
<td>Commercial organisation (&lt; 250 employees)</td>
<td>144</td>
<td>8.3%</td>
</tr>
<tr>
<td>Governmental body</td>
<td>141</td>
<td>8.2%</td>
</tr>
<tr>
<td>Commercial organisation (&gt;250 employees)</td>
<td>115</td>
<td>6.7%</td>
</tr>
<tr>
<td>Association</td>
<td>113</td>
<td>6.5%</td>
</tr>
<tr>
<td>Other</td>
<td>218</td>
<td>12.6%</td>
</tr>
</tbody>
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**References**

supporting transnational collaborative research. These actions are established ones with proven European value added. However, there was also widespread support for launching European Technology Initiatives with new objectives and to stimulate the creativity of basic research (81% of responses). Concerning the development of infrastructures of European interest and the coordination of national programmes, the support was high (86% and 85%, respectively).

3. Concerning other aspects of supporting research by the European Commission, there is particularly high importance attached to improving science and society relations (92% of responses); to supporting innovation (88% of responses) and research by and for SMEs (88% of responses); and to the importance of focusing EU efforts on topics of major European interest (88% of responses).

Other important objectives that were supported by the vast majority but less than 85% of respondents

1. Stimulating the creativity of basic research through competition between teams at European levels (81.2%). There was a clear difference depending on the respondents, e.g. universities/higher education tended to rate this objective more highly (88%) than average while large companies rated it lower (72%). Most comments on this point are in favour of improving support for basic research at a European level with excellence as the sole selection criteria, evaluation by international peer review and no predefined priorities. Overall, there is strong recognition that the right kind of competition can stimulate new ideas and creativity, although there was some concern that too much competition between researchers can be counterproductive.

2. Improving coordination of national programmes (84.5%). Support was slightly lower from large companies (78%). Concerns were raised by some participants that coordination could in some way weaken national programmes, although others considered that it improves their quality by allowing researchers to learn from each other. I personally think that the wish to strengthen research in the 10 new member states of the European Union is incompatible with the idea of opening national funding to the pan-European market. These countries would suffer from the competition by research groups from countries with greater potential and better infrastructure allowing them to propose more promising research projects. In my view national programmes should therefore remain closed to scientists from other countries.

Other major objectives of the respondents that deserve to be highlighted

1. Making Europe more attractive to the best researchers:
   a. Attracting young people
   b. Role of women
   c. Transfer of knowledge
   d. International dimension
   e. Lifelong learning and career development
   f. Increasing the quality, structuring and mutual recognition of research training across Europe is needed.

2. Doing better to do more:
   a. Reductions in the level of administrative burden, bureaucracy and proposal preparation costs in the Framework Programme, as well as faster administrative procedures.

Conclusions

Overall, the opinions raised in the online consultation are in agreement with the principles identified by Achilleas Mitsos, Director-General of the European Commission’s Research Directorate General, and published in “The ELSO Gazette” (Journal of the European Life Scientist Organization, issue 19, April 2004). He identified four main principles for future funding instruments. First, decisions about priorities should be driven by science, not by policy considerations, in a “bottom-up” approach. Second, scientific excellence should be the only selection criterion. Third, individual groups as well as networks should be funded; there should be no requirement for international consortia. Fourth, European funding should move towards grants based on trust and away from the cost-sharing models that have entailed a heavy bureaucratic burden.

Finally, an important issue that should be taken into consideration is the increase in the investment in research. If the European Union wants to compete in research with the USA we not only need to be more creative and work harder but we should have at least similar research budgets. In 2001 Europe invested e.g. 171 billion Euros in research and development, whereas USA invested 315 billion Euros. To correct this imbalance the Commission has decided to gradually increase European investment in research and development to reach 3% of the GDP by 2010. I hope that the above-mentioned objectives and modifications of research policy as well as the increase in the research funding will help in developing a more dynamic and powerful research system in Europe.

Jordi Vila
ESCMI Scientific Affairs Officer

GlaxoSmithKline donates bacterial isolate collection to scientific community for research

GlaxoSmithKline is donating the entire 10-year (1992-2001) European Alexander Project Surveillance Isolate Collection to the Antibiotic Resistance Monitoring & Reference Laboratory, Health Protection Agency in Colindale in the UK (previously called the Public Health Laboratory Service). This unique collection of over 20,000 isolates, comprising mainly S. pneumoniae and H. influenzae, is now available to the scientific community for research purposes. In addition, isolates from several non-European countries involved in the Project for several years are also included in the collection. GSK has provided this collection to encourage research in a number of areas such as resistance mechanisms and the development of resistance.

For information on how to obtain isolates from the collection, please contact: Antibiotic Resistance Monitoring & Reference Laboratory, Health Protection Agency-Centre for Infections, 61 Colindale, Avenue, London, NW9 5HT, UK; (Tel +44 20 8327-6511).
ESCMID and four of its Study Groups (ESGAP, ESGARS, ESGNI and ESGEM) have been running a DG Research Concerted Action on antibiotic resistance, prevention and control (ARPAC) for the past three years.

Over 200 hospitals from around Europe have been contributing data on infection control and antibiotic policies, antibiotic consumption and resistance. ARPAC work-package members have been studying the relationship between these areas to identify possibilities for improved control of antibiotic resistance in all European hospitals.

On 22 November approximately 200 delegates including representatives from 80 ARPAC hospitals, gathered in Amsterdam for a three-day consensus conference. The Conference was co-organised by SWAB, the Dutch professional organisation for the control of antibiotic use and resistance and held under the auspices of the Dutch Government who held the European Presidency at the time.

The Conference was opened by Dr Anna Lonroth from DG Research in Brussels and then a series of plenary lectures presenting the core ARPAC data were chaired by Prof H. Verburgh, President of SWAB and Prof. J. Vila, Scientific Affairs Officer of ESCMID.

The second day was fully occupied by four workshops whose contents reflected the four main areas of ARPAC work: antibiotic resistance surveillance; antibiotic policies and guidelines; antibiotic consumption; and infection control policies.

Each workshop included guest speakers presenting expert views on the subject (R. Canton, H. Grundmann, V. Jarlier, D. Nathwani, H. Kolmos, I. Gyssens, R. Polk, C. Brandt, G. Zanetti, A. Voss, C. Suetens, S. Harbarth, J. Green, K. Levi). Then ARPAC Steering Group members presented detailed ARPAC data on the subject and the workshop participants spent the rest of the day (and much of the evening in some cases!) drafting essential and desirable recommendations for hospitals, National Health authorities, European Health Authorities and research. The ARPAC Steering Group then worked late into the night to harmonise these recommendations.

On the final day of the Conference these recommendations were presented by the workshop rapporteurs (G. Duckworth, B. Cookson, D. Monnet and M. Struelens). This plenary section was chaired by Dr I. M. Gould, Scientific Co-ordinator of ARPAC and Prof M. Struelens, President of ESCMID. There was enthusiastic discussion of the recommendations with many useful points made by the delegates being taken on board by the ARPAC Steering Group. Major recommendations, based on ARPAC evidence, were made in areas such as antibiotic formularies, education on antibiotic resistance and prescribing, auditing of prescribing, measurement of antibiotic consumption, hand hygiene, isolation facilities, surveillance, screening and typing of antibiotic resistant alert organisms. Although there was, inevitably, some overlap with output from previous European con-

Figure. Members of the ARPAC Steering Committee answering questions from the audience.
ferences such as Copenhagen and Rome, it was felt that this was necessary in areas where poor progress had been made in implementation of previous recommendations.

There was tremendous support amongst the ARPAC hospital delegates for the success of the project, particularly in enabling them to measure and benchmark their antibiotic consumption data. Anna Lonroth was particularly enthusiastic about the value for money that the project had delivered. Unfortunately, this type of project, a concerted action, is no longer to be offered by the Commission, so that it is difficult to see how the network of hospitals can be maintained on a formal basis. One possibility is for the individual ESCMID Study Groups to maintain the network in their individual areas of expertise and for ESCMID to maintain the ARPAC website as a forum for continued interaction between the Study Groups as well as a vehicle for driving forward implementation of the ARPAC recommendations. Another possibility is re-union of the network for a VIth or VIIth Framework submission to DG Research and there was unanimous agreement that the subject of any such research should be the control of MRSA across Europe.

The Conference finished on an enthusiastic note regarding its success which was, in part, inspired by the beautiful venue (a converted church), in part by the superb Dutch hospitality which had included excellent food and a Conference dinner held on a candle lit barge touring the beautiful canals of Amsterdam and last but not least, by the dedication and untiring enthusiasm of Fiona MacKenzie, the ARPAC Project Co-ordinator, without whom ARPAC would not have been such a major success for all concerned. Finally I hope that ARPAC will be a template for future successful collaborations between the ESCMID Study Groups. Thanks to all and well done!

Ian Gould
ARPAC Scientific Coordinator

Acknowledgements
The ARPAC Steering Group included:
I. M. Gould, M. J. Struelens, H. Goossens, K. J. Towner, F. M. MacKenzie, J. van der Meer, V. Krcmery, B. Cookson, P. van den Broek, L. Dijkshoorn, J. Vila, G. Cornaglia, F. Baquero, D. Monnet, J. Mollinson, J. Bruce, D. Wagner, M. van Looveren. Thanks also go to J. Cooper and K. Milne for much patience and help and Peter Schoch for his and ESCMID’s support.

Note
Further ARPAC results will be presented at ECCMID 2005 in Copenhagen in a symposium on Saturday afternoon and at the European Network Corner. The Consensus Recommendations will be summarised on Sunday afternoon in another symposium and are currently being prepared for publication.

Clinical Challenges in Diagnosis and Management of Atypical Pneumonia

32nd ESCMID Postgraduate Education Course
Riga, Latvia, 20–21 June 2005

The focus of this course is on respiratory tract infections caused by “atypical” bacteria.

For further information please contact: Dr. Arta Balode, Phone +371 946 08 66, Email a.balode@stradini.lv or consult the internet at www.escmid.org, Courses & Workshops.
ESCMID Study Group on Molecular Diagnostics

Molecular diagnostics has become a common technology in the routine clinical laboratory where it has helped transform clinical laboratory medicine by providing more rapid and sensitive diagnostic results and by crossing the traditional boundaries between disciplines such as clinical chemistry, genetics, haematology, microbiology, and virology.

Over the past 10–15 years molecular technologies have been rapidly transferred from the research laboratory into the routine clinical diagnostic laboratory. For the diagnosis of infectious diseases, molecular technologies now form the foundation of the clinical diagnostic process in many cases.

Since the development of in vitro nucleic acid amplification in 1986, this technique has acquired increasing importance in many aspects of clinical microbiology: from diagnosis and patient management, to surveillance and epidemiological studies. In recognition of the increasingly utility of molecular diagnosis in microbiology, an ESCMID Study Group for Molecular Diagnostics, the ESGMD, was informally established in the early 1990s. The ESGMD was formalised in 1995 under its first Chairman Prof. M. Altwegg in collaboration with Prof. J. Verhoef.

About the Study Group

The objective of the Study Group is to study all aspects of the use of molecular techniques for the diagnosis and management of infectious diseases. This implies the extension of knowledge on procedures, best practice, and technical aspects relating to both commercial and non-commercial molecular test systems used in clinical diagnosis. The ESGMD aims to achieve this through the development of joint projects. These projects are either with other European study groups or through external collaborations with recognised experts within the international infectious disease community.

The projects focus on currently important technical and clinical issues within the molecular field, and can be extremely valuable to individual laboratories that have limited resources and may not have access to specific methodology and best practice approaches. In addition, where molecular tests are being applied to the diagnosis of rare diseases, there are often insufficient clinical data and patient information available to both promote good laboratory practice and support the diagnosis and clinical decision process.

The overall aims of the Study Group are to promote communication between interested parties all over Europe and to provide a forum for those involved in molecular diagnostics to communicate with one another and to establish links between already existing networks which help advance the use and acceptance of molecular diagnostics as standard practice where appropriate. Improving the quality of molecular diagnostic testing is one of the important goals of the Study Group.

To achieve these goals it is essential that clinicians, mainly infectious diseases specialists, microbiologists and representatives of the industry actively participate in the ESGMD.

ESGM Membership

As for all Study Groups, individual membership is open to all members of the ESCMID with an active involvement and interest in this area, including corporate members. The membership application has to be approved by the Study Group’s Executive Committee. The membership assembly defines the membership fee. The Executive Committee consists of a chairperson, a secretary and a treasurer. Additional members are elected to assure a balanced representation from different European countries. Members of the Executive Committee are elected for 2 years and can be re-elected. At present Prof. Dr. M. Ieven chairs the Executive Committee. Prof. M. Altwegg, Dr. P. Savelkoul and Dr. G. Noordhoek are co-chairperson, secretary and the member assuring quality control issues, respectively.

The ESGMD has presently 60 members including medical microbiologists, molecular biologists and scientists from hospitals, public health laboratories, universities and research laboratories across the whole of Europe.

The Executive Committee meets at regular intervals or communicates via e-mail. It is responsible for the organisation of membership meetings and scientific meetings in collaboration with local organisers. The Executive Committee also defines joint projects and raises the necessary funds. A general membership assembly is held during each ECCMID, during which elections to the Executive Committee take place, and changes in the statutes are approved (this can also be done by postal ballot).

ESGMD Activities

Since 1999, the ESGMD has co-organised the bi-annual European Meeting on Molecular Diagnostics, the “Scheveningen Meeting,” (1999, 2001, 2003). Also, during each of the recent annual ECCMID meetings a scientific symposium or workshop was organised. These have included the following subjects: Quality control and standardization (Scheveningen, 1999), Recent innovations and clinical practice (Stockholm, 2000), Quality control in molecular diagnostics in microbiology: organization, pitfalls and solutions (Istanbul, 2001), Molecular diagnostics (Milan, 2002), Quality control in molecular diagnostics (Glasgow, 2003), The clinical relevance of rapid diagnostic tests (Prague, 2004). Each of these Symposia consisted of four presentations on recent evolutions in the field; examples of subjects discussed over the last years include: Clinical virology and standardisation in molecular diagnostics, Composition, evaluation and control of external quality control panels, Rapid detection of respiratory viruses, when and how?, Molecular diagnostic techniques – are they cost effective? These meetings reflect the gradual progress in the molecular diagnostic technology made over the years i.e. from entirely manual procedures and locally developed protocols, based exclusively on ampiclon detection by gel electrophoresis, to the use of commercialised reagents and comprehensive kits.

Over the years the technology has expanded considerably by the development of multiplex formats to allow syndromic diagnostic approaches, i.e. the detection of one of multiple possible etiologic agents in a clinical syndrome such as meningitis or respiratory tract infections, and by the development of different technical platforms. The sensitivity of the multiplex formats still has to be carefully compared with that...
of the individual tests because of the possibility of decreased sensitivity within multiplex reactions. Different amplification techniques such as PCR and NASBA must be compared in all aspects, including cost-effectiveness. A special problem in validation studies is that of the comparison of a new test with a reference test, when the new test has a higher sensitivity than the traditional test. This is often the case for amplification tests. In this case appropriate method evaluation, validation and statistical procedures have to be applied, which must be in line with the laboratories regulatory requirements.

More recent advances have included the use of real-time amplification techniques whose advantages are increased rapidity, possible automation, improved protection against cross-contamination in the laboratory and easy development of quantitative determinations. The latter are becoming increasingly important, especially for the antimicrobial management of patients with chronic infections such as hepatitis C virus, HIV and CMV infections. In these infections it is not always possible to eradicate the infection but monitoring of the residual virus load is very important. Besides the detection of infectious agents by nucleic acids, amplification techniques are also increasingly applied for the rapid detection and identification of antibiotic resistance determinants.

As complete genome sequences of an increasing number of microorganisms are known, it is now also possible to detect and characterise uncultivable or uncultivated agents or even previously unknown organisms through the successive application of broad range primers and subsequent sequencing of the amplicons. The main challenge for the near future is to define the optimal use of the most appropriate amplification techniques in the routine diagnostic laboratory and to determine and communicate the clinical relevance of their results.

A collaborative study was initiated on the detection of Mycoplasma pneumoniae in respiratory specimens comparing two extraction methods and two different amplification and detection protocols. The results indicated that none of the laboratories was free of false-positive or false-negative results(1). A collaborative study on the presence of Chlamydia pneumoniae in atherosclerotic arteries concluded not only that C. pneumoniae was absent in the lesions but also that the immunohistochemical detection of the organism resulted from an un specific binding of the antibody (2).

The immense enthusiasm due to the enormous potential that molecular diagnostic procedures could have in infectious diseases, was rapidly confronted with the problems of false-positive and false-negative test results, and the necessity for careful fine-tuning and standardisation of the procedures. Therefore, the ESGMD from its start emphasised the need for quality control of molecular diagnostics. Originally, during the meetings of 1999-2000 the subject was addressed in collaboration with the Quality Control Concerted Action of the European Society for Clinical Virology (EU-QCCA), funded by the European Commission. As the EU-QCCA concentrated exclusively on the detection of viruses, collaboration with ESGMD resulted in the expansion of the programme to include bacterial agents as well. Proficiency panels for the detection of Chlamydia trachomatis were prepared and distributed. The results were analysed during the Istanbul meeting in 2001 and published in 2003 (3). The results of proficiency panel testing for Mycobacterium tuberculosis were also presented and discussed during that meeting (4). However, sponsoring of EU-QCCA by the European Union ended in 2001. One of the objectives of the EU-QCCA was to establish a self-sufficient organisation to continue and expand the external quality assessment activities, particularly also in the area of bacterial targets. Thus, EU-QCCA was superseded by QCMD, Quality Control for Molecular Diagnostics, an independent non-commercial organisation, managed by experts in the field. The Executive and Scientific Advisory Boards of QCMD work in close collaboration with the ESGMD, the chairperson of the ESGMD being one of its board members. The objective is still to improve the quality of existing and evolving nucleic acid amplification methods through proficiency testing and standardisation and support of best practice.

Through this collaboration, the ESGMD is able to influence and define the type, range and design of the quality control activities that QCMD delivers within the microbiological area. The aim is that in collaboration with the ESGMD, QCMD will gradually expand its QC activities to include more pathogens and applications (such as detection, quantification, genotyping, sequence analysis) as well as support the development of standards and working reagents through its international network.

Another important objective for the future is the elaboration of recommendations for the accreditation of laboratories applying molecular techniques in the field of infectious diseases.

In conclusion, the ESGMD will continue to concentrate on quality issues and the evaluation of new developments in molecular diagnostics.

The Study Group has a website (www.escmid.org/ESGMD). Full details of past activities of the Study Group can be found there as well as future plans. ESCMID members who are interested in the activities of the ESGMD Study Group can contact one of the Executive Committee members, mentioned on the website.

Margaret Ieven
ESGMD Chairperson

References
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Harmonization of Antimicrobial Breakpoints in Europe – Can It Be Achieved?

Abstract

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is convened by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and supported by representatives of almost all European countries. It is financed by ESCMID, the European Union, and the national breakpoint committees of France, Germany, Norway, Sweden, the Netherlands, and the United Kingdom. The Committee has recently published harmonized European breakpoints for aminoglycosides, fluoroquinolones, glycopeptides, and linezolid and is currently addressing aztreonam, carbapenems and cephalosporins. EUCAST has recognized the inconsistencies between clinical breakpoints primarily aimed at predicting better (susceptible) versus worse (resistant) outcome and epidemiological cutoff values for early detection of antimicrobial resistance development. EUCAST clinical breakpoints are based primarily on pharmacokinetic-pharmacodynamic relationships but do take into account other factors, such as differences in dosing regimens, toxicity, resistance mechanisms, clinical outcome data, and wild-type MIC distributions. EUCAST has devised a system for collecting MIC distributions of wild-type bacteria and for setting epidemiological cutoff values. The output of EUCAST is freely available via the EUCAST website (www.eucast.org).

Several different guidelines for antimicrobial susceptibility testing are used in European countries. This was highlighted some years ago with the introduction of the European Antimicrobial Resistance Surveillance System (EARSS), which organizes surveillance of resistance in bacteria causing invasive infections in 28 countries (www.earss.rivm.nl). To the best of our knowledge, there are seven internationally recognized committees defining antimicrobial minimum inhibitory concentration (MIC) breakpoints used in European countries for categorizing bacteria and fungi into susceptible (S), intermediate (I), and resistant (R). In alphabetical order, these are the BSAC (British Society for Antimicrobial Chemotherapy Working Party on Antimicrobial Susceptibility Testing, United Kingdom) (1), CA-SFM (Comité de l’Antibiogramme de la Société Française de Microbiologie, France) (2), the Commissie Richtlijnen Gevoeligheidsbepalingen, The Netherlands (3), DIN (Deutsches Institut für Normung, Germany) (4), NCCLS (National Committee for Clinical Laboratory Standards, United States) (5), Norwegian Working Group on Antimicrobials, Norway (6), and the SRGA (Swedish Reference Group of Antibiotics, Sweden) (7). The origins of these groups go back to the 1960s and 1970s. Their output is provided as professional recommendations, but occasionally, national agencies and/or programs (accreditation, quality assessment) may convert some aspects into “rules and regulations.” The formal authority generally rests with national health authorities and/or drug evaluation agencies, such as the Food and Drug Administration (FDA) in the U.S., national agencies in Europe, and more recently, the European Medicines Evaluation Agency (EMEA). The FDA and EMEA are required to determine breakpoints as part of the process for registering new drugs, so official breakpoints are determined early in the life of a drug. The professional breakpoint committees usually address the breakpoints for a new drug at a later stage, often several months later, and consequently, breakpoints may be different from those set by the national agencies. The European national committees are appointed by national medical societies and are bodies of specialists, most often in clinical microbiology and infectious diseases but also in other specialties. A few committees also have representatives from industry. Each of the committees consists of 10 to 15 members. Apart from determining antimicrobial breakpoints, all are involved in educational aspects of antimicrobial use and susceptibility testing. Some of them (BSAC, DIN, CA-SFM, and SRGA) support complete “systems” of antimicrobial susceptibility testing, publishing not only MIC breakpoints, but also zone diameter breakpoints for diffusion methods, together with detailed recommendations on methodology and quality assurance. Several committees are involved in national surveillance of antimicrobial resistance and in external quality assurance programs. The Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) have formed a joint committee addressing antifungal chemotherapy, the Nordic Reference group on Methods in Medical Mycology (www.srqa.or/svamp/index.html). The different national committees have certainly influenced one another, but until recently, there has been no formal attempt to harmonize their output. Thus, Europe has at least seven different sets of antimicrobial breakpoints and a wealth of methods and abundant versions thereof. The introduction of automated systems has had little if any harmonizing effect, as the manufacturers feel obliged to comply with customer demands regarding national breakpoints.

ESCMID and EUCAST

The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) (www.escmid.org) set up the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in 1997. The committee was formed with a representative from each European country and six representatives from industry but with no formal relationship to the national breakpoint committees. Since the national breakpoint committees were not involved in EUCAST, they independently continued to do what they had always done. Europe then had the EUCAST guidelines in addition to the six active national committee recommendations and in some countries a substantial following for NCCLS. In the spring of 2002, EUCAST was restructured, and the major responsibility for the professional output of EUCAST was given to the active national breakpoint committees in Europe. A steering committee, consisting of representatives from each of the national breakpoint committees, two representatives of the EUCAST General Committee (which has a representative from each European country), a scientific secretary, and a chairperson, was formed. A new decision-making process was agreed on whereby tentative decisions made by the steering
committee and the national breakpoint committees are distributed for consultation to the EUCAST General Committee, to affiliated groups, and to industry. The final decision is taken by consensus in the steering committee, taking into account any comments made during the consultation process. In this way, the considerable expertise and traditions of the national breakpoint committees are utilized, and the national committees take responsibility for implementation of the decisions made by EUCAST.

EUCAST is funded by ESCMID, the national breakpoint committees, and, for the next 3 years, by a grant from the Directorate General for Health and Consumer Affairs of the European Union. Industry does not contribute financially, but industry members are asked to supply the committee with the data needed for determining breakpoints for new and existing antimicrobials, to give opinions on interpreting data, and to comment on proposed breakpoints.

Following the restructuring in 2002, EUCAST has achieved several goals. All national committees have agreed to express breakpoints in a common format, as S≤ and R≥, which is also the format chosen by EMEA. A series of documents on methodological aspects, terminology, the determination of MIC values in bacteria and fungi, breakpoints, etc., have been published in *Clinical Microbiology and Infection* and are now available on the EUCAST website ([www.eucast.org](http://www.eucast.org)) (8–15). The website was created for the publication of EUCAST breakpoint tables, recommendations, news, and all other aspects of EUCAST activity. The concept of “epidemiological cutoff values,” sometimes called “species-specific microbiological breakpoints” (16), for the sensitive and early detection of phenotypic resistance development has been described (17) and implemented for four classes of drugs (aminoglycosides, fluoroquinolones, glycopeptides, and oxazolidinones). A website for the collection of large quantities of species-specific MIC distributions has been constructed, and software to collect and present these on the internet has been developed (see below). The clinical breakpoints for aminoglycosides, fluoroquinolones, glycopeptides, and linezolid have been re-evaluated, and the harmonized breakpoints have been published after a new procedure for harmonizing breakpoints for existing drugs was followed. Furthermore, a procedure for determining breakpoints for new drugs has been developed and is currently available for comment on the EUCAST website. Together with EMEA and industry, a standard operating procedure (SOP) for this is being developed. The SOP will describe the formal role of EUCAST in determining breakpoints for new drugs and will allow it to be involved at an early stage in the registration process for new drugs.

### EUCAST rationale for determining antimicrobial breakpoints for new and existing drugs

It must be recognized that the process for establishing antimicrobial breakpoints is a compromise among clinical, epidemiological, and methodological aspects. The perfect antimicrobial breakpoint (i) has clinical value, i.e., there is a correlation between categorization as “susceptible” and therapeutic success and between “resistance” and clinical failure; (ii) has epidemiological value, i.e., the breakpoint will distinguish between microorganisms lacking acquired or mutational mechanisms of resistance and microorganisms with resistance mechanisms; and (iii) allows reproducible susceptibility testing in the laboratory. Rarely is it possible to achieve these goals simultaneously with only a single breakpoint. EUCAST has recognized this and differentiates between clinical breakpoints, which are aimed primarily at predicting better versus worse outcomes and epidemiological cut-off values, which are aimed primarily at early detection of resistance. EUCAST has placed considerable emphasis on ensuring that the clinical breakpoint allows reproducible susceptibility testing of important target microorganisms, and in order to achieve this, the breakpoint must not divide wild-type MIC distributions of major target microorganisms.

In recent years, the measurement of resistance and resistance development has increased in importance. Investigation and description of the forces driving antimicrobial resistance development and intervention programs designed to influence the rates of resistance require breakpoints that correctly separate microorganisms with and without resistance mechanisms. For this reason, EUCAST aims not only to harmonize clinical breakpoints for Europe but also to develop a set of breakpoints for epidemiological use (17). These epidemiological breakpoints are referred to as epidemiological cutoff values so that they are not confused with clinical breakpoints. The effects of using the latter were recently investigated by applying them to the EARS database (18). The differences in resistance rates as measured by the various clinical breakpoints were at times pronounced. The single epidemiological breakpoints were not contentious and clearly indicated strains with resistance mechanisms. With *Escherichia coli* and ciprofloxacin, various clinical breakpoints gave resistance rates of 3.9 to 8.3%, whereas the epidemiological cut-off value gave a microbiological resistance rate of 12%; with *Streptococcus pneumoniae* and erythromycin, various clinical breakpoints gave resistance rates of 16.0 to 24.1%, and the epidemiological cut-off value gave a microbiological resistance rate of 24.1%. Both clinical breakpoints and epidemiological cut-off values are available on the EUCAST website.

The setting of breakpoints for clinical categorization of microorganisms is largely, but not exclusively, based on scientific considerations. Factors with a sound scientific basis are microbiology (drug activity against target species, resistance mechanisms and their effect on MIC values and clinical outcome, and methodological factors, such as inoculum density), pharmacology and toxicology (and their constraints on dosing and the variation of pharmacokinetic properties in the patient population intended for treatment), and pharmacokinetic-pharmacodynamic relationships. Other factors are less scientific and include the effect a decision may have on antibiotic policies and clinicians’ choice of drugs, on economy (for individual patients, for society, in reimbursement systems, and for manufacturers), whether there are viable alternatives, and the “level playing field,” i.e., the fairness of a breakpoint decision in relation to other drugs in the same class. Breakpoint committees need to change their original decisions, resulting in an evolution of antimicrobial breakpoints.

### Antimicrobial breakpoints need to evolve

A formal process is lacking by which the breakpoints for a drug or a class of drugs are re-evaluated either at intervals or when a new class member is presented for registration. Factors such as evolving therapeutic indications and practices, new resistance mechanisms, changing dosages, new pharmacokinetic knowledge, and the need to evaluate older compounds within a
class of antimicrobials as new compounds are introduced emphasize the need for antimicrobial breakpoints to evolve. However, the evolution of breakpoints is painful because (i) a multitude of documents need to be amended, distributed, and implemented by authorities, manufacturers, and laboratories; (ii) manufacturers of antimicrobial susceptibility testing devices need to make alterations to media, dilutions, algorithms, package inserts and manuals, and interpretive criteria in automated systems; (iii) laboratories across the world need to implement the new breakpoint in their antimicrobial susceptibility testing systems, sometimes having to wait for the manufacturer of an automated system to make the necessary (and sometimes expensive) changes – laboratory manuals, SOPs, and computer systems also need to be updated; (iv) the education of clinicians, medical students and laboratory personnel is affected; and (v) the rates of antimicrobial resistance in resistance surveillance programs are often affected, sometimes drastically, by a change in a breakpoint. This was recently demonstrated when a single change in the NCCLS cefotaxime breakpoint for S. pneumoniae brought the overall cefotaxime resistance rates in 2001 down from 24.9% to 16.0% for a large set of data (19).

The FDA, EMEA, and national medicine evaluation agencies are required to define breakpoints as part of the registration process for a new drug. However, they are not required to re-evaluate breakpoints unless formally requested to do so, and in practice, that is likely to happen only when there is a request for a higher breakpoint than that originally set by the agency. When breakpoint committees, lacking the legal constraint of the “agencies,” decide to re-evaluate breakpoints, it usually results in a lowering, not raising, of the breakpoints. In doing so, the committees are aware that the amount of work involved is quite daunting.

**EUCAST procedure for setting breakpoints**

EUCAST has formalized the procedure for setting breakpoints for new and existing antimicrobials. Before harmonizing breakpoints for existing drugs, it is important to determine whether the breakpoint differences can be explained by differences in dosing, chemical formulations, clinical indications, or target organisms. Therefore, information from each of the committees on how the drug is perceived and used nationally is collected at an initial stage. The target organisms are defined and agreed on. Wild-type distributions of MIC values for target organisms are collected, and epidemiological cut-off values are determined. Resistance mechanisms and their effects on drug activity and clinical outcome are identified. Pharmacological, toxicological, and pharmacokinetic data are collected, and a set of pharmacokinetic variables (concentrations following standard dosages, protein binding, half-life, area under the curve, etc.) are defined and used to determine a theoretically correct breakpoint based on pharmacokinetic-pharmacodynamic relationships, including Monte Carlo simulations (20). The theoretical breakpoint is compared with existing breakpoints (if breakpoints already exist) set by the national committees, including the NCCLS, and with the wild-type MIC distributions of target microorganisms to ensure that wild-type MIC distributions are not divided. In that case, the breakpoint for one or several species or groups of species may be shifted one dilution step up or down to prevent poor reproducibility in the laboratory. In these cases, explanatory comments are provided, and in some instances, notes are added regarding the dosing regimens. Finally, checks that the breakpoints are not in conflict with clinical outcome data are made. The tentative breakpoint decision made by the steering committee in concert with national breakpoint committees is distributed according to the formal consultation process described above. The final decision is taken by the EUCAST steering committee, and a table of breakpoints for the class of antimicrobial is published on the EUCAST website and in *Clinical Microbiology and Infection*. A document describing the rationale for the decision is published on the EUCAST website when, or shortly after, the breakpoints are posted. Implementation of the new breakpoints rests with the national breakpoint committees, who subsequently need to change their national inhibition zone diameter breakpoints to reflect the EUCAST breakpoints.

**Wild-type distributions and epidemiological cut-off values**

When comparable methodologies are used, the MIC distribution for any given drug for the wild-type population of any given microbial species is the same worldwide. The proportion of organisms no longer belonging to the wild type (microorganisms with acquired or mutational resistance) varies considerably and is, for many organism-antimicrobial combinations, increasing all over the world. The fact that the MIC distribution for a wild-type microorganism is the same irrespective of when and where in the world the microorganisms were collected and irrespective of whether the strains are of human or veterinary origin is fundamental for setting epidemiological cut-off values. The typical MIC distribution for wild-type organisms covers three to four twofold dilution steps, e.g., for penicillin and *S. pneumoniae*, MICs range from 0.016 to 0.064 μg/ml (Fig. 1); for ciprofloxacin and *E. coli*, from 0.06 to 0.032 μg/ml (Fig. 2); for vancomycin and *Staphylococcus aureus*, from 0.5 to 2 μg/ml; and for fluconazole and *Candida albicans*, from 0.064 to 0.5 μg/ml. Definition of the MIC distributions for wild-type microorganisms by collecting large volumes of MIC data from all over the world has several benefits and is one of the tasks EUCAST has prioritized, the benefits include the following: (i) availability of defined wild-type MIC distributions permits the setting of breakpoints that do not divide the wild-type distributions, which would preclude reproducibility of susceptibility testing; (ii) wild-type MIC distributions are used to define epidemiological cutoff values (microbiological breakpoints) that separate the wild-type from the non-wild-type microorganisms; (iii) the aggregated wild-type MIC distributions provide a downloadable reference for the individual investigator, laboratory, manufacturer of susceptibility testing devices, pharmaceutical company, etc.; and (iv) wild-type MIC distributions provide a public reference to the expected MIC value of a particular drug for a particular organism that has not developed resistance to the drug in question. EUCAST has undertaken the task of collection and public display on the Internet of aggregated species- and drug-specific MIC distributions. (For further description of the concept of MIC distributions of wild-type bacteria, see [www.eucast.org](http://www.eucast.org) and reference 17). The epidemiological cut-off values can be applied to species-specific MICs (18) or inhibition zone diameter distributions (21) of strains collected in antimicrobial resistance surveillance programs or be included in the software of automated susceptibility testing devices.
While there is no formal decision-making relationship between EUCAST and the NCCLS, the former and current chairman of EUCAST have served since 1999 as formal Advisors to the NCCLS Subcommittee on Antimicrobial Susceptibility Testing. Also, there is an increasing tendency to share data and views on breakpoint setting. EUCAST, while harmonizing European breakpoints for existing drugs, tries to avoid making decisions that will generate new minor differences between the breakpoints of the two committees. Through initiatives in CEN (the European Standards Organisation) and ISO (International Standards Organisation), the two groups are jointly involved in describing an international reference method for determining MIC values for non-fastidious microorganisms.

### References


4th ESCMID School of Clinical Microbiology and Infectious Diseases

Szeged, Hungary, 25 June – 2 July 2005

A one-week course dedicated to postgraduate and continuous medical education. The programme covers most of the relevant topics in clinical microbiology and infectious diseases, thus being of particular interest to young MDs at the end of their specialty training as well as those wishing to broaden their professional knowledge. By providing short reviews and well-selected case studies, the ESCMID School helps the students to prepare for their examination.

For details and registration see the ESCMID homepage at www.escmid.org. ESCMID School.

Organised by the ESCMID Education Committee under the auspices of the University of Szeged.
Streptococcus bovis Endocarditis with a Medico-legal Angle

We are pleased to occasionally publish interesting and educational case reports. Please make your own judgement. The outcome of the case described below will be revealed in a later issue of ESCMID News.

The Editor

Case Reports with a Twist

Streptococcus bovis Endocarditis

The patient
Mr. Y, then 51 years old, a farmer’s hand.

Past medical history
Aged 1 year: Eczema diagnosed by paediatrician.
Aged 18 years: Hyperthyroidism with goitre and exophthalmos treated with carbimazole and thyroxine.
Aged 22 years: Decompressive surgery for exophthalmos in right eye.
Aged 35: Epididymo-orchitis.
Aged 43: Hypothyroidism.
Aged 44: Non-Hodgkin’s lymphoma involving thyroid gland (open biopsy), treated with radiotherapy and chemotherapy.
Aged 47: Uvullectomy, atopic dermatitis, infected eczema.
Aged 51: Basal cell carcinoma on the left lower eyelid was diagnosed and required further radiotherapy.

First presentation
October 2002: Mr. Y attended casualty (A&E) in an average sized district general hospital (DGH) with cellulitis of left leg following blunt injury to left foot, allegedly due to a cow falling on him a few days earlier (“Primary condition” in legal terms). He also claimed that he had suffered a laceration to his right forearm as a result of contact with a broken handle on tractor three weeks earlier and that had become infected but settled spontaneously.

It was recorded in the notes that he was lethargic and complained of weight loss (half a stone in last few weeks), night sweats and shortness of breath. Medication was recorded as prednisolone and thyroxine. He had been on prednisolone for several years as treatment for his eczema. Heart signs and chest findings were normal. A diagnosis of cellulitis was made and he was admitted to hospital. Erythromycin and ciprofloxacin were prescribed and he was discharged 3 days later.

History of present illness
December 2002: Re-admitted 22 days following discharge, complaining of sudden difficulty in using the right side of the body, together with visual disturbances and breathlessness. He claimed he was continuously unwell since his last admission in October with loss of appetite, weight loss, night sweats and chills. His temperature was 39.2°C. His speech and swallowing were normal but there was a right temporal field defect. The optic fundus were normal and there was no abnormality to be found on examining the limbs neurologically. A heart murmur was noted and a subsequent echocardiogram showed vegetations on both mitral and aortic valves.

A diagnosis of infective endocarditis associated with transient stroke was made. In view of his allergy to penicillin he was prescribed IV Teicoplanin (to continue for 4 weeks) + Gentamicin (to continue for 2 weeks). Blood cultures grew Streptococcus bovis 48 hours after admission. It was decided to discharge Mr Y home 20 days after admission with a plan for daily return for IV antibiotics.

He was readmitted 6 days later with sudden weakness of left limbs and difficulty in speech. A diagnosis of left-sided hemiplegia as a result of septic embolism from endocarditis was made. CT showed multiple brain infarcts in the right temporo-parietal and left occipital regions but no sign of haemorrhage was seen. Repeat echocardiography showed persistently large vegetations.

January 2003: Cardiac catheterisation performed, showing severe aortic valve incompetence but good left ventricular function with normal left coronary artery system as well as 80% stenosis in mid right coronary artery.

February 2003: Renal failure noted, urea 18.4 mmol/L, creatinine 142 mmol/L. Aortic and mitral valve replacements with mechanical valve prosthesis were performed as well as a coronary artery bypass graft (CABG), using a saphenous vein graft from the leg.

March 2003: INR of 7.1 corrected by fresh frozen plasma. This was followed by drainage of massive bilateral pleural effusion. An abdominal ultrasound was performed and only revealed an enlarged front right lobe of the liver (Riedel lobe), which was put down to a probable congenital anomaly. CT scan of abdomen was of poor quality (non-contrast due to patient’s phobia of needles) and detected no abnormality.

April 2003: Discharged home.

July 2003: Grand mal seizures, anti-convulsants prescribed. Left-sided weakness, speech and visual defects noted.

October 2003: Mr Y claimed he was improving slowly but his leg remained weak and there was little movement in his left arm. He could only walk a short distance with help. On examination, he still had a mild dysphasia and there was a left homonymous hemianopia as well as weakness of tongue movements to the left and mild impairment of left sided facial sensation. The fundal examination was normal. Power was reduced in both left limbs but more so in the arm. Dysesthesia was present down the whole of the left side of the body. His lungs sounded normal, blood pressure was 145/90 and the prosthetic valve sounds were normal. There were no residual signs of the limb injuries.

Legal claim
Mr Y sued his employer (the farm owner) for negligence. His legal team recruited expert witnesses who asserted that there is a possible connection between patient’s injuries and subsequent endocarditis/strokes. The argument is that the source of the infection may have been external and related to Mr Y’s former occupation as a farm labourer. There is a history of laceration to the forearm and cellulitis both occurring within 3 months of his presentation with endocarditis. Further, in the absence of a demonstrable lesion in the lower gastro-intestinal tract (GIT), the
close temporal relationships between the injuries and the endocarditis would indicate that the source of infection was probably from contaminated material from the farm.

Discussion

The organism and its incidence in endocarditis: The genus *Streptococcus* causes the majority (≥50%) of cases of endocarditis. *Streptococcus bovis*, the cause of endocarditis in the patient, is a member of this group and its association with endocarditis is well documented. A recent study by Kupferwasser compared patients with *Streptococcus bovis* endocarditis to patients with endocarditis secondary to other causative microorganisms. In this study, 177 cases were reported, with 22 cases (12.5%) caused by *Streptococcus bovis*. In a further study by Gonzales-Juanatey the incidence was 16.8%.

Source of the organism: In all cases endocarditis is preceded by a bacteraemia. The Health Protection Agency (HPA) reported that *Streptococcus bovis* caused 187 cases of bacteraemia in England and Wales in 2001 www.hpa.org.uk/infections/topics_az/strepto/non_pyogenic/data_strepto_abrep.htm. The source of the bacteraemia resulting in endocarditis is usually the gastrointestinal or urinary tract. In the case of *Streptococcus bovis* it is generally acknowledged to be the gastrointestinal tract. *Streptococcus bovis* is a common inhabitant of both animal and human gastrointestinal tracts and hence it is commonly found in soil. The source of the organism in the human gastrointestinal tract may be intrinsic / endogenous or due to contact with various ruminant animals or birds, their carcasses or meat products and working in a farm is not necessarily a pre-requisite for colonisation by this organism. Identification of *Streptococcus bovis* strains of human origin in clinical settings has been problematic due to variations in biochemical tests as compared to ruminal strains of *Streptococcus bovis* and other streptococcal species. Whitehead et al using molecular typing found that *Streptococcus bovis* strains of human origin are different from those of ruminal origin. Further, on his initial presentation to A&E in October 2002, Mr Y was already complaining of weight loss (half a stone in last few weeks), night sweats and shortness of breath (possibly of shorter duration). These symptoms are consistent with endocarditis and may be an indication that his endocarditis was already well underway, his leg injury not being causal as it occurred only a few days earlier.

Skin lesions and relationship to source: The vast majority of cases of cellulitis (as diagnosed in patient’s left leg in October 2002, following blunt trauma) and wound infection (including that to lacerations as sustained by the patient on right forearm in September 2002) are caused by beta haemolytic streptococci belonging to Lancefield Groups A, C & G as well as *Staphylococcus aureus*. *Streptococcus bovis* is not an organism normally associated with cellulitis or wound infection and this association has not been referred to in any of the review papers listed here or in recognised Infectious Diseases textbooks (e.g. Mandell et. al.) In fact *Streptococcus bovis* is rarely associated with any human infections other than endocarditis.

Predisposing factors: There is a strong association between *Streptococcus bovis* bacteraemia / endocarditis and bowel carcinoma (≥ 50% of cases), bowel polyps (biotype 1) and hepatobiliary disease (biotype 2). In the Gonzales-Juanatey study 77% of patients with *Streptococcus bovis* endocarditis had colonic neoplasms. Bowel ulceration may further enhance bacteraemia and endocarditis and it is notable that the patient had been taking steroids for several years as a treatment for eczema. Steroid therapy may be associated with bowel ulceration, impaired healing of existing bowel ulcers as well as some impairment of the immune system in its ability to combat infection. Further, long term oral steroid therapy for eczema is controversial and it is common practice that most patients would be treated topically, with or without short courses of steroids. Additionally, the patient was diagnosed with Non-Hodgkin Lymphoma when 44 years of age and had subsequent radiotherapy and chemotherapy. Further, a basal cell carcinoma on the left lower eyelid was diagnosed aged 50 (a year prior to this episode) and required further radiotherapy. Both the disease (cancer) and the treatment would suppress or impair the immune system further and thus increase susceptibility to infection. Prior to the patient’s heart surgery in February 2003 he was noted to have carious teeth, which were duly extracted. Dental caries is a common and accepted risk factor for streptococcal endocarditis and good dental care is an essential preventative measure. Those facts are clearly relevant to the current case.

Complications, cerebral and other: The Kupferwasser study showed that *Streptococcus bovis* endocarditis is a severe infection. The duration of fever and raised inflammatory markers after the onset of treatment was longer than with infective endocarditis caused by other bacteria. Multiple valve involvement and valvular damage was also more frequent. Cerebral emboli are not uncommon and can cause cerebral infarction, arteritis, mycotic aneurysms, haemorrhage, cerebritis, and meningitis. In Ballet’s study 22 of 53 cases (~40%) had emboli and 11 cases (~20%) had strokes. Gastrointestinal lesions were observed in nearly 50% of patients. Mortality rates from the Kupferwasser study were 45% for *Streptococcus bovis* and 25% for non- *Streptococcus bovis*
endocarditis. This is higher than the 7.5-38% mortality range reported previously. Mortality was related not only to the virulence of *Streptococcus bovis* but also to a more frequent occurrence of underlying extra-cardiac disease from which patients died during follow-up care. Surgical treatment (valve replacement) is also more common in patients with *Streptococcus bovis* endocarditis. In the Kupferwasser study, surgical treatment was performed in 73% of patients with *Streptococcus bovis* endocarditis but only in 34%, 34%, and 41% of patients with endocarditis caused by other streptococci, staphylococci, or other bacteria, respectively. The above clinical features fit well with the patient’s clinical history related to his endocarditis episode (multiple valve involvement, mitral and aortic valve replacements, February 2003) and the subsequent complications he suffered: cerebral infarcts / strokes (December 2002), Grand mal seizures (July 2003). Indeed, his recovery is a testament to the adequacy of his medical and surgical management.

**Adequacy of hospital management:**
From the information available it appears that the patient’s hospital management (diagnosis, medical and surgical treatment) was generally satisfactory. However, certain aspects of management are not entirely clear:

- **Biotyping / further patient investigation:** The *Streptococcus bovis* isolated from the patient belonged to biotype 1 (API #5040573). As already mentioned this biotype is associated with bowel tumours (benign polyps and carcinoma). It is unclear, however, whether this association is causal, i.e. whether the presence of bowel tumours predisposes to bacteraemia and subsequent endocarditis, though this is likely. Further, it is unclear whether (in view of the above finding) the patient was fully investigated for bowel tumours. An abdominal ultrasound was performed in March 2003 and only revealed an enlarged front right lobe of the liver (Riedl lobe), which was put down to a probable congenital anomaly. It is fair to point out, however, that ultrasound scans are not particularly sensitive at detecting gut pathology. An abdominal CT scan was also performed in March 2003 without contrast since the patient refused IV cannulation. This rendered the scan much less sensitive than would have been otherwise and again no abnormality was detected. The most sensitive investigation in the circumstances would have been a colonoscopy with or without a barium enema but there is no record of this having been performed.

- **Antibiotic treatment:** The patient’s allergy to Penicillin would have rendered treatment for endocarditis more difficult. However, the patient appears to have been adequately treated with antibiotics as per BSAC recommendations. Insufficient information is available concerning dosage, compliance with treatment following discharge from hospital.

- **Surgical treatment:** In view of the large vegetations on the patient’s heart valve, antibiotic treatment alone would have been unlikely to result in cure. Endocarditis is an almost invariably fatal disease in the absence of cure. Thus it is commendable that the patient had early surgery for valve replacements following antibiotic treatment.

**Conclusions**

*Streptococcus bovis* is not a common cause of endocarditis, occurring in 12-17% of cases. The resultant endocarditis is more severe than average, often involves multiple valves and is commonly associated with bowel neoplasms. Both sides of the legal argument agree that it is most likely that the brain infarcts / strokes suffered by the patient, as well as the resultant seizures, originated from the vegetations associated with endocarditis and that the patient’s hospital management appears to have been satisfactory. The prosecution’s viewpoint is that in the absence of a demonstrable lesion in the lower GIT, the close temporal relationships between the injuries and the endocarditis would indicate that the source of infection was probably from contaminated material from the farm. On the other hand, the defence maintains that the patient had several recognised risk factors for bacteraemia and endocarditis, most notably his curios teeth. It follows that it is most unlikely that the injuries sustained by the patient (lacerations to right forearm in September 2002, cellulitis left leg in October 2002 following blunt trauma) had any causal relationship to the subsequent endocarditis and its complications.

**Selected references**


Michael Morgan
Consultant Microbiologist
In 1994 I received an ESCMID training grant in support of my research project in the laboratory of Prof. Jos van der Meer, at the University Medical Centrum Nijmegen, The Netherlands.

Our research was addressed to the mechanisms involved in the increased susceptibility to infections of rheumatoid arthritis (RA) patients undergoing therapy with anti-TNF agents. Cytokines are important effectors of the immune system and they have a pivotal role in the induction of a proper immune response towards different pathogens. Consecutively, we hypothesised that a disturbance at the cytokines level might contribute to the increased susceptibility to infections seen in these patients. Therefore, our first aim was to assess the production of different cytokines upon stimulation of whole blood with heat-killed microbes in a group of RA patients that were preparing to start a therapy with TNF blockers and in a healthy control group. We chose the whole-blood system to closer mimic the in vivo situation, and we used for stimulation intracellular microorganisms, such as Salmonella typhimurium or Mycobacterium tuberculosis, because most of the infections reported in these patients were due to these germs. We investigated the production of IFN-gamma, IL-1 beta, IL-6 and IL-10, as important cytokines involved in the cellular immune response. Our results showed a marked decrease in IFN-gamma production in the patients group compared with healthy controls (Figure). IFN-gamma plays a key role in the activation of cellular immunity. IFN-gamma knock-out mice are highly susceptible to M. tuberculosis and individuals lacking receptors for IFN-gamma suffer from recurrent sometimes lethal mycobacterial infections. In addition, M. tuberculosis is responsible for the most infections seen in RA patients treated with anti-TNF agents. We hypothesized therefore that the low IFN-gamma production in RA patients is likely to account for the higher susceptibility to infections.

To evaluate the influence of anti-TNF therapy on cytokine production, we followed-up our RA group for 14 weeks. We observed that anti-TNF therapy did not influence the capacity of whole-blood from RA patients to release IFN-gamma, IL-6 and IL-1beta. Unfortunately, we could not measure endogenous TNF production due to the presence of therapeutic antibodies in our samples. We concluded that, although short-term therapy with anti-TNF agents did not further decrease the release of other proinflammatory cytokines, the combination of defective IFN-gamma production in basal conditions and TNF neutralisation during anti-TNF therapy is likely to be responsible for the higher susceptibility to infections in patients with RA.

The data obtained by us served for the writing of an article that was recently accepted for publication (Popa C, Netea MG, Barrera P, Radstake TR, van Riel PL, Kullberg BJ, van der Meer JWM. Cytokine production of stimulated whole blood cultures in rheumatoid arthritis patients receiving short-term infliximab therapy. Cytokine 2004, in press.).

The mechanisms that render these patients more susceptible to infections are not completely elucidated. We would like to continue our investigation on the recognition of pathogens by toll-like receptors, a mechanism situated upstream to cytokine production.

I would like to thank ESCMID for supporting this project.

Calin Popa
Timisoara, Romania

Figure 1. Production of IFN-gamma from stimulated whole-blood cultures in healthy controls (white bars) and RA patients (black bars) prior to receiving infliximab. Heat-killed C. albicans, S. aureus, S. typhimurium, A. fumigatus and MTB sonicates were used as stimuli. RPMI: culture medium. Values are expressed as means ± SD. p values, calculated using Man-Whitney U-test, are as follows: *p<0.05, **p<0.002, ***p<0.0004
Carl Julius Salomonsen and the Start of Medical Microbiology in Denmark

Introduction

Carl Julius Salomonsen (1847–1924) was the first medical microbiologist in Denmark (Figure 1). At the turn of the year 1873–74 he made a series of bacteriological investigations, where he demonstrated streptococci in pus from an infected patient and postulated that they were the cause of the patient’s disease (1). This is one of the earliest records in the medical literature, which convincingly links streptococci with clinical disease; however, it is virtually unknown outside Scandinavia, because it was only published in Danish. In this paper Salomonsen’s observations are, for the first time, presented in an international context.

Salomonsen grew up in Copenhagen as the son of a district physician and matriculated at the medical faculty of Copenhagen University in 1865. From his early study years he was familiar with germ theory and its practical implications. Thus, he saw Lister’s antiseptic dressing in use, while he got his clinical training in the surgical department at the Copenhagen Municipal Hospital in the late autumn of 1867.

When Salomonsen qualified as an MD in 1871 the germ theory was about to replace the miasma theory as the predominant explanatory model of infectious diseases. However, this new paradigm was still based on assumptions rather than on clinical facts. At autopsies the presence of bacteria could often be demonstrated in infected organs, but it remained unsettled whether they had already been present in vivo, or whether they only represented a post mortem phenomenon. Furthermore, it was still a matter of controversy, whether or not they should be regarded as the etiology of infection. In November 1873 Salomonsen had a position as a registrar at a newly established mixed surgical-medical department at The Copenhagen Municipal Hospital (Figure 2), where he served under Carl Rasmussen MD, a pupil of Virchow. This formed a basis for fruitful scientific work, and a few weeks later he started his experiments.

Case History

On 4 December 1873 a 21 year-old man was admitted to the Copenhagen Municipal Hospital with a severe inflammation of his right foot. Shortly before he had suffered from a paronychion of the third finger of his right hand, which had been incised and was now well drained. Over the next days the inflammation progressed proximally, gradually involving his whole right leg. His right knee joint was swollen and fluctuating degrees of severity, and the patient became progressively septic. On 10 December Salomonsen punctured his inflamed knee joint, using Dieulafoy’s small aspirator (Figure 3A). He succeeded in aspirating a few drops of thin pus, from which he made wet-mount specimens for microscopic examination. Using a Hartnack microscope (Figure 3B) he was able to identify “…some cocci in straight or slightly curved chains of 2-8 links. Streptococcus” (1). Similar results were obtained, when he examined pus from the patient’s right foot one week later. Over the next weeks the condition gradually worsened. Pustules appeared all over his trunk, and the patient’s right shoulder joint became inflamed with fluctuating severity. On 28 December Salomonsen aspirated pus from the shoulder joint, and “… In the aspirated pus some streptococci were found of the same sort as those described above”. In an attempt to control infection the joint cavity was flushed with a sulphurous acid solution, a substitute for carbolic acid. However, the next day the accumulation had regenerated, and pus was aspirated once more. Microscopy of this material showed “… 1) very numerous red blood cells, of which the majority were discoloured and pasted together in larger or smaller clusters (effect of the injected sulphurous acid solution); 2) a few streptococci; 3) huge amounts of bacterium termo.” On 9 January Salomonsen made a final aspiration of pus, this time from the patient’s right peroneus. He found...
that "...Of the pus cells many were in clear decay, and serum was rich in masses of detritus; inside as well as outside these large amounts of streptococci were found; some of the chains were very long; no other bacterial forms were found". Two days later the patient died.

Of the pus that Salomonsen had aspirated from his patient on 9 January he inoculated, on the same day, a droplet into both the right pleural cavity and the peritoneal cavity of a young rabbit, which died four days later. Autopsy showed signs of severe inflammation with pus in both cavities. Salomonsen states that "...In the pus streptococci were found in abundant amounts, but no other bacterial forms". A droplet of the pus collected from the pleural cavity of the dead rabbit was inoculated 24 hours later into the right pleural cavity of another young rabbit, which died after eight days. At autopsy the right pleural cavity showed obvious signs of inflammation with pus. At microscopy Salomonsen found "...in addition to pus cells immense amounts of streptococci in general containing 8, 10 or even more links; where the pus cells had passed together to larger flakes, the chains were evenly mixed with those; in places small groups of chains were also found alone, loosely tangled, but never tighter than each chain was clearly discernible; giococci or other bacterial forms were not found."

**Discussion**

With today’s knowledge there is little doubt that the patient suffered from a generalised infection due to *Streptococcus pyogenes*, arising from a paranchymon. Salomonsen himself was reluctant to draw any firm conclusion. In his article he wrote: "This case history of course proves nothing with regard to the causal relationship between streptococcus and pyaemia; however, at any rate it seems to me that it is of some value as a contribution to the not very numerous reports on the occurrence of bacteria in metastatic foci of live human beings". Seen in retrospect this statement may seem too cautious. On the other hand, it reflects the problems that scientists were faced with, when trying to prove a causal relationship between an organism and a disease. It was only in 1884 that Koch formulated his four postulates, which still serve as the reference for establishing a causal relationship between an organism and a disease. They state that

1) the organism must regularly be isolated from cases of the disease,
2) it must be grown in pure culture in vitro,
3) inoculation of a pure culture of the organism into a susceptible animal must result in typical disease, and
4) the organism must again be isolated from such experimentally induced disease.

Whereas he was close to fulfill the first, third and fourth postulates, Salomonsen was unable to grow streptococci in pure culture. A major obstacle to this was the lack of solid media. These were not available until after 1881, when Koch introduced gelatine-based solid media. Even staining methods for bacteria were largely unknown at the time when Salomonsen performed his experiments; methylene blue staining was only introduced in 1877, and Gram staining in 1883 by his pupil, Christian Gram. Salomonsen’s animal experiments were inspired by a recent publication by Orth (2).

Salomonsen was probably fully aware of the scientific importance of his observations. It may therefore seem strange that they were first published five years later, and not in an international journal (1). One reason may be that he read the Austrian surgeon, Theodor Billroth’s book on “Cocobacteria septica”, which came out in 1874, immediately after Salomonsen had conducted his experiments (3). In his book, Billroth reports several case histories, in which he demonstrated streptococci and other bacterial forms in pus from living patients. However, in contrast to Salomonsen, he did not believe that they played any etiologic role, and he even contested that the different types of organisms seen at microscopy represented genetically stable forms. According to Billroth, all bacteria belonged to one species, Cococbacteria septica, which could assume different phenotypes (rods, cocci in chains or clusters, etc), dependent on factors associated with the host and the environment. Salomonsen was still young and inexperienced, and the prospect of a confrontation with someone in a capacity like Billroth may have discouraged him from publishing his results immediately.

Another reason for hesitating with publication may be that Salomonsen planned to include his data in a thesis on the role of streptococci in pyaemia. However, his plans were disturbed, when his mentor, Valdemar Rasmussen, fell ill and had to retire. Salomonsen instead addressed Peter Ludvig Panum (1820–1885), professor of physiology at the University of Copenhagen. Panum was the most renowned scientist at the medical faculty, and had the only laboratory in Copenhagen with facilities for bacteriological experiments. He agreed to be his new mentor, but immediately rejected the idea of a thesis based on clinical bacteriological data. Instead he advised Salomonsen to concentrate on more basic issues, which could serve to elucidate the natural history of bacteria and which could be tested in simple laboratory experiments. According to Panum, there was no point in elucidating the etiologic role of bacteria in human disease, as long as the basic knowledge about bacteria was still very sparse. From a clinical point of view we may regret Panum’s decision. However, from a scientific point of view he was undoubtedly right. Writing a thesis on the clinical significance of streptococci in pyaemia was a risky business, with the question about their genetic stability being unsettled. If Billroth was right, Salomonsen could easily end up in a blind alley with a thesis focusing one-sidedly on streptococci.

A major reason for doubting the genetic stability of bacterial phenotypes was the lack of technologies for producing pure cultures. Microorganisms could still only be cultivated in liquid media, and pure cultures could easily be contaminated with irrelevant organisms, which in turn could raise doubt about the genetic stability of phenotypes and favour the view held by Billroth. Salomonsen’s revised plans for a thesis set out to clarify these issues. In 1876 through 1877 he performed a series of laboratory experiments with putrefying...
In 1877 Billroth, together with his co-worker Ehrlich, published a new paper on Cocccobacteria septica in clinical specimens (7). They described a number of case histories, where they had demonstrated streptococci from e.g. subcutaneous abscesses and inflamed joints of patients with septicaemia. None of the case histories are very detailed, and they did not really add anything new to Bilroth’s observations from 1874. Billroth still contested a causal relationship of streptococci with clinical disease, and he maintained the concept of Cocccobacteria septica. It was the reading of this article that prompted Salomonsen to publish his nearly five-year-old clinical study (1). The results from his thesis had convinced him that Bilroth’s concept of Cocccobacteria septica was wrong, and it therefore made good sense to focus on streptococci as a phenotypic entity and try to prove a causal relationship with pyaemia in humans. Compared with the standards of his time Salomonsen’s clinical studies are of high quality, and we may regret that he did not publish them earlier and in an international journal. This would have made him one of the very first to link streptococci with clinical disease. Today Billroth is given the credit for this (8), which is history’s irony, since he neither believed in streptococci as a stable phenotype, nor in their causative role in disease (3, 7).

One important observation in the above-referred case history did not fit with Salomon’s hypothesis that streptococci were the cause of the patient’s disease. On 29 December, when he punctured the patient’s shoulder joint for the second time, he not only demonstrated streptococci, but also huge amounts of Bacterium termo, a motile rod. The day before he had punctured the same joint and only found streptococci, and after aspiration of pus he had instilled a sulphurous acid solution for disinfected the joint cavity. His own explanation for this unexpected finding was that the new organism had been introduced from outside in conjunction with the aspiration and instillation procedures. This seems probable, since they were performed without antiseptic precautions. As such it may be regarded as one of earliest records of a bacterially-verified hospital-acquired infection.

Closing Remarks

Over the next decades Salomonsen had a glorious career as a medical microbiologist. In 1883 he was appointed lecturer (from 1893 on as professor) at a newly-created chair in bacteriology at the University of Copenhagen, which is considered the first of its kind in Europe. The same year he sent his younger assistant, Christian Gram, to Carl Friedländer’s laboratory in Berlin, where he invented the Gram stain. And in 1895 he started Danish production of immune sera against diphtheria. This led, on his initiative, to the foundation of the State Serum Institute in 1902, where he served as its first director until 1910.

This paper was based in part on a previous article published in the Danish journal, Bibliotek for Læger (9).

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7. Billroth T, Ehrlich F. Untersuchungen über Cocccobacteria septica. Archiv für klinische Chirurgie (Langenbecks Archiv) 1877; 20: 403–33
Prolonged Restaurant-associated Outbreak of Multidrug-resistant Salmonella Typhimurium with Patients from Several European Countries

Abstract

This report concerns a prolonged restaurant-associated outbreak of infection caused by a multidrug-resistant (AS-SuT) strain of Salmonella Typhimurium, phage type U302, which took place during July and August 2003 and affected people from Denmark and neighbouring countries who had attended a specific restaurant. The outbreak comprised 67 laboratory-verified cases and ten probable cases; however, the actual number of patients was estimated to be more than 390. The outbreak strain was isolated from a buffet which was probably contaminated by an assistant chef who was found to excrete the epidemic strain. An attack rate of 7.3% was estimated and long incubation periods were observed, including one extreme instance of 27 days. This outbreak underscores the importance of conscientious personal hygiene, including frequent washing of hands, for professionals handling food.

Introduction

Food-borne Salmonella infections are a considerable public health problem throughout the Western World. In most countries Salmonella enterica subspecies enterica serovar Typhimurium (S. Typhimurium) is the foremost or second-most prevalent serotype. Although most cases of S. Typhimurium appear to be sporadic, outbreaks are an important means of transmission of this agent, and the literature describes a number of different modes of transmission. The detection and resolution of outbreaks, as well as an understanding of their epidemiology, are important in the direct and indirect control of this agent.

The number of S. Typhimurium cases peaked in Denmark in the late 1980s because of a high level of infection in domestically-produced poultry, and again in the early 1990s, primarily because of infection in pigs. Large-scale national efforts to control Salmonella infections in the farm-to-fork chain have resulted in a steady decline in the number of infections. However, the control of infection in production animals, and the subsequent reduction in both sporadic cases and outbreaks caused by contaminated meat, may have little effect on outbreaks mediated by infected individuals. This report describes a prolonged outbreak of S. Typhimurium infection traced to a single restaurant and, in all likelihood, to a single member of staff found to excrete the organism involved.

Results

The outbreak

The outbreak was first suspected when a woman, hospitalised with severe gastroenteritis on 31 July 2003, indicated a particular restaurant as the possible source of her infection. The Regional Food Authority (RFA) responsible for the supervision of the restaurant in question was notified the same day and an inspection was carried out. Samples for bacteriological examination were taken from the kitchen and the prepared food, but there were no visible problems and the general hygiene standards were found to be acceptable. At the same time, a rise in the number of S. Typhimurium isolates (antigenic profile O:4,12:H;i,1.2) with a particular antibiotic resistance profile (ASSuT; i.e., ampicillin, streptomycin, sulfamethoxazole and tetracycline resistance) was noted at the Statens Serum Institut. Patient interviews were initiated on 7 August and, after learning that four patients became ill after eating at the same restaurant, the RFA was contacted. The Swedish Institute for Infectious Disease Control contacted the RFA independently because of the appearance of an unusually high number of Swedish patients infected with S. Typhimurium who reported visiting Copenhagen. The RFA closed the restaurant on the morning of 8 August, and no further cases were reported subsequently. Faeces samples were collected from the kitchen staff, and S. Typhimurium was isolated from the sample of one of the employees, as well as from samples taken from the buffet served in the restaurant.

The investigation of the restaurant

The restaurant involved in the outbreak is one of 35 restaurants located in an amusement park in operation since the 18th century, and is thus frequented by both local visitors and tourists. Most guests at this restaurant select a buffet which consists of a variety of meat, potato and pasta dishes, and a large selection of raw vegetables. The RFA inspected the restaurant on 31 July and took two samples from the buffet for microbiological examination – one from a bowl with cold cooked pasta, and one pooled from four bowls containing chopped tomatoes, cucumber, green peppers and iceberg lettuce, respectively. These samples were chosen as the initial case reported eating “pasta salad” from the buffet. Laboratory analysis revealed S. Typhimurium in 25 g of material from both samples. In addition, faecal coliform bacteria were found at counts of 2300 CFU/g in the pasta and 360 CFU/g in the pooled raw vegetables.

Faecal samples from the three individuals employed in the kitchen were taken on 8 August; one sample was positive for S. Typhimurium, and the two other samples were negative. The staff member excreting the bacteria, who had worked in the restaurant daily during the period from 17 July to 7 August, was not ill and did not remember having had diarrhoea or...
Table 1. Overview of patients forming part of the outbreak

<table>
<thead>
<tr>
<th>Nationality of cases</th>
<th>No. of confirmed cases</th>
<th>No. of probable cases eating at the restaurant</th>
<th>Total no. of patrons in groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danish</td>
<td>40</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>Swedish</td>
<td>22</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Norwegian</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>German</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>10</td>
<td>59</td>
</tr>
</tbody>
</table>

other signs of enteritis. The restaurant was closed by the RFA on the morning of 8 August, and all personnel were dismissed by the owners. On the owners’ initiative, a private professional bacteriological analysis was undertaken the same evening. Twenty-four samples of food items in stock and swabs of surfaces in the kitchen were negative for Salmonella.

A buffet was prepared on 11 August to determine whether the problem persisted. Eight samples were taken by the RFA, including the pasta and the vegetables that had initially tested positive and the three types of meat served, i.e., ham, beef and spare-ribs, all of which were negative for Salmonella or other pathogenic bacteria. Special attention was given to the spare-ribs, which were delivered raw and frozen every 2–3 days from the same supplier and from the same import dealer, and which were thus potentially implicated in the infections. However, 25 g of material were negative for Salmonella on four different occasions: on export from the country of production, on sampling at the restaurant on 8 and 11 August, and again in October when the RFA tested four additional samples from the remainder of the batch at the supplier.

The RFA inspection of the restaurant on 31 July revealed only one breach of regulations, namely a non-functional staff toilet, necessitating that staff and customers used the same toilet facilities. Otherwise, the apparent hygienic level and the hygienic procedures, as reported by the manager, were acceptable, and included the separation of raw and ready-to-eat products, discarding all left-overs at the end of each day, and washing the kitchen utensils and the buffet containers. The various cooling systems were adequate. The restaurant was allowed to reopen on 14 August, at which time it had been thoroughly cleaned, had received new deliveries of all food, and had undergone a complete change of staff.

### Attack rate and incubation periods

The attack rate of the outbreak was estimated in three different ways. All patients but one visited the restaurant on one occasion only, and all did so in the company of others. There were 59 groups, ranging in size from 2 to 16 (median 4), accounting for a total of 306 people, most of whom had eaten from the buffet (see Table 1). Seventy-seven confirmed and probable cases among these 306 individuals gives an attack rate for salmonellosis of 25.2%. However, this calculation was based on groups of people in which one person is bound to have been ill. Excluding one patient from each group, there were 18 patients among a total of 247 individuals, which gives an attack rate of 7.3%. Finally, a third estimate was based on the total number of known patients relative to all exposed persons, i.e., all customers of the restaurant. The total of 77 known cases, in conjunction with a total of 5357 paying customers between 17 July and 4 August (as indicated by the restaurant accounts), gives a minimal attack rate of 1.4%.

The incubation periods (Fig. 3) could be estimated for 64 of the confirmed patients because they had visited the restaurant on one occasion only and clearly remembered the date of the visit, and because the chance that a patient who had eaten at the restaurant and was infected by the outbreak strain had acquired the infection elsewhere was extremely low. Four days was the median period between eating at the restaurant and the first symptoms. One-quarter of the patients had incubation periods of 26 days, and two patients had very long incubation periods of 26 and 27 days, respectively. One of these, a 42-year-old woman, was among a group that became ill after eating at the restaurant, and may theoretically have contracted the infection by secondary transmission. The other was a 27-year-old woman who was otherwise healthy and had received no medication in the period between eating at the restaurant and the onset of symptoms.

### Discussion

Although the outbreak was traced to the buffet of a particular restaurant, and terminated following closure of the restaurant, the question of transmission was not resolved. An important characteristic of the outbreak was that patients became infected over a period of 3 weeks, which may be explained by: (i) continuous use of a single batch of contaminated food; (ii) continuous contamination of food via contaminated utensils or surfaces; or (iii) contamination of food via restaurant personnel excreting the bacterium. The first possibility seems unlikely since extensive sampling at the restaurant revealed no contaminated products. The duration of the outbreak and the fact that food was prepared fresh daily in a generally hygienic setting argues against the second possibility. The discovery of a member of the kitchen staff infected with the outbreak strain makes the third possibility the most likely. This hypothesis is supported by further information: (i) the discovery of faecal coli bacteria, which are generally a sign of contamination with human faeces, in the samples from the buffet; (ii) the fact that the outbreak strain was found in cooked pasta and salad, indicating that cross-contamination occurred in the kitchen of the restaurant; (iii) low attack rates and long incubation periods, which both indicate low-grade contamination of food, again consistent with the hypothesis of contamination by an excreting member of staff. Although the route of infection of the staff member is not known, the presence of the outbreak strain in several unrelated sporadic cases indicates that the strain is circulating in the community at a low rate, an idea supported further by finding the outbreak type among human S. Typhimurium isolates from Denmark from the year 2002 and from a Danish meat sample. Therefore, it seems possible that the staff member acquired the infection via the community and introduced it into the restaurant. Alternatively, he may have been among the initial victims of the out-
Outbreaks spread by excreting restaurant staff are rare. There have been few such outbreaks within the last decade among more than 10 000 restaurants in Denmark, with the most prominent being a large 6-week outbreak of S. Enteritidis PT 34 infection which originated at a Chinese restaurant in central Copenhagen during the summer of 1999. However, although rare, these outbreaks may affect more people than restaurant outbreaks caused by contaminated food because they may last longer. The period in which individuals infected with non-typhoid Salmonella strains shed the bacteria varies with age and serotype, but 40% of non-symptomatic infected cases overall have been found to excrete Salmonella after 4 weeks, falling to 14% after 8 weeks. An investigation by the Minnesota Department of Health showed that 10% of staff at restaurants associated with Salmonella outbreaks shed the bacteria, with most of the positive staff being asymptomatic.

Several other noteworthy features of this outbreak relate to its size, attack rate, incubation periods, multidrug-resistance, sub-typing and surveillance. The outbreak comprised 40 independent culture-confirmed patients, making it one of the larger S. Typhimurium outbreaks in Denmark to date. Furthermore, the outbreak was international, spreading into Sweden and Norway, and probably to other countries. The scope of the outbreak was probably a result of a prolonged period of contamination in a restaurant which attracts many visitors from a large geographical region. Warm summer weather may also have contributed to the magnitude of the outbreak.

All the attack rates, which were calculated in three different ways, were fairly modest, which was an indication of low-grade contamination of the food. The minimal attack rate of 1.4%, based on the assumption that no more than the 77 registered patients could be found, represents an under-estimate because the national laboratory surveillance of Salmonella, and interviews with verified cases, records only a fraction of the total cases in the community. The maximal attack rate, on the other hand, represents an over-estimate as it is based on a selection for groups eating at the restaurant in which at least one member acquired salmonellosis. The third way of calculating the attack rate circumvents this problem by excluding the
index patient from each group, although this may lead to some under-estimation of the true attack rate. A rough estimate of the true size of the outbreak would be 390 individuals (7.3% of 5357), with the lower limit being 77 (the known patients) and the upper limit being 1350 (25.2% of 5357).

The 4-day medium incubation period number is long compared to the textbook periods of 6–72 h, which is again consistent with a low-grade contamination of the restaurant food. The relationship between a low infectious dose and long incubation periods and low attack rates in outbreaks of *Salmonella* infection has been described previously on several occasions. An incubation period of almost 4 weeks was found in two instances in this outbreak; although these patients may have acquired the infection from elsewhere, this possibility was regarded as unlikely. We are not aware of other studies in which incubation periods of similar length for non-typhoid *Salmonella* have been reported.

The outbreak described in this study was caused by a multidrug-resistant (MDR) *S. Typhimurium* strain of phage type U302. MDR U302 deserves to be monitored closely in the light of experience with the related *S. Typhimurium* phage type MDT DT104, which has been emerged rapidly in many western countries. It is possible that U302, like DT104, is a “success-clone”, and that this may have been a contributing factor in the propagation of this outbreak. However, MDR outbreak strains also pose the unwelcome problems of potential treatment failure and spread of resistance genes. Indeed, a recent Danish study has documented an increased mortality of MDR compared to sensitive *S. Typhimurium* strains.

All Danish *S. Typhimurium* strains are routinely phage typed and tested for antibiotic resistance, and at the time of the outbreak, they were also subjected to real-time PFGE. The results of the resistance testing were the first to be available; the outbreak was recognised initially on the basis of antibiograms alone. Antibiograms remain important outbreak surveillance tools – at least for *S. Typhimurium* where resistance genes are frequently present.

This outbreak also underscored the strengths and weaknesses of the laboratory-based surveillance system. The system efficiently detects all outbreaks of a certain size, especially if the strain involved possesses a special trait – in this case, a distinct resistance profile. However, outbreaks are not recognised immediately because of certain features of the system: patients with salmonellosis will typically tolerate symptoms for several days before seeing a doctor; the sample must be transported to the laboratory and await isolation, typing and possibly subtyping of the infectious agent; and the results must be recorded in the designated database and brought to the attention of an epidemiologist. In this particular instance the system functioned effectively and the various institutions involved in the process cooperated smoothly. The outbreak was detected and the source was determined almost simultaneously via the laboratory surveillance system and the fieldwork of the food authorities. Although the swift intervention of the latter in closing down the restaurant probably contributed to timely containment, the outbreak nevertheless continued for 3 weeks and was responsible for illness in a very large number of people.

The limitations of the power of the food authorities is another issue. Under Danish legislation, faecal samples can only be obtained if the individuals in question volunteer to submit them. Obtaining such samples was highly important in resolving the current outbreak, and the willingness of the restaurant’s managers and staff to cooperate was an important factor in the successful investigation of this outbreak. Last but not least, this outbreak also highlighted the importance of conscientious personal hygiene and frequent washing of hands on the part of all individuals handling food for public consumption.

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News in Brief

Infectious Diseases

**Chlamydia can inhibit host cell apoptosis**

Programmed cell death or apoptosis can be induced when cells are infected by obligate intracellular pathogens and this can lead to the death of the intracellular pathogen. A recent study from a group in Munich, Germany has shown that Chlamydia can inhibit this apoptosis and thus protect itself from destruction. In cells infected with *Chlamydia trachomatis* or *Chlamydia pneumoniae* the BH3-only pre-apoptotic proteins BIM, BAD and Puma were not present, although levels of mRNA were normal. Cytochrome c was still present in the mitochondria but in infected cells, it was not released.

*Fischer et al., J Exp Med. 2004; 200: 905*

**Cryptococcus genome sequenced**

Cryptococcus neoformans is a pathogenic dimorphic yeast which causes a range of human infections, including meningitis, and is often found in patients infected with HIV. The genomes of two phenotypically distinct strains have been sequenced and have revealed that they are rich in transposons, which may drive karyotype instability. The genomes of two strains have variation in gene content as well as sequence polymorphisms.


**New drug inhibits ATP synthase of M. tuberculosis**

Scientists at Johnson & Johnson in Beerse, Belgium have discovered a diarylquinoline (R207910) with a novel mode of action against *Mycobacterium tuberculosis*. The compound inhibits the proton pump of ATP synthase and has activity against drug-resistant strains of *M. tuberculosis*. In infected mice, the compound was highly active, and was more bactericidal that isoniazid or rifampin. The drug has been well tolerated.

*Andries et al., Science 2005; 307: 223*

**Structure of pneumococcal adhesin determined**

*Streptococcus pneumoniae* adheres to a polymeric immunoglobulin receptor in human cells and then invades them; it is the only bacterium known to use this method. Recent work on the principal adhesin, choline binding protein A (CbpA), has shed light on the precise mechanism of this binding. Various structural features of CbpA are shown to be conserved in most pneumococcal strains and they are important for high-affinity binding.

*Loe et al., EMBO J 2005; 24: 34*

**Warning issued regarding testing for Lyme disease**

CDC (US) has issued a warning in the MMWR regarding the number of commercial laboratories offering testing for Lyme disease using inadequate assays or testing inappropriate samples. The FDA (US) has approved a number of serologic assays and this information is available, similarly recommendations have been published in Europe and in Canada. Details are included in the article in MMWR.

*MMWR Weekly 2005; 54: 125*

**Resistance**

**Vancomycin-resistant *E. faecium* outbreak in Hungary**

An outbreak of vancomycin-resistant *Enterococcus faecium* occurred in a haematology and a stem cell transplantation unit in a Hungarian hospital during 2004. The isolates were all the VanB phenotype, with vancomycin MICs of 48-128 mg/L and teicoplanin MICs of 1-2 mg/L. A total of 14 patients was involved. This is the first such outbreak to occur in Hungary. The source was not identified.

*Eurosurveillance Weekly 2005; 10:4*

**New mechanism of resistance to aminoglycosides identified**

The emergence and dissemination of a new mechanism of resistance to aminoglycosides in Gram-negative bacilli has been described by the Institute Pasteur, Paris, France. The new mechanism uses post-transcriptional methylation of ribosomal RNA using S-adenosyl-methionine as a co-factor. The gene has been named as *armA* (aminoglycoside resistance methyltransferase) and confers resistance to the 4,6-di-substituted deoxystreptamines; this includes kanamycin, amikacin, gentamicin, netilmicin and tobramycin. MICs of these compounds ranged from 256 to 1024 mg/L. The gene has been detected in isolates from three hospitals in Paris, two hospitals in Sofia, Bulgaria and from isolates in the laboratory collection.

*Eurosurveillance Weekly 2005; 10:4*

**Apramycin can restore drug susceptibility to resistant bacteria**

A method of restoring drug susceptibility to various drug-resistant strains of bacteria has been reported by a group from the University of Illinois (US). This has been demonstrated with apramycin, which is a compound that mimics a short section of RNA from *E. coli* and It has the ability to adhere to and interfere with the replication of a plasmid mediating resistance to ampicillin. The plasmid is then ejected by the bacterium, which becomes susceptible to ampicillin. The toxicity of apramycin precludes its clinical development but it is hoped that other molecules may be found with similar properties.

*DeNap et al., J Am Chem Soc 2004; 126: 15402*

Viral Infections

**New coronavirus identified in pneumonia patients**

A new group 2 coronavirus has been identified by a group in Hong Kong in an elderly patient with pneumonia who had recently travelled to China. Samples were negative for SARS virus but were positive for a new virus, CoV-HKU1. Another patient in Hong Kong was also found to have the virus.

*Woo et al., J Virol 2005; 79: 884*

**Norovirus grown in laboratory for the first time**

A group from the Washington University School of Medicine announced in November that they had grown the mouse strain of norovirus (MNV-1) successfully in a mouse cell line. This is the first time a norovirus has been grown in culture.

*BioCom on line news 30 Nov 2004*
**Avian influenza**

The WHO reports that the number of people in Vietnam to have H5N1 avian influenza since December 2004 totals 13, 12 of whom have died. The first case of avian influenza has been confirmed in Cambodia; this was in a 25 year old woman who has died.

*WHO Weekly Epidemiological Record 2005; 80 (6) 49*

The possible person-to-person transmission of H5N1 avian influenza has been investigated in a family cluster in Thailand. Previously the majority of patients had had close contact with poultry and there had been no evidence of person-to-person contact. This study indicates, however, that two of the patients contracted the disease from the patient they were nursing.

*Ungchusak et al., NEJM 2005; 352: 333*

An analysis of the avian influenza outbreak in the Netherlands in 2003 has revealed that the rate of transmission from birds to humans was far higher than originally thought. The virus in the Netherlands outbreak was influenza A H7N7 and involved many commercial poultry farms. This study used questionnaires and extensive collection of serum samples from those who had contact with poultry and those involved in controlling the outbreak. A modified assay for H7 antibodies showed that large numbers of people were positive causing concern that humans may act as "mixing vessels" for influenza viruses.

*Eurosurveillance Weekly 2005; 10: 1*

to enter the mammalian cell. This indicates that the virus is changing over time and caution needs to be taken over the use of these vaccines in humans.

*Yang et al., Nature 2004; 428: 561.
Yang et al., Proc Natl Acad Sci. 2005; 102: 797*

**Smallpox vaccine to be “fast-tracked”**

Acambis has announced that its ACAM2000 smallpox vaccine has been granted “fast-track” status by the US Government. This follows an extensive review of the safety of the vaccine after three volunteers were found to have inflammation of the heart. The Company has already delivered over 180 million doses of vaccine to the US Government and they already have “fast track” status for their MVA smallpox vaccine, a form designed for use in the elderly and in pregnant women.

**Production of Chiron influenza vaccine still suspended**

A further 3-month suspension of production of Chiron’s influenza vaccine, Fluvirin™, was enforced in December by the UK’s Medicines and Healthcare products Regulatory Agency. The Agency emphasised that no additional safety problems were involved but that the Company needed more time to complete the remedial work necessary. The suspension of production of Fluvirin™ in October 2004 had a major effect on the stocks of vaccine for the US, a major customer.

**GlaxoSmithKline Kline wins contract from US for supplying influenza vaccine**

The US Government has agreed to purchase 1.2 million doses of GlaxoSmithKline’s influenza vaccine Fluarix™. The vaccine will have to be used as an investigational new drug as it does not have approval for use in the US. This means that patients have to sign a consent form before receiving the vaccine.

**GlaxoSmithKline gains European approval for new vaccine for hepatitis B**

GSK Biologicals have developed a new vaccine (Fendrix™) for hepatitis B using a new adjuvant (MPL) from the US firm Corixa. A drawback to their established vaccine Engerix-B™ is the poor response seen in some patients with renal problems who have a poor immune system; in contrast Fendrix™ has increased immunoprotency in such patients and will only need to be given twice rather than three times. This is the first vaccine to be approved using the new adjuvant.

**More studies show no link between autism and MMR vaccine; doctor discredited**

A research team from the London School of Tropical Medicine and Hygiene (UK) reported their results recently of a large and comprehensive study designed to show if any link could be found between the development of autism and the use of the MMR (mumps, measles and rubella) vaccine in children. A general practitioner raised concern of such a link in the UK in 1998 and the adverse publicity surrounding this allegation has led to a drop in the uptake of the vaccine, with only 82% of children in the UK now receiving it. The study was published in the Lancet. Soon after, a television documentary was shown in which it was alleged that the doctor who made the original claims had filed a patent for the use of a single measles vaccine. The programme also claimed that much of the original work was of poor scientific merit. The Doctor’s work is currently under investigation by the General Medical Council in the UK and he currently resides in the US where he promotes products aimed at helping autistic children.

BMJ 2004; 329: 1254 and 1293*
Prions

Merck’s HIV vaccine enters Phase II

Merck is working in collaboration with the HIV Vaccine Trials Network (HVTN) to test their investigational HIV vaccine which has now entered Phase II. The vaccine will be tested in a ‘proof of concept’ study in North and South America, Australia and the Caribbean. The vaccine is based on a modified adenovirus which transports three synthetically-produced HIV genes into the mammalian cell.

BSE confirmed in a goat in France and suspected in a goat in the UK

A case of BSE has been confirmed in a goat slaughtered in France in 2002. The remainder of the herd were slaughtered and no other animals showed any signs of disease. Confirmatory tests on the infected goat have been performed in mouse bioassays. In view of this result the BSE testing of goats will be increased but no changes are planned in the current consumption of goat milk, cheese and milk from healthy animals. This is the first case of BSE confirmed in a goat.

As a result of this case, there is now a strong suspicion that another goat confirmed previously as having scrapie, a TSE normally affecting sheep, may have had BSE. Bioassays are needed to confirm this. These take about two years to complete.

First case of vCJD in Japanese patient

The Japanese Ministry of Health, Labour and Welfare announced on 4 February 2005 that a case of variant CJD had been confirmed in a Japanese patient. This is the first such case in Japan and the patient, who died in December 2004, had visited the UK in 1988. It is assumed that he contracted the disease while in the UK. There are restrictions in Japan on blood donors who have lived in the UK for more than one month. Between 2001 and 2004 there have been 14 cases of BSE in cattle in Japan; there is a strict regime for testing carcasses for BSE and no imports of beef or beef products are allowed from countries with BSE.

Prions found in many body organs

It had been assumed that the presence of abnormal prions causing BSE was restricted to the central nervous system and immune system but work published by Aguzzi, one of the leading experts in this field, reveals the disturbing finding that the prions can be detected in many other tissues. Aguzzi’s group had reported previously that they found prions in the muscles of humans with vCJD but this is the first time that this has been shown in animals. Mice infected with a TSE were used and an inflammatory response was created in the infected mice. This resulted in large amounts of prion being detected in a range of tissues (kidneys, pancreas, and spleen). It is hypothesised that the immune system responsible for the inflammatory response is helping the prions replicate.

Industry and Drugs

GSK and ViroLogic sign agreement on testing HIV drugs

ViroLogic is a biotechnology company located in California (US) and they have an assay system to identify patients infected with drug-resistant HIV. GSK (GlaxoSmithKline) has a number of promising candidates (especially entry inhibitors) for treatment of HIV infection. The two companies announced in February that they have entered into an agreement whereby ViroLogic’s assay methods will be used to identify patients for entry to trials and to monitor progress while on treatment with GSK’s drugs.
Editor of The Lancet criticises relationship between drug companies and journals

A House of Commons select committee on health (UK) is investigating the relationship between the media and drug companies. Various newspaper medical correspondents and the editor of The Lancet (Richard Horton) have given evidence to the committee. Comments were made that writers would like the regulatory process in the UK to be made transparent, whereas it is currently confidential. Richard Horton claimed that financial incentives were frequently offered to medical journals and that drug companies often attempt to exert pressure on journals to publish a paper. Some papers submitted, including review articles and leading editorials, have clearly been ‘ghost’ written by companies.

Eaton, BMJ 2005; 330: 9

Warning re co-administration of rifampin with saquinavir or ritonavir

Roche and the FDA have issued a warning that rifampin should not be given to patients who are also receiving HIV treatment with saquinavir and/or ritonavir. The combination carries the risk of liver damage; this was revealed in a Phase I study in volunteers who received 1000 mg saquinavir boosted with 100 mg ritonavir twice daily plus once daily 600 mg rifampin. Several volunteers developed drug-induced hepatitis, which was resolved when the drugs were discontinued.

Roche’s Pegasys™ approved for use in Switzerland for HBV

Roche’s pegylated interferon, Pegasys™, already marketed for the treatment of hepatitis C, has been granted approval for the treatment of chronic hepatitis B in Switzerland. Approvals are anticipated from the US and the EU.

New European pharmaceutical company launched

Archimedes Pharma is a new company launched by various ex-pharmaceutical company senior personnel. The new company’s first acquisition is the nasal drug delivery technology from the American company, West Pharmaceutical Services, purchased for 7.1 million dollars. The main investor, Warburg Pincus, has put 40 million dollars into the new company.

Pharma Times online 11 Feb 2005

European Matters

European Centre for Disease Prevention and Control appoints Director

The new European Centre for Disease Prevention and Control (ECDC) announced that Zsuzsanna Jakab has been appointed as the first Director. Jakab is Hungarian and has wide experience of international public health, having spent some years in the European office of the WHO since 1991. The ECDC, although welcomed by some, has been criticised by others as it has no laboratory capacity and will function via a network of experts in the control of disease throughout the EU.

The Scientist 22 Dec 2004

UK considers first antibiotic to be sold without prescription

The UK has traditionally been antagonistic to the principle of having antibiotics available to the public without prescription, but the Medicines and Healthcare products Regulatory Agency (MHRA) is now considering allowing chloramphenicol eye drops to be sold through pharmacies. The move is criticised by some who see it as a possible route to increasing resistance to the drug but the MHRA said that the situation would be monitored.

BBC News online 25 Nov 2004

Public health response to the tsunami

The tsunami which struck many Asian and east African countries on 26 December 2004 caused widespread damage and loss of life. The WHO Health Action in Crises network was activated in SE Asia to give an early warning of emerging disease threats. Within Europe, most national health ministries and public health institutes have issued news and advice to those returning from or travelling to the affected areas. Most of this advice is available online.

Eurosurveillance Weekly 2005; 10: 1

Dutch GPs protest at modernisation plans

The Dutch government is calling for modernisation of general practice but there are no plans to provide any funds for this. The plans include larger multidisciplinary practices and a market-driven health insurance scheme. In addition general practice is to be excluded from a new no-claim bonus scheme for public health insurance. The GPs are dissatisfied with the progress of discussions and have taken action by referring patients to hospitals sooner than previously and have held a rally attended by more than 3000 GPs.

Sheldon, BMJ 2005; 330: 326

Will Austrian medical schools be flooded by German students?

University education in Germany has been free for many years but following a recent decision that allows universities to charge, there are now plans to introduce fees in many German states. Austrian medical schools already have a small number of German students since the language is common and the countries are geographically close, but currently access is restricted to study for one year only. Following an EU decision, access will be open to all Europeans and it is now feared that there may be a great influx of more German students as the Austrian fees are low or non-existent.

Tuffs, BMJ 2005; 330: 328

Pamela Hunter
Medical Writer
Dear Colleagues and Friends

On behalf of the Organising Committee, we have the honour and pleasure to invite you to the 16th ECCMID to be held on April 1–4, 2006 in Nice, France.

In a world of increasingly mobile populations, whether for leisure or through necessity, international cooperation in all aspects of health is proving essential to control the spread of infectious diseases. Coordinated efforts in prevention and control, standardised diagnostic procedures and management, global surveillance and timely information sharing should provide the necessary tools to prevent or contain future epidemics. Examples such as the recent outbreaks of SARS or of avian influenza are there to warn us of the potential for new pandemics to arise, while re-emergence of diphtheria and whooping cough are a reminder that sustained prevention remains mandatory.

In such a context the 16th ECCMID will provide an opportunity to bring together participants involved in all aspects of infectious diseases to share their expertise and describe new developments in biomedical research, diagnostic procedures, vaccines, anti-infective agents and public health issues. The annual ECCMID is one of the largest international meetings on infectious diseases and microbiology. With thousands of participants, including clinicians, clinical microbiologists, biomedical scientists, public health specialists and trainees from over 80 countries, the ECCMID offers an interdisciplinary forum to share knowledge in a collegial atmosphere.

We are pleased that Nice has been selected to host the ECCMID 2006. Located on the French Riviera, in its spectacular setting between the Mediterranean shore and the Southern Alps, the city offers the unique combination of a French atmosphere with the Italian influence reflected in its architecture and traditional cuisine.

We warmly invite you to share and enjoy with us a stimulating scientific programme and the beauty of the “Costa d’Azur”!

Prof. Pierre Dellamonica
President of the 16th ECCMID

Prof. Marc Struelens
President of ESCMID

www.escmid.org/eccmid2006

Visit the 16th ECCMID website featuring:
- Continuously updated scientific programme
- Online abstract submission (deadline 17 November 2005)
- Online registration as well as hotel & tours reservations
- Option to compose your personal congress programme
- Details about the industrial exhibition
- Information on the congress venue and the city of Nice

For further information please contact:

Administrative Secretariat
16th ECCMID 2006
c/o AKM Congress Service
P.O. Box
CH-4005 Basel
Switzerland
Phone +41 61 686 77 11
Fax +41 61 686 77 88
E-mail info@akm.ch
Forthcoming ESCMID Events

More detailed information about ESCMID courses and conferences as well as general information about other events can be found on the ESCMID website at www.escmid.org under Courses & Workshops, ECCMIDs & Conferences, or Calendar of Events, respectively.

**ESCMID events**

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<tr>
<td>23–28 May 2005</td>
<td>31st ESCMID Postgraduate Education Course: 1st Training Course in Multilocus Variable Number Tandem Repeat-Genotyping of Mycobacterium tuberculosis</td>
<td>Institut Pasteur de Lille; Phone: +33 3 20 43 86 72; Email: <a href="mailto:marie-jose.truong@pasteur-lille.fr">marie-jose.truong@pasteur-lille.fr</a></td>
</tr>
<tr>
<td>20–21 June 2005</td>
<td>32nd ESCMID Postgraduate Education Course: Clinical Challenges in Diagnosis and Management of Atypical Pneumonia</td>
<td>Contact: Dr. Arta Balode; Email: <a href="mailto:a.balode@internet.lv">a.balode@internet.lv</a></td>
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<tr>
<td>25 June–2 July 2005</td>
<td>4th ESCMID School of Clinical Microbiology and Infectious Diseases</td>
<td>Contact: C&amp;T Hungary Ltd.; Phone: +36 62 548 485; Internet: <a href="http://www.congresstravel.hu/ESCMIDschool2005/">www.congresstravel.hu/ESCMIDschool2005/</a></td>
</tr>
<tr>
<td>1–4 April 2006</td>
<td>16th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)</td>
<td>Contact: AKM Congress Service; Phone: +41 61 686 77 11; Email: <a href="mailto:info@akm.ch">info@akm.ch</a></td>
</tr>
<tr>
<td>31 March–3 April 2007</td>
<td>17th European Congress of Clinical Microbiology and Infectious Diseases/25th International Congress of Chemotherapy (ECCMID/IJC)</td>
<td>Contact: AKM Congress Service; Phone: +41 61 686 77 11; Email: <a href="mailto:info@akm.ch">info@akm.ch</a></td>
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**Endorsed by ESCMID**

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<tr>
<td>6–7 May 2005</td>
<td>Crossing the Species Barrier: Place: Rovereto, Italy</td>
<td>Emmezeta Congressi, Milano; Phone: +39 02 6680 2323; Email: <a href="mailto:piera.guaglini@mzcongressi.com">piera.guaglini@mzcongressi.com</a>; Internet: <a href="http://www.mzcongressi.com">www.mzcongressi.com</a></td>
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<tr>
<td>11–14 May 2005</td>
<td>7th International Meeting on Microbial Epidemiological Markers (IMMEMY)</td>
<td>Place: Victoria, B.C., Canada; Contact: ASM Conferences; Phone: +1 202 942 92 61; Email: <a href="mailto:conferences@asmusa.org">conferences@asmusa.org</a>; Internet: <a href="http://www.asm.org/Meetings/index.asp?bid=27725">www.asm.org/Meetings/index.asp?bid=27725</a></td>
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<tr>
<td>24–26 May 2005</td>
<td>IACMAC Conference on Antimicrobial Therapy</td>
<td>Place: Moscow, Russia; Email: <a href="mailto:iacmac@microbiology.ru">iacmac@microbiology.ru</a>; Internet: <a href="http://www.iacmac.ru/iacmac/en/">www.iacmac.ru/iacmac/en/</a></td>
</tr>
<tr>
<td>8–9 June 2005</td>
<td>Challenges in HIV Infection</td>
<td>Place: Basel, Switzerland; Contact: AKM Congress Service; Phone: +41 61 686 77 11; Email: <a href="mailto:info@akm.ch">info@akm.ch</a></td>
</tr>
<tr>
<td>18–21 June 2005</td>
<td>4th International Conference on Rickettsiae and Rickettsial Diseases</td>
<td>Place: Logroño (La Rioja), Spain; Contact: Congresos e Incentivos Rioja; Phone: +34 941 202664; Email: <a href="mailto:cr@rickettsia.net">cr@rickettsia.net</a></td>
</tr>
<tr>
<td>13–14 October 2005</td>
<td>4th European Meeting on Molecular Diagnostics</td>
<td>Place: Scheveningen, The Hague, the Netherlands; Email: <a href="mailto:molecule@wens.nl">molecule@wens.nl</a>; Internet: <a href="http://www.wens.nl/molecule/">www.wens.nl/molecule/</a></td>
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**Imprint**

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