Section of a nematode showing Wolbachia bacteria (blue) concentrated in the lateral cords around the uterus and within the microfilariae (see page 42)
Dear Colleagues,

This edition of ESCMID News follows the recent, highly successful annual ECCMID meeting in Prague. In addition to the excellence of the congress and its venue, there have been a number of notable consequences. The process of developing a single European Congress in Microbiology and Infectious Diseases has taken an important step forward by the agreement between ESCMID and the International Society for Chemotherapy to hold a joint congress in Germany 2007.

One of the integrated symposia in Prague highlighted the current concerns over the rapid decline in antibacterial drug development which appears to be linked to not only the difficulties in developing traditional “blockbuster” agents with broad indications but also to the recent major industrial mergers and the greater emphasis on developing drugs for chronic diseases such as HIV, hepatitis C and lifestyle-associated disorders. This has been compounded by the failure to deliver genomic based products and the increasing regulatory and economic hurdles required for licensing and marketing.

In June, the Society organised an important 2-day workshop in Stockholm in which these issues were further discussed and developed by speakers expert in drug development, licensing, clinical trials and clinical practice. The press coverage of this meeting was impressive. The Society is considering a position paper on this topic.

A particular issue that underscores the need for new solutions is the rapid emergence of resistance among community Escherichia coli, which although multifactorial has been most recently linked to extended spectrum beta-lactamase production in the UK, France and Italy, among other countries. The significance of this issue has recently become apparent in relation to the treatment of urinary infections where the only effective oral agents have sometimes been limited to nitrofurantoin and fosfomycin.

The pathogenic role of superantigens in causing a repertoire of staphylococcal disease is widely recognised. However, the speed with which new antigens are being identified has rapidly increased. For example, by 2000 the number of enterotoxins identified was 10 (designated alphabetically A–J). Sequence data has since expanded the number by a further 5, but the vagaries of the time to publication of the original research has required the revision of designation of the more recent enterotoxins SEK, SEL, SEN and SEO. The international nomenclature committee for staphylococcal superantigens has recently proposed a procedure for newly described antigens compatible with this age of genomics.

The Society has input to the Advisory Group of the EU 6th Framework Programme for Research and Technological Development. It is pleasing to see that the recently published 3rd call includes a number of topics of direct interest to members, such as “Lower Respiratory Tract Infection” (Network of Excellence); Mobile genetic elements and resistance genes (Specific Targeted Research Project, STREP) and Ecological factors impacting on fitness/virulence/resistance (STREP). Many of you will be busy over the next few months preparing your submissions for the November deadline.

This edition of ESCMID News has much of interest and provides a snapshot of the enormous energy and vitality of the Society and its membership. I draw your attention to the announcement of a new award sponsored by bioMérieux (page 10); an update on the progress being made by EUCAST in conjunction with European national breakpoint committees (page 26); and revised affiliation scheme for national societies of clinical microbiology & infectious diseases which was discussed and supported at the recent European Council (page 8) and which will be introduced shortly. This will create a real opportunity for the professional and scientific societies in Europe to raise issues within a central forum where they can be carefully considered and if supported become part of the future policy and strategy of ESCMID.
Message from the President

Marc Struebels

Dear Colleagues,

Last spring, the 14th annual edition of the ECCMID achieved great success, attracting over 6500 participants and staging 2500 communications on the latest developments on a broad range of topics in microbiology, infectious disease and public health. Let me thank many of you for your active participation and our sponsors for their support that made this success possible. I also wish to thank Prof. Jarmila Jelinkova for her charming hospitality and the National Committee for contributing to the superb scientific programme developed by the Programme and Organising Committees led by Prof. Patrick Francioli. To recognise outstanding accomplishments of European scientists and encourage young investigators, several awards and fellowships were presented at the last ECCMID, as reported in this issue, which also provides information on new awards open for nominations. We were privileged to hold the congress in the ancient city of Prague on the historical day when the Czech Republic and nine other countries joined the European Union, bringing together more closely the destiny of 450 million people speaking 20 different languages. Europe, as a political concept in search of itself, is in tension between dream and deed. To quote Friedrich Nietzsche: “The continuous repetition of a dream may well turn it into a reality felt and judged”, as we increasingly realise as European citizens. Our congress bore testimony to the enthusiasm of the infectious diseases and microbiology community to work together in advancing science and creatively addressing the challenges we are facing.

During the congress, the meetings of the ESCMID European Council and Assembly of Members were well attended and gave the opportunity for lively debates on a number of important issues and proposals (see Minutes pages 4 and 8). The reform of the Council was adopted and will be implemented during the coming months to develop stronger links with national and continental organisations active in the infection disciplines. On the other hand, a proposed statutory amendment on the duration of senior officers’ terms in the Executive Committee was turned down for the sake of preserving continuity and visibility of the President as figurehead of the Society. These debates indicate the democratic maturity of our Society as we are striving for the best balance between efficacy and accountability.

As reported in this issue, progress was also made in Prague towards building concrete partnership with several major organisations. An agreement was signed with the International Society for Chemotherapy to hold a joint Congress in 2007 in Germany, to be named 17th ECCMID/25th ICC (page 21). A Memorandum of Collaboration was signed with the Federation of European Microbiology Societies (FEMS) inaugurating joint initiatives such as research fellowships, symposia and cutting-edge scientific meetings (page 25). ESCMID also participated in the preparation of a proposal entitled “Improving Patient Safety in Europe (IPSE)”. This collaborative programme linking the EU, WHO, professional organisations, academic institutions and public health institutes aims at improving surveillance, prevention and control of healthcare-associated infections and antimicrobial drug resistance, notably by means of improved professional training. It has now been selected for funding by the DG SANCO programme of the European Commission.

The Society’s publication Clinical Microbiology and Infection has almost doubled its latest impact factor. As explained by the Managing Editor Judith Crane (page 15), this remarkable progress is the fruit of the quality of authors’ contributions and of the editorial work of previous years, particularly that of Prof. Emilio Bouza and the Madrid team of editors. We are most pleased to recognise their accomplishment on behalf of the Society. I have no doubt that CMI will further progress in quality and impact under the current Editor-in-Chief Dr Kevin Towner and his team. The time to publication of accepted papers has now been significantly shortened and this makes the journal increasingly attractive for authors and readers alike.

In the burning field of antimicrobial resistance, ESCMID helped review the research priorities during an EU conference co-organised with DG Research last November in Rome and the conclusions of which appeared in CMI in April. We are pleased to note that the third call for proposals under the 6th Framework Programme (http://fp6.cordis.lu/fp6/call_details.cfm?CALL_ID=148) included several of the research needs and opportunities identified at this conference. The current trend toward decreasing anti-bacterial drug research and development programmes in major pharmaceutical companies is cause for concern. This issue was addressed in depth at an ESCMID international symposium held in Stockholm last June with participants from academia, industry and regulators (see page 22). ESCMID is willing to contribute to creative approaches to support the pre-clinical and clinical development of novel anti-infective drugs where needed as well as public-private cooperation in fostering appropriate use of the drugs that we have at hand.

Marc Struebels
ESCMID President
Assembly of Members 2004

Minutes

1 WELCOME
Marc Struelens welcomed the 135 attending members to this largest Assembly since many years. He observed that the minutes of last year’s Assembly have been published in ESCMID News 2-2003 and that the invitation to the Assembly 2004 had been correctly sent out as stated in the Statutes. The proposed agenda was accepted without objection.

2 PRESIDENT’S ADDRESS AND REPORT
In the reporting period the Society has again extended its range of activities and reached more people than before. Marc Struelens mentioned with great pleasure that this ECCMID not only seems to be the largest in history but that in the previous year some 500 people, mostly young professionals, have enjoyed educational activities organised or supported by ESCMID. Important achievements in 2003 were the securing of the Society’s finances, as will be explained by the treasurer, and that we are making progress in establishing cooperation with related partner organisations:

i) with the International Society of Chemotherapy (ISC) an agreement was reached to organise in 2007 a joint congress, called 17th ECCMID/25th ICC, in Germany;

ii) with the Federation of European Microbiological Societies (FEMS) a Memorandum of Collaboration was signed concerning joint educational activities and fellowships.

Comment by Jean-Claude Piffaretti, Bellinzona, Switzerland: as FEMS liaison officer for ESCMID, Jean-Claude Piffaretti expressed his satisfaction about the Memorandum and confirmed the commitment of FEMS to work with ESCMID to achieve common goals in microbiology in Europe.

3 REPORT OF THE SECRETARY GENERAL
According to figures presented by Giuseppe Cornaglia, ESCMID has currently 2730 regular members. This is 300 more than at the same time last year which is very encouraging. The best-represented country is the UK with 200 members, followed by Germany, Italy and the US. Especially pleasing is the remarkable increase in the number of members from Russia. As explained in more detail at the European Council meeting on May 1 Giuseppe Cornaglia then summarised the proposal for a new European Council and a revised affiliation scheme: all European specialist societies in the infection field will be invited to sign an affiliation agreement with ESCMID. This entitles them to become members of the ESCMID European Council and to receive an electronic information bulletin for distribution to their members three times per year. The European Council shall meet during ECCMID, preferably on Saturday afternoon prior to the opening of the congress, be comprised of the affiliated societies’ presidents (or their nominees) and be chaired by the ESCMID President. The main objective of the proposal is to upgrade the European Council to a forum which drives an agenda to strengthen the cooperation and cohesion among the European specialist societies and to address the professional challenges in Europe. The annual costs for affiliation are between EUR 50 and EUR 250 per society, depending on their size.

Question by Panayotis Tassios, Athens, GR: What about ESCMID Study Groups? Answer: The Study Groups are considered to be part of ESCMID. Their concerns should be represented by the Science Advisory Committee and the Scientific Affairs Officer. We thus don’t see a need to include the ESCMID Study Groups in the Council.

Question by Richard Bax, London, UK: What is the reason for wanting a President for one year only? Answer:

4 REVISION OF THE STATUTES
Marc Struelens pointed out that only the proposed changes of the Statutes, which are highlighted in the distributed document and on screen, are open to decision. He explained them one-by-one:

i) Allowing for a corporate membership ($3). No request to speak.

ii) Executive Committee ($4):

– Past President to become a normal member of the Executive with regular voting rights. No request to speak
– Term in office of the President, President-elect and Past President to be reduced from two years to one year.

Answer: We cannot force the societies to organise elections. How they nominate their representatives is their business.

Proposal by Martin Steinbakk, Nordbyhagen, NO and Hilary Humphreys, Dublin, IE: The affiliated societies should be represented in the European Council by their presidents or a nominee. Asking for permanent nominees is asking for too much. Giuseppe Cornaglia agreed with the proposal as did obviously the majority of the audience.

Question by Hajo Grundmann, Bilthoven, NL: Can “networks” also participate? Answer: In principle, yes. If their participation is considered relevant to advance professional affairs in Europe they should be able to join the European Council.

Question by Hartmut Lode, Berlin, Germany: The number of societies in each country differs considerably across Europe. How do you prevent an imbalance in the European Council? Answer: All regular societies with statutes and activities in the infection fields should be able to apply. The European Council should primarily be a forum to interact, discuss, plan and coordinate activities and not to vote on controversial issues. The Council itself has no legal power. We thus think that a certain national imbalance can be accepted.

Proposal by Panayotis Tassios, Athens, GR: What about ESCMID Study Groups? Answer: The Study Groups are considered to be part of ESCMID. Their concerns should be represented by the Science Advisory Committee and the Scientific Affairs Officer. We thus don’t see a need to include the ESCMID Study Groups in the Council.

Question by Richard Bax, London, UK: What is the reason for wanting a President for one year only? Answer:
An important argument is the fact that a shorter term will limit the total duration of successive mandates in the Executive and allow more countries to come forward with a President. In addition, running the Executive is a team affair. As President-elect and Past President there are also many opportunities for contribution.

Comment by Michel Glauser, Lausanne, CH: The proposal deserves support. ESCMID has matured. The professional infrastructure and support by the Executive Office guarantees continuity and allows for a shorter presidential term.

Comments by Hartmut Lode, Berlin, DE; Fernando Baquero, Madrid, ES; Ian Phillips, Malaga, ES; Gunnar Kahlmeter, Växjö, SE: They all were against a shorter term, invoking similar arguments: running the Executive is a delicate task which requires balancing out different subjective and national interests. One risks finishing his/her term before really having achieved this. Being President is a mandate and not an honorary position. A strong President is needed as there are still plenty of challenges ahead. Presidents popping in and out too frequently would not even be recognised by many members of the Society.

Comment by Matthew Falagas, Athens, GR: The actual term according to the proposal must be seen as one of 3 years: President-elect, President, and Past President. If the Executive works as a team an individual can achieve quite a bit during this period. IDSA is doing well with a one-year arrangement.

Comment by Roger Finch, Nottingham, UK: The Executive was not unanimous about the proposal. It actually relates to the style of an organisation. Being an effective President involves a learning process.

Proposal by Pramod Shah, Frankfurt, DE: The proposed changes of the Statutes refer to different issues. He proposed to vote on each of them separately or to postpone the decision about presidential term in office by one year. Marc Struelens recommended to vote on each of the three issues separately but opposed postponing any of the decisions on agenda items.

iii) Revision of the European Council and affiliation scheme as explained by Giuseppe Cornaglia. No requests to speak.

5 PROPOSAL OF NEW MEMBERSHIP FEES
The proposal as it was communicated to the entire membership with the invitation to the Assembly was as follows: With this change the Executive wants to achieve, as explained by the President, that the membership fees for young and retired members cover at least the subscription for CMI and also contribute a small amount to the other costs of the membership services. This is currently not the case. The reduced fee for members choosing the print edition of CMI results even in a substantial deficit.

Marc Struelens summarised the revision of Statutes as decided by the Assembly: the President’s term of office will remain two years; the nominees representing the affiliated societies in the European Council are not required to be “permanent”; all other amendments as proposed by the Executive were approved.

6 APPROVAL OF THE REVISED STATUTES (VOTE)
Marc Struelens asked for hand votes on the proposed changes of the Statutes as explained before:
1) Are you in favour of postponing the decision about the term of the President (proposal by Pramod Shah)?
   Yes: 6; No: vast majority
2) Do you agree with the allowance of a corporate membership (§3)?
   Yes: vast majority; No: 2; Abstentions: 2
3) Do you agree with the proposed change of §4 concerning the one-year term of the President?
   Yes: 9; No: vast majority; Abstentions: 5
4) Do you agree with the other proposed changes of §4 (including the revised European Council consisting of the affiliated societies’ presidents or nominees (omitting “permanent”)?
   Yes: vast majority; No: 2; Abstentions: 2

7 APPROVAL OF THE NEW MEMBERSHIP FEES (VOTE)
Marc Struelens asked for the hand vote on the new membership fees as explained above: do you agree with the proposed increase of the reduced rate of the ESCMID membership fee from EUR 40 to EUR 65 (CMI print & online) and from EUR 33 to EUR 37 (CMI online)?
Yes: vast majority; No: 13; Abstentions: 2

8 PRESENTATION OF THE ESCMID RESEARCH FELLOWSHIPS
The ESCMID Research Fellowships 2004 were presented by Roger Finch, Past President and Chairman of the Award Committee, to:
- Roy Sleator, PhD, born 1975, Department of Microbiology, BioSciences Institute, University College, Cork, Ireland. He has also been selected to receive the first joint ESCMID/FEMS Research Fellowship.
- Jean-Denis Doquier, PhD, born 1974, Centre for Protein Engineering, University of Liège, Liège, Belgium.
- Laurent Poirel, PhD, born 1969, French National Institute of Health and Medical Research (INSERM), Department of Microbiology, Hôpital Bicêtre, University Paris XI, Paris, France.

Roger Finch congratulated the recipients (applause) who were given each a cheque of EUR 5000.

<table>
<thead>
<tr>
<th>Membership</th>
<th>current fees (EUR)</th>
<th>new fees (EUR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual full, regular rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CMI print &amp; online</td>
<td>85</td>
<td>85 (unchanged)</td>
</tr>
<tr>
<td>- CMI online</td>
<td>57</td>
<td>57 (unchanged)</td>
</tr>
<tr>
<td>Individual full, reduced rate*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CMI print &amp; online</td>
<td>40</td>
<td>65</td>
</tr>
<tr>
<td>- CMI online</td>
<td>33</td>
<td>37</td>
</tr>
</tbody>
</table>

*: for young (<35 years) and retired members
9 FINANCIAL REPORT OF THE TREASURER

Andreas Voss presented the preliminary profit and loss accounts and the balance sheet for the year 2003. In contrast to the previous year, the Society has balanced accounts this year: total expenses, including a reserve of EUR 100’000 for tax payments, of EUR 811’615 are nearly balanced by revenues of EUR 797’233. The reason for this satisfactory result is a higher surplus from the 13th ECCMID in Glasgow, a more restrictive cost management and regular budget controls.

The balance sheet showed a profit carried forward of EUR 813’378. This corresponds roughly to the annual financial needs of the Society and provides security in case of a large financial “catastrophe”.

10 FORMAL APPROVAL OF THE ACCOUNTS (VOTE)

Marc Struelens asked for a hand vote of approval of the financial report. It was approved unanimously.

11 REPORT OF THE EDUCATION OFFICER

Carl Erik Nord, CMI Supplement Editor, gave the educational report on behalf of Claude Carbon who apologised for not being able to attend the Assembly.

In 2003 the following educational activities were held:

i) 2nd ESCMID School, Utrecht, NL, June 28 – July 4, 2003 (organised by the ESCMID Education Committee, 31 students attended)

ii) Four Postgraduate Courses or Workshops were held under the auspices of and supported by ESCMID:
- Challenges in HIV Infection, Basel, Switzerland, May 7–8, 2003 (organised by the Swiss Society of Infectious Diseases)
- Measuring, Auditing and Improving Antimicrobial Prescribing, Troon, Scotland, May 9–10, 2003 (organised by ESGAP)
- Training Course in Hospital Epidemiology, Antalya, Turkey, November 5–9, 2003 (co-organised by ESGN and SHEA)
- Role of Clinical Microbiology in the Management of Community-Acquired Infections, Smolensk, Russia, December 12–14, 2003 (co-organised by IACMAC and ESGARS)

The activities in the current year include the 3rd ESCMID School to be held in Athens, six Postgraduate Courses or Workshops, and four pre-ECCMID Teaching Courses. Furthermore, CARRINE, a Network of Excellence on antibiotic resistance in respiratory infections, in which ESCMID and ERS would be responsible for the educational platform, is being revised for re-submission to DG Research.

Exploratory activities are ongoing concerning possible funding of at least part of ESCMID’s educational activities through the Marie Curie-Programme of the European Commission.

12 REPORT OF THE PROFESSIONAL AFFAIRS OFFICER

CLINICAL MICROBIOLOGY

Elisabeth Nagy reported that EBACM (European Board for Accreditation of CME in Clinical Microbiology), a joint venture of UEMS and ESCMID, has been implemented and has already accredited several educational activities. The Board consists of 3 members from the Microbiology Commission of the UEMS Section for Medical Biopathology and 2 members from the ESCMID Executive.

The ESCMID workshop held in Leuven in March 2004 (see item 14 below) addressed many key professional issues awaiting resolution. A position paper is in preparation for publication later this year.

There is still a lack of reliable data from individual countries on the status of CM, especially in Eastern and Central Europe. A questionnaire addressing this deficiency is in preparation in order to collect information, as e.g., on the recognition of the specialty, subspecialties, degrees obtainable, training programmes, admission to training, CME systems, etc. across Europe.

13 REPORT OF THE PROFESSIONAL AFFAIRS OFFICER
INFECTIOUS DISEASES

Ragnar Norrby reported that he will also work on the questionnaire as outlined by Elisabeth Nagy. One of his main concerns was to include also infection control, paediatric ID and hospital epidemiology. This should eventually be reflected in a core curriculum starting with a common training for all ID specialists and allowing sub-specialisation in the mentioned disciplines at a later stage.

14 REPORT OF THE CHAIR OF THE EU TASK FORCE

At the Assembly 2003 Marc Struelens announced that ESCMID has initiated an EU Public Affairs Programme with the objective of establishing a dialogue with EU institutions to ensure input of ESCMID members and support the Society’s activities. This initiative has resulted in a number of promising activities:

Professional Affairs:
- Leuven Workshop, March 17–19, 2004, “Progress toward Meeting the Challenges in Clinical Microbiology and Infectious Diseases”. A Consensus Declaration addressing the needs and means in these fields is soon to appear.

Public Health:
- EUCAST: 60% funding by DG SANCO during 2004–2007
- ESCMID is a partner of EU-funded projects: ESAC, EARSS
- Partner for 2nd call applications: EU-REQUAS, IPSE
- European CDC: position paper published, liaison with the European Commission, permanent representatives of member states and members of the European Parliament

Science:
  A comprehensive meeting report has been published in CMJ.
- Partner in CARRINE application
- Partner in European Science Foundation Report on “Research in Infectious Diseases”

In summary, ESCMID has acquired an advisory role on EU research and health policy issues. We will closely monitor progress in cooperation with UEMS, the European Commission and others. A continuing obligation will be the promotion of the recognition of CM and ID across Europe.
16 REPORT OF THE CHAIR
OF THE PUBLICATION
COMMITTEE

In his report as Chair of the Publication Committee Roger Finch first thanked Kevin Towner, the new CMI Editor-in-Chief, for the transition which he and his dedicated team successfully mastered. In 2003 Carl Erik Nord has taken responsibility as CMI Editor for supplements which is important for the economics of the Journal. The submission rate has increased in 2003 by some 30%. This positive trend and an inherited backlog of accepted papers from the previous editor have made it necessary to increase rejection to the current rate of 52%. The still too long publication time and the rejection rate will normalise before the end of 2004. In February 2004 EarlyOnline has been introduced by Blackwell. Through this feature manuscripts are made available to subscribers a few days after acceptance. In 2003 the number of personal and institutional subscriptions only slightly increased. A large increase of 67% however was noted in the online readership. This is indicative of good visibility and penetration of CMI which will eventually result in a higher impact factor.

17 REPORT OF THE PRESIDENT AND PROGRAMME DIRECTOR
OF THE 14th ECCMID

Jarmila Jelinkova, President of 14th ECCMID, briefly reviewed a most successful Congress, which was attended by 6609 participants (including the exhibitors’ personnel and accompanying persons) from 89 different countries. This made the 14th ECCMID the largest ECCMID ever. She thanked her many colleagues in the Czech Republic and abroad who made this success possible.

Patrick Francioli, CMI Programme Director, reviewed the scientific programme which comprised 126 scientific sessions. The integrated symposia arranged by the industry are enriching the programme and are a sign of good health. A record number of 2644 abstracts have been received, 7% of which were accepted for oral presentation, 56% for poster presentation, and 19% for publication in the abstract book. This last category was primarily introduced for practical reasons as space for only 3 x 500 posters was available.

Jarmila Jelinkova then handed over the “challenge cup” to the President of the 15th ECCMID 2005, Niels Hoiby from Copenhagen. This cup is a silver plate with the engraved ESCMID logo and list of all ECCMID venues since 1983. Niels Hoiby thanked her for her achievements and praised this most charming ceremony. He is aware of the heavy burden and promised to do his best to make “his” Congress as successful as “hers”.

18 RELEASE FROM RESPONSIBILITY
OF THE EXECUTIVE COMMITTEE

Marc Struelens asked for a hand vote about the exoneration of the Executive Committee. This was approved unanimously.

19 ANY OTHER BUSINESS

No request to speak.

CLOSE OF THE MEETING

Marc Struelens thanked the Members for attending. He adjourned the meeting at 13:45 h.

Basel, June 10, 2004

Signed,

Marc Struelens, President

Giuseppe Cornaglia, Secretary General

Peter Schoch, Managing Director

New Statutes and Bylaws

The ESCMID Statutes and Bylaws have been revised taking into consideration the decisions made during the Assembly of Members in Prague. They are published on the ESCMID website at www.escmid.org. ESCMID, for those who want to look at them.
MEETING DURING
14TH ECCMID 2004, PRAGUE, CZECH REPUBLIC, ON MAY 1, 2004 AT 14:00 H

1 WELCOME AND PRESIDENT’S ADDRESS
Marc Struelens welcomed the 75 participants to the meeting of the European Council 2004. He noted that the meeting agenda was distributed on time and that the meeting minutes for 2003 were published in ESCMID News 3-2003. The proposed agenda was accepted without objection. This year’s meeting is of special importance as we are going to propose a new constituency and function of the European Council which is linked to a revised affiliation scheme for European specialist societies. This will be explained later by the Secretary General, Giuseppe Cornaglia. Not only this proposal for a new European Council but all our activities in 2003 must be seen in the context of ESCMID’s mission to improve public health in Europe through the promotion of education, research and professional affairs. In his opening address Marc Struelens briefly reviewed the main achievements in 2004. For a more complete account of the Society’s activities he referred to the Assembly of Members (minutes published in this ESCMID News).

Addressing “Education” he referred to ECCMID which is expanding the number of pre-ECCMID teaching courses and meet-the-expert sessions. The number of travel grants and free registrations reached a record number of 104 this year. Last year some 500, mostly young professionals participating in ECCMID, ESCMID School or Postgraduate Courses or Workshops enjoyed direct or indirect support by ESCMID. ESCMID’s scientific “branch” is the 12 study groups. For their activities and membership regulations see our homepage. Several study groups are currently running clinical and other studies, are engaged in educational activities or are developing practice guidelines. Another asset that deserves to be mentioned is the Society’s scientific journal Clinical Microbiology and Infection (CMI). CMI currently receives a record number of submissions and has just gone through the successful transition to a new editorial team. Under the title “Professional and European Affairs” Marc Struelens referred to the recent Leuven workshop in March 2003, during which the challenges in our disciplines were discussed as they relate to specialist training, CME, needs and models for healthcare services as well as to infectious disease surveillance, alert and response systems. Another successful endeavour is EUCAST, the European Committee for Antimicrobial Susceptibility Testing, which works under the umbrella of ESCMID towards the harmonisation of methodology and breakpoints in Europe. It is receiving financial support from the European Commission (DG SANCO) for three years starting May 2004. For a society like ESCMID, partnerships are important as no organisation can achieve major advances on its own. Marc Struelens was pleased to note that effective cooperative relationships exist between ESCMID and UEMS, FEMS, ISC, ASM, SHEA, DG SANCO and DG RTD from the European Commission and European societies such as ERS, ESICM and others.

2 PROPOSAL OF A NEW AFFILIATION SCHEME AS BASIS OF A RENEWED EUROPEAN COUNCIL
Affiliation is a special relationship between European specialist societies and ESCMID with the objective to cooperate and promote the wider interests of both organisations. A year ago the Executive decided to terminate the current pilot affiliation with three societies and to propose a revised scheme that supports the general principles of affiliation and is cost neutral for ESCMID. This revised scheme, which will be offered to all European societies active in the infection field, is linked to a renewed European Council. It was presented by Giuseppe Cornaglia, Secretary General. ESCMID’s natural partners to advance science, education and professional affairs in Europe are the national and other European specialist societies. This goal shall be pursued by a renewed European Council consisting of societies affiliated with ESCMID. The relevant paragraph in the new Statutes proposed to the ESCMID members for adoption at the Assembly 2004 reads as follows:
The European Council shall strengthen the cooperation and cohesion among the European specialist societies in the infection field and serve as an advisory board to the Executive Committee. Its constituent members are the European societies which signed an affiliation agreement with ESCMID. Each affiliated society is represented in the European Council by its President or a nominee. Affiliation is subject to approval by the Executive Committee. The European Council shall meet during the annual congress of the Society. The President of the Society shall serve as chairperson. In other words, all European national and continental specialist societies active in the fields of microbiology, infectious diseases and related disciplines will be invited to become affiliated with ESCMID. UEMS, EU-supported research networks, or similar organisations are also eligible for affiliation. Any application for affiliation must be approved by the ESCMID Executive Committee. Giuseppe Cornaglia made clear that ESCMID does not exert any external control on the affiliated societies’ organisation, activities and internal electoral procedures through affiliation. On the other hand, membership to the ESCMID European Council does not give affiliated societies the right to interfere with the ESCMID organisation, activities and internal electoral procedures. The European Council meets at least once a year, preferably on the ECCMID opening day. The inherent travel and accommodation expenses are not borne by the ESCMID. It is foreseen that the agenda of the European Council meeting is developed under the responsibility of the Secretary General with the active participation of the affiliated societies, and sent out at least 4 weeks prior to the meeting. The ESCMID President acts as chairperson. The Secretary General acts as the Council’s secretary and gives a progress report of the activities...
and achievements related to the European Council during the past year. Recommendations prompted by the European Council and the complete minutes of the Council meetings, signed by the ESCMID President and Secretary General, are published in ESCMID News and in the abridged version dispatched to all affiliated societies for distribution among their members.

The benefits to affiliated societies are related to the advancement of their professional objectives:

i) Membership to the ESCMID European Council

ii) Individual members become affiliated ESCMID members

iii) The affiliated societies are entitled to receive an abridged version of ESCMID News as an electronic information bulletin 3 times a year by e-mail (May, September, January) as well as electronic mailings about professional issues of general interest

iv) Subscription to CMI at a preferential rate

v) Section in ESCMID News and ESCMID web site to announce and report on activities of affiliated societies

vi) Co-organisation of ESCMID educational events.

According to Giuseppe Cornaglia the fees and requirements for affiliation are modest in order to allow many European societies to enter into a cooperative relationship with ESCMID:

i) The mailing process is decentralised through the affiliated societies which are responsible for distributing the information provided by ESCMID among their individual members.

ii) Annually affiliated societies provide ESCMID with the name of the formal representative to the European Council and with the updated number of individual members.

iii) Annual affiliation fee per society: EUR 50 (<300 members), EUR 100 (300 to 1000 members) or EUR 250 (>1000 members).

In summary, the main objective of the revised affiliation proposal is to upgrade the European Council to a forum which drives an agenda to strengthen the cooperation and cohesion among the European specialist societies and to address the professional challenges in Europe.

Question by Hilary Humphreys, Dublin, Ireland: Since the new European Council is more focussed on active participation than on representation he was wondering

i) whether membership to FEMS affects membership to the European Council, and

ii) how ESCMID responds to the situation that some countries have many national societies and would thus have many representatives in the European Council.

Answer: Giuseppe Cornaglia does

i) not see a conflict between FEMS membership and membership to the European Council, and

ii) also foresees a certain national imbalance between the number of representatives from different countries. Since the European Council as a discussion forum has no executive power such an imbalance is acceptable.

Proposal by Robert Read, Sheffield, UK: Since some countries might have up to ten representatives and others only one he recommended that the voting power of the representatives is graded according to their membership counts. Answer by Marc Struelens: The European Council is not a federation; votes on political issues are not foreseen.

Proposal and question by Pramod Shah, Frankfurt, Germany:

i) the proposed European Council might become the “European Parliament” for professional and public health issues in the infection disciplines. Rules should therefore be established for the voting process.

ii) What are the rules for accepting European societies to become members to the European Council?

Marc Struelens answered that rules for formal votes might be considered in the future should this be required. Regarding the rules for accepting new members of the Council Giuseppe Cornaglia mentioned that we will adopt a liberal approach: each established society with statutes and proven activities will be invited to become a member.

Comment by Teresita Mazzei, Italy: She expressed her concern that the European Council will be an ineffective discussion forum devoid of real power. Peter Schoch answered that ESCMID wants to remain a society based on individual membership and not become a federation. Our individual members have the full power to vote at the Assembly. The Council however has no executive power and is a forum to discuss, plan and coordinate professional activities and initiatives. Giuseppe Cornaglia promised that we will encourage the members of the European Council to make real contributions to the agenda of the Council meeting next year.

Comment by Giorgio Palu, Padua, Italy: He was wondering who is lobbying on behalf of the professional community in the infection disciplines in Brussels if not ESCMID, especially taking into consideration that so many networks and pressure groups are present in Brussels. Answer: Marc Struelens replied that ESCMID is indeed the natural platform to unify all these players and provide them a voice in Brussels. Lobbying activities based on consensus propositions of the Council are no problem. If controversies prevail the decision about future action must be left to the Executive. According to the statutes the Executive is responsible to the Assembly and not to the Council. Should the European Council prove to become an active forum and need a more legal voice and stronger representation in the Executive the rules would need to be reviewed at a later stage.

Proposal by Pramod Shah, Frankfurt, Germany: Why not allow the European Council to elect its own chairperson to strengthen its authority? Answer by Giuseppe Cornaglia: This is a proposal that we might consider in the future.

Question by Jan Kazar, Bratislava, Slovak Republic: He was asking for more information about the position of ESCMID concerning the planned European CDC. Marc Struelens answered that ESCMID has issued a position paper which has been published in ESCMID News and on the website. It has also been sent to many key persons in the European Union. Several points have been taken into consideration in the final decision on the organisation and activities of the ECDC as reported in ESCMID News 1-2004. In addition, the 14th ECCMID scientific programme features several talks addressing this issue.

Comment by Elisabeth Nagy, Szeged, Hungary: She expressed her strong
support for a more relevant European Council. This is especially important to Central and Eastern European countries. The European Council will improve their information and offer a platform for their interacting with the rest of Europe.

Comment by Milena Svabic-Vlahovic, Belgrade, Serbia-Montenegro: With the current proposal the Serbian microbiologists and infectious disease specialists would not be adequately represented in the European Council since the relevant Serbian society is essentially an agricultural society.

Answer by Giuseppe Cornaglia: In your case the representative should obviously not be the President of your society but a nominee who is able to adequately represent the infection disciplines of your country.

Comment by Alexander Firsov, Moscow, Russia: He expressed mixed feelings about the proposed system. What are the criteria to accept or reject applications for affiliation? In many former socialist countries there still exist “mock societies” without real agendas and democratic legitimation.

Marc Struelens answered that caution is well taken and that we will go through a learning process. We will certainly have to look carefully at the applications and ask for statutes and activities. It is our goal to get the real representatives of the active and relevant national societies into the Council.

3 TOWARDS A SINGLE EUROPEAN CONGRESS IN THE INFECTION DISCIPLINES

Marc Struelens delivered the good news that the International Society of Chemotherapy and ESCMID have agreed to organise a joint congress in 2007 in Germany. The congress shall be called 17th ECCMID / 25th ICC 2007. By this an undesirable waste of resources, competition and programme overlap can be avoided.

The agreement between the two societies specifies the rationale for organising a joint congress and defines the organisational, financial and contractual arrangements.

This will be the first joint congress in the infection disciplines organised by two large societies in Europe. To mark this historical moment a Memorandum of Understanding was publicly signed by Jean-Claude Péchère, ISC President, and Marc Struelens, ESCMID President. (For a facsimile of the Memorandum and picture of the signing ceremony see page 21 of this ESCMID News). Future negotiations will show whether this model can be extended to joint ECCMID / ECCs in the following years.

4 ANY OTHER BUSINESS

No requests to speak.

Marc Struelens thanked the participants for the interesting discussion and adjourned the meeting at 16:00 h.

Basel, June 13, 2004

Marc Struelens
ESCMID President

Peter Schoch
Managing Director

bioMérieux and ESCMID Award 2005 for Advances in Clinical Microbiology

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) is pleased to announce an award of EUR 10'000 sponsored by bioMérieux to recognise excellence and/or major contributions to progress in clinical microbiology by young scientists from Central and Eastern Europe.

The award expresses the shared mission of ESCMID and bioMérieux to advance laboratory practice of clinical and diagnostic microbiology across Europe.

Application

Nominations of Central and Eastern European scientists born in 1964 or later are to be submitted in writing. They must contain a description of the nominee’s career, his/her postal and email address, place and date of birth, list of publications, research interests and major contributions to the development of clinical microbiology. Two supporting letters from outside the nominating institution must be included. Self-applications will not be considered. Seven copies of all materials, plus one colour photograph (on paper or electronically as tif, jpg or eps file) must be sent to the ESCMID Award Committee.

The selection of the recipient will be made by the ESCMID Award Committee. Members of the ESCMID Executive Committee are ineligible. No correspondence beyond that necessary for the application will be accepted.

The deadline for submission is October 1, 2004. Applicants will be notified of the decision by March 15, 2005. The Award will be granted at 15th ECCMID 2005 in Copenhagen.

Please send your application to:
ESCMID Executive Office
P.O. Box 6, Clarastrasse 57
CH-4005 Basel, Switzerland
Phone +41 61 686 77 99
Email peter.schoch@escmid.org
Turning the Tide of Resistance: Research Grant 2005 by ESCMID and AstraZeneca

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) is pleased to announce an unrestricted research grant of EUR 40,000 by AstraZeneca for research in the field of antibiotic resistance. This fourth consecutive research grant is based on the collaboration of ESCMID and AstraZeneca to overcome antibiotic resistance.

The objective of this research grant is to contribute to overcoming antibiotic resistance. Appropriate projects may be laboratory or clinically based, or a combination thereof. However, proposals with clear clinical relevance will be preferred.

Application

Applications are to be submitted in writing. They must contain a detailed research plan, a description of the applicant's present research, his or her CV, a list of publications plus two letters of recommendation. Applicants must include their complete postal and e-mail address, telephone and fax number and send five copies of all materials plus one colour photograph (preferably electronically) to the ESCMID Executive Office.

The selection of the recipient will be made by the ESCMID Award Committee. Members of the ESCMID Executive Committee or the ESCMID European Council are ineligible. No correspondence beyond that necessary for the application will be accepted.

The deadline for submission is November 30, 2004. Applicants will be notified of the decision by March 1, 2005.

Please send your application to:
ESCMID Executive Office, P.O. Box 6, Clarastrasse 57, CH-4005 Basel, Switzerland
Phone +41 61 686 7799; Email peter.schoch@escmid.org

ARPAC Consensus Conference

AMSTERDAM, THE NETHERLANDS, 22 – 24 NOVEMBER, 2004

Control of Resistance in European Hospitals... ...Informing Future Evidence-Based Practice

The European Commission-funded project “Antibiotic Resistance: Prevention And Control” (ARPAC) culminates with this meeting which is being co-hosted by ESCMID and The Dutch Working Party on Antibiotic Policies (SWAB).

The ARPAC project aimed to
i) lay the foundations for a better understanding of the emergence and epidemiology of antibiotic resistance in human pathogens and
ii) evaluate and harmonise strategies for prevention and control of antibiotic resistant pathogens in European hospitals.

The Consensus Conference will present an overview of the key ARPAC findings to all delegates. Delegates will then split into one-day workshops to further explore the data gathered and modelled by ARPAC and the ESCMID Study Groups: ESGAP, ESGARS, ESCNI and ESGEM. The workshops will involve extensive discussion of the ARPAC findings in the context of the world-wide situation. The deliverables of each workshop will be a set of high priority strategic goals likely to be broadly feasible and to have a significant impact on antibiotic resistance.

For further information and the registration form please go to www.abdn.ac.uk/arpac or contact Dr. Fiona M. MacKenzie (f.m.mackenzie@abdn.ac.uk). A limited number of attendance grants will be available.
Jean Paul Butzler, born 1941 in Brussels, Belgium

Professor of Clinical Microbiology and Epidemiology at the Free University of Brussels, in recognition of his outstanding contributions in research, teaching and international cooperation in the fight against infectious diseases related to poverty, in particular diarrhoeal diseases. Throughout his medical career he has translated the concerns about poverty and poor health care in the developing world into collaborative research programmes. He has been instrumental in establishing reference microbiology laboratories in some of the most deprived regions, notably in Central Africa. In addition, he has trained and promoted many foreign and Belgian students who are now among the new generation of opinion leaders in the infection disciplines.

Research Interests
Jean-Paul Butzler’s early research concentrated on the diagnosis and treatment of enteric diseases. In 1974 he was the first to show that “Related Vibrio”, now called Campylobacter jejuni/coli, was a frequent cause of acute human enteritis and that early administration of erythromycin significantly reduced the duration of both diarrhoea and faecal excretion in patients with severe campylobacter enteritis. In 1972, he started the laboratory of clinical microbiology at the hospital of malnourished children in Lwiro, Bukavu, Congo where he concentrated on the rapid diagnosis and treatment of septicaemia and the management of hospital infections. In 1980 the WHO appointed Jean-Paul Butzler Director of the WHO Collaborating Centre for Enteric Campylobacter. From 1985 to 1990 Jean-Paul Butzler focused his research on HIV infections in Rwanda. His teams at the St Peter’s University Hospital in Brussels and the Kigali Hospital, Rwanda, in conjunction with the Institute for Tropical Medicine in Antwerp, were the first to show that HIV could be heterosexually transmitted. Today Jean-Paul Butzler supervises a team of young medical doctors both at the hospital for malnourished children in Lwiro, Bukavu, Congo and at the St Peter’s University Hospital in Brussels. Their current research focus is on emerging potential enteric pathogens and infection control.

Marc Lecuit, born 1966 in Paris, France

MD, Department of Infectious Diseases and Tropical Medicine, Necker University Hospital, and Pasteur Institute, Paris, France, in recognition of his outstanding contributions to our understanding of the molecular pathogenesis of Listeria monocytogenes infection based on laboratory investigations, animal models and human epidemiological studies.

Research Interests
Marc Lecuit’s research is focused on the pathophysiology of human infectious diseases. As a clinician and a researcher, he is particularly interested in understanding the specific host and organ tropisms of microbial pathogens, and the mechanisms they deploy to breach physiological barriers such as the intestinal barrier, the blood-brain barrier and the maternofetal barrier. His research has mainly focused on the Listeria model. He has investigated the molecular mechanism by which this bacterial species enters non-phagocytic cells, and discovered the species-specificity of Listeria monocytogenes. This led to the generation of a transgenic mouse model for human listeriosis. His current research focuses on the molecular mechanisms accounting for microbial central nervous and/or maternofetal tropisms. A complementary area of Marc Lecuit’s interest is the putative infectious origin of orphan diseases. Recently, he has coordinated a study on the microbial origin of a rare form of intestinal lymphoma (IPSID) known to respond in its early stages to antibi-
This led to the discovery of an association between this type of lymphoma and *Campylobacter jejuni*.

The two Young Investigator Awards are sponsored by Pfizer.

**INTERNATIONAL SEPSIS FORUM AWARD 2004**

**Tom Sprong,**
born 1975
in s’Hertogenbosch, the Netherlands

MD, University Medical Centre St Radboud Nijmegen, Department of General Medicine, in recognition of his excellent poster presented at 14th ECMID on the complement activation during meningococcal disease. His data demonstrate that the initial activation of the complement system during meningococcal infection is highly correlated with disease severity and that complement activation occurs via the alternative and lectin pathways, whereas classical pathway engagement develops only after 24 hours.

**Research Interests**
Sepsis, complement, cytokines and cytokine receptors and *Neisseria meningitidis*

The ISF Award 2004 is sponsored by the International Sepsis Forum.

**ESCMID RESEARCH FELLOWSHIPS**

**Jean-Denis Doquier,**
born 1974
in Liège, Belgium

PhD, Centre for Protein Engineering, University of Liège, Liège, Belgium

**Research Interests**
Jean-Denis Doquier’s research interests mainly concern the β-lactamase-mediated resistance mechanisms to β-lactam antibiotics in *Gram-negative* bacteria, including the molecular and genetic characterisation of multiresistant isolates, and the biochemical characterization of new enzymes. His present work is particularly focused on the study of the emerging acquired metallo-β-lactamases of the IMP- and VIM-type, whose production confers to the host a broad resistance profile usually including carbapenems and classical β-lactamase inactivators. In this area, his studies also aim at understanding the genetic mechanisms involved in the horizontal dissemination of the *bla*<sub>nov</sub> and *bla*<sub>ov</sub> genes and the structure-function relationships of these important metallo-enzymes, for which no clinically useful inhibitor is currently available.

**ESCMID / FEMS RESEARCH FELLOWSHIP**

ESCMID and FEMS have agreed on a joint initiative to foster outstanding research in microbiology by young Europeans. Every year each organisation will select one individual among their recipients of research fellowships to receive an additional amount of EUR 1000 from the other organisation. We are delighted to announce that the first combined ESCMID / FEMS fellowship goes in 2004 to Roy Sleator from Cork, Ireland.

**Roy Sleator,**
born 1975
in Kerry, Ireland

PhD, Department of Microbiology, BioSciences Institute, University College, Cork, Ireland

**Research Interests**
In the post-genomic era, Roy Sleator’s research will focus on the relationships between the genome, the proteome, and most importantly, the functionality of whole organisms. The most important functionality attributes of *Listeria monocytogenes* lie in its ability to survive and grow in foods and cause disease in humans. Both attributes are predicated on the ability of the organism to sense and respond in an appropriate manner to changes in its environment. One of the most efficient ways in which to convert a physical or biological signal into an appropriate biological response is to use two-component signal transduction systems (2-CS). The LisRK system is unique in that it is the first 2-CS identified in *Listeria*, which has a demonstrable role in the virulence of the organism, in addition to playing a role in its ability to respond to environments external to the host. His analysis of this system will provide valuable insights into the stress sensing capabilities of this important pathogen, and the role that such stress sensing plays in its virulence.
The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and AstraZeneca are proud to announce the recipient of the EUR 40’000 research grant for research in the field of antibiotic resistance. The grant, sponsored by AstraZeneca, was announced under the logo Turning the Tide of Resistance during 13th ECCMID 2003 in Glasgow. The recipient selected by the ESCMID Award Committee is:

Dr. Michael Niederweis
Department of Microbiology
University of Erlangen
Erlangen, Germany

He was selected for his project on: Synergy of Outer Membrane Permeability Barrier and Multidrug Efflux Pumps in the Intrinsic Antibiotic Resistance of Mycobacterium tuberculosis

His project aims at the identification and functional characterisation of an outer membrane channel of Mycobacterium tuberculosis, which is the central part of the most effective drug efflux pump systems. These drug efflux pumps and the very low permeability of the outer membrane act synergistically to render M. tuberculosis resistant to many antibiotics. The project is driven by the hypothesis that inhibition of the outer membrane channel enhances the susceptibility of M. tuberculosis to existing antibiotics.

A short award ceremony took place during the 14th ECCMID in May 2004 in Prague.

We would like to congratulate him on this success.

ESCMID Award Committee

Scanning electron microscopic picture of mycobacteria and host cells
CMI Impact Factor almost Doubles

The current Impact Factor for CMI (2.24), which was announced in June 2004, is nearly double the first rating. The factors responsible for this increase – and for the fact that CMI has an Impact Factor at all – are various and not always obvious.

THE ROLE OF AUTHORS
The degree to which Authors are dependent on the Impact Factors of the Journals in which they publish is widely known, often discussed and, in general, regarded as inappropriate but inevitable. However, the degree to which the Impact Factor of a given journal is dependent upon the Authors who publish in it may not be fully recognised. Indeed, Authors play a crucial role – probably the most crucial – in the complete scenario of Impact Factors. In the case of CMI, it is not simply the Authors whose papers were cited directly prior to a given rating who deserve credit, but also those who have attracted citations previously and have contributed to the heightened profile of CMI during the last ten years. The authors whose work was deemed sufficiently relevant and topical to merit inclusion of CMI in the Institute for Scientific Information (ISI) database, thus making it possible to acquire an Impact Factor, are those who published between 1995 and 1999. The current Impact Factor reflects upon both the Authors and the second Editorial Team who was responsible for the issues from which it was calculated.

THE ROLE OF PUBMED
Back up even further, it must be remembered that no paper, however “cite-worthy”, will receive very many citations unless the journal in which the paper appears is indexed in PubMed. Prior to the visibility afforded by PubMed, the only people who had access to articles published in CMI were the subscribers. Even these people are more likely to proceed with a PubMed search when writing their own papers than they are to remember to cite an article they read in CMI. The attainment of indexing in PubMed was a lengthy process that took place during the term of the founding Editorial Team. The long-awaited inclusion in PubMed made it possible for CMI to finally acquire an Impact Factor. The realisation of that possibility, however, was necessarily three years in the future.

THE ROLE OF THE FORMULA
The calculation of an Impact Factor involves a formula: the total number of citations received during one year to articles published in the journal during the two previous years is divided by the total number of citeable items (source items) published in the journal during those two years. The current Impact Factor is thus an estimate of the frequency at which the average article published during the two-year period preceding the past year was cited during the past year (see inset). Since the data used for the calculation of the Impact Factor extends over three years, and the calculation itself requires almost a full year on the part of the ISI, it was impossible for CMI to receive a rating before the summer of 2003. For this initial rating, the authors who deserve credit for attracting citations are those who submitted papers between 1999 and 2000, which were published during 2000 and 2001. Once CMI had an Impact Factor, the rate of submission naturally increased, and the Impact Factor increased accordingly.

THE ROLE OF JOURNAL SCOPE
Among the 84 journals in the field of microbiology which have been accorded an Impact Factor, CMI ranks in position 31, having advanced from position 53 last year. Among 41 journals in the field of infectious diseases, CMI moved from position 28 last year to position 15 this year. Keeping in mind that many of the journals ranking above CMI are dedicated review journals, which provide a more concentrated source of information and will always have an Impact Factor superior to that possible for journals that publish primarily original articles concerning a single aspect of a subject, CMI now compares well with other longer-established international journals. Clearly, the scope of a journal, and the manuscript categories included and prioritised, affects the Impact Factor in a straightforward way. However, there is a less obvious way in which journal content comes into play. Although the process of calculating an Impact Factor involves determining the total number of citations, it also involves a decision by ISI concerning those articles that are deemed citable (source items). For example, reviews, original articles and case reports figure in the denominator of the equation, while certain other manuscript categories do not. Since reviews and original articles are cited frequently, they contribute favourably to the potential Impact Factor, but because case reports tend to be cited infrequently, they have a detrimental effect. The converse is the case for editorials and abstracts; even if they attract only a few citations, they will be beneficial because they are not considered source items (i.e., they are not included in the denominator of the formula for calculation). Similarly, articles in Supplements are necessarily beneficial because they are cited second in frequency to review articles, and they are not considered source items.

The Impact Factor (IF) is calculated using the following formula:

\[
\text{IF} = \frac{\text{Citations received in 2003 to articles published in CMI in 2001–2002}}{\text{Number of source items published in CMI in 2001–2002}}
\]

First Impact Factor 2003 : 1.20 = Citations received in 2002 to articles published in CMI in 2000–2001

Number of source items published in CMI in 2000–2001


Number of source items published in CMI in 2001–2002
of parameters in addition to the relevance and topicality of the contents. These criteria include the timeliness of publication, the peer review system, adherence to international standards for format, the composition of the editorial board, the reputation of the publisher, and the profile and standing of the affiliated society. The favourable assessment of all of these criteria took place between 1995 and 1999, and for this achievement, credit is due to the founding Editorial Board which was appointed by the Society in 1995 and the original Publisher, Decker Europe. Similarly, the significant rise in the Impact Factor correlates with the increased stature of ESCMID and the growing importance of ECCMID, as well as the increased recognition of CMI as a journal with a wide readership and increasing visibility in which it is beneficial to publish important research findings.

Judith Crane
CMI Managing Editor

CMI Timeline

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation period for PubMed</td>
<td>Evaluation period for ISI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| approx. period of submissions of MS responsible for 1st Impact Factor |
| approx. period of submissions of MS responsible for 2nd Impact Factor |

1 – 4 May, 2004, Prague

14th ECCMID Highlights

ESCMID’s largest international event ever, 14th ECCMID 2004, was a great success. For the first time in ESCMID’s history, ECCMID took place in Prague, a country with a long history and rich culture. The Czech representatives are grateful to the ESCMID Executive Committee of 2001 for the decision to hold it in Prague. We are proud to report a record number of 6609 participants, including 344 accompanying persons, and 750 personnel from 55 exhibiting companies. 89 countries were represented with the highest attendance from the UK, Greece, Spain, and the USA.

The Congress had never before been held in this part of Europe. As it happened, the opening day coincided with the entrance of 10 new countries into the European Union, including the Czech Republic. Congress participants had the opportunity to witness the celebration of this historic event in the country’s capital.

The scientific and social programmes reached a laudatory level, due to both topical and organisational aspects. The superb Scientific Programme was developed by the Programme Committee under the leadership of Patrick Francioli and with input from the members of the National Committee, Jiri Beran and Paula Kriz. The cutting-edge programme included 126 scientific sessions: 2 plenary sessions, 5 keynote lectures, 40 official 1- or 2-hour symposia, 22 oral 1- or 2-hour sessions, 15 integrated symposia arranged by the industry, 18 meet-the-expert sessions, 17 guided poster walks, 7 satellite and other meetings.
A record number of 2644 abstracts were received on the 26 given topics. The evaluation of the abstracts was a difficult task for the anonymous reviewers. It was followed by a 2-day meeting of the Organising Committee during which the final programme and the free communication sessions were constructed: 190 (7%) abstracts were accepted for 10-minute oral presentations, 1490 (56%) for poster presentations, 489 (19%) for publication only, and 475 (18%) were rejected. Guided poster walks, which were introduced at Glasgow in 2003, were successfully organised again. Whether the newly-introduced abstract category, “for publication only”, will become a standard feature at future ECCMIDs remains to be decided. Incidentally, the National Committee was very satisfied to see 115 abstract submissions by Czech authors.

The scientific programme on the whole was of high professional quality. Presentations focused on the latest findings in laboratory and clinic diagnostics as well as on therapy and prevention of infections, including interdisciplinary perspectives and public health aspects. Topical symposia and talks on SARS, avian influenza, STD, antibiotic resistance, etc. were included. As at ECCMID Glasgow in 2003 a special last-minute hot topic lecture was set up and this year held by Albert Osterhaus, Rotterdam: “Catastrophes after crossing species barriers: lessons from SARS, avian influenza...”. Moreover, the role of the newly-decided EU institution, the European Centre for Disease Prevention and Control (ECDC), was intensively discussed on several occasions. Its activities will begin in Stockholm by early 2005. At the press conference on May 1, Marc Struelens, ESCMID President, stated: “Infectious diseases know no boundaries. We are looking forward to sharing breakthroughs and advances in the clinical management of infectious diseases to progress to common standards across Europe. We plan to focus attention on the need for effective international cooperation, especially with the ECDC coming close to being a reality”.

Abstracts of presentations and posters can be found in CMI, Vol. 10, Supplement 3, May 2004 or on the internet at www.escmid.org, ECCMIDs & Conferences. The weight of the abstract book is impressive: 1504 grams! The complete abstract book and the presented posters were also recorded on CD-Rom and made available to the Congress participants thanks to our sponsors.

The social programme started on Saturday with the usual Opening Ceremony, commenced by the Congress President’s welcome speech and followed by messages from Pavel Bem, Mayor of the City of Prague, Jaroslav Blahos, President of the Czech Medical Association of Jan Evangelista Purkyne, Marc Struelens, ESCMID President and Georgios Gouvras, Public Health Directorate, European Commission. The ceremony was completed by an elegant choreographic performance of the unique Prague Black Light Theatre Company. After that, the Mistress of Ceremony, dressed in powder blue, accompanied the delegates to the welcome cocktail offered on all floor foyers of the Congress Centre with its marvellous views of Prague.

The traditional President’s Dinner for the 240 invited speakers and guests took place at the Big Ball Games Palace, a renaissance building with graffiti decoration constructed for the King’s family in 1567-9. The structure is situated in the Royal Garden at the Prague Castle. It was a special pleasure for me to open the evening with a brief address about this politically and culturally significant place in Central Europe since the beginning of the second millennium. Marc Struelens, underlined the role of and need for an event like ECCMID for the infection disciplines in Europe. Jaroslav Spizek, President of the Czechoslovak Society for Microbiology (established in 1928) gave a short address on behalf of the Czech Academy of Sciences. Niels Hoiby, President of the 15th ECCMID presented his cordial invitation to come to Copenhagen in 2005.

A classical concert performed on Monday by the Czech National Symphony Orchestra took place in the famous Antonin Dvorak Hall of the Rudolfinum, a neo-renaissance building situated on the banks of the Vitava River.

Finally, I wish to express my sincere thanks to all those who contributed to making the 14th ECCMID a big success, including our sponsoring companies and the congress organisers from AKM and Czech-in. We had a good time in Prague.

I hope that all delegates will remember their experience in Prague for many years to come and look forward to seeing you next April in Copenhagen!

Jarmila Jelinkova
President, 14th ECCMID 2004
1–4 May, 2004, Prague

14th ECCMID Photo Gallery

Marc Struelens, ESCMID President, giving his address at the Opening Ceremony

One of the 126 scientific sessions

Patrick Francioli, ECCMID Programme Director, chairing a session

Rafael Canton explaining his poster during one of the ‘Guided Poster Walks’

Jean Paul Butzler, ESCMID Excellence Awardee 2004, during his talk on Campylobacter
Arianna Loregian being given one of the ESCMID Young Investigator Awards 2004 by Roger Finch

Reception in front of the Ball Game Hall prior to the President's Dinner for the invited speakers

The large exhibition featured many beautiful stands, here that of Merck

A youngster at the Pfizer stand: practice makes perfect

ECCMID’s most precious asset: the delegates

Jarmila Jelinkova, ECCMID President, being thanked for a job well done
Dear Colleagues and Friends

It is a great pleasure to invite you to participate in the 15th ECCMID in Copenhagen April 2–5, 2005!

ECCMID is the major annual European Congress on Clinical Microbiology and Infectious Diseases in Europe. The yin-yang symbiosis of our two important specialties within modern medicine means that they will always co-operate, although at times compete in the best cultural and scientific traditions, for the benefit of patients the world over.

We are closely interconnected with the environment including animals, birds, fish, and plants and many of the new infectious diseases like SARS originate from animals which have long been domesticated. The programme of the 15th ECCMID will reflect this interconnection between human beings and microbes from the living and innate environment in addition to the major area of recent developments in well-established, emerging and re-emerging infectious diseases. The 15th ECCMID will also focus on the molecular biology revolution. This is causing major changes in our ability to perform rapid diagnostic tests on infectious diseases and in our ability to design exciting new antimicrobials and maybe also to combat the threat of antimicrobial resistance. The 15th ECCMID will be held in Copenhagen Congress Center which housed the EU summit when Denmark chaired the negotiations in December 2002 opening up EU membership in 2004 to many new European countries and thereby a new exciting era also for ECCMID.

On the cultural side Copenhagen is famous for the Tivoli garden, its castles, museums, churches, old city and waterfront. In addition, the impressive new Opera at the waterfront opposite the Royal castle will open in 2005 and welcome the participants of the 15th ECCMID as part of the social programme.

Our opening ceremony of the 15th ECCMID on April 2nd, 2005 takes place on the 200th birthday of Hans Christian Andersen. This is the great author of many world famous fairy tales including “The Little Mermaid” which is the symbol of Copenhagen. We sincerely hope that many of the scientific contributions to the 15th ECCMID will be longstanding evergreens like the fairy tales of Hans Christian Andersen.

Welcome to Copenhagen!

Prof. Niels Hoiby
President 15th ECCMID

Visit the 15th ECCMID website featuring:
• Continuously updated scientific programme
• Online abstract submission (deadline November 18, 2004)
• Online registration as well as hotel & tours reservation
• Possibility to compose your personal congress programme
• Details regarding the industrial exhibition
• Information on the congress venue and the city of Copenhagen

For further information please contact:
Administrative Secretariat
15th ECCMID 2005
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

www.escmid.org/eccmid2005
ESCMID and the International Society of Chemotherapy (ISC) have agreed to hold a joint congress in Germany in 2007. The Memorandum of Understanding below was signed at the 14th ECCMID in Prague.

Organisational arrangements
1 A joint congress is to be organised in 2007.
2 It shall be called 17th ECCMID / 25th ICC 2007
3 The congress will take place in Germany. The selection of the city is to be based on strategic arguments concerning quality and cost of congress infrastructure, hotel capacity, transport connections, city attractiveness, and overall financial issues.
4 The Congress president is proposed by ISC, subject to approval by ESCMID (Bremen, Augsburg, Leibniz).
5 The Programme Director is proposed by ESCMID, subject to approval by ISC (Andreas Vosa, Nijmegen).
6 Composition of the Programme Committee (25 members):
   - 4 ex officio ESCMID officers: programme director (Chair), president, education officer, scientific officer
   - 4 members proposed by ISC/FESC
   - 3 local representatives proposed by the Congress President
   - 4 representatives of the ESCMID Study Groups
   - 10 free members proposed by the Programme Director on the basis of their scientific competence only

7 Composition of the Organising Committee (6 members):
   - ESCMID President
   - ISC President
   - Congress President (Chair)
   - Programme Director
   - Host country Scientific Coordinator (proposed by the Congress President)
   - Secretary General (proposed by the Congress President)

Financial and contractual agreements
The financial agreements and contractual arrangements with the PGo will be dealt with by the Boards of both Societies and the Congress Organising Committee.

Signed by:

Marc Struelens, ESCMID President, and Jean-Claude Péchère, ISC President, signing the above Memorandum for a joint Congress in 2007
Antimicrobial resistance has resulted in a continuous need for new therapeutic alternatives. Despite that, we see very few new anti-infective drugs against bacteria, viruses, fungi and parasites. Reasons are the increasing costs for development of new drugs and the fact that, when they reach the market, they tend to be reserved for special patient groups. As a result the economic return is so small that some pharmaceutical companies have decided to leave the field of infectious diseases. The ultimate threat is that we may end up with patients who cannot be treated due to lack of effective drugs. On June 1st and 2nd in Stockholm a number of experts from pharmaceutical companies, biotechnological companies, regulatory agencies and academia met to discuss the situation and to consider what should be done. The conference was jointly organised by ESCMID, the Karolinska Institute and the Swedish Institute for Infectious Diseases Control.

Speakers’ extended abstracts and PowerPoint presentations are available on the Society’s website (www.escmid.org, News & Current Issues). Some highlights from the conference follow.

SESSION I: THE NEED FOR NEW ANTIMICROBIAL AGENTS

In the first session Prof. Hartmut Lode, Berlin, discussed the need for new antibiotics. He mentioned that strains resistant to all available antibacterial agents have recently been found. Disturbances of ecosystems, more high risk populations such as immunocompromised patients, increased frequency of invasive medical interventions and survival of patients with chronic debilitating diseases have amplified the problem. The number of hospital-acquired infections such as those caused by methicillin-resistant staphylococci, vancomycin-resistant enterococci, multiresistant Pseudomonas and Acinetobacter strains and extended-spectrum betalactamase-producing enterobacteria is now increasing in many European countries. Community-acquired pathogenic bacteria such as multiresistant Mycobacterium tuberculosis and Streptococcus pneumoniae are also found more often. He concluded his presentation by pointing out the importance of more prudent use of antibacterial agents and the urgent need for new antibacterial agents.

Prof. Frank C. Odds, Aberdeen, gave an overview of fungal infections from common skin diseases such as dermatophytosis and genital thrush to disseminated visceral infections in immunocompromised patients. He mentioned that the market for antifungal agents for treating superficial mycoses is well saturated with inexpensive and effective agents. The need for new agents to treat life-threatening mycoses is obvious. Mortality rates from invasive Candida and Aspergillus infections are still very high. A commercially viable agent must be active against the most prevalent causes of fungal infections, i.e. all common Candida and Aspergillus species.

Prof. Giorgio Palù, Padua, described a novel strategy to inhibit viral replication by the disruption of viral protein-protein complexes by peptides or peptidomimetics that mimic the interface structure of either one of the interacting subunits. Antiviral agents for the treatment of herpesvirus infections include acyclovir and derivatives, ganciclovir, foscarin and cidofovir, which all inhibit herpesvirus DNA polymerases. The interest in the search for new anti-herpesvirus inhibitors has been renewed because of the emergence of drug-resistant viral strains,
particularly in immunocompromised patients, and because some of these antiviral agents, e.g. ganciclovir and foscamet, have toxic side-effects. The identification of new structures, which interfere with protein-protein interactions of enzymes involved in DNA replication, is relevant for understanding the pathogenesis of viral infections and the development of new antiviral agents. This new mechanism for inhibition of viral replication might thus be used for the development of future drugs.

Prof. Peter L. Chiodini, London, discussed the need for new antiparasitic agents. He has noticed that there are very few new drugs for treatment of parasitic infections. Chloroquine-resistant *Plasmodium falciparum* malaria is now established in Africa. The development of new classes of antimalarial agents and increased use of combination therapy is therefore urgent. Pentavalent antimonials for treatment of visceral leishmaniasis are no longer effective in India.

**SESSION II: THE REGULATORY SITUATION**

The first speaker in this session, Prof. Francis A. Waldvogel, Geneva, noted that science in industry and in academia have gone separate ways during the last decades. The advent of biotechnology has changed the modern drug finding strategy. Increasing collaboration between the pharmaceutical industry and small biotechnological companies and/or universities in the last years has progressively turned out new ideas and drugs from joint projects. However, the association between industry and academia creates the need for new regulations for patents, licences and other legalities. European harmonisation must be established as soon as possible, and the ethical issues concerning the relationship between industry and academia should also be addressed.

Prof. Johan W. Mouton, Nijmegen, discussed whether pharmacokinetics/pharmacodynamics investigations could replace clinical trials. The most important feature of antimicrobial agents is that their action is directed against microbial receptors, whereas for other drugs human receptors are the targets. The action of any drug obeys a concentration-effect relationship. Many investigations have shown that the effect of an agent can be predicted from the pharmacological properties and pharmacokinetic/pharmacodynamic relationships. Prof. Mouton holds that phase 1 trials are still necessary to determine the pharmacokinetic profile of the antimicrobial agent, such as protein binding, distribution and elimination, as well as toxic effects. He stated that phase 2 and 3 trials can be redesigned to take pharmacokinetics and pharmacodynamics into account and thereby allow including fewer patients in the trials.

Dr. Bo Aronsson, European Medicines Agency (EMEA), London, gave a presentation on "EMEA and CPMP – hurdles or opportunities?". He focused on the recently-revised guidance document on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 1). The objective of that document is to assist applicants in the development of antibacterial products. The Committee for Proprietary Medicinal Products (CPMP) encourages attempts to validate and confirm the PK/PD data during the clinical trials. The CPMP also encourages investigations on the treatment duration. In more serious infections with resistant microorganisms, EMEA is prepared to discuss and accept an initial marketing authorisation based on limited data. EMEA also accepts that it may be justified in performing uncontrolled trials for certain infections caused by resistant bacteria, e.g. in endocarditis and meningitis. Extrapolating efficacy results between indications may also be acceptable. The PK/PD relationships are important in these cases. A flexible approach is now taken by EMEA for authorisation of agents for treatment of infections caused by multi-resistant bacteria.

**SESSION III: IMPROVING THE FUTURE**

The third session began with a presentation by Prof. Staffan Normark, Stockholm, on antivirulence drugs. He described the identification of bacterial gene products such as those for Type III secretion, an anti-host effector delivery system e.g. in *Salmonella*, *Shigella*, *Yersinia*, *Escherichia coli*, *Pseudomonas* and *Chlamydia*. Several compounds have been identified that inhibit type III secretion. Another target for anti-virulence drugs has been the prevention of biofilm formation. By identifying genes present in all human pathogenic bacteria, new potential targets have recently been found. These approaches might pave the way for new antibacterial agents in the near future.

Dr. Göran Ando, Celltech Group plc, Slough, Berkshire, discussed the role of the biotech industry. He stressed that discovery research into new antibiotics significantly declined in the 1990s. The need for cost containment measurements has contributed to making antibiotic research and development less attractive for pharmaceutical and biotech companies. Only 5 of 400 new drugs in development are antibacterial. Biotech companies and academia are generally good sources of...
innovation; this applies also to anti-infectives. Modifications of regulatory demands and creation of incentives is required to increase the return on investment and make antibiotics more attractive to the industry. More than 3,000 biotech companies are now established worldwide with a significant skill base and resources in target identification and validation. These companies are flexible, rapidly moving, and they seize opportunities. Unlike major pharmaceutical companies, small biotech companies need much lower peak sales to make a business opportunity attractive. This should be exploited to increase the flow of new antibiotics.

Prof. Roger Finch, Nottingham, gave a presentation on the improvement of clinical trial design. Antibiotics are unique among therapeutic agents since they target bacteria and not pathophysiological processes in the human body. They are also prescribed for a short period to most patients. During recent years, clinical trial design has been mainly influenced by academia and regulatory agencies. Double-blind randomised controlled trials are the gold standard. Many advances have been made but problems still remain. Few studies are placebo-controlled and the choice and dose of the comparative agent does not always reflect that of medical practice. Most trials are designed to show equivalence and non-inferiority, which rarely advance the evidence to improve disease management. The emergence of antibiotic resistance must be predicted and managed. Better microbiological surveillance of target organisms as well as of the impact of antibiotic resistance on disease management should be introduced, along with pharmacokinetic and pharmacodynamic modelling. Improved standardisation of safety and tolerability data distinguishing between adverse events, adverse drug reactions and reasons for drug withdrawal are still important issues. Better international cooperation between industry, academia and regulatory agencies should be encouraged.

Dr. Barbara Hampel, Bayer HealthCare, Wuppertal, gave her views on the role of big and small pharma in the development of new infectious disease treatments. She confirmed that the pharmaceutical industry is reducing its antibacterial research and development investments. The costs and the complexity of drug discovery and development have shifted investment from drugs with short therapies for acute infections to those for long treatment of chronic diseases. The anti-infective agents have thus lost their attractiveness for big and small pharma. The investment of EUR 800 million for the clinical development of an antibacterial agent has increasingly come into question by many pharmaceutical companies. She stressed that the situation can and must be improved. One important step is that the communication and cooperation between the involved parties must be intensified. Recent initiatives by FDA to give continuous guidance are appreciated by the industry. Such an approach should also be adopted by EMEA. Better harmonisation between FDA and EMEA is also needed and may lead to improved communication between industry and regulatory agencies. Other measures that were discussed and are of equal importance relate to the creation of regulatory and economical incentives to make antimicrobial research and development profitable again.

Dr. Jordi Llinares Garcia, EMEA, London, reported about the Orphan Drug Option. The regulation was published in December 1999 in order to stimulate research, development and marketing of drugs against diseases which are neglected by the pharmaceutical industry due to their rarity or low commercial interest. Patients with rare diseases should have the same right to be treated with safe and effective agents as patients with more common diseases. Dr. Llinares Garcia presented the criteria for medical orphan drugs. The sponsor of an orphan application can be a company or an individual, i.e. a scientist, investigator, doctor or patient in the European Union. So far there have been only few orphan applications for medicinal products against infectious diseases. An example of a successful orphan designation is infection with Pseudomonas aeruginosa in patients with cystic fibrosis. The orphan drug option is suitable for pharmaceutical and biotechnological companies, academia and hospitals.

Prof. Alf A. Lindberg, Stockholm, gave a presentation on vaccines as alternatives to antimicrobial agents. He described the current bacterial vaccines’ ability to influence colonisation, elimination and eradication of pathogens in humans. Haemophilus influenzae type B vaccine has significantly reduced the number of invasive HIB disease cases in the last ten years. The conjugate pneumococcal vaccines have caused reduction of vaccine type pneumococci. Replacement of vaccine type with non-vaccine type pneumococci has been noticed particularly in day-care centres. No therapeutic effects of new bacterial vaccines have been seen.

Prof. Jaap T. van Dissel, Nijmegen, discussed the role of immunotherapy of infectious diseases. In the past, immunotherapy by vaccination or serum therapy proved to be effective in the prevention or treatment of infectious diseases caused by bacterial pathogens. Examples are diphtheria, pneumococcal pneumonia and meningococcal meningitis. These immunotherapeutic interventions were replaced by antibacterial chemotherapy in the 1940’s. Several developments have renewed the interest in immunotherapy of infectious diseases. Cytokines such as G-CSF, GM-CSF, M-CSF and IFN-gamma have received attention as non-specific immunomodulators in adjunctive treatment of different bacterial, viral and fungal infections. However, clinical experience with immunotherapeutic agents is limited and often investigational. Comparative controlled clinical trials are needed to evaluate the safety, efficacy and indications for these drugs.

CONCLUSIONS

From the above presentations at this symposium, it can be concluded that the lack of development of new anti-infective agents is a threat, which must receive more attention in the near future. If that is not done, the risk of emerging micro-organisms which are untreatable due to resistance is obvious. Actions must be taken by all parties involved: academia, the biotech industry, the pharmaceutical companies and the regulatory agencies. ESCMID is presently preparing a position paper on the above problems, which will remain in the focus of the Society’s future activities.

Carl Erik Nord
Professor

S. Ragnar Norrby
Professor, Director General
ESCMID and FEMS Pulling together

During the ECCMID 2004 in Prague Marc Struelens, ESCMID President, and Jean-Claude Pifaretti, FEMS delegate, signed the “FEMS and ESCMID Memorandum of Collaboration” (below). The document outlines a scheme of cooperation between the two organisations.

Marc Struelens and Jean-Claude Pifaretti signing the Memorandum on May 2, 2004
EUCAST (the European Committee on Antimicrobial Susceptibility Testing) and its Subcommittee on Antifungal Susceptibility Testing (EUCAST AFST) is convened by ESCMID and the European national breakpoint committees in France, Germany, the Netherlands, Norway, Sweden, and the United Kingdom. It is financed by ESCMID and the national breakpoint committees and by a grant received from DG Sanco of the European Union. EUCAST has four Steering Committee meetings and one General Committee meeting per year. EUCAST activities cover: harmonising breakpoints for existing drugs; setting breakpoints for new antibacterial and antifungal drugs; collecting multiple distributions of MIC values for any antimicrobial agent and species to be published on the EUCAST website for antimicrobial MIC wild type distributions; and collaborating with ESCMID study groups, EARSS, the EMEA, NCCLS and the pharmaceutical and susceptibility testing device manufacturing industries. Further details are given on websites run by EUCAST (see www.eucast.org). Here we briefly present some of our recent activities.

BREAKPOINTS FINALISED FOR AMINOGLYCOSIDES, FLUOROQUINOLONES, GLYCOPROTEINS AND LINEZOLID

At the Steering Committee meeting held in conjunction with the 15th EC-CMID in Prague, May 2004, EUCAST finalised a first set of common European breakpoints. Several rounds of consultation with the EUCAST General Committee, the pharmaceutical industry and antimicrobial susceptibility testing manufacturers were concluded in preparation for the Steering Committee meeting where consensus was reached. The EUCAST breakpoints are available on the EUCAST website (www.eucast.org). EUCAST has commenced work on harmonisation of breakpoints for cephalosporins, the carbapenems and aztreonam. Again we urge anyone in possession of MIC distributions for any of the drugs in these or any other groups or for any bacterial species to contribute them to the EUCAST database. Please contact the chairman of EUCAST.

BREAKPOINT TABLES

The EUCAST breakpoint tables, as exemplified by fluoroquinolones in Figure 1, are organised in such a way that each class of drugs has its own table. EUCAST may decide to omit a drug from a class table, usually because the drug is only marketed in one or two countries, in which case the user is referred to the national breakpoint committee of that country. From the breakpoint table the user can directly access the internet-based EUCAST MIC wild type distribution programme. Later this year the user will also be able to reach the drug-specific documents indicating the rationale for the breakpoint decisions made by EUCAST. The breakpoints are organised according to species or groups of species and the organisation of the table is the same irrespective of drug class. A dash signifies that the drug in question cannot be expected to have any useful activity against the species. The letters IE indicate “insufficient evidence” and suggest the lack of any formal indication and/or insufficient evidence to set a breakpoint. The breakpoints are given in the format 0.5/0.5 (interpreted as \( S \leq 0.5 \text{ mg/L}, R > 0.5 \text{ mg/L} \)).

CHANGES TO EUCAST CONSTITUTION 2004

To improve our channels of information and to clarify how EUCAST is funded, a number of changes were made to the EUCAST constitution, which is available on the EUCAST website.

COLLABORATION BETWEEN EUCAST, EMEA AND THE PHARMACEUTICAL INDUSTRY IS BEING EXPLORED

A formalised collaboration between EUCAST, EMEA, and the pharmaceutical industry is being explored. The goal is to identify a procedure to allow EUCAST to formally address the question of breakpoints in the process of registration of new antimicrobial drugs. A preliminary standard operating procedure is being discussed among the three parties.

DOCUMENTS DESCRIBING THE RATIONALE BEHIND BREAKPOINT DECISIONS TO BE PUBLISHED ON WEBSITE

The rationale behind each of the EUCAST breakpoint decisions will be published on the website in 2004. Background data has been obtained from scientific papers, the six national breakpoint committees, experts within and outside the EUCAST Steering Committee and General Committee, the pharmaceutical industry, antimicrobial resistance surveillance organisations and national reference laboratories. In setting breakpoints the Steer-
ing Committee, in collaboration with the national breakpoint committees, has followed the procedure set down in the EUCAST document European antimicrobial MIC breakpoints through EUCAST and the National Breakpoint Committees, which is available on the EUCAST website.

EUCAST DOCUMENTS
Discussion Documents will no longer be printed as inserts in Clinical Microbiology and Infection. From now on they will be published on the EUCAST website for at least 3 months, during which comments will be invited. Definitive documents will continue to be published in CMI and will also be available on the EUCAST website.

FUNDING OF EUCAST
EUCAST is funded by the national breakpoint committees of France, Germany, Norway, Sweden, the Netherlands and the United Kingdom, the ESCMID and, since May 2004, by a grant from DG Sanco of the European Union. The available funds cover EUCAST Steering Committee meetings (four meetings per year), activities of the EUCAST AFST, website activities and two workshops in 2005 and 2006.

POWERPOINT PRESENTATION OF EUCAST TO GO ON WEBSITE
The Steering Committee is preparing a PowerPoint presentation of EUCAST to go on the EUCAST website. It should provide an opportunity to present to audiences the ongoing process of harmonising European breakpoints. It can be run on the website or be downloaded from the website. The presentation will be updated regularly.

REFERENCE METHODOLOGY FOR MIC DETERMINATION THROUGH CEN AND ISO
Following an initiative in CEN, and through an ensuing collaboration between CEN and ISO, a joint international reference method for the determination of MIC in non-fastidious microorganisms will be published. It will be based on the broth microdilution method already published by EUCAST and NCCLS.

SUBCOMMITTEE ON ANTIFUNGAL SUSCEPTIBILITY TESTING (AFST)
The AFST is continuing its excellent work by setting European breakpoints for Candida species. Wild type MIC distributions are being collected and will eventually be made available on the EUCAST website. The EUCAST document Determination of minimum inhibitory concentrations by broth microdilution of fermentative yeasts will now be submitted for publication in CMI as a Definitive Document.

EUCAST SUSCEPTIBILITY DEFINITIONS
The EUCAST definitions of clinical and epidemiological categories of susceptibility are shown in Table 1.

Gunnar Kahlmeter
EUCAST Chairman
Email: gunnar.kahlmeter@ltkronoberg.se

Table 1: EUCAST definitions of susceptibility categories and breakpoints

Clinical Susceptibility Categories and Breakpoints

Clinically Susceptible (S)
- a micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success.
- a micro-organism is categorized as susceptible (S) by applying the appropriate breakpoint in a defined phenotypic test system.

Clinically Intermediate (I)
- a micro-organism is defined as intermediate by a level of antimicrobial activity associated with indeterminate therapeutic effect.
- a micro-organism is categorized as intermediate (I) by applying the appropriate breakpoints in a defined phenotypic test system.

Clinically Resistant (R)
- a micro-organism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure.
- a micro-organism is categorized as resistant (R) by applying the appropriate breakpoint in a defined phenotypic test system.

Clinical breakpoints may be altered with legitimate changes in circumstances. Clinical breakpoints are presented as S<x mg/L; I>x, <y mg/L; R>y mg/L.

Epidemiological Susceptibility Categories and Cut-off Values

Wild type (WT)
- a micro-organism is defined as wild type (WT) for a species by the absence of acquired and mutational resistance mechanisms to the drug in question.
- a micro-organism is categorized as wild type (WT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- wild type micro-organisms may or may not respond clinically to antimicrobial treatment.

Microbiological resistance - Non-Wild Type (NWT)
- a micro-organism is defined as non-wild type (NWT) for a species by the presence of an acquired or mutational resistance mechanism to the drug in question.
- a micro-organism is categorized as non-wild type (NWT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- non-wild type micro-organisms may or may not respond clinically to antimicrobial treatment.

Epidemiological cut off values will not be altered by changing circumstances. The wild type is presented as WT<x mg/L and non-wild type as NWT >z mg/L.
Intestinal infections caused by *Clostridium difficile* are an increasing problem in hospitals and the community because of the greater use (and abuse) of antibiotics and chemotherapeutics, and the increasing population age. An enormous amount of data has been gathered in the last decade to address this important health issue, including information on advances in diagnosis and epidemiology of *C. difficile* disease, toxins produced by the organism and their mode of action, and development of genetic tools. The objective of the FICDS was to bring together participants active in various fields of *C. difficile* research: clinicians, epidemiologists, microbiologists, molecular biologists, toxicologists and research students, to discuss past achievements and plan future developments. About 100 participants from 19 countries registered for what was a productive, stimulating and, most importantly, fun two days.

The first session set the stage with an excellent historical overview by Peter Borriello of early work on the initial isolation of a bacterium, called *Bacillus difficilus* at the time that was eventually shown to be a cause of pseudomembranous colitis and antibiotic-associated diarrhea, and the identification of two toxins as the main virulence factors. The session continued with a description of some well-known problems caused by *C. difficile* from the clinical point of view by Dale Gerding. Finally, to conclude the introduction of the meeting, an interesting description of *C. difficile* as an emerging animal pathogen was given by Glen Songer.

**Meeting Report**

**First International Clostridium difficile Symposium (FICDS)**

organised by the ESCMID Study Group on *Clostridium difficile* (ESGCD) from May 5th to 7th in Kranjska Gora, Slovenia


**CLINICAL ASPECTS: DIAGNOSIS AND EPIDEMIOLOGY, PREVENTION AND TREATMENT**

As mentioned by Dale Gerding there are three major needs that remain to be addressed concerning *C. difficile* infection: 1) better methods to prevent and control nosocomial *C. difficile*-associat-

ed disease, 2) a more sensitive test for *C. difficile* with a rapid clinical turnaround time, and 3) improved treatments that do not result in the ~20% recurrence rate observed with the current treatments.

Two sessions were devoted to diagnostic procedures and epidemiology. Michel Delmee started the sessions with a comprehensive overview of available methods for the diagnosis of *C. difficile* disease, pointing out some of the limitations of current EIA kit methods. Mark Wilcox then talked about general strategies for control of *C. difficile*: prevention of horizontal spread using barriers (gloves), hand washing, cleaning and disinfection (of rooms and disposables) and isolation methods (or cohorting). He then went on to discuss how restricting antibiotic use influences the incidence of *C. difficile* infections. Tom Riley described the epidemiology of *C. difficile*-associated disease (CDAD) in detail, highlighting the economic consequences of the large increases in CDAD seen in the industrialised world in the last 20 years. Jon Brazier then reviewed methods available for typing *C. difficile*. This has become increasingly important in recent years, as several potentially more virulent clones of *C. difficile* have emerged. Additionally, some novel typing and diagnostic methods were presented, such as multi-locus sequence typing (Ludovic Lemee), use of the real-time PCR for diagnosis (Renate van den Berg) and possible use of rectal NO values as a measurement of intestinal inflammation (Anders Enoksson). To conclude these sessions a round-table discussion was held on important diagnosis issues. It was agreed that the single most important issue to resolve was to develop a simple, sensitive, specific and rapid test to diagnose CDAD that could be used in a wide range of laboratories. It was conceded that not all laboratories could undertake PCR assays and that for the immediate future these would be available only to larger facilities. Several avenues for treatment and control of the disease were presented. An excellent summary of the early work with animal models, and on recent advances in *C. difficile* vaccine
C. difficile found in domestic animals and, in particular, dogs and horses.

**C. DIFFICILE – AN INTERESTING ORGANISM**

Ian Poxton summarised pathogenesis and host responses – entry into host, adherence, multiplication, evasion of immune response, damage to the host and release and spread – as well as some still unanswered questions: 1) are there differences in virulence between A’B’ and A’B’ strains, 2) why are some types more virulent than others, 3) what makes patients susceptible, and 4) which additional immune system factors are involved in the pathogenesis?

Several oral and poster presentations dealt with surface proteins involved in adherence and colonisation. Among molecules and structures mediating adhesion are S-layer proteins, cell wall proteins, proteases, flagella, fimbriae and the capsule. The S-layer in C. difficile, discussed by Neil Fairweather, is a para-crystalline layer around the cell and is composed of two proteins, both derived from a common precursor protein SpiA. Adherence of C. difficile to host cells could be inhibited by antibodies against the high molecular weight S-layer protein.Vinulin, an intracellular protein interacting with actin, was identified as the host cell target for S-layer proteins. Because C. difficile is regarded as an extra-cellular pathogen, the events involved in this interaction and their physiological relevance are still unclear. Severine Pechine focused on the other adhesins and flagellin proteins: cell wall protein Cwp66, and flagellar proteins FlID (cap protein) and FlIC (flagellin). She studied variability among strains, different expression and the host immune response to them, suggesting that surface epitopes could play a role in antibody-mediated protective immunity.

**MOLECULAR BIOLOGY OF C. DIFFICILE**

This area of research started several years ago with the study of mobile genetic elements and was overviewed by Peter Mullany. First described were transposons which code for different antibiotic resistances and could be exchanged between C. difficile, Bacillus subtilis, Staphylococcus aureus and Entercoccus faecalis. Our knowledge of molecular biology (other than molecular biology of toxin genes) proceeded with identification of group II introns and a unique genetic mobile element IStron (combining features of insertion sequences and group I introns) found only in C. difficile. Only few plasmids are well studied, but phages are now being re-investigated and were shown to potentially increase the cytotoxicity of the strains by an as yet unknown mechanism as reported by Shan Goh.

Julian Rood described recent developments in C. difficile genetics. The lack of tools for the genetic manipulation of C. difficile has long been an obstacle in pathogenesis research. Two main approaches, the use of modified C. difficile plasmids or use of C. perfringens shuttle vectors, now enable the introduction of genes into C. difficile thus allowing detailed studies on toxin regulation (especially the role of the gene ttxE) and different two-component signal transduction systems important in gene regulation.

The genome sequencing of C. difficile strain CD630 is finished and now at the annotation stage (www.sanger.ac.uk/Projects/C_difficile). This information was presented by Brendan Wren. With the genome sequenced, new possibilities for C. difficile research have emerged. One of them is the current construction of a microarray and use of proteomics for detailed study of virulence potential, expression patterns, etc.

Sporulation was covered by Linc Sorneshein. This is an important feature of C. difficile as spores are the infectious agent, and synthesis of toxins TcdA and TcdB occurs during the stationary phase and is linked to sporulation. The C. difficile sporulation genes, as well as genes involved in the regulation of sporulation and toxin production (such as codY), are homologous to those found in B. subtilis. In C. difficile, two sporulation phenotypes could be differentiated (spo+ and spo−) depending on the presence (spo+) or absence (spo−) of a phage-like genetic element whose excision during sporulation is necessary for synthesis of mature spores.

Another important aspect of gene regulation in bacteria is the use of quorum sensing (cell-density dependent coordinate control of gene expression) and specific details on C. difficile were presented at the meeting by Nigel Minton. Up to now two diffusible autoinducers (AIs) have been found. The
first corresponds to AI-2, a universal pheromone described in both Gram-negative and Gram-positive bacteria. The second pheromone resembles the “substance A” of *C. perfringens*. It can be detected in culture medium from late log phase *C. difficile* cultures and stimulates the production of TcdA when added to fresh cultures.

**C. DIFFICILE TOXINS (TCDA AND TCDB, BINARY TOXIN CDT)**

Toxins A (TcdA) and B (TcdB) are well-studied virulence factors of *C. difficile*. Christoph von Eichel-Streiber refreshed our knowledge on the biochemical properties of TcdA and TcdB, and the molecular biology and variability of the specific PaLoc region coding for the toxins. Ingo Just discussed functional properties and possible use of the toxins as tools in cell biology, and Bruno Dupuy presented an update on the regulation of TcdA and TcdB production. TcdA and TcdB are large single strand protein toxins with a three-domain structure. The catalytic N-terminal domain harbors glucosyltransferase activity, the middle domain is involved in translocation and the C-terminal repetitive domain in receptor binding. Toxins TcdA and TcdB modify small GTP-binding proteins belonging to the Ras superfamily, which are molecular switches regulating the actin cytoskeleton, gene expression, apoptosis and cell transformation. Modification inactivates the GTP-ases and thereby prevents downstream signaling. Most of the new information presented in several posters was on toxin binding and entry into the host cell, and on novel intracellular mechanisms affecting gene expression. The production of toxins TcdA and TcdB is regulated by various environmental factors such as carbon sources, antibiotics and temperature, and is mediated by regulation of the expression of TxeR (now renamed in TcdR). This protein is an alternative sigma factor, belonging to a new subgroup of the σ54 family involved in toxin production of pathogenic Clostridia. Studies identifying additional regulatory factors, a two-component signal transduction system (VirRI, VirRII) and a carbon catabolite regulator (CcpA) are under way. Some *C. difficile* strains produce a third toxin, binary toxin CDT. It is unrelated to TcdA and TcdB and belongs to the clostridial iota-like binary toxins, produced also by *C. perfringes* type E and *C. spiroforme*. Current data about clostridial binary toxins were presented by Michel Popoff and Bradley Stiles. The role of binary toxin in *C. difficile* infection is still unknown; however, as judged by the number of posters on binary toxin-producing *C. difficile* strains, interest in such strains is rising. In addition to reports on the prevalence of binary toxin positive strains and their correlation with specific ribotypes, some data have indicated that such strains are likely to cause more severe diarrhoea than binary toxin negative strains. Studies in animal models support the role of binary toxin as an additional virulence factor, but its effects depend on the animal model used. Strains that produce only binary toxin, and no TcdA or TcdB, do not cause disease in hamsters, but are enterotoxic in the rabbit ileal loop assay. Finally, a round table was held on the nomenclature of the *C. difficile* toxins TcdA and TcdB, and associated toxin genes. In parallel with recent developments in the molecular biology and biochemistry of *C. difficile*, several different nomenclature systems have been applied to the toxins and their associated genes. With an increasing number of research groups working on the molecular biology of *C. difficile* or using its toxins as tools in cell biology, and with the imminent completion of the first *C. difficile* genome sequence, the need for a unified nomenclature has become apparent. A revised nomenclature was agreed to by the research groups currently active in the field and will be published shortly. This will also be available on the ESGCD web page.

**CONCLUSIONS**

The response to this meeting, from both attendees and presenters, has been very positive. *C. difficile* is now clearly the most important Clostridium species from a clinical and economic perspective. We plan to hold these meetings on a regular basis in the future to build on the good relationships established at the FICDS. For further information, and regular updates, please consult the ESGCD web page: www.escmid.org. Study Groups, ESGCD.

**ACKNOWLEDGEMENTS**

The Organising Committee would like to thank all speakers and other presenters, chairs and participants again for making this meeting such a great event and to acknowledge the support received from ESCMID and various industry sponsors.

**Maja Rupnik**, Ljubljana, Slovenia

**Tom Riley**, Perth, Australia
Within the framework of the ESCMID strategic intervention plan in Eastern Europe, the international conference, *Actual questions of antimicrobial therapy in the Republic of Belarus*, was held on June 24–25 in Minsk. This event was jointly organised by ESCMID and the Belorussian State Medical University, in cooperation with the Belarus Society of Infectious Diseases, the Research Institute of Microbiology and Immunology, and the Municipal Committee of Public Health. More than 50 physicians (Infectious Diseases specialists, pulmonologists, intensive care unit specialists, clinical microbiologists) attended.

The conference was co-chaired by Prof. Igor Karpov, main Infectious Disease specialist at the Ministry of Public Health, and by Dr. Giuseppe Cornaglia, ESCMID Secretary General, who greeted the first ESCMID members from Belarus and underlined the mission of ESCMID to support the scientific societies active in the infection fields in Eastern Europe, and to promote and strengthen their partnership with centres of excellence within this geographical area. The conference focused on the need for effective co-operation between clinicians and clinical microbiologists to improve and optimise the diagnostic procedures as well as the antimicrobial therapy of the most prevalent infectious diseases in the Republic of Belarus. Thus, it involved both infectious diseases specialists and microbiologists, and its programme covered the most relevant epidemiological, laboratory and clinical issues in infectious diseases and clinical microbiology as regards community- and hospital-acquired infections in our country.

The lectures were delivered by Giuseppe Cornaglia (Verona, Italy), Javier Garau (Barcelona, Spain), Igor Karpov (Minsk, Belarus), Roman Kozlov (Smolensk, Russia), Helmut Mittermayer (Linz, Austria), Leonid Titov (Minsk, Belarus), and John David Williams (London, England). Lectures were always followed by highly involving discussions. The clinical microbiology lectures overviewed the principles for rational laboratory diagnosis of infections in different body sites, and made a critical appraisal of antibiotic susceptibility testing rationale and methods.

The clinical issues debated included management of patients with lower respiratory tract, urinary tract, catheter-related, and MRSA infections, as well as sepsis and meningitis. Participants were provided with the basic, integrated knowledge necessary for understanding the need to perform microbiological tests, as well as the need for correct identification and reporting.

Special attention was paid to the role of the various antibiotics in managing community- and hospital-acquired infections, to monitoring antibiotic resistance of the most important pathogens and to making proper use of epidemiological data for both clinical and public health purposes. The conference received very high appraisal from all participants and represented an excellent starting point for an expanding co-operation between specialists in Belarus and ESCMID.

Elena Kachanka, MD and Igor Karpov, MD
Department of Infectious Diseases
Belorussian State Medical University,
Minsk, Belarus
The UEMS Section for Medical Biopathology, Commission of Microbiology, and ESCMID are pleased to inform the scientific community that a joint European Board for the Accreditation of CME in Clinical Microbiology (EBACM) has been established. The purpose of this joint initiative is to support providers of CME in the field of medical and clinical microbiology in applying for European CME credits. EBACM is linked up with EACCME, the European Accreditation Council for CME, which is an institution of UEMS in Brussels.

BACKGROUND INFORMATION
1) Continuing Medical Education (CME) is part of CPD (Continuing Professional Development), which is considered an ethical obligation and ongoing responsibility throughout the career of each clinical microbiologist.  
2) Medical education, specialist training and professional accreditation/certification is subject to national regulation. An increasing number of European countries require proof of CME and have established national CME accreditation boards.  
3) UEMS has set up a mechanism for European accreditation of CME activities. This allows medical specialists to earn CME credits for educational activities taking place outside of their home countries. This mechanism is based on the European Accreditation Council for CME (EACCME), an institution of UEMS in Brussels, and requires the CME provider to comply with predefined quality criteria. European CME credits issued by EACCME are recognised by most European countries represented in UEMS.  
4) In principle, in order to obtain European accreditation by EACCME, the CME activity must be pre-accredited by the national CME authorities of the host country. However, since many European countries are still lacking functional CME accreditation boards operating under uniform European quality standards EACCME can base the accreditation of a CME activity in the field of Clinical or Medical Microbiology on the assessment by EBACM.  
5) Providers of educational activities with multinational participation can thus first apply either directly to the CME authorities of the host country or to EBACM for accreditation (for the latter case see the flow chart below). In both cases the accreditation must be followed by accreditation from EACCME to be recognised throughout Europe.  
6) Applicants for CME accreditation by EBACM must use the online form on www.ebacm.org. For further information about EBACM, including the online application form and the costs of accreditation see www.ebacm.org.

Elisabeth Nagy, on behalf of EBACM

ESCMI/ SHEA Training Course in Hospital Epidemiology

This intensive training programme is aimed at those who have responsibility for hospital epidemiology and infection control programmes. It is organised by the ESCMID Study Group of Nosocomial Infections (ESGNI) and the Society for Healthcare Epidemiology of America (SHEA). The course is taught by renowned experts from the US and Europe, dedicated to continuous quality improvement in infection control and the application of epidemiology within the hospital setting. The course offers an advanced module in addition to the basic module.

For further information please contact: Dr Markus Dettenkofer
email: markus.dettenkofer@uniklinik-freiburg.de or consult the websites at www.hosp-epi-course.org or www.escmid.org

Elisabeth Nagy, on behalf of EBACM
Epidemiology Typing Workshop

The 24th Postgraduate Education Course of ESCMID and the ESCMID Study Group on Epidemiological Markers (ESGEM) was held in Warsaw, Poland, on the 25th–30th April 2004. It was organized in the National Institute of Public Health (NIPH) in Warsaw by Prof. Waleria Hryniewicz (NIPH, main supervisor), Dr. Lenie Dijkstra (Leiden University Medical Center, the Netherlands), Prof. Alex van Belkum (Erasmus Medical Center, Rotterdam, the Netherlands), Dr. Panayotis T. Tassios (University of Athens, Greece), Dr. Joanna Empel (NIPH), and Dr. Marek Gniadkowski (NIPH). The Organizing Committee was strongly supported by other NIPH scientists, including Dr. Magdalena Kawalcik, Anna Olczak, M. Sc., Dr. Ewa Sadowy, Janusz Fiett, M. Sc., Radek Irdebski, M. Sc., and Marcin Kadlubowski, M. Sc.

Financial and/or material support was received from the following organisations and companies: ESCMID, ESGEM, NIPH, American Society for Microbiology, Werkgroep Epidemiologische Typering (WET, the Netherlands), Stichting Microbiële Typering (the Netherlands), Fundacja “Centrum Mikrobiologii Klinicznej” (Poland), Bio-Rad Poland, Applied Biosystems Applera Poland and Bayer. The announcement of the course met with wide interest; 72 applications were received in total. The applicants represented 26 countries from Europe, Africa and Asia. Twenty-four participants from 16 countries were selected, based mostly on their professional interests, research fields, and their intention to directly apply the knowledge and skills gained during the workshop in their laboratories. Participants’ educational background included medicine, infectious diseases, microbiology and/or molecular biology.

The programme consisted of 12 lectures and 4 practicals over a five-day period. Nine 30-minute lectures referred to principles of microbial typing and taxonomy, molecular typing methodology, and application of molecular biology methods in basic and epidemiological studies of bacterial infections and microbial identification. They covered various aspects of basic microbiology, mostly genetics and population genetics of bacteria, but also important issues of laboratory performance, computer-based analysis of typing data, data interpretation and management, standardisation of typing methods and development of new techniques. Many examples of advanced research with the use of various molecular typing approaches were presented, including studies on pathogenicity and antimicrobial resistance in bacteria. Participants were thus acquainted with such typing methods as PFGE, ribotyping, plasmid fingerprinting, RAPD, AP-PCR, REP-PCR, PCR-RFLP, AFLP, binary typing, MLST and typing with the use of DNA microarrays.

During practicals participants performed their own PFGE, RAPD and PCR-RFLP analyses, as well as the computer-assisted analysis of the DNA fingerprints generated by the above methods. They worked in pairs (from different countries) and the entire group was split into two subgroups of six pairs each. In the PFGE analysis, the participants carried out the whole procedure of bacterial DNA preparation in agarose plugs, restriction digestion, and pulsed-field gel electrophoresis of the resulting DNA fragments. Subgroup 1 analysed 24 clinical isolates of Staphylococcus aureus, whereas subgroup 2 worked with 24 isolates of Escherichia coli. The PCR practicals started with preparation of total DNA from 24 isolates of Acinetobacter spp. for subgroup 1, and 24 isolates of E. coli for subgroup 2. RAPD analysis was carried out on DNA from both sets of isolates and included a single PCR reaction for each isolate and separation of the reaction products by electrophoresis. In the PCR-RFLP analysis, the students worked with the DNA preparations of Acinetobacter spp. and performed the identification of Acinetobacter genomic species by the ARDRA approach. Laboratory practicals were preceded by detailed instructions at the start of each day, and included trouble-shooting and results interpretation sessions, during which all technical and application aspects were discussed for each of the methods. Bacterial isolates that were used during the course were derived from the culture collection of the NIPH and their comparison illustrated various epidemiological situations, which the participants may encounter in their future work. The earlier performance of the laboratory programme by teachers themselves allowed the organisers to guarantee the good quality of all reagents prepared for the course.

The last practical was the computer-assisted analysis of DNA fingerprints done with the Fingerprinting II Informatix software (Bio-Rad). It consisted of a tutorial, during which participants were acquainted with the software itself and its possible applications. For the computing practical, participants were split into three groups of pairs, each working in a separate room and supervised by different teachers. All members of the teaching faculty were present in the course area at all times and were available for discussions and additional explanations. Each participant received a protocol book containing the programme and schedule, protocols for the laboratory work, results sheets, and appendices with the full Pulse-Net USA protocols for PFGE of enterobacteria, reference documents for the ARDRA approach for Acinetobacter identification, and the Fingerprinting II Informatix Software Tutorial (Bio-Rad).

The course also had a social programme which included a guided sight-seeing tour in Warsaw, a visit to the Historical Museum of Warsaw, a guided tour in the Old City, and a guided visit to the Chopin’s family house in Żelazowa Wola and to an aristocratic residence of the Radziwill family at Nieborów, in combination with fine dinners.

At the end of the course, participants anonymously filled out evaluation questionnaires, which revealed a high level of satisfaction and encouragement to repeat the course in the near future. News items about the course appeared in the largest Polish newspaper and on Polish TV. These included short interviews with faculty members (L. Dijkstra, W. Hryniewicz, A. van Belkum) and participants. The official opening and closing of the course was done by W. Hryniewicz. All participants received certificates of attendance at the end of the course.

Alex van Belkum
ESGEM Chairperson
The 3rd ESCMID School was held from June 26 to July 2, 2004 in Athens, Greece. It was organised by the ESCMID Education Committee and hosted by Alfa HealthCare and “Henry Dunant” Hospital. Thirty six fellows were hosted by Alfa HealthCare and “Henry Dunant” Hospital. Thirty six fellows attended the School, a 56% and 16% increase compared to the 1st and 2nd ESCMID Schools, respectively. Five participants were supported by ESCMID grants to attend the School (one from each of the following countries: Albania, Cyprus, Turkey, Romania, and United Kingdom).

There were twenty 50-min lectures (including a 10-min question/answer period), six 90-min small group tutorials, and six 90-min case presentation sessions. The overall assessment grade of the 3rd ESCMID School by the participants was 9.63 (on a scale of 1 to 10). The participants also evaluated the presentations of the 20 lecturers with a mean grade of 8.90 (range 7.89 to 9.61). The mean grade of the 7 persons who served as the main faculty and facilitators for the duration of the School was 9.45.

The overall high degree of satisfaction of participants makes clear that the ESCMID School has become a successful tradition. A report by a participant appears below. The Education Committee of ESCMID is committed to maintaining the achieved level of educational value and the didactic format in subsequent editions of the ESCMID School.

I would like to thank my assistants, Ioannis Bliziotis, MD, Sofia Kasiakou, MD, Antonia Karavasiou, MSc, Konstantinos Paraschakis, BSc, Evi Papastamataki, RN, Fotini Helvatzoglou, RN, and Antigoni Nenti, RN for their help with several practical aspects of the School. Also, I would like to thank Wyeth Hellas and Cana Pharmaceutical Laboratories for their support as well as the president of the Hellenic Red Cross, Dr. Andreas Martinis, and the administration of “Henry Dunant” Hospital, the venue of the course, for their contribution to the success of the 3rd ESCMID School.

On behalf of the ESCMID Education Committee, the 3rd ESCMID School Coordinator, Matthew E. Falagas, MD, MSc Adjunct Assistant Professor of Medicine, Tufts University School of Medicine, Boston, MA, USA Scientific Director, Alfa HealthCare SA, Athens, GR Director, Infectious Diseases Clinic, “Henry Dunant” Hospital, Athens, GR


**Review of the 3rd ESCMID School 2004 in Athens**

The ESCMID School... ...is gaining an increasingly good reputation. I attended the School this year and had an unforgettable week in Athens, Greece. There were thirty six participants in total, from Albania (1), Belgium (1), Bosnia (1), Cyprus (1), Greece (21), Portugal (3), Turkey (2), Romania (1), Saudi Arabia (1), and UK (4). Including the six facilitators, thirteen nationalities were represented.

The School opened with an address from Professor Claude Carbon, chair of the ESCMID Education Committee. This was followed by the first two of a series of educationally valuable lectures. During dinner at the “Alexandros Hotel”, there was a less formal opportunity for delegates and facilitators to get to know each other.

The course was very well organised. Each morning, there were four lectures. These were of very high quality and clinical relevance. In each question time, the participants contributed enthusiastically, given the informal, yet, inspiring atmosphere. The topics included epidemiology and public health (STDs, preparedness plans for the control of infectious diseases in the 21st century), microbiology (mechanisms, impact and control of microbial resistance, new antituberculosis agents), infectious diseases (brucellosis, rickettsial diseases, the use of steroids in infectious diseases, chronic hepatitis B and C, developments in antiretroviral therapy and control of vertical transmission).

Each afternoon was divided into two sessions. For the first session, we were divided into small groups for tutorials by the facilitators. These were an excellent opportunity to learn and study interactively. In the second session, participants presented their own clinical cases. Some fascinating cases were discussed and a number will be submitted for publication.

The social events complemented the educational programme. On two occasions we went on a tour of Athens and to the Greek Island of Hydra, and enjoyed the beauty of the area, excellent food and traditional music.

I echo the opinion of all of the participants in that it was a fabulous week and I would highly recommend the ESCMID School to interested trainees and specialists. We would like to extend our thanks to our hosts in Athens, especially Professor Matthew Falagas and to the members of the ESCMID Education Committee, Professor Claude Carbon, Dr Geoff Scott, Dr George Schmid, Dr Achim Schwenk, as well as the other two facilitators, Dr Helen Moraitou and Dr Antonios Vassiloyannakopoulos.

Dr Alice Chi Eziefula
Senior House Officer in Tropical Medicine and Microbiology, Hospital for Tropical Diseases, University College London Hospitals, London, UK
Forensic Microbiology: an Old Science, a New Approach

In the beginning of the 21st century, forensic microbiology can be a useful approach to the interpretation of a wide range of situations in which legal issues are related to infectious diseases. Although not yet considered as a discipline in its own right, with its own rules and requirements, its crucial role in certain public health threats and its great impact in other contexts will eventually lead to its recognition as a special component of the microbiologists’ domain. A brief overview of this specialised area of microbiology will make evident its widespread repercussions in the context of forensic investigations.

First of all, a definition is called for: forensic microbiology should be understood as the application of microbiology to forensic investigation. This definition goes beyond the impact of clinical microbiology on legal investigations. Applied environmental microbiology can also be used by forensic investigators to compare soils by bacterial community profiling or to demonstrate microbial degradation of pollutants. However, this review will only deal with the implications of clinical microbiology in forensic investigations.

Useful Approach, Special Situations

In which situations is clinical microbiology useful to forensic specialists? Firstly, it can help establish the cause of death whenever a fulminating infectious disease is suspected or should be ruled out in cases where a diagnosis has not been made ante-mortem. Secondly, it can be a useful approach in clinical situations concerning suspected malpractice, which can lead to prosecution and even conviction. Moreover, forensic microbiology is concerned with the molecular characterisation of any pathogen responsible for a biocrime.

BACTERIAL FULMINATING INFECTIONS

Is sudden unexpected death of infectious origin underestimated? Now, living in the post-antibiotic era, can one imagine a fulminating bacterial infection causing the death of an otherwise healthy individual? Microbiological post-mortem analysis has long been used as a complementary tool for pathologists although medical examiners and forensic pathologists have been traditionally more interested in criminal issues than in natural causes of death. However, early recognition of potential risks to public health is among the primary responsibilities of medical-legal officers. There are a wide variety of pathogens, the detection of which is to be reported to public health authorities in order to diminish the risk of secondary cases or outbreaks. These pathogens include Neisseria meningitidis, Mycobacterium tuberculosis and those from the CDC Category A. Under some circumstances, the diagnosis of diseases due to these pathogens is not undertaken soon enough after the onset of symptoms and the patient dies before being diagnosed. In such cases, and those that may involve malpractice, forensic microbiology comes into play in determining the cause of death.

Sudden death caused by meningococcal disease could be underestimated when unspecific or mild signs of infection progress rapidly to a fatal outcome, and the only post-mortem finding is adrenal haemorrhage. Although the typical pattern of meningococcal meningitis is a generalised rash, with fever, meningeal signs and vomiting, sometimes the symptoms are vague and cutaneous manifestations may be entirely absent, making it indistinguishable from other infections. Moreover, in individuals with dark complexion, petechiae are few and can be easily overlooked. In most of these cases post-mortem findings are characteristic of the Waterhouse-Friderichsen syndrome, but in others adrenal haemorrhage may be focal and observed only microscopically. To complicate matters further, other organisms such as Strep-
tococcus pneumoniae or Haemophilus influenzae are also involved in infectious fulminating sudden deaths and Waterhouse-Friderichsen syndrome. Thus, the prompt identification of the pathogen responsible for death is critical. Because of the difficulties of post-mortem cultures, other methods must also be used. The antigenic latex agglutination tests can provide a presumptive diagnosis that has to be confirmed with specific PCR techniques. Indeed, the development of real-time PCR assays designed to distinguish between the different meningococcal serogroups allows serogrouping in only a few hours, and provides vital information for the correct management of individuals who have been in contact with the index case.

Group A Streptococcus pyogenes is another bacterium that can cause progressive and fatal infections detectable only by forensic analysis. Necrotising fasciitis caused by this agent has been reported in the context of recent surgical treatment, but also as a consequence of injuries inflicted during an assault. This microorganism has also caused fulminating empyema diagnosed after death. Moreover, both meningococcal and Streptococcus pyogenes infections have been detected in several individuals found dead in their homes under circumstances suggestive of an assault. In those cases, investigation of the scene and the subsequent microbiological forensic analyses revealed that blood stains on the floor and bed linen were not due to an assault, but could be attributed to a bleeding wound.

THE SUDDEN INFANT DEATH SYNDROME

Sudden unexpected death in infancy is always the subject of legal investigation since a crime must be excluded. There are guidelines to ensure that vital evidence of inherited metabolic diseases, infection, or non-accidental injury is not lost or overlooked. For this reason, a complete post-mortem protocol should include biochemical, pathological, toxicological and microbiological analysis. Sudden infant death syndrome (SIDS) is the most common cause of post-neonatal infant mortality in the developed world. This is a diagnosis of exclusion with peak age of incidence between 2 and 56 months. Fifty to 63% of these infants have a pre-existing upper respiratory tract infection prior to death. It has been hypothesised that the immature immune system may be altered by a primary infection, preventing a protective response after second-
Typical syncytia due to Respiratory Syncytial Virus (RSV) in a sudden infant death

Myocarditis

Myocarditis is the most common cause of heart failure in children and adolescents and it is also considered an important predisposing factor for dilated cardiomyopathy. The introduction of endomyocardial biopsy has facilitated the clinical diagnosis, although its routine use is still not extensive, especially in children. Viral infections are thought to be the most frequent cause of myocarditis. Thus, postmortem analysis of fatal cases of myocarditis could be useful in the assessment of its etiology. Traditionally, classical microbiological procedures have been hampered by formalin-fixation of tissues, which prevents microbial culture and makes analysis by PCR difficult; thus, the final etiology of the infectious disease remains unknown in most cases. However, the application of new molecular techniques to detect viral genetic material in paraffin-embedded myocardium offers a promising strategy for establishing a viral origin of myocarditis.

SEXUALLY TRANSMITTED DISEASES

There are other legal situations calling for microbiology for reliable and conclusive data in court. One of them is the diagnosis of sexually transmitted diseases (STD) in suspected victims of sexual abuse, especially in children. In these cases, diagnostic tests should be chosen mainly on the basis of specificity. As a false-positive test for a STD can lead to erroneous reports of sexual abuse, unjustified prosecution, and even inappropriate convictions and incarcerations, the diagnosis should always entail isolation of the organism. However, not all culture methods for sexually transmitted pathogens are easy to perform or standardised, and a new generation of commercial kits based on molecular diagnoses is being launched. The inappropriate use of these non-culture tests could be avoided by the development and diffusion of special guidelines for the evaluation of infection in the realm of sexual abuse. So as to guarantee quality, only those laboratories with high standard control criteria should be authorised to analyse the samples involved in these legal situations. Molecular microbiologists could make a contribution by developing highly discriminative markers for strain typing. There are some pathogens that show extensive variation between strains due to horizontal gene transfer. One of them is Neisseria gonorrhoeae, in which some polymorphism markers with good discrimination potential have been described. Chlamydia trachomatis, also involved in STD, shows a great variety in ompT, the gene that encodes the major outer membrane protein, but the study of some housekeep-
ing gene loci demonstrated little sequence variation, thus limiting the subtyping to omp1. In addition, the methods used in pathogen strain profiling are usually tedious and time-consuming; electrophoresis on long agarose gels will sometimes provide identification of defined alleles by different size, but most frequently, sequencing will be the technique of choice.

In order to provide evidence of sexual contact between the victim and the suspect, it must be demonstrated that the suspected abuser carries the same strain as the victim once the pathogen has been isolated in both victim and abuser. However, the significance of a concordant strain typing must be interpreted in terms of the distribution of strain types in the local population, since the victim could have received the pathogen from another contact. Consequently, local population databases must be generated to determine the alleles’ frequency for each marker. Interestingly, phylogenetic analyses of HIV-1 and HCV have been admitted in court and used as evidence in some criminal cases, although their acceptability at court can be hampered by the absence of statistical confidence in the conclusions. This problem may be avoided with the development of methods allowing a statistical evaluation concerning the likelihood of each sample belonging to a given group, a relevant question in many forensic and epidemiological analyses of molecular sequences. For this reason, the integration of other related areas, such as epidemiology, is essential to achieve the goals of forensic microbiology.

**BIOTERRORISM**

Another issue concerning forensic microbiology is the need to identify the pathogens and toxins potentially used as biological weapons. Recently, a programme to improve the capabilities for determination of the use of pathogenic agents in an illicit manner has been sponsored by the U.S. Government. Microbial Forensics is a programme defined as a “scientific discipline dedicated to analysing evidence from a bioterrorism act, biocrime, or inadvertent microorganism/toxin release for attribution purposes”. The aim of this forensic investigation is not only to identify the causative agent and its source, so that appropriate and preventative measures can be implemented, but also to determine the association of this source with a specific individual or group. The foundations of this programme are the creation of a national bioforensics laboratory, a specialised laboratory network and a scientific working group, as well as the promulgation of quality assurance guidelines.

**Diagnosis Based in New Technologies**

Forensic microbiology requires a comprehensive combination of molecular and antigenic techniques, as well as some classical microbiological techniques. Various molecular techniques, such as PCR, gene sequencing and real time PCR, have become an essential part of the diagnostic armamentarium for rapid, specific and sensitive identification of pathogens in forensic samples. In order to link a pathogen with a crime and a perpetrator, strains must be subtyped by means of molecular biological tools similar to those used by forensic geneticists: single nucleotide polymorphisms (SNPs) characterisation, variable number tandem repeat analysis, pathogenicity array analyses, 16S rRNA sequencing, other molecular phylogenetic analyses, antibiotic resistance gene identification and modern robotic systems once they are further developed. Finally, toxins will be detected by immunoassays, biofunctional assays and mass spectrometry.

In summary, forensic microbiology is an increasingly useful discipline, involving methods that are at an interface between those of classical microbiology and those of forensics genetics. Throughout the last decade, the great advances in human genetics have been applied to forensic genetic identification, and today access to genetic tools makes it possible for the specialists to solve difficult criminal cases. This technology should be extended to the forensic identification of other microorganisms causing infections with medical-legal implications. Since the bioterrorism-associated anthrax investigation of 2001 in the United States, society in general, as well as the authorities, have become more aware of the importance of forensic microbiology and a great effort is being made to develop specialised and standardised methods to detect and identify any pathogen capable of serving as a weapon. Although such studies are important in the context of potential bioterrorism, this technology should be extended to encompass the identification of other pathogens involved in forensics, with a broader range of medical-legal applications. Standardising the diagnosis of the pathogens involved in sudden death and sexually transmitted diseases in victims of sexual abuse is also a matter of extreme urgency, not only in the context of health, but also for its judiciary consequences.

Amorro Fernández-Rodríguez, Clinical Microbiologist, Pharm. D., National Institute for Toxicology and Forensic Sciences, Madrid Email a.fernandez@mju.es

**FOR FURTHER READING**


Hammerschlag, MR. Implications of inappropriate STD testing go beyond pure diagnostics. ASM News 2003; 69 (2): 74–79
Diagnostic Research in Clinical Microbiology: a Resource Pack for the Novice Researcher

ABSTRACT
Novice researchers in diagnostic microbiology often overlook the fact that successful research is not based on inspiration alone. There is in fact a structure to planning and carrying out a research study. This paper examines the basic principles involved from selecting the research question, searching the literature, formulating the study design to the reporting of essential statistics. The architecture of diagnostic research is discussed in detail with emphasis on the uniqueness of the microbiological research process. The paper is not intended to be exhaustive but merely to act as a guide to the main issues faced by the microbiological researcher.

INTRODUCTION
Good quality research does not depend entirely on inspiration but also on how the research is structured; a fact often overlooked by the novice researcher. The aim of this resource pack is to provide a guide to both new and less experienced researchers in microbiology as to how to develop a new diagnostic method in the routine clinical microbiology laboratory. This resource pack is not exhaustive and is intended as a guide to the main issues faced in diagnostic microbiology. The main areas to be discussed will focus on selecting the research question and searching for appropriate literature, formulating the study design, what statistics need to be reported. The situation with microbiology is uniquely different to that of the other laboratory disciplines in that the main goal is the isolation or detection of living organisms that are responsible for causing disease. Therefore, when the term diagnostic test is referred to it usually relates to either a method of isolation, identification or detection of specific microorganisms. Improvements are continually sought with regard to the above for many reasons including cost and time needed to carry out existing methods. This resource pack will not cover issues relating to costs and staffing that also may require consideration when developing diagnostic tests.

DEVELOPING THE RESEARCH QUESTION
The most important aspect of any research is the question being asked. How do these questions come about? Research questions are rarely based on inspired ideas but are developed by following a suitable strategy. There are no formal rules that can be given for this process but a good starting point for further information is Chapter 3 in Research in Health Care by Crombie and Davies1. They described the following strategy:

• Review existing practice
• Challenge accepted ideas
• Look for conflicting views
• Investigate geographical variation
• Identify Cinderella topics (those that may have been overlooked)
• Let the imagination loose.

The most important of these are the review of existing practice and the use of imagination. In the light of existing information the imagination can consider various aspects and challenge current practice. These ideas must not be subjected to the normal rules of critical assessment as they may contradict conventional wisdom or they might never be raised because they might be deemed as foolish!

A similar notion is expressed by Bourner2 where he identifies the two most common avenues by which research questions arise, i.e. awareness of a problem and may even suggest areas of further research. These ideas must not be subdivided into the normal rules of critical assessment as they may contradict conventional wisdom or they might never be raised because they might be deemed as foolish.


Full instructions are available there and specifically for using MeSH terms at: www.ncbi.nlm.nih.gov/entrez/query/static/help/pmhelp.html#MeSHDatabase

A useful example of using a search strategy can be found here: www.med.ualberta.ca/ecbm/diagbasics.htm#filter

The question being asked. How do these questions come about? Research questions are rarely based on inspired ideas but are developed by following a suitable strategy. There are no formal rules that can be given for this process but a good starting point for further information is Chapter 3 in Research in Health Care by Crombie and Davies1. They described the following strategy:

• Review existing practice
• Challenge accepted ideas
• Look for conflicting views
• Investigate geographical variation
• Identify Cinderella topics (those that may have been overlooked)
• Let the imagination loose.

The most important of these are the review of existing practice and the use of imagination. In the light of existing information the imagination can consider various aspects and challenge current practice. These ideas must not be subjected to the normal rules of critical assessment as they may contradict conventional wisdom or they might never be raised because they might be deemed as foolish.

A similar notion is expressed by Bourner2 where he identifies the two most common avenues by which research questions arise, i.e. awareness of a problem and may even suggest areas of further research. These ideas must not be subdivided into the normal rules of critical assessment as they may contradict conventional wisdom or they might never be raised because they might be deemed as foolish.


Full instructions are available there and specifically for using MeSH terms at: www.ncbi.nlm.nih.gov/entrez/query/static/help/pmhelp.html#MeSHDatabase

A useful example of using a search strategy can be found here: www.med.ualberta.ca/ecbm/diagbasics.htm#filter
subject headings by which the literature is indexed in the database whereas; textword searches look for specific words in the articles’ bibliographic record. The best approach is to attempt both types of search to reduce the chances missing an important article. Starting with a broad search and progressively narrowing to reduce the number is a useful approach. Searching too specifically in the beginning may miss an important reference. An electronic database search using MeSH terms makes it possible to carry out searches using combinations of headings. This is very useful because by selecting combinations of headings you can greatly reduce the number of irrelevant results. Many databases have specific features that can be applied either alone or in combinations to vary the sensitivity and specificity of the search, i.e. to filter out irrelevant results to more easily find what you are looking for. Table I shows the most common of these.

Once the literature has been reviewed the research question should be clearly focussed. A clearly focussed question will reduce the chances of over elaboration in the collection of data. The question must specify in detail the purpose of the study, the methodology to be used and the measurements to be collected. Once the question has been formulated you are now ready to carry out the research.

ARCHITECTURE OF RESEARCH
There is a defined way of carrying out diagnostic research; one cannot just devise a new method or test and then introduce it into practice. Sackett and Haynes have recently described diagnostic research broken down into four phases:

- **Phase I:** Do test results in patients with the target disorder differ from those in healthy people? This is basically an evaluation of the test using positive and negative controls.
- **Phase II:** Are patients with certain test results more likely to have the target disorder than patients with other test results? There is a change in direction of conclusion from test result to diagnosis, rather than from diagnosis to test result as in Phase I.
- **Phase III:** Do test results distinguish individuals with and without the target disorder from patients in whom it is clinically reasonable to suspect that the disease is present? This is an assay validation in a real clinical setting.
- **Phase IV:** Do patients who undergo this diagnostic test have a better clinical outcome than similar patients who are not tested? This is the ultimate question to be asked: what are the benefits of this test? Sometimes they will be self-evident, as in diagnosing life-threatening disease, on other occasions they are not. It is often the case that phase IV testing is subjected to randomised control trials where the patient undergoes either the test of interest or another (or no) test.

Using the above framework most, if not all, clinical microbiological research can be carried out. The majority of published research often reports an analytical and, most importantly, a clinical evaluation.

### VALIDITY OF DIAGNOSTIC RESEARCH
The first thing to remember with a diagnostic test in clinical microbiology, as with other diagnostic tests, is that they are seldom 100% accurate. False positive and false negative results will occur. A good test will detect a high proportion of true positive results and exclude most if not all true negative results. In order to validate diagnostic research the test or method that has been developed must be compared to another test or method. This comparison is usually against an established “gold standard” or reference method. The “gold standard” method is that which is generally accepted to provide strong evidence of a positive diagnosis. For most areas of clinical microbiology these standards can be found in good quality textbooks such as *The Manual of Clinical Microbiology*. The most important aspect of this comparison is that it is independent and blind. All subjects or organisms must be tested against both the research and reference methods without prior knowledge of the result in either test to allow unbiased comparison.

---

**Table I: Common features for database searching**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Key</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truncation</td>
<td><em>(or $ or :)</em></td>
<td>Placed at the end of a word will include terms with all variable endings to the beginning of the word in the search, e.g. anal* will search for analytic, analytical, analyse, etc.</td>
</tr>
<tr>
<td>Focus</td>
<td>*</td>
<td>Placed at the beginning of a word searches for articles in which the word is a major focus of the paper.</td>
</tr>
<tr>
<td>Explode/expand</td>
<td>Explode or exp</td>
<td>Placed before a term will search for all possible related options.</td>
</tr>
<tr>
<td>Wildcards</td>
<td>?</td>
<td>Placed within a word indicates that the letter it replaces is a variable or absent. The search will include all permutations of the word, e.g. gynaecology will search for gynaecology and gynecology</td>
</tr>
<tr>
<td>Boolean</td>
<td>AND</td>
<td>Boolean operators are used between terms to link them. Article must include both terms, e.g. MRSA AND isolation.</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>Article can include either term.</td>
</tr>
<tr>
<td></td>
<td>NOT</td>
<td>Excludes articles, which include the term following NOT, e.g. Salmonella NOT typing.</td>
</tr>
<tr>
<td>Proximity</td>
<td>NEAR</td>
<td>Terms linked must occur close to each other, e.g. molecular NEAR typing</td>
</tr>
<tr>
<td>Limits</td>
<td></td>
<td>Can be used to restrict a search by publication type, year, language or other characteristics. Limits can also direct the search for terms to a particular part of the document. Many databases also have a limits option, which can be selected by clicking on it.</td>
</tr>
<tr>
<td>Related</td>
<td></td>
<td>Clicking on this hyperlink when you have found a useful reference will search for similar articles in the database.</td>
</tr>
</tbody>
</table>

*adapted from Jones-Harris 2003."
Traditionally, in clinical microbiology culture is regarded as the final arbiter as to whether a clinical specimen is truly positive or not for a given pathogen. This has certainly been the case in the development of rapid antigen testing for group A β-haemolytic streptococci in cases of pharyngitis. Vaspolder et al. used culture for Neisseria gonorrhoeae as the “gold standard” in their research into a molecular detection method for N. gonorrhoeae and showed that the molecular method performed well as a suitable screening and diagnostic test for gonorrhoeal infection in men and women. The use of molecular methods in routine clinical laboratories is perceived as expensive and developmental research in this area is often confined to laboratories associated with academic medical centres. Reference or “gold standards” may appear to be “cast in stone” but can change over time in response to research evidence. An example of this is the detection of genital Chlamydia trachomatis infection. The accepted “gold standard” for the detection of this pathogen was by culture in cell monolayers. This method has a sensitivity of 70–85% but the advent of molecular research methodologies now can produce a test that has sensitivity approaching 100% and is now recommended as the preferred laboratory test. Not all microbiological “gold standards” are by culture, especially those that provide the reference method for identification of organisms. leven et al. used a reference method taken from the Manual of Clinical Microbiology for their work developing a rapid and economical method for species identification of clinically significant coagulase-negative staphylococci. They compared their own rapid method with two commercial systems and the reference method and reported percentage agreement with the reference method identifications. In some areas of clinical microbiology it may be inappropriate to use a true “gold standard”. This may be due to the standard being too expensive, time consuming to carry out or an area where there has been a plethora of new developments such as specific culture media. In such cases where the goal of the research is to find a better method than the one currently in use by the laboratory it is acceptable to use the latter as the reference standard for comparison. This must be clearly stated in the research question and in any method section. Gurran et al. used this approach for their work on selective broth medium for the detection of methicillin resistant Staphylococcus aureus (MRSA). They used as reference standards Mannitol Salt Agar (MSA) containing oxacillin and Baird-Parker (BP) medium containing ciprofloxacin. They reported that MSA had been used in national and international studies to determine the frequency of MRSA and that BP was chosen because of the prevalence of ciprofloxacin resistance of MRSA in their locality and also, that it had been shown to be more sensitive than MSA. These statements were all backed up by suitable references. They reported a two-stage design with the first stage using MSA and BP as reference standards and the second stage using only BP. In conclusion they reported that selective mannitol broth (SMB) had a sensitivity and specificity of 100% for screening nasal swabs but overall the sensitivity and specificity dropped to 85.1% and 43.6% respectively when tested against other screening samples. Another example of the use of a local reference standard is given by the work of Perry et al. who looked at the use of a novel “suicide substrate” alafosfalin as a selective agent for the isolation of Salmonella from clinical samples. They modified a commercially available agar (ABC), incorporated alafosfalin as a selective agent and compared its selective and isolation properties against unmodified ABC and a “traditional” agar called Hektoen Enteric agar (HE). Both the unmodified ABC and HE agars served as reference standards.

EVALUATION RESEARCH

This is an area of clinical microbiological research that is often overlooked. It is usually involved when a commercial method or test is introduced into the laboratory. The issue addressed is about reliability: does the new test or method yield consistent results and is it replicable. There may be a comparison with a reference standard and the design of the study follows the criteria already established. A different design is needed when the new system is to potentially replace a current commercial system that is in use in the clinical laboratory. Here the reference standard is the current system in use. An example of this is the recent work of Davies et al. who evaluated a new commercial latex agglutination test for the serogrouping of β-haemolytic streptococci against four internationally used commercial systems. The four other systems acted in part as reference standards for the new system. The approach of testing the system is essentially the same as in diagnostic research, i.e. the results were blinded and tested independently to reduce potential bias.

CALCULATION AND REPORTING OF STATISTICS

Statistical analysis can often frighten the novice researcher and some may even try to avoid it “at all costs”. Knowing some basic statistics is essential when undertaking any type of research but especially in diagnostic clinical microbiological research. A good book to brush up on basic statistical methods is Statistics at Square One published by BMJ Books. Any diagnostic study requires essential statistics, which are described in the following sections.

SENSITIVITY AND SPECIFICITY

Most microbiological diagnostic tests classify disease qualitatively into two groups according to presence or absence of a particular organism or identify an organism on the basis of particular traits. This binary test then must be quantified to assess the ability of the test to discriminate between organisms or conditions of interest. This is achieved by using a 2 x 2 table as shown in Table 2. The performance of diagnostic tests is usually described in terms of sensitivity and specificity, which are defined as follows.

Sensitivity

This is the true positive rate, the proportion of true positive results that are correctly identified by the test. This can be calculated by dividing the true positive tests by the total disease positives: a / (a + c)

Specificity

This is the true negative rate, the proportion of true negatives that are correctly identified by the test. This can be calculated by dividing the true negative tests by the total disease negatives: d / (b + d)

Ideally a test should be 100% sensitive and specific. This is not always possible when dealing with live organisms as there will always be aberrant results due to mutations. The closer the test can be to 100% the more useful it is in microbiology.
Table 2: 2x2 table for diagnostic testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Disease</th>
<th>+ve</th>
<th>-ve</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ve</td>
<td>True +ve</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>-ve</td>
<td>False -ve</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
<td>n</td>
<td></td>
</tr>
</tbody>
</table>

POSITIVE AND NEGATIVE PREDICTIVE VALUES (PPV & NPV)

Sensitivity and specificity define the performance of a test in terms of the samples being tested but give no indication of what proportion of positive test results are truly positive, i.e. they give no interpretation of the value of a test result on an individual sample. To accomplish this we need to use PPV and NPV. These are defined as follows.

Positive predictive value

This is the proportion of samples with a positive test result that are correctly diagnosed as disease positive. This can be calculated by dividing true positive results by total positive results: PPV = a / (a + b)

Negative predictive value

This is the proportion of samples with a negative test result that are correctly diagnosed as disease negative. This can be calculated by dividing true negative results by total negative results: NPV = d / (c + d)

Tests with high sensitivity and specificity will not necessarily have high PPV and NPV values. To obtain high specificity the price may be to accept a high rate of false negative results. High numbers of false positives or negatives will lead to lower predictive values as they reduce the proportion of true results.

ACCURACY

This measures the performance of the diagnostic test by showing the proportion of all tests that have given the correct result, i.e. true positives and true negatives as a proportion of all results: (a + d) / (a + b + c + d)

CONFIDENCE INTERVALS (CI)

Altman\(^1\) argues that the emphasis of research should not aim at obtaining “statistical significance” and focus on the actual level of difference achieved. He argues that it is more useful to present sample statistics as estimates of results that would be obtained if the total population had been studied. The degree of precision can be shown by the use of a confidence interval. Confidence intervals give a measure of the uncertainty inherent in a study in absolute units. They do not take account of any additional uncertainty that might relate to other aspects such as bias in study design. Imprecision of measurement decreases as the sample size increases. Confidence intervals are calculated to determine whether the precision of the test is sufficient for its intended use.

It is now common to present diagnostic statistics together with their associated confidence intervals. These are normally given as 95% confidence intervals, indicating that with 95% probability the interval contains the true value obtained if the entire population was studied.

To calculate confidence intervals it is easier to use a statistical package than to attempt the calculation by oneself. If you do not have access to a suitable statistical package then a simple programme can be downloaded gratis from the following location: [www.sghms.ac.uk/depts/phs/staff/jmb/jmbsoft.htm](http://www.sghms.ac.uk/depts/phs/staff/jmb/jmbsoft.htm) or a web based calculator can be accessed at: [www.members.aol.com/johnp71/ctab2x2.html](http://www.members.aol.com/johnp71/ctab2x2.html). These will allow you to calculate sensitivity, specificity, PPV and NPV with 95% confidence intervals.

An example follows based on a rapid biochemical screening test for Salmonella. Table 3 shows the 2x2 table for the screening test. Based on the data in Table 3 the following calculations are used to determine the values for sensitivity, specificity, PPV, NPV and accuracy.

Sensitivity = 49 / (49 + 1) = 0.98
Specificity = 212 / (3 + 212) = 0.986
PPV = 49 / (49 + 3) = 0.942
NPV = 212 / (1 + 212) = 0.995
Accuracy = (49 + 212) / (49 + 3 + 1 + 212) = 0.985

Using the web based calculator the following 95% confidence intervals were determined:

Sensitivity = 98% (90.8% to 99.9%)
Specificity = 98.6% (96.9% to 99%)
PPV = 94.2% (87.3% to 96.1%)
NPV = 99.5% (97.8% to 100%)

To calculate confidence intervals it is easier to use a statistical package than to attempt the calculation by oneself. If you do not have access to a suitable statistical package then a simple programme can be downloaded gratis from the following location: [www.sghms.ac.uk/depts/phs/staff/jmb/jmbsoft.htm](http://www.sghms.ac.uk/depts/phs/staff/jmb/jmbsoft.htm) or a web based calculator can be accessed at: [www.members.aol.com/johnp71/ctab2x2.html](http://www.members.aol.com/johnp71/ctab2x2.html). These will allow you to calculate sensitivity, specificity, PPV and NPV with 95% confidence intervals.

Using the web based calculator the following 95% confidence intervals were determined:

Sensitivity = 98% (90.8% to 99.9%)
Specificity = 98.6% (96.9% to 99%)
PPV = 94.2% (87.3% to 96.1%)
NPV = 99.5% (97.8% to 100%)

Graeme Wilson
gwilson44@btinternet.com

ACKNOWLEDGEMENTS

This paper was commissioned as part of the Professional Doctorate in Biomedical Science programme at the University of Portsmouth, United Kingdom.

REFERENCES

7. Sackett DL and Haynes RB. The architecture of diagnostic research. BMJ, 2002;324:539–541

Table 3: 2x2 table for Salmonella screening test

<table>
<thead>
<tr>
<th>Salmonella</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>49</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>212</td>
<td>213</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>215</td>
<td>265</td>
</tr>
</tbody>
</table>
The Achilles’ Heel of the Endosymbionts

In the early 1960s in Egypt English archeologists discovered a well-preserved mummy of a high priest presumably from the 18th dynasty. Upon investigating the mortal remnants, they found a peculiar alteration of the genital organs, which opens the path to the cause of the hydrocele: a dilatation of the lymphatic vessels caused by parasites. Both testicles were so enlarged that they had been tied up with a cloth. Histopathologic investigation showed the fact that these parasites are nematodes, probably *Wuchereria bancrofti*. Since the Egyptian priest contracted lymphatic filariasis some 3000 years ago, knowledge about the classical tropical illness has dramatically increased. In the last ten years therapeutic approaches have been developed which, for the first time, make eradication of the parasites possible. Among the multitude of tropical pathogens the filarial worms are particularly unusual parasites. Despite the fact that these parasites are nematodes, they are not found in the intestine, but, depending upon species, in skin, blood, lymphatic vessels, and even in the eye of their host. They have an obligatory developmental phase in blood-sucking mosquitoes or flies, and these vectors transfer the next generation of the infectious agent to humans. In contrast to other multicellular parasites they do not produce eggs, but bear living offspring, which opens the path to the propagation of the filariasis. About a billion people live in areas of risk. While untreated the disease eventually leads to chronic skin inflammation and blindness, lymphatic filariasis leads to elephantiasis of body parts, in particular the genital organs, which opens the path to mockery from those around them. As if that were not bad enough, the parasite’s propagation is as successful as the reproduction strategy’s extravagance. In Africa, Asia, South America, the Pacific and Caribbean more than 200 million persons suffer from one or another type of filariasis. About a billion live in areas of risk. While untreated “river blindness” (onchocerciasis) leads to chronic skin inflammation and blindness, lymphatic filariasis leads to elephantiasis of body parts, in particular the genital organs, which opens the path to mockery from those around them. As if that were not bad enough, the course of time elephantiasis of the lower extremities turns the affected individuals into invalids.

Since recently, filariasis has also become more important to clinical microbiologists in Europe. On the one hand increasing numbers of tourists, business persons or development workers spend weeks or months in typical endemic areas and become infected. On the other, the number of visitors, immigrants or refugees from endemic areas, who come to Europe increases. In both cases patients with uncharacteristic skin alterations or recurring lymphangitis turn up. Laboratory diagnosis is based on the presence of microfilariae in blood, lymph, urine or skin samples and detection of specific antibodies. Eosinophilia, an increase in IgE serum as well as increased concentrations of IL-4 and IL-5 are frequently present.

For more than 50 years tropical-medical research has been striving to find a suitable therapy against filarial nematodes. The drugs used thus far, Diethylcarbamazine (DEC) since 1947, and the anti-helmintics, ivermectin and albendazole, have all a common drawback: they
work only against microfilariae. Macrofilariae are not impaired and continue to produce their tiny descendants in assembly-line fashion. The only substance, which works against the macrofilariae is suramin, a drug synthesised in 1920 in Germany for the treatment of sleeping sickness. It is, however, much too toxic for practical usage. Because of the macrofilariae’s long life span, one would have to treat all potential filarial carriers in an endemic area regularly over at least one decade, in order to interrupt transmission completely. Such an approach is not only expensive; it is also logistically complicated and requires high compliance from the population.

Against this background the discovery by a group of German researchers that filariae possess a sort of therapeutic “Achilles’ heel”, was a quantum leap in tropical medicine. Achim Hörauf’s group (formerly at Bernhard-Nocht-Institute in Hamburg, now Institute for Parasitology at the University of Bonn) found out that the most important human-pathogenic filariae species harbour endobacteria of the Wolbachia species, which are sensitive to tetracycline. After tetracycline treatment, the endobacteria in the uteri of the macrofilariae die. Consequently, the female parasites become sterile and degenerate. Hence, microfilariae are no longer produced.

First shown in animal models, chemotherapy targeting Wolbachia has been successfully confirmed by several human phase IIa studies in different African countries. In 1993 the American parasitologist, John McCall of the University of Georgia, had already observed that giving tetracycline to certain animals with filarial infections inhibited the development of sexually-mature worms. However, he drew the wrong conclusion that the antibiotic had a direct effect on the filariae. The Hamburg researchers first recognised the true connection. Wolbachia, present in the filariae, are genuine endosymbionts, also found in many insects. Phylogenetic analyses show that Wolbachia, which are related to Rickettsia, have been living in filarial nematodes for millions of years and similar to mitochondria, are transferred to the next generation through the fertilised egg (vertical transmission).

Since Wolbachia belong to the order Rickettsiales and are closely related to Ehrlichia spp, which all respond well to the antibiotic tetracycline, Achim Hörauf and colleagues added “two plus two” and got rid of Wolbachia with this antibiotic. Indeed, a standard therapy of six weeks with tetracycline led to an irreversible degeneration of macrofilariae. If one administers one dose of the anthelminthic ivermectin, in addition to doxycycline, this results in more than 90 per cent of all patients completely free of microfilariae on a long-term basis. The validity of the thesis that killing the endosymbionts by tetracycline is the crucial therapeutic step is supported by the observation that administering this antibiotic had no effect on the few filariae species, which do not harbour Wolbachia. The new therapeutic approach concurrently clarified another mystery about the exotic parasitic disease. For a long time it had been assumed that the chronic complications from onchocerciasis and lymphatic filariasis are not caused by the pathogens themselves, but by an inappropriate immune response. However, which mechanism keeps the immune system in a permanently hyperactive condition leading to tissue destruction was so far unknown.

Now it is clear that Wolbachia is the actual culprit. Lipopolysaccharide (LPS) - like molecules of Wolbachia activate mechanisms of natural immunity. For example corneal opacity in onchocerciasis is triggered by a lipopolysaccharide receptor, the Toll-like receptor 4, on host cells. Wolbachia LPS activates neutrophile granulocytes circulating in the blood, which thereupon migrate to the eye, eventually leading to corneal opacity. In addition, the sometimes dramatic adverse events of the drugs used so far can be explained by the release of Wolbachia LPS. When microfilariae are killed, for example by administering DEC, massive amounts of Wolbachia are released into the bloodstream and LPS enters the circulation. Consequently, the patient exhibits transient septicaemia-like symptoms, which the physicians had difficulty explaining.

**What will elimination succeed?**

In 1993 a world-wide campaign under WHO patronage was launched to eliminate lymphatic filariasis as an illness. To this end the entire population of endemic areas is annually treated with one or more filaricial drugs. In Africa and South America usually the combination of DEC and ivermectin or albendazole and ivermectin is used, in Asia DEC is predominantly administered alone. Doxycycline is not used in the mass treatment campaigns, since approximately 40 per cent of the target population are children or pregnant women, who should not be treated with a tetracycline. The success has been impressive. In the past year 80 million persons in 38 countries were treated in Africa alone and 50 million in India. The drugs are donated by the manufacturers and the logistical organisation of the mass treatment is financed by a global alliance for filariasis elimination. The WHO’s goal to eliminate lymphatic filariasis as a public health problem by 2020 seems realistic.
News in Brief

Infectious Diseases and Outbreaks

GROUP A STREPTOCOCCAL DISEASE IN BELGIUM
An outbreak of severe, invasive disease caused by Group A streptococci (GAS) was reported in Belgian hospitals. During a two-month period (April and May 2004) there were 55 cases in three regions (Flanders, Brussels and Wallonia). Six of the patients (two children and four adults) died. A working group on invasive GAS disease was set up and monitoring was enhanced. This pathogen is already monitored on a voluntary basis but hospitals have now been asked to report every incident of invasive GAS infection. Isolates are being typed at a reference laboratory. Of the isolates typed from this outbreak 16 were emm type 1 and 10 were emm 100–104. Isolates were susceptible to β-lactams and macrolides but are thought to be more virulent than previous strains. Eurosurveillance Weekly 8 (26) June 24, 2004

OUTBREAK OF NOROVIRUS INFECTION IN PORTUGAL
An outbreak of vomiting and diarrhoea involving 31 cases occurred in a school in the north of Portugal early in 2004. Control measures were taken quickly to limit the spread of the disease. The causative organism was isolated from two stool samples and shown to be norovirus by the use of RT-PCR. The virus was isolated in a Portuguese laboratory and samples were sent to the reference laboratory at Colindale (UK) for characterisation. It was found to belong to genogroup II and is similar to strains circulating in the UK. Tap water, dishes and the hands of kitchen staff were negative and it was concluded that the outbreak was not water or food borne. The probable route of transmission was faecal-oral and airborne from fomites. Eurosurveillance Weekly 8 (13) March 25, 2004

LESIONNAIRES’ DISEASE ASSOCIATED WITH WHIRLPOOLS AT EXHIBITION
Three cases of Legionnaire’s disease occurred in men all of whom had attended an exhibition and had stood by a whirlpool. Infection with Legionella pneumophila was confirmed by a urinary antigen test. One man aged 65 developed multi-organ failure, necessitating haemodialysis and mechanical ventilation for 11 days. Immunofluorescence tests on tracheal washings confirmed that the L. pneumophila belonged to serogroup 1. Tests were being carried out on the whirlpool to confirm whether it was the source of infection. Eurosurveillance Weekly 8 (15) April 8, 2004

Viral Infections

DEATH FROM RABIES IN A CHILD FROM LITHUANIA
A five-year-old boy from southern Lithuania died of rabies in March. There was no history of an animal bite and rabies was not suspected until late in the progression of the disease. Investigations following the confirmation of rabies revealed that between October and December 2003 two cases of animal rabies had been detected near where the child lived, one in a dog and one in a mongoose, but none had been reported during 2004. The parents said that the child had no contact with animals.

Resistance

THIRD CASE OF VRSA REPORTED
A third case of a patient infected with a vancomycin resistant strain of Staphylococcus aureus (VRSA) has been reported by CDC (US). The patient is a 63 year old woman in a long-term care facility in New York who has a history of diabetes, multiple sclerosis and a chronic urinary tract infection. In addition she had previously had infections with a vancomycin-resistant enterococcus (VRE) and a methicillin-resistant Staphylococcus aureus (MRSA). A urine culture from the patient contained a VRSA with an MIC of vancomycin of >256 (determined using an Etest). The isolate contained the mecA gene and the vanA gene but appears unrelated to the previous two cases. The isolate was susceptible to linezolid, chloramphenicol, minocycline, Synercid, rifampin and trimethoprim-sulfamethoxazole. MMWR 2004; 53: 322

INVESTIGATION OF THE SECOND CASE OF VRSA AND COMMENTS ON THE SITUATION
A detailed account of the second case of VRSA has been published in Clinical Infectious Diseases. An editorial commentary summarises the situation regarding the first two cases of VRSA. These two and the latest case have similarities in that the patients all had serious underlying conditions but had not received vancomycin immediately prior to the isolation of the VRSA. They did however have MRSA and VRE infections. In addition, these strains all retain susceptibility to a number of older and newer agents.
Whitener et al. CID 2004; 38: 1049 and Bush (Editorial) CID 2004; 38: 1056

CDR Weekly 14 (23) June 4, 2004 and 14 (28) July 8, 2004

CDR Weekly 14 (23) June 4, 2004 and 14 (28) July 8, 2004
with domestic or wild animals but that a piglet had died in the area from unknown causes. The animal was not examined by a veterinarian and was buried. Rabies is relatively rare in Lithuania with only 11 human deaths occurring between 1960 and 2004 although it is more common in animals. A surveillance and control programme was instituted in 2002 and vaccination of wild animals is to be undertaken.

Eurosurveillance Weekly 8 (16) April 15, 2004

HUMANS CONTRACT NEW VIRUS FROM BUSHMEAT
Hunting and eating monkeys and chimpanzees (bushmeat) is common in Central Africa and is thought to have been the original source of HIV since chimpanzees have been shown to carry the closely-related SIV. Simian foamy virus (SFV) occurs in a range of primates but causes no apparent disease in the animals. A study reported in the Lancet was carried out in the Cameroon and describes how ten people out of just over 1000 sampled carried antibodies to SFV. They had no overt signs of disease but clearly there is a risk of more unknown diseases passing to man. DNA sequencing indicated that there were at least three non-human primate sources of the virus: these were a gorilla, mandrill and De Brazza’s guenon.

Wolfe et al. Lancet 2004; 363: 932

SARS
SARS cases continue to be reported sporadically. In China there have been eight confirmed cases this year but WHO reports that the chain of human-to-human transmission has now been broken, with the last two patients in intensive care and no more cases having occurred. The source of the latest infections is still unknown and this is a cause for concern. Several of the latest patients were researchers at the National Institute of Virology in Beijing but the last two patients were not working with live virus. WHO urges all Member States to review their biosafety procedures and have issued safety guidelines.


A new rapid method of detecting SARS has been described by a group from Japan and Vietnam. It is a one-step technique termed real-time loop-mediated isothermal amplification (RT-LAMP) which involves amplification of the DNA in a single tube heated to 63°C. The authors assayed 49 throat and nasal samples from patients in Vietnamese hospitals during a SARS outbreak and compared the results with those from conventional RT-PCR. The RT-LAMP assay proved to be far more sensitive (100%) and highly specific (87%). The time required is between 11 minutes and 1 hour. The authors claim that the technique is not only rapid, specific and sensitive but it does not require skilled personnel or expensive equipment.


Two recent publications in the June edition of the Journal of Pathology, one from Holland and one from China, suggest that the SARS virus may be both more contagious than previously thought and more widely distributed in human tissues. The group from Groningen (the Netherlands) have looked at the distribution of a metallopeptidase, angiotensin converting enzyme (ACE2), which has been identified as the functional receptor for the SARS coronavirus. They found that the ACE2 protein was expressed on the surface of lung alveolar epithelial cells and enterocytes in the small intestine, suggesting that these sites could be the route of entry of the virus. In addition ACE2 was present in arterial and venous endothelial cells and arterial and smooth muscle cells.

The group from Guangzhou (China) looked at the distribution of the SARS coronavirus in a range of tissues from patients who had died of the infection. They used a murine monoclonal antibody specific for the virus nucleoprotein and probes specific for the viral RNA polymerase gene fragment. The virus was found to be widely distributed in many tissues of the respiratory and intestinal tract, kidneys and sweat glands. This suggests that the virus may be excreted through the faeces, urine and sweat.


A group from Taiwan has detected the presence of the SARS coronavirus in throat washes and saliva from patients suspected of having SARS. They used a quantitative RT-PCR assay. The number of viral particles present was high, suggesting that this could be a useful test for diagnosis.


A mouse model of SARS coronavirus infection has been developed in BALB/c mice by a group from New York (US). Although the SARS virus has been isolated from a range of animal species, previous attempts to establish an infection in mice had not been successful. The authors used infection by the intranasal and the oral routes simultaneously and found that they could isolate SARS coronavirus from lung tissue and intestinal tissue. Virus particles were first detected on day 7 post-infection and then increased dramatically between day 10 post-inoculation and day 28. This model may help in developing and testing antiviral agents and vaccines.


WEST NILE VIRUS (WNV)
A new study by a group in the Pasteur Institute in Paris (France) has shown experimentally how the virus variant responsible for the 2002 outbreak in North America preferentially infects the neurons in the central nervous system. In murine neural cell cultures, infection of the neurons was accompanied by a cytopathic effect and physiopathological changes. These results agree with the observations that an increase in neuropathogenicity in humans has been noted with recent isolates.

Ceccaldi et al. FEMS Microbiol Lett 2004; 233: 1

In April 2004 MMWR published an update of the results of the screening of blood donations and transfusion-associated transmission of WNV in the US for 2003. In spite of screening of blood samples, six cases of transfusion-associated transmission occurred indicating that low levels of virus can go undetected. Nucleic acid amplification tests have been used to screen samples and this has enhanced the safety of transfusion but the lower limit of virus that can lead to infection in recipients of infected blood is not known.

MMWR 2004; 53: 281

West Nile Virus infections have occurred earlier this year than previously with two cases reported by
the end of May and by June 8 there were seven cases, six in Arizona and one in New Mexico. By July 20 182 cases had been reported from 12 states, 69% of these being from Arizona. A large number of dead birds, 1264 corvids and 130 other birds had been found to have WNV.


**AVIAN INFLUENZA**

A report in the *Lancet* summarises the findings of an investigation carried out in the Netherlands following a highly lethal outbreak of avian influenza caused by influenza A subtype H7N7, to determine the risks of poultry transmitting the virus to humans. Workers in poultry farms and persons in close contact with infected patients were included in the study. Eye and throat swabs were collected and both cell culture and RT-PCR were used to determine the presence of influenza A virus, subtype H7N7. Over 450 people reported various health complaints, 77% of whom (349/453) had conjunctivitis and 20% of whom had an influenza-like illness. H7N7 was detected in 78 people with conjunctivitis, in five with conjunctivitis and flu-like symptoms, in two with flu-like symptoms and in four other patients. There was clear evidence of human-to-human contact as 83/453 with various symptoms had no respiratory symptoms. The patient, who had been exposed to dead chickens, was admitted to hospital in March 2004 with rapidly progressive pneumonia. A rapid test for influenza A on nasopharyngeal aspirates proved negative and the patient was not given antiviral agents. She died later with severe respiratory distress syndrome and multiorgan failure.


An outbreak of avian influenza in British Columbia, Canada has let to massive culling of affected poultry. Two poultry workers contracted the disease, both presenting with conjunctivitis and nasal discharge. Both have been treated with oseltamivir and have recovered. Workers involved with the culling are being vaccinated with the current anti-influenza vaccine. This will not protect against avian influenza but will prevent them being co-infected with circulating human strains and reduce the possibility of genetic reassortment between avian and human strains.

**Eurosurveillance Weekly 8 (15) April 8, 2004**

Atypical avian influenza, caused by influenza A subtype H5N1, has been reported from Thailand. The authors describe the clinical symptoms in a patient who had fever and diarrhoea but no respiratory symptoms. The patient, who had been exposed to dead chicken, was admitted to hospital in March 2004 with rapidly progressive pneumonia. A rapid test for influenza A on nasopharyngeal aspirates proved negative and the patient was not given antiviral agents. She died later with severe respiratory distress syndrome and multiorgan failure.


The genetic transition of the virus causing the avian influenza outbreak in Hong Kong in 1997 and subsequent avian outbreaks in 2001 and 2002 have been described in a recent paper published in *Nature*. A dominant H5N1 genotype (Z) in chickens and ducks was the result of genetic reassortment. The authors believe that domestic ducks play a major role in the maintenance of this virus and wild ducks probably aid in its dissemination. These viruses have pandemic potential and would not be easy to eradicate. Long term control measures are needed.

**Li et al. Nature 2004; 430: 209**

The WHO has expressed grave concern regarding the continuing outbreaks of avian influenza, H5N1. It states that while effective tools exist to control outbreaks in poultry, assessing the risks to human health is less certain. The ability of these avian viruses to infect humans appears to be low but there have been some human cases and there is a risk that they may develop a greater ability to infect humans. WHO urges that risk assessment be undertaken as soon as possible. It is now clear that the virus is more widespread than previously thought and a pool of infection exists in wild birds. WHO also urges that all virus isolates and clinical specimens be made available for investigation. People involved in culling poultry flocks must be protected with antiviral chemotherapy and trials of experimental influenza pandemic vaccines should be accelerated.

**WHO on-line update; July 8 2004. www.who.int/csr**

**Vaccines**

**AVENTIS RECALLS RABIES VACCINE**

Aventis Pasteur has recalled its rabies vaccine world-wide because a quality assurance test on samples not yet released for the market revealed the presence of a non-inactivated viral component of the vaccine. The Pitman-Moore rabies virus is an attenuated strain but one batch of product contained live virus. All batches manufactured at the same time have been recalled as a precaution even though they passed EU and US regulatory tests for virus inactivation.

**Eurosurveillance Weekly 8 (15) April 8, 2004 and MMWR 2004; 53 (Dispatch) 1**

**ACAMBIS SUSPENDS TRIALS ON SMALLPOX VACCINE**

Following three cases of myopericarditis (inflammation of the heart and the surrounding tissues), the UK biotechnology company Acambis suspended its Phase III studies on smallpox vaccine. The trial was a comparison with Dryvax, another smallpox vaccine and the company has not clarified whether there were similar effects with Dryvax. Such effects have been reported previously with smallpox vaccines.
PLAGUE VACCINE UNDER DEVELOPMENT
Scientists at the NIAID (US) have tested a vaccine (F1-V) against bubonic plague and report that good protection was seen in vaccinated mice challenged by allowing infected fleas to feed off them. Fourteen out of 15 of the control mice that had received only the adjuvant developed plague but all 15 of the vaccinated mice survived. The vaccine was developed at USAMRID and has shown protection in conventional models in mice, ferrets and monkeys, where the animals are challenged by injection. This is the first time a more natural method of infection has been used.

Prions
UNUSUAL TYPE OF SCRAPIE DETECTED IN SHEEP
There is a theoretical risk that sheep, some of whom are infected with scrapie (a TSE) might become infected with BSE and the presence of scrapie could then mask the BSE. BSE has not been found in sheep but during the epidemic of BSE in the UK in the 1980s, some sheep were fed cattle-derived meat and bone meal. Recently an unusual type of scrapie was detected in a sheep carcass in the UK. Based on a battery of tests this TSE does have some characteristics similar to BSE but using histochemical tests it was decided that it is not BSE.

Industry and Drugs
TELITHROMYCIN APPROVED BY FDA
Telithromycin (Ketek™, Aventis) has finally gained approval by the FDA. It is approved for use in treating mild to moderate cases of community-acquired pneumonia, sinusitis and acute exacerbations of chronic bronchitis. It is restricted to treating those aged over 18 years.

FOSAMPRENAVIR APPROVED FOR USE IN EUROPE
The new anti-HIV drug, fosamprenavir (Telzir™), to be jointly marketed by GSK and Vertex, has gained approval for use in Europe. The protease inhibitor is already marketed in the US as Lexiva™. The drug is approved for use in combination with ritonavir (Norvir™, Abbott).

Schering-Plough (S-P) has finalised a deal with Toyama to licence the des-fluoro(6)-quinolone antibacterial agent, garenoxacin. S-P has the worldwide rights to garenoxacin, excluding Japan, Korea and China.

BAYER BUYS ROCHE’S OTC BUSINESS
Bayer has bought the over-the-counter sector of Roche for approximately EUR 2.4 billion, more than the original anticipated price. The European headquarters will be in Basle. Bayer has also acquired five Roche production sites.

AVENTIS MERGES WITH SANOFI
After months of speculation, the takeover battle of Aventis, the Franco-German firm, has been amicably resolved by a merger with Sanofi-Synthelabo, the French firm. Novartis had originally bid for Aventis but the French Government did not approve the proposed merger. Sanofi then put in a hostile bid and after lengthy discussions, a ‘friendly’ offer was made by Sanofi and accepted by Aventis. The new company will be named Sanofi-Aventis and will be the largest pharmaceutical company in Europe and the third largest in the world.

European Matters
FRENCH RESEARCH WORKERS PROTEST OVER GOVERNMENT CUTS
In March there was a rally outside the Paris City Hall of approximately 15,000 French research scientists, part of a movement called “Save Research”, protesting against the Government’s proposed cuts. Following this there was another march together with hospital workers complaining about plans to overhaul the public hospital system. Currently France ranks fourth in world expenditure on research into health, behind Japan, the US and Germany.
BMJ 2004; 328: 662

SWEDEN BANNS PRIVATISATION OF HOSPITALS
New legislation is planned by the Swedish government to prevent the privatisation of hospitals. Some local authorities had privatised state hospitals that had expanded into private care. Private companies will no longer be allowed to buy regional or University hospitals but existing private hospitals will be able to continue and new hospitals may be set up. They are not, however, allowed to take state insured patients.
BMJ 2004; 328: 484

UK GOVERNMENT Launches AN INQUIRY INTO THE PHARMACEUTICAL INDUSTRY
The UK government is planning an inquiry into the influence of the pharmaceutical industry on health policy, health outcomes and future health needs. A spokesman stated that this proposal was not a response to various recent issues surrounding drug safety or clinical trial disclosures. The Association of the British Pharmaceutical Industry (ABPI) has officially welcomed the plan and stated that it is “looking forward to co-operating fully with the committee as the enquiry progresses”. Comments will be gathered until mid-August with a report anticipated early in 2005.
Pharmatimes (on line) June 21, 2004 and ABPI press release June 18, 2004
Pamela Hunter
Medical Writer
Forthcoming 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

<table>
<thead>
<tr>
<th>Event Details</th>
<th>Dates</th>
<th>Location</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>8–9 October 2004</td>
<td>Infections in ICU</td>
<td>Place: Sochi, Russia</td>
<td>Dmitry Galkin, MD</td>
</tr>
<tr>
<td>17–20 October 2004</td>
<td>ESCMID/SHEA Training Course in Hospital Epidemiology</td>
<td>Place: Freiburg, Germany</td>
<td>Dr Markus Dettenkofer</td>
</tr>
<tr>
<td>2–5 April 2005</td>
<td>15th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)</td>
<td>Place: Copenhagen, Denmark</td>
<td>AKM Congress Service</td>
</tr>
<tr>
<td>1–4 April 2006</td>
<td>16th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)</td>
<td>Place: Nice, France</td>
<td>AKM Congress Service</td>
</tr>
<tr>
<td>5–9 October 2004</td>
<td>1st Middle East Conference on Infection Prevention</td>
<td>Place: Riyadh, Saudi Arabia</td>
<td>Contact: Infection Control Forum, Riyadh</td>
</tr>
<tr>
<td>22–24 November, 2004</td>
<td>ARFAC Consensus Conference</td>
<td>Place: Amsterdam, the Netherlands</td>
<td>Dr. Fiona MacKenzie</td>
</tr>
<tr>
<td>28–29 January 2005</td>
<td>10th International Symposium on Infections in the Critically Ill Patient</td>
<td>Place: Porto, Portugal</td>
<td>Contact: McCann Meetings</td>
</tr>
<tr>
<td>1–2 March 2005</td>
<td>1st European Consensus Conference on the Treatment of Chronic Hepatitis B and C in HIV Co-infected Patients</td>
<td>Place: Paris, France</td>
<td>Contact: Wells Healthcare</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</td>
<td>Congressos E Incentivos Rioja</td>
</tr>
</tbody>
</table>

Supported by ESCMID

22–24 September 2004 European Helicobacter Study Group XVII International Workshop Place: Vienna, Austria | Contact: Email: ehsg@medacad.org | Internet: www.medacad.org/ehsg2004 |

Imprint

ESCMID News: Newsletter of the European Society of Clinical Microbiology and Infectious Diseases

Editors and Editorial Office: Peter Schoch, Managing Director; Roger Finch, Chairman Publication Committee; Dianne White, Publication Assistant; Pamela A. Hunter, Medical Writer; Editorial Office: ESCMID Executive Office, PO Box 6, CH-4005 Basel, Switzerland. Email: info@escmid.org

Manuscripts and Copyright: Submission of unsolicited manuscripts, graphics and photographs for publication is highly welcome. In addition, the editors actively solicit or commission articles from ESCMID members, officers, study groups and third parties. Colour illustrations are encouraged. Copyright for articles accepted for publication is shared between ESCMID and the author(s).

Editorial Statement: Despite careful editing and setting, ESCMID, the editors and Interrepro AG cannot be liable for any errors or inaccuracies in this publication. Opinions expressed are those of the contributing authors.

Number of Issues & Editorial Deadlines: ESCMID News appears three times per year in April, September and December. Manuscripts must arrive at the Editorial Office (preferably by email) by the 15th of the previous month if they are to be considered for publication in the next month’s issue.

Distribution and Circulation Number: ESCMID News is personally distributed to all registered ESCMID members and spread at international conferences for promotion of ESCMID. Circulation number: 4500

Change of Address: Notice of change of address should be sent to Ms B. Menzemeier, ESCMID Secretariat, PO Box 1131, D-82018 Taufkirchen, Germany. Email: birgit.menzemeier@escmid.org

Printer: ESCMID News is produced by Interrepro AG, Pumpwerkstrasse 11, CH-4142 Münchenstein, Switzerland.

ESCMID Executive Committee

M. Struelens, President, Brussels, B
C. Carbon, Education Officer, Paris, F
G. Cornaglia, Secretary General, Verona, I
R. Finch, Past President, Nottingham, UK
P. Francioli, ECCMID Programme Director, Lausanne, CH
E. Nagy, Professional Affairs Officer, Clinical Microbiology, Szeged, H
S.R. Norrb, President-elect, Professional Affairs Officer, Infectious Diseases, Stockholm, S
A. Voss, Treasurer, Nijmegen, NL
J. Vila, Scientific Affairs Officer, Barcelona, E

Ex Officio Members:
J. Jelinkova, President 14th ECCMID 2004, Prague, CZ
N. Høiby, President of 15th ECCMID 2005, Copenhagen, DK
C.E. Nord, Editor CMI Supplements, Stockholm, S
K. Towner, CMI Editor-in-Chief, Nottingham, UK
P. Schoch, Managing Director, Basel, CH